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INVITED SPEAKER PRESENTATIONS

I1
PReS13-SPK-1478: New developments in our care & understanding of JIA
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Recent years have seen a rapid change in speed of translation from basic science into the clinic: the benefits of this are now being felt right across pediatric rheumatology. There is an increasing awareness that our patients need first class science to be done to answer major questions and develop better treatments: in fact patients and their families often ask why we are not making faster progress, and wish to contribute to this work.

To this end more and more large collaborative studies and networks are growing in our specialty that enable all children to be part of such studies. In this session we will review some of the most exciting novel developments that have happened in the year of 2012-2013 in basic science, including novel results from genetics, molecular and functional biology.

We will consider how these new findings relate to patients with chronic autoimmune and inflammatory diseases, and how those developments may translate to better care and outcomes for our patients.

Disclosure of interest: None declared.

I2
PReS13-SPK-1253: Challenges in nursing care with the new biologics for JIA
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Sam was diagnosed with extended oligoarticular Juvenile Idiopathic Arthritis at the age of 18 months. He began Etanercept at the age of 10 years old in March 2007 after an inadequate response to non-steroidal medications, methotrexate and numerous steroid preparations. Seventeen months later he was switched to Adalimumab with the expectation that this would have an improved response for him. Sam hated Adalimumab and was struggling to tolerate the injections. Encouraging Sam to persevere was difficult but he did so. After seven months, Sam refused anymore Adalimumab and had fourteen months only on Methotrexate, with numerous joint injections and intravenous steroid pulses. He was then commenced on Abatacept. Sam was seen every 4 weeks and his active joint disease remained apparent. By fourteen months only on Methotrexate, with numerous joint injections and requiring frequent joint injections and occasional intravenous pulses of steroids when he allows it, Sam is getting very fed up with the fortnightly infusion and the associated day out of school. Now at 16 years of age and struggling with his GCSE exams, Sam wants to know what will work for him. Despite his parent’s strong reluctance, Sam wants to know if he can have a bone marrow transplant and believes the quoted 10% risk of mortality is worth it.

Sam’s case is not unique but it does highlight many issues with these newer ‘biological’ therapies. This presentation will highlight many of these issues including injection site reactions, adverse events, changing therapies and perhaps most importantly; managing patient expectations.

Disclosure of interest: None declared.

I3
PReS13-SPK-1034: looking for new monogenic forms of lupus
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We can expect that a better understanding of the pathogenesis of systemic lupus erythematosus (SLE) will eventually lead to improved treatments for this devastating disorder (‘translational medicine’). And if lupus is not a single disease entity, then different treatment regimens might be appropriate in different patients (‘personalized medicine’).

As one approach to improving our understanding of why some people develop lupus, we are interested in the identification and analysis of monogenic (i.e. Mendelian) forms of SLE - thinking that they will not only provide clues to disease causation in specific cases, but that they will also help to define general molecular concepts of immune tolerance/dysfunction in humans, and thus inform the experimental approaches of other researchers (by highlighting potentially important disease pathways e.g. the ‘type I interferonopathies’).

Drawing on a well-proven strategy taken in other ‘complex diseases’ (e.g. certain types of cancer, motor neuron disease, Parkinson disease, Alzheimer disease etc.), we hypothesise that populations of children affected by lupus will likely be enriched for Mendelian forms. We are therefore harnessing the power of next-generation sequencing technology to identify highly penetrant genetic susceptibility loci for
Neuropsychiatric (NP) manifestations pose diagnostic and therapeutic challenges in systemic lupus erythematosus (SLE). Less than one-third of these events can be directly attributed to SLE; accordingly attribution to SLE remains a considerable challenge. Increased generalized SLE disease activity or damage, previous or concurrent major neuropsychiatric SLE (NPSLE) events, and persistently positive moderate-to-high antiphospholipid antibody titers are established risk factors. NPSLE patients have increased genetic burden and novel genomic approaches are expected to elucidate its pathogenesis. In animals with disturbed blood-brain barrier, autoantibodies against the NR2 subunits of the N-methyl-D-aspartate receptor and 16/6 idiopathic NP cause diffuse NP manifestations through neuronal apoptosis or brain inflammation; data in humans are still circumstantial. In NPSLE, advanced neuroimaging uncovers structural and metabolic abnormalities in brain regions with normal appearance on conventional magnetic resonance imaging. The European League Against Rheumatism (EULAR) has published evidence and expert based opinion for the management of NPSLE(1). According to them, diagnostic evaluation is guided by the presenting manifestation with MRI used to visualize brain or spinal pathologies. For neuropsychiatric events believed to reflect an immune or inflammatory process, or when these events occur in the context of active generalized disease, evidence (primarily from uncontrolled studies) supports the use of glucocorticoids alone or in combination with immunosuppressive therapy. In refractory cases, uncontrolled studies suggest a beneficial role of rituximab. Antiplatelet and/or anticoagulation therapy is recommended for NPSLE manifestations related to antiphospholipid antibodies, especially for thrombotic cerebrovascular disease. For the future, we anticipate novel biomarkers and advanced neuroimaging tests will better define the underlying pathologic mechanisms of SLE-related neuropsychiatric disease, and help guide therapeutic decisions.

Disclosure of interest: None declared.

PReS13-SPK-1033: Neonatal lupus
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Children born from mothers positive for autoantibodies against SSA/Ro and/or anti-SSB/La ribonucleoproteins may develop heart conduction tissue damage resulting in atrioventricular block and/or transient skin rash. In addition, enzyme abnormalities and anaemia/thrombocytopenia.

Additional transient electrocardiographic abnormalities (sinus bradycardia, QT interval prolongation) have been reported. Such clinical and laboratory manifestations are included in the so-called Neonatal Lupus Syndromes, independently whether the mother is suffering from a systemic autoimmune disease or is totally asymptomatic. The prevalence of the congenital heart block is around 2%, of neonatal lupus rash around 20%, while laboratory abnormalities in asymptomatic babies can be detected in up to 30% of cases. The risk of recurrence of complete heart block is almost ten times higher in the following pregnancies. Most of the mothers are asymptomatic at delivery and are identified only by the birth of an affected child. Their longterm outcome is generally more reassuring than previously assumed and arthralgias and xerophthalmia are the common symptoms.

A standard therapy for heart blocks detected in utero is still matter of investigation, although fluorinated corticosteroids have been reported to be effective on myocarditis signs when present. Serial echocardiograms and obstetric sonograms, performed at least every two weeks starting from the 16 weeks’ gestation, are recommended in anti-Ro/SSA positive pregnant women: the goal is to detect early fetal abnormalities, that might precede complete atrioventricular block and that might be a target of preventive therapy. Transplacental passage of maternal anti-SSA/SSB IgG is thought to be pivotal in inducing tissue damage. However, the discordant appearance of the syndrome in twins does suggest a role also for foetal or environmental factors.

Disclosure of interest: None declared.

PReS13-SPK-1137: New developments in our care & understanding of JIA
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Despite significant advances in our care and understanding of patients with Juvenile Idiopathic Arthritis (JIA), many continue to have severe, debilitating disease. A holistic multi-disciplinary approach to the care of children and their families is critical to maximise the child’s physical and psychosocial development. Landmark clinical trials including more recently those of a range of biologics have significantly improved outcomes. These include trials of tocilizumab, canakinumab, and other ongoing trials that are the result of important international collaborative efforts. However predicting which children will respond in a timely manner remains an evolving art as children may be exposed to potentially toxic agents whilst finding the most suited for them. Long-term safety, as well as efficacy, is critically important.

Knowledge translation that arises in the day to day care of children into driving forward ever greater understanding of the biological basis that underpins JIA and its sub-types is ever more crucial. Similarly, our
understanding of the underlying biological processes and our ability to manipulate the immune pathways with ever more accuracy offer enormous clinical opportunities, yet also challenges. Involvement of the multidisciplinary team will ensure that best care is provided going forward. An overview of recent advances in our care and understanding of children with JIA will focus on recent and novel treatments that are now being introduced into our care of patients.

Disclosure of interest: None declared.

18
PReS13-SPK-1590: Relevance of cytokine in pediatric inflammatory disease
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Pediatric Rheumatology 2013, 11(Suppl 2):18

Cytokines are pleiotropic mediators that play a major role in inducing and orchestrating the inflammatory and the immune response. They play a major role in the response to damage or infections. In some pathological condition abnormal regulation of the production of cytokines leads to pathological events and subsequent damage to target tissues. Dissecting the role of each single mediator in the plethora of cytokines and in the complex networks has been one of the aims of biomedical research that has led to relevant applications in rheumatic diseases. In the presentation we will briefly review the evidence leading to the identification of the role of some cytokines (IL-1, IL-6 and TNF) as key mediators and therapeutic targets in pediatric rheumatic diseases.

Disclosure of interest: None declared.

19
PReS13-SPK-1472: Science of muscle training in inflammatory disease
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Idiopathic inflammatory myopathies (IIMs) embody a heterogeneous group of conditions with a chronic autoimmune inflammatory process affecting a variety of muscle, skin and internal organs. IIMs are clinically characterized by (proximal) muscle weakness and decreased muscle endurance. Exercise training is increasingly utilized as a non-pharmacological intervention in the clinical management of pediatric patients with chronic inflammatory conditions; however, the efficacy, safety and effects on the course of the conditions should be topic of investigation. Clinicians attempting to prescribe exercise training in children with chronic inflammatory conditions face a dilemma. Exercise and physical training may encourage exercise training is increasingly utilized as a non-pharmacological intervention in the clinical management of pediatric patients with chronic inflammatory conditions; however, the efficacy, safety and effects on the course of the conditions should be topic of investigation. Clinicians attempting to prescribe exercise training in children with chronic inflammatory conditions face a dilemma. Exercise and physical training may encourage

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110
PReS13-SPK-1082: Catastrophic antiphospholipid syndrome
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In the 1980’s, isolated case reports appeared in the world literature documenting patients who appeared to suffer from an often fatal complication associated with the demonstration of antiphospholipid antibodies (aPL). The clinical picture comprised widespread multi-organ thrombosis and consequent organ failure and was referred to by the authors as a “devastating non-inflammatory vasculopathy”, “occlusive vasculopathy” or “acute disseminated coagulopathy-vasculopathy” when describing individual cases. In 1992, ten patients with this unusual condition were first reviewed and, in an attempt to define its acuteness and severity, the eponym “catastrophic” was attached to the variant of the antiphospholipid syndrome (APS). Although less than 1% of patients with the APS develop this complication, its potentially lethal outcome, despite all recommended therapies, emphasizes its importance in clinical medicine today. The majority of these patients end up in Intensive Care Units (ICU) with multi-organ failure and, unless the condition is considered in the differential diagnosis by the attending physicians, it may be completely missed with a disastrous outcome for the patients.

The rarity of the syndrome makes it extraordinarily difficult to study in any systematic way. In order to put together all the published case reports as well as the new diagnosed cases from all over the world, an International Registry of patients with catastrophic APS was created in 2000 by the European Forum on Antiphospholipid Antibodies (“CAPS Registry”). The initial results of the project have been already presented in several original papers. Currently, it documents the entire clinical, laboratory and therapeutic data of more than 400 patients whose data has been fully registered and it is expected that the periodical analysis of these data will allow us to increase our knowledge of this condition. The purpose of this presentation is to focus on the current management of these patients and some of the potential new therapeutic approaches.

Disclosure of interest: None declared.

111
PReS13-SPK-1240: New aspects on APS pathogenesis
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Antiphospholipid antibodies (aPL) are both diagnostic markers for, and pathogenic drivers of, antiphospholipid syndrome (APS). Beta 2 glycoprotein I (Beta2GPI)–dependent aPL, the most important subset, mediate different—and not necessarily alternative—thrombogenic mechanisms, mainly on the basis of their reactivity with Beta2GPI expressed on cells that participate in the coagulation cascade. In vivo experimental models showed that Beta2GPI cannot be detected in vascularized organs in resting conditions, while it can be over-expressed after pro-inflammatory stimulus. In this condition autoantibodies recognize the molecule, fix complement (C) and eventually induce clotting. This finding is in line with the observation that although the presence of aPL is a necessary pre-condition, APS-associated clotting is triggered by an additional ‘second hit’, frequently related to innate inflammatory immune responses. Recurrent pregnancy complications associated with aPL cannot be explained solely by thrombosis, and alternative pathogenic mechanisms have been reported. Although one in vivo model of fetal loss supports a mechanism of aPL-mediated acute placental inflammation, other models and the histopathological examination of APS placentae do not support an inflammatory signature. Beta2GPI can be detected on endothelial cells of uterine vessels in resting conditions and its presence is increased during pregnancy in uterine endothelium and trophoblast. This finding does support the hypothesis that Beta2GPI -dependent aPL recognize their antigen on placental tissues. There is evidence that the antibodies may inhibit the growth and differentiation of trophoblasts, and eventually cause defective placentation so explaining the APS obstetric manifestations.

Why antibodies with similar antigen specificity produce different clinical manifestations is not clear. The formation of immune complexes on the membrane of cells with different biological functions may at least in part explain the diverse effects mediated by the autoantibodies (i.e. clotting versus defective placentation). Altogether this finding strongly supports the pivotal role of Beta2GPI as the main tissue target for aPL. Accordingly, new approaches have been tried in order to interfere with the antibody binding and its consequences. A synthetic peptide displaying a similarity in the PL-binding region of the Vδ domain of the Beta2GPI was shown to compete with the molecule binding to the membrane of cells involved in the pathogenesis of the syndrome (i.e. endothelial cells, monocytes and trophoblasts). The passive infusion of the peptide was protective against the
effect of polyclonal human APS IgG fractions on experimental thrombus formation and fetal loss induction. Moreover, a human monoclonal antibody against the immunodominant epitope of the Beta2GPI (Domain I) was shown to induce fetal loss and to trigger clotting by fixing C⃞ in naïve mice. A similar monoclonal antibody lacking the CH2 fragment in the Fc gamma portion was still reacting with the Beta2GPI but no more able to activate C⃞. The C⃞ non-fixing monoclonal antibody was protective by competing with the pathogenic one when passively infused in naïve mice and evaluated for both the induction of thrombus formation and the induction of fetal loss.

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112 PreS13-SPK-1277: Role of B2GPI in APS
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β2-Glycoprotein I (β2-GPI), also known as apolipoprotein H, is a 50 kDa protein that was described for the first time in 1961, and in 1968 the first apparently healthy person was identified deficient in this protein. As no function could be attributed to β2-GPI, the protein did not receive much attention and on average a single publication per year appeared in the literature. From 1990 onwards, the interest in this apparently obsolete protein has increased significantly when β2-GPI was identified as the most important antigen in an autoimmune disease called the antiphospholipid syndrome (APS). APS is an auto-immune disease characterized by thrombotic complications in both arteries and veins as well as pregnancy-related complications in combination with the presence of so-called antiphospholipid antibodies in the plasma of these patients. It is now generally accepted that these auto-antibodies are not directed against negatively charged phospholipids but towards proteins bound to these phospholipids. Animal studies have shown that the most prominent antigen in APS is β2-GPI, a protein with relatively low affinity towards anionic phospholipids. The importance of antibodies against β2-GPI was demonstrated by injection of these antibodies in mice, which resulted in increased thrombus formation when challenged and they showed an increased resorption of fetuses when pregnant. Despite the obvious importance of β2-GPI in the pathophysiology of APS, these in vivo experiments did not reveal a physiological function for this protein. It was already known for a long time that no circulating immune complexes could be detected in plasma of patients with APS, suggesting that the epitope recognized by the auto-antibodies was cryptic. Moreover, different studies have shown that the presence of auto-antibodies against domain I of β2-GPI correlates much better with clinical manifestations than auto-antibodies against the whole protein. This assumption was confirmed by the observation that β2-GPI can exist in at least two conformations, a circular conformation and a stretched conformation. In plasma, β2-GPI predominantly circulates in the circular conformation in which N-terminal domain I interacts with the C-terminal domain V. When β2-GPI binds to anionic phospholipids, it is converted into the stretched conformation. This conformation exposes an otherwise cryptic epitope in domain I and the protein can be recognized by the circulating auto-antibodies. In recent years, novel and exciting data have become available that suggest an important function of this protein in innate immunity. β2-GPI was found to scavenge lipopolysaccharide (LPS) and was able to clear unwanted anionic cellular remnants such as microparticles from the circulation. The scavenger function of β2-GPI is dependent on the stretched conformation. After binding of LPS, β2-GPI is cleared by monocytes. The new indications regarding a possible physiological role of β2-GPI could also shed light on the events that cause the formation of auto-antibodies against the protein, and why auto-antibodies against this protein results in an increased risk for thrombo-embolic complications and fetal losses.

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114 PreS13-SPK-1322: Autoinflammatory in nature: what patients teach us
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The autoinflammatory syndromes are a group of multisystem disorders characterized by recurrent episodes of fever and systemic inflammation affecting the eyes, joints, skin, and serosal surfaces. These syndromes differ from autoimmune diseases by several features, including the periodicity whereas autoimmune diseases are progressive, and the lack of signs of involvement of adaptive immunity such as association with HLA haplotypes, high-titer autoantibodies or antigen-specific T cells. Thus, autoinflammatory syndromes are recognized as disorders of innate immunity. This definition is supported by the a dramatic therapeutic response to IL-1 blocking. Indeed, the rapid and sustained response to a reduction in IL-1 activity on an "ex adjuvantis" basis is the best hallmark of most of these diseases. Due to the rarity of these conditions, most of the studies aimed to unravel the pathogenic consequences related to the mutation of genes involved in inherited autoinflammatory

Introduction: The antiphospholipid antibody syndrome (APS) is a multisystem autoimmune disease characterized by thromboembolic events, pregnancy morbidity, hematologic, dermatologic, neurologic and other manifestations in the presence of elevated titers of antiphospholipid antibodies (aPL). In recent years, APS has been increasingly recognized in various pediatric autoimmune and non-autoimmune diseases, but the relatively low prevalence and heterogeneity of APS in childhood made it very difficult to study in a systematic way.

Objective: To evaluate the prevalence of thrombotic and nonthrombotic clinical manifestations in children with positive aPL and determine the long-term outcome of children with APS.

Methods: A retrospective study with longitudinal follow-up of an unselected group of children who tested positive for at least one aPL subtype (aCL, anti-β2GPI and/or LA) was conducted for assessment of the prevalence of clinical features associated with aPL in children. Testing for aPL was requested by treating physicians given the clinical suspicion of aPL-related clinical manifestations. Data from the European registry extended internationally of pediatric patients with APS (Ped-APS Registry) were used for assessment of the long-term outcome of children with APS. To be eligible for enrollment the patient must meet the preliminary criteria for the classification of pediatric APS and the onset of APS must have occurred prior to the patient's 18th birthday.

Results: A total of 163 patients (76%) were positive for at least one aPL subtype (aCL, anti-β2GPI and/or LA) at the time of or within the first three months after the disease presentation were enrolled. There were 98 (62%) females and 61 (38%) males with mean age at disease presentation 11.4 years (range: 1-18 years). Mean follow-up period was 6.2 years. During this period 25 (16%) patients had thrombotic event (16 venous and 9 arterial), 48 (30%) patients developed hematological manifestations, 25 (16%) patients nonthrombotic neurological manifestations, 19 (12%) patients skin manifestations and 5 (3%) patients cardiac valve disease. Two out of 25 (8%) patients with thrombosis had recurrent thrombotic event. Underlying systemic autoimmune disease was identified in 55 (35%) of patients. The clinical characteristics and outcome was compared with 140 children with APS included in the Ped-APS Registry. Venous thrombosis occurred in 86 (61%), arterial thrombosis in 43 (31%), small vessel thrombosis in 7 (5%) and mixed arterial and venous thrombosis in 4 (3%) patients. Associated non-thrombotic clinical manifestations included hematological manifestations (39%), skin disorders (19%) and non-thrombotic neurological manifestations (16%). Mean follow-up time from the time of APS diagnosis was 6.1 years. Recurrent thrombosis was observed in 19% of pediatric patients with initial venous thrombosis and 21% of patients with initial arterial thrombosis. Sixty-eight (49%) patients included in the Ped-APS Registry had underlying autoimmune disease.

Discussion: Nonthrombotic clinical manifestations were more frequent than thrombotic events (16%) in an unselected group of children with positive aPL. Children with APS have significantly higher thrombosis recurrence rates as compared with adult APS patients.

Disclosure of interest: None declared.
diseases were based on the analysis of in vitro transfected cells or animal models. These approaches have the clear advantage to facilitate the availability of material for these studies and also to reduce the variability associated to clinical and genetic variables (type of mutation, active versus inactive disease, ongoing treatment, etc.). On the other hand, the use of patients’ primary cells strongly increase the possibility that the observed phenomena could be indeed pertinent to the pathogenesis of the disease and not influenced by possible artifacts linked to the study of transfected cells or animal models.

In the present lecture we will review the contribution of the study of primary cells from patients affected by inherited autoinflammatory diseases gave to the understanding of the role of IL-1 in the pathogenesis of these disorders.

Disclosure of interest: M. Gattorno Grant/Research Support from: Novartis, Consultant for: Novartis, SOBI, Speakers Bureau: Novartis, SOBI.

PReS13-SPK-1182: Six years of eu paediatric regulation - what was achieved for paediatric rheumatology

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PaeDiatric Rheumatology 2013, 11(Suppl 2):115

EU Paediatric Regulation was adopted by the European Parliament and the Council in December 2006. First meeting of the Paediatric Committee took place in July 2007.

1. Paediatric investigation Plans (PIPs)

In 2007-2013 The European Medicines Agency (EMA) and its Paediatric Committee have agreed more than 600 Paediatric Investigation Plans (PIPs) with pharmaceutical companies, to provide data on the efficacy and safety of medicines for diseases of children.

- For treatment of JIA PIP was agreed for the following substances: abatacept, adalimumab, anakinra, anti-BAFF antibody, anti-IL-6 antibody, anti-IL-17 antibody, anti-IL-17A antibody, apremilast, baricitinib, canakinumab, certolizumab, denosumab, etanercept, givinostat, golimumab, ololizumab, sarilumab, tocilizumab, tofacitinib and ustekinumab.

- For treatment of SLE in children PIP was agreed for anti-BAFF, belimumab and epratuzumab.

- For treatment of CAPS PIP was agreed for anakinra, anti-IL-1beta antibody and canakinumab.

2. Clinical trials

More paediatric clinical trials were done (data from EudraCT, accessible at the European Clinical Trials Register).

3. New authorised indications for children

- 12/11/2009: canakinumab for treatment of CAPS.
- 25/08/2008: adalimumab - treatment of active polyarticular juvenile idiopathic arthritis in adolescents from 13 to 17 years of age.
- 20/01/2010 abatacept - treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients 6 years of age and older.
- 18/03/2011: adalimumab - treatment of active polyarticular juvenile idiopathic arthritis in the paediatric population aged from 4 to 12 years.
- 01/08/2011: tocilizumab - treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older.
- 24/08/2011: etanercept - polyarticular juvenile idiopathic arthritis (JIA) from the age of 2 years.
- 24/08/2012: etanercept - treatment of RF+ and RF- polyarthritis, extended oligoarthritis from 2 years of age, psoriatic arthritis and ERA from 12 years of age.
- 17/01/2013 - adalimumab - treatment of active polyarticular juvenile idiopathic arthritis in the paediatric population aged from 2 to 4 years old.
- 25/04/2013 - tocilizumab - treatment of polyarthritis (RF+, RF- and extended oligoarthritis) from 2 years old (EC decision pending at the time of abstract submission).

4. A network of paediatric research networks

Enpr-EMA works by fostering collaboration from within and outside the European Union (EU), including between members, patients associations, academia and the pharmaceutical industry.) PRINTO and JSWG of PRes are members of Enpr-EMA.

5. Expert meetings at EMA:

Paediatric rheumatology (2009, 2010), Gastroenterology and rheumatology (2010).

6. Development of scientific guidelines (JIA, SLE, GIOP).

7. Pharmacovigilance

Disclosure of interest: None declared.

PReS13-SPK-1408: New EU scientific guidelines for JIA, SLE and GIOP from the European Medicines Agency

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PaeDiatric Rheumatology 2013, 11(Suppl 2):16

Background: Development of EU guidelines: Guideline (GL) in the pharmaceutical legislative framework represents a harmonised EU approach based on the most up-to-date scientific knowledge to facilitate planning the overall pharmaceutical product development, the preparation of applications for marketing authorisations by the pharmaceutical industry and the assessment, approval and control of medicinal products in the European Union. It has no legal force (“soft law” non-legally binding but quasi-binding character). Alternative approaches may be taken, provided that these are appropriately justified.

Methods - EU guideline development steps:

- Development, adoption and release for consultation of concept paper.
- Preparation and release for consultation of draft guideline.
- Preparation and adoption of final guideline for publication and its implementation.
- All steps are transparent, published on EMA website http://www. ema.europa.eu/ema/.

Results - Development of scientific guidelines for JIA, SLE and GIOP:

1. Juvenile idiopathic arthritis (JIA)

EMA paediatric rheumatology expert meetings 2009, 2010, identified a need for new guideline and discussed its principles. Concept paper on the need for revision of the guideline has been released for public consultation in 2012. Draft GL is prepared to be published at the time of abstract submission.

Main principles:

- Link to adult development.
- Lowering the minimum age from 6 to 1 year, need of PK studies.
- Study design, primary and secondary endpoints, extrapolation.
- Development in JIA uveitis, vaccination sub-studies.
- Need for pharmacovigilance studies.

2. Systemic lupus erythematosus (SLE)

Consultation with experts from PRINTO and SLE WG of PRES for the section on paediatric SLE was conducted. Draft GL on clinical investigation of medicinal products for the treatment of SLE, cutaneous lupus and lupus nephritis was released for public consultation (May 2013).

Main principles (for paediatric SLE)

- Use of PRINTO criteria in children.
- PK studies in 5 to 12 years old.
- Extrapolation from adult studies - need for CNS and renal involvement to be included.

3. Glucocorticoid induced osteoporosis (GIOP)

Existing GL for primary osteoporosis needs to be amended to add GIOP. Concept paper on the need for revision was published in 2012. Public consultation closed, draft guideline to be published.

Main principles:

- Need for treatment in GIOP, differences between paediatric and adult GIOP.
- Primary and secondary endpoints (fractures, bone mineral density, biomarkers).
- Study design (placebo control).

Disclosure of interest: None declared.
I17
PReS13-SKP-1587: New biologic targets for the future and basic science behind them
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The treatment of pediatric rheumatic diseases has made great progress in the last decade. The introduction of the biologicals meant (after the introduction of MTX) the second therapeutic revolution. This together with many improvements in related areas has greatly improved the quality of life of patients with rheumatic diseases. At present however, despite the introduction of more biological agents directed at immune targets the progression has stalled. The next challenge will be to:
1) Better understand the immune pathogenesis underlying the heterogeneity of the disease.
2) Identify patients at risk at the onset of disease and stratify them according to risk factors.
3) Personalize treatment based on their risk profiling.
4) Develop strategies that are aimed not only at suppressing disease but also at maintaining disease remission after withdrawing immune suppression.

Over the last years much progress has been made in all these areas. In this presentation we will discuss this progress, focusing on a better understanding of the mechanisms of immune tolerance, leading to new targets for intervention.

Disclosure of interest: B. Prakken Grant/Research Support from: Dutch Arthritis Foundation.

References:

I18
PReS13-SKP-1030: Juvenile dermatomyositis
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Juvenile Dermatomyositis (JDM) is a systemic, inflammatory, idiopathic disease, mainly affecting the skin and the muscles, starting before the age of 16 with an incidence around one case per million children. Some patients display typical features of JDM without skin involvement or even without muscle involvement, however both tissues are affected over time in most cases. Diagnosis criteria have been established by Bohan and Peter 35 years ago, based on the presence of typical skin rash and proximal muscle involvement. Other conditions have to be ruled out before making a diagnosis of JDM, such as other connective tissue diseases, polymyositis, infectious/post-infectious myositis, genetic diseases, metabolic or drug-induced myopathies. Unlike adult-onset dermatomyositis, JDM is exceptionaly associated with a malignant disease. JDM may also affect several organs including the lungs and the digestive tract. In a subset of patients, glucose intolerance, lipodystrophia and/or calcinosi develop. Delay in treatment initiation or inadequate treatment may favour diffusing, debilitating calcinosis. JDM patients have to be referred to reference pediatric centers with a multidisciplinary team to properly assess disease activity, disease-related damage (including low bone density in most cases) and define the best treatment. Long-lasting corticosteroid therapy remains the gold standard, together with physiotherapy. Physiotherapists often play an important role not only through their participation to patients care but also by assessing disease activity at each stage, using several tools including CMAS and MMT assessment of muscle strength. Other tools have been developed to assess extra-muscular disease and disease-related damage. Patients quality of life also needs to be properly assessed. Several collaborative efforts have been conducted to improve the way we assess patients health and response to treatment. Most patient respond to treatment, relapses are frequent but a complete disease remission is achieved in most cases before adulthood, with or without sequelae. Ongoing clinical trials are assessing the effect of several immunosuppressive and immunomodulatory drugs; preliminary results from aPRINTO international trial suggest that both methotrexate and cyclosporine may help controlling the disease, reducing the rate of early flares and may hence have a corticosteroid-sparing effect. On the short term, methotrexate seems better tolerated. Some preliminary data suggest that other drugs may also be of interest.

Disclosure of interest: None declared.

I19
PReS13-SKP-1469: Juvenile scleroderma
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Pediatric Rheumatology 2013, 11(Suppl 2):I19

Juvenile localized scleroderma, also known as morphea, is the more frequent subtype of scleroderma in childhood. It comprises a group of distinct conditions which involve the skin and subcutaneous tissues. They range from very small plaques of fibrosis involving only the skin, to diseases which may cause significant functional and cosmetic deformity. The most widely used classification divides JLS into five general types: circumscribed morphea (CM), linear scleroderma, generalized morphea (GM), pan sclerotic morphea and the new mixed subtype where a combination of two or more of the previous subtypes is present.

Circumscribed morphea (CM) is characterized by oval or round circumscribed areas of induration surrounded by a violaceous halo. When there are four or more plaques with individual plaques that are larger than 3 cm and they become confluent involving at least two out of seven anatomic sites (head-neck, right upper extremity, left upper extremity, right lower extremity, left lower extremity, anterior trunk, posterior trunk) it is called Generalized Morphea (GM).

Linear scleroderma, the most common subtype in children and adolescents, is characterized by one or more linear streaks that can extend through the dermis, subcutaneous tissue, and muscle to the underlying bone, causing significant deformities. The upper or lower extremities can be affected but also the face or scalp, as in the en coup de sabre variety (ECS). The Parry Romberg syndrome (PRS), characterized by hemifacial atrophy of the skin and tissue below the forehead, with mild or absent involvement of the superficial skin is considered the severe end of the spectrum of ECS and for this reason is included in subtype of linear scleroderma.

Pansclerotic morphea, an extremely rare but severe subtype, is characterized by generalized full-thickness involvement of the skin of the trunk, extremities, face and scalp with sparing of the fingertips and toes. A recent multinational study reported that almost one fourth of the patients present extra-cutaneous manifestations such as arthritis, neurological findings, associated autoimmune conditions or ocular abnormalities. Antinuclear antibodies (ANA) are present in more than 40% of patients with JLS.

The management of JLS is challenging and the detection of disease activity and progression remains a fundamental problem. Clinical examination is subjective, classical skin scoring methods, utilized in the assessment of systemic sclerosis, cannot be applied. Among the new tools which have been proposed for the assessment of the skin lesions, infrared thermography (IRT), computerized skin score (CSS), ultrasound (US) and magnetic resonance imaging (MRI) are those most frequently used.

Over the years, many treatments have tried for localized scleroderma. Circumscribed morphea generally is of cosmetic concern only, and therefore treatments with potentially significant toxicity are not justified. When there is a significant risk for disability, such as in linear and deep subtypes, systemic treatment methotrexate (MTX) in combination with corticosteroids should be considered.

Disclosure of interest: None declared.
I20

PReS13-SKP-1588: Recurrent fevers

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Pediatric Rheumatology 2013, 11(Suppl 2):I20

Fever is common in childhood, usually due to infections. Some children however experience recurrent episodes of seemingly unprovoked fevers. These so-called periodic fever syndromes are rare diseases. Clinically they are characterized by generalized inflammation and differences in localization of tissue inflammation. Skin and joints are often affected in these patients and the long-standing inflammation can lead to irreversible organ damage due to tissue deposition of inflammatory amyloid proteins. Especially the kidney is vulnerable to the so-called AA-amyloidosis. The spontaneous sterile inflammation in the absence of autoantibodies is the periodic fever syndromes in the same category as systemic juvenile idiopathic arthritis; the group of autoinflammatory diseases. Often these are genetically determined.

Over the past 15 years genetic defects have been identified underlying more than twenty such genetic autoinflammatory diseases. These are disorders like Familial Mediterranean Fever, caused by mutations in MEFV, TNF receptor associated periodic syndrome (TRAPS), caused by mutations in TNFRSF1A gene and the Chronic Infantile Neurological Cutaneous Articular (CINCA) syndrome, caused by mutations in the NLRP3 gene.

Identification of the responsible genes has led to understanding of the pathophysiology and hence to effective targeted therapy. Interleukin-1 has proved to be the central mediator in many of these disorders. This finding in the congenital autoinflammatory diseases has led to novel therapies in more common disorders like interleukin-1 blockade in systemic Juvenile Idiopathic Arthritis. The rarity of the periodic fever syndromes hampers evidence based therapy. International collaboration in the EUROFEVER network has enabled us to better define the clinical picture of these disorders and to select targets for therapeutic research. However, many children currently defy genetic diagnosis. Next generation genetic sequencing efforts will hopefully identify the cause of inflammation in this group of patients.

The functional consequences of autoinflammatory diseases are primarily related to the unpredictable fever episodes. However irreversible sequelae, such as hypertrophic arthropathy, chronic renal failure, impaired vision or hearing do occur. Since these are largely preventable by adequate control of inflammation, effective therapy is essential.

Disclosure of interest: None declared.

I21

PReS13-SKP-1332: Assessment of disease activity and damage in juvenile idiopathic arthritis

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Pediatric Rheumatology 2013, 11(Suppl 2):I21

A vast array of instruments are available for measuring disease activity in juvenile idiopathic arthritis (JIA). However, due to the high variability in the clinical presentation and course of JIA, no single measure can reliably capture disease activity in all patients. On the other hand, assessment of all measures individually may cause methodological and statistical problems, especially when these measures are employed as endpoints in clinical trials. Several approaches can be followed to achieve a more rational and standardized evaluation. One of these approaches is based on the so-called composite disease activity scores, which are made of a pool of individual measures and are aimed to quantify the absolute level of disease activity by providing one summary number on a continuous scale. Recently, the first composite disease activity score for JIA, named Juvenile Arthritis Disease Activity Score JADAS, has been developed. In validation analyses, it was found to have good metrologic properties, including the ability to predict the disease outcome. The cutoff values of the JADAS that corresponded with the states of inactive disease and minimal disease activity, or reflected the physician’s, parent’s or child’s subjective rating of remission or the parent’s or child’s satisfaction with the outcome of the illness were established recently. These cutoffs represent an additional clinical tool that, if applied regularly in daily practice, may allow tighter control of therapy, support the optimization of treatment on an individual patient basis, and help prevent the development of joint damage and physical disability. JIA is characterized by prolonged synovial inflammation that may cause irreversible alterations in joint structures. Permanent changes may also occur in extra-articular organs/systems, such as the eye (as a complication of chronic anterior uveitis), or may result from side effects of medications. The Juvenile Arthritis Damage Index JADI was devised to enable a thorough detection of articular and extra-articular damage in children with JIA. The JADI is aimed to capture damage, defined as persistent changes in anatomy, physiology, pathology or function, which may be the consequence of previous active disease, side effects of therapy, or co-morbid conditions, is not due to currently active arthritis, and is present for at least 6 months. Damage is often irreversible and cumulative and, thus, damage scores are most frequently expected to increase or remain stable over time. However, because some forms of damage may improve or even resolve in growing children, in some cases scores may decrease. The index is composed of two parts, one devoted to the assessment of articular damage (JADI-A) and one devoted to the assessment of extraarticular damage (JADI-E). In validation analyses, the JADI was found to be feasible and to possess both face and content validity; furthermore, it exhibited good convergent construct validity, excellent reliability (intrarater agreement and internal consistency), and strong discriminative validity in a large cohort of JIA patients with long-standing disease.

Disclosure of interest: None declared.

I22

PReS13-SKP-1028: Activity and damage - we have to measure them

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Pediatric Rheumatology 2013, 11(Suppl 2):I22

Background: Childhood-onset SLE is a complex multiorgan disease. In order to judge the need of medical interventions and the patient benefits from them, measurement disease activity and damage are key. Furthermore, important improvement and deterioration of disease needs to be ascertained. Such measurement are the basis for clinical trial aimed at identifying improved medications and are needed to judge the benefits of medical interventions in general.

Methods: An overview will be provided about current surrogate and biological markers of global and disease specific disease activity and damage. Focus will be placed on the relevance for children with SLE and current research activities, particularly NPSLE and lupus nephritis.

Results & deliverables: Upon completion of the presentation the audience will have a firm understanding about the suitability of individual measures of disease activity and their differences. Measures include the various versions of the SLEDAI and BILAG, as well as SLE flare tools. The SLICC Damage Index and its pediatric version will be discussed in addition to previously validated measures of clinically relevant improvement and disease flare. Additionally, biomarkers of lupus nephritis as they are suited to help diagnose kidney disease and anticipate changes in the activity and chronicity of kidney lesions will be available. Some novel imaging biomarkers of neuropsychiatric damage will be reviewed.

Disclosure of interest: None declared.

I23

PReS13-SKP-1582: Activity and damage - we have to measure them

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Pediatric Rheumatology 2013, 11(Suppl 2):I23

"You can’t manage what you don’t measure."

The world community–led by the IMACS and PRINTO groups–has developed robust core criteria to measure disease activity and damage for Juvenile Dermatomyositis studies. These measures are tremendously useful in clinical practice, and not just for research. More problematic has been determining clinically meaningful change. The current definitions of change may not be adequate for clinical trials. Problems include mathematical theoretical ones (e.g. using percent [relative] change for non-ratio measures, and trying to calculate continuous scores
from ordinal measures), and practical ones (not incorporating patients’ subjective assessments properly).

Proper measures have an important place in the clinical care of children with dermatomyositis; we have made a very strong start, but there is still work to do.

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Disclosure of interest: None declared.

I24
PReS13-SPK-1247: Activity and damage in juvenile systemic sclerosis- we have to measure them
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Pediatric Rheumatology 2013, 11(Suppl 2):I24

Juvenile systemic sclerosis (jSSc) is an orphan disease. There are no established activity and damage indices for the juvenile form. In the adult form the are prospective studies aiming to validate the activity and damage indices. The assessment of the activity and damage is important in jSSc too to be able to stage the severity of the disease, judge the response to the therapy.

One of the main organ involvement in jSSc is the skin involvement. The modified Rodnan skin score, the pivotal measure of skin involvement. This is not validated prospectively in children with jSSc and it has specific problems in the assessment in a growing child. They are suggestion to adopt it considering the Tanner stage of the child. Newer methods like the assessment of the skin with durometer are perhaps more sensitive and have less interrater variability.

The 6 minute walk test, is a pivotal measure in any study to evaluate cardiopulmonary function an required to be used by the licensing agencies to evaluate an effect of a new medication on pulmonary hypertension. It is not validated either, but recent research established norm values for healthy children as a first to apply it in jSSc patients.

The standardisation of assessment of nailfold capillary changes in jSSc is still evolving, they are few studies looked at the range of changes of the nailfold capillaries in healthy children. They clear changes like capillary loss, which are pathognomic for jSSc. The composite Medsger index, where all organ involvement are scored and assessed is prospectively in adults with systemic scleroderma is not validated either, but recent research established norm values for healthy adults to evaluate an effect of a new medication on pulmonary hypertension. It is not validated either, but recent research established norm values for healthy adults to evaluate an effect of a new medication on pulmonary hypertension.

Proper measures have an important place in the clinical care of children with dermatomyositis; we have made a very strong start, but there is still work to do.

Disclosure of interest: None declared.

I25
PReS13-SPK-1576: Unmeet needs in JIA treatment
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Pediatric Rheumatology 2013, 11(Suppl 2):I25

Conducting clinical trials in paediatric rheumatology has been difficult in the past mainly because of the lack of funding for academic studies and the lack of interest by pharmaceutical companies for the small and non-rewarding paediatric market. The situation changed dramatically few years ago with the introduction of the Best Pharmaceuticals for Children Act in USA and of a specific legislation for paediatric medicines development (Paediatric Regulation) in the European Union (EU).

The main reasons for success are: the availability of two large international non-for-profit networks working in close collaboration, such as the Pediatric Rheumatology Collaborative Study Group (PRCSG at http://www.prscsg.org), covering North America, and the Paediatric Rheumatology International Trials Organisation (PRINTO at http://www.printo.it), covering more than 50 countries worldwide; the availability of validated measures to evaluate response to therapy, now called JIA American College of Rheumatology (ACR) criteria, accepted by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA); last but not least the advent of the biologic therapies (anti TNF, Anti IL 1 and 6, anti CTL4) which have revolutionized juvenile idiopathic arthritis (JIA) treatment.

Some problems however remain still to be solved: There is a need to harmonise all the regulatory aspects related to drugs that are used in the treatment of paediatric rheumatic diseases and in particular in JIA; the issue of me too drugs; the issue of proper pK studies; the ethics of drugs provision and of trial implementation; the implementation of proper pharmacovigilance systems. This presentation will review the reasons for success and the problems that still remains to be solved for conducting trials in JIA.

Disclosure of interest: None declared.

I26
PReS13-SPK-1586: Biological agents for the treatment of rheumatic diseases: present and future targets of biologic therapy
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Pediatric Rheumatology 2013, 11(Suppl 2):I26

The last decade has seen the advent of a variety of novel biologic agents, which are now used widely across a range of the inflammatory rheumatic diseases. Normally introduced after the trial and failure of conventional disease modifying anti-rheumatic drugs (DMARDs) the biologic class of medicines has been a revolutionary in terms of the scope and depth of response now sought in treating rheumatic diseases. Those best characterized are TNF, IL-6R, rituximab and abatacept, all of which bring about improvement in clinical signs and symptoms, and variously mitigate articular destruction and improve function. Application of drugs developed for other indications but now being tested in rheumatic diseases has raised interest in the possible value of agents such as ustekinumab (inhibiting IL-12/23), and several antibodies that block the biology of IL-17. The latter appear to exhibit especial benefits in the spondyloarthropathies and psoriatic variants of inflammatory arthropathy. Other studies targeting GM-CSF receptor have similarly shown benefit in early studies in rheumatoid arthritis. The long promised possibility that chemokines and their receptors would deliver benefit now has some tentative evidence for benefit. In this presentation I shall describe the successes and failures of recent biologic therapeutic studies in the rheumatic disease, and wider inflammatory arena, and from this draw inferences as to new emerging understanding of the molecular taxonomy of the inflammatory diseases.

Disclosure of interest: None declared.

I27
PReS13-SPK-1579: Biologic agents for the treatment of rheumatic diseases
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Pediatric Rheumatology 2013, 11(Suppl 2):I27

Since the middle 1990s biologics have been available for rheumatic diseases. The initial experiments showed efficacy for symptoms and signs but concern was expressed about tachyphylaxis and absence of a true DMARD effect. Combining the antibodies with methotrexate answered some of these criticisms and since that time the number of agents available for rheumatoid arthritis, psoriatic arthritis and spondyloarthropathy has grown.

It is clear these agents work, what is less clear is how they should be used to produce optimum cost benefit. The ever expanding market has...
attracted a large number of pharmaceutical players to this area and this shows no sign of abating. Also there are number of new drugs including oral synthetic DMARDs becoming available. 

Disclosure of interest: None declared.

I28
PReS13-SPK-1577: ‘Asia’- autoimmune (auto-inflammatory) syndromes induced by adjuvants
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In the last decades four enigmatic medical conditions were described, all of which were characterized by an hyperreactive immune response as well as similar clinical and laboratory manifestations. These conditions, namely siliconosis, the Gulf war syndrome (GWS), the macrophagic myofascitis syndrome (MMF) and post vaccination phenomena represent environmental factors that may play a role in inducing or aggravating autoimmunity and auto-inflammation. 

Vaccines, administered to animal and humans, are clearly one of the best achievements of modern medicine and are commonly and safely inoculated to the vast majority of subjects. However in rare occasions vaccines may induce autoimmune or auto-inflammatory conditions both in animals and in humans. These conditions, either defined diseases such as Gullian Barre syndrome or enigmatic ones, have been reported following different vaccines and vaccination protocols. The susceptibility factors and the temporal association between vaccines and these rare immune mediated reactions are yet to be defined, however the similarities between vaccines and infections and the addition of an adjuvant (i.e. alum, squalene etc.) to almost every vaccine are considered major contributors to such adverse events. Perhaps the most evaluated condition is MMF, in which a cause was clearly delineated. MMF is a rare condition caused by deposition of alum, used to adjuvant different vaccines, which bring about an immune mediated muscles disease. Thus, in only a minority of genetically prone, i.e. HLA-DRB1*01 patients, alum may induce this syndrome. Another immune mediated phenomena leading to autoimmune diseases is exposure to silicones (i.e. breast implant). In a large study Fryzek et al showed that a group of 1546 patients with silicone breast implants had a statistically significant increase in 16 of 28 investigated symptoms when compared to a group of 2496 women who underwent reduction mammoplasties. Many of these symptoms satisfied several criteria for fibromyalgia and chronic fatigue syndrome, which is congruent with the FDA’s finding that there is a statistically significant link between fibromyalgia and ruptured silicone gel implants. 

A common denominator to each of these four syndromes as well as to various infectious agents is the trigger entailing adjuvant activity (7). Thus, herein we would like to suggest to include these four conditions under a common syndrome entitled the “Autoimmune (Auto-inflammatory) Syndrome induced by adjuvants” (ASIA). We propose several major and minor criteria that may aid in the diagnosis of this newly defined condition (ASIA).

Disclosure of interest: None declared.

I29
PReS13-SPK-1350: Autoimmune responses following vaccination in healthy populations
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Pediatric Rheumatology 2013; 11(Suppl 2):I29

Vaccinations against infectious diseases are one of the major achievements in medicine in the last century and the most effective method for preventing infections. Concern about safety of vaccinations has been heightened by several reports of possible vaccine-induced autoimmune phenomena following various vaccinations. So far no study was able to show a casual connection between any vaccine and autoimmune syndrome. Few studies were published showing that induction of autoantibodies following various vaccination is possible, but without clinical significance. In few cases antibodies after vaccination were elevated even 6 months after vaccination. Induction of autoantibodies, mainly antiphospholipid antibodies, in selected apparently healthy individuals was reported after influenza, hepatitis B and hepatitis A vaccination. Autoimmune manifestations reported have been only temporally related to the respective vaccine. Gullian Barre syndrome was described following vaccination against influenza and few other vaccines, multiple sclerosis and arthritis were mainly reported after hepatitis B vaccination. There are some evidence to suggest a connection of reactive arthritis and rubella vaccine. Dermatomyositis was described following hepatitis B, tuberculosis, influenza and tetanus vaccinations. Recently a new syndrome Autoimmune-Autoinflammatory syndrome induced by adjuvants-ASIA has been described.

Highlights of lecture:
- autoimmune adverse events following vaccinations is possible in selected individuals but the risk of autoimmune disease after vaccination is, comparing to advantages of vaccination, negligible. 
- induction of autoantibodies in selected individuals after vaccination has no clinical significance.
- new generation vaccine, mainly oriented on finding safer and effective adjuvants, are needed. At present few effective adjuvants are considered safe for use in humans.

Disclosure of interest: None declared.

I30
PReS13-SPK-1212: Vaccination in paediatric patients with auto-immune and autoinflammatory diseases
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Pediatric Rheumatology 2013; 11(Suppl 2):I30

N.M. Wulfsaat and MW Heijstek, Department of pediatric rheumatology, UMC Utrecht, The Netherlands
In order to develop evidence-based recommendations for vaccination of pediatric patients with auto-immune and/or auto-inflammatory diseases, a EULAR task force performed a systematic literature review. Available evidence was critically appraised using a customary scoring system for the level of evidence. The strength of each recommendation was determined. The majority of papers considered influenza (44) or pneumococcal (20) vaccination. Very few studies were found for the live-attenuated vaccines. Considering composite vaccines, it is recommended to adhere to national guidelines for the meningococcal serogroup C conjugate, Hib, pneumococcal, hepatitis A and B, DTaP, HPV, Japanese encephalitis, tick-borne encephalitis, typhoid fever, rabies and cholera vaccination (Grade C-D). Seasonal influenza vaccination is recommended (Grade D). Patients on anti-CD20 therapy must receive tetanus specific immunoglobulines when indicated, since rituximab lowers responses to tetanus toxoid (Grade D).

Since the publication of these recommendations, we concluded a randomised controlled trial for the effects of booster MMR in 139 children (60 using MTX and 15 using a biological) with JIA in the age of 4 to 9 years. Disease activity measured by the JADAS 27 did not differ between the revaccinated and the non-vaccinated groups. As expected seroprotection rates were higher in the revaccinated group. Methotrexate and biologicals did not affect humoral responses, but low numbers precluded definite conclusions.

Disclosure of interest: N. Wulfsaat Consultant for: Pfizer, Novartis, Roche, AbbVie.

I31
PReS13-SPK-1321: Expanding clinical spectrum of autoinflammatory diseases
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Pediatric Rheumatology 2013; 11(Suppl 2):I31

The term autoinflammation was initially introduced to denote a group of diseases that lacked the usual features of autoimmunity (high-titer autoantibodies and antigen-specific T cells), and were subsequently
recognized as disorders of the innate immune system. Patients with autoinflammatory disorders present with chronic and recurrent bouts of systemic inflammation that are medi-ated by the cells of the innate immune system such as neutrophils and macrophages. The concept of autoinflammation started with hereditary recurrent fevers, but has grown substantially to include both monogenic and polygenic diseases. Hereditary recurrent fevers are the prototypic monogenic disorders, whereas Behçet disease, Crohn disease, gout, spondyloarthropathies, type-2 diabetes are all considered complex autoinflammatory diseases. The monogenic autoinflammatory diseases are inherited in an autosomal-recessive or autosomal-dominant fashion, and many of disease-causing mutations are found in genes that regulate the IL-1 signaling pathway. More recently, new pathways such as the IL-36, immunoproteasome, HOIL-1 deficiency, and phospholipase C2 pathways have been identified in the pathogenesis of autoinflammation. Some of these new autoinflammatory diseases and relevant pathways will be discussed at the meeting. Despite major advances, a substantial number of patients have no mutations in the known autoinflammatory genes. The present challenge is how to find the as-yet undiscovered genes, considering that most cases are sporadic or occur in small families that are not suitable for linkage analysis. New approaches and tools such as next-generation sequencing are the most likely methods to be successful. Such research might require collaborative studies in order to increase the number of patients presenting with a rare phenotype.

Disclosure of interest: None declared.

132
PReS13-SPK-1292: Gut microbiome and metabolism
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Pediatric Rheumatology 2013, 11(Suppl 2):132

The enormous number and diversity of microorganisms in the human gastrointestinal tract support the host in many functions such as digestion of complex carbohydrates. The relationship between the gut microbiota and energy homeostasis, metabolic dysfunction and inflammation and their role in the pathogenesis of obesity-related disorders is increasingly recognized. Obesity developing in genetically or diet-induced obese mice is characterized by impressive changes in the composition and metabolic function of the gut microbiota. Importantly, colonization of germ-free mice with an “obese-gut-derived” microflora results in a much greater increase in total body fat and leads to obesity. Similar alterations as in experimental models have been observed in human obesity. The gut microbiota is able to directly regulate host gene expression and thereby control host energy expenditure and storage. This may take place by various mechanisms such as regulation of Fiaf, AMPK or short chain fatty acids. Furthermore, it is increasingly recognized that diet may have a fundamental effect on the composition of our microbiota. The innate immune system is another important player controlling microbiota composition. Animals deficient for toll-like receptor 5 (TLRs) or certain members of inflammasomes such as Caspase1 or ASC develop a dysbiosis which is associated with obesity, metabolic syndrome and fatty liver disease. Whereas knowledge in various models is increasing, data in humans are still in its infancy. This is especially true for interventional studies manipulating the gut microbiota e.g. by using antibiotics, pro- or prebiotics. A first human study using fecal transplantation recently showed that insulin sensitivity might be improved via such a strategy. Overall, data suggest an important role for the microbiota in metabolic dysfunction, type 2 diabetes and obesity.

Disclosure of interest: None declared.

133
PReS13-SPK-1107: Development of an academic pediatric rheumatology program
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Pediatric Rheumatology 2013, 11(Suppl 2):133

The development of the Pediatric Rheumatology Program in Toronto began in 1984 with the recruitment of 3 junior but well-trained pediatric rheumatologists. Their goal, to create the finest pediatric rheumatology program in the world, was predicated on the need to both create and disseminate new knowledge. This required that all the elements of a strong academic program would be supported: (1) scholarly clinical care; (2) education at all levels including medical student, resident, fellow and continuing education; and (3) research, both clinical and basic. Early salary support from The Arthritis Society was critical to the recruitment and the hiring of a clinical fellow.

Recognition of the expertise of the individual staff provided opportunities to pursue specific interests in a collegial and non-competitive environment. The shared vision was embraced such that individual goals and successes all contributed to the greater good and allowed each member to share in the successes of the others; each achievement not only advanced an individual’s program but the entire division benefited. Early provision of resources by the institution (space, nursing, rehabilitation, social work) provided the opportunity to rapidly build the clinical program. The development of subspecialty interests was encouraged leading to a variety of specific clinics that built clinical experience and expertise, provided large cohorts for clinical research and allowed trainees to see a large number of patients with rare diseases even if they had otherwise limited exposure to rheumatology. The strong Research Institute affiliated with the hospital provided excellent scientific support for both clinical and basic science research endeavours. Presentation and publication of our work and international meetings gave us early credibility and highlighted training opportunities. To date, over 70 trainees from 27 countries have come through the program, and graduates continue to promote the program as a centre of excellence for clinical and research training.

The presentation will review the development of the program and highlight the elements that have allowed the Toronto program to remain one of the leading academic programs for pediatric rheumatology in the world.


134
PReS13-SPK-1127: Pediatric rheumatology in India
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Pediatric Rheumatology 2013, 11(Suppl 2):134

Pediatric Rheumatology took birth in India with the formation of an interest group of the Indian Academy of Pediatrics and the first conference in 2001 in Mumbai. Now 11 conferences old, it has about 200 members and 12 centers offering part time or whole time care.

With a population of over 1000 million, it may be extrapolated from Western data that India should have at least 400000 children with rheumatologic disease - JIA, JDM, SLE and vasculitides (excluding KD and HSP) Disease patterns are similar to a Western clinic and a little over a third of children attending a rheumatology clinic in Mumbai are diagnosed to have non rheumatologic musculoskeletal disease, notably leukemia, genetic disorders and chronic pain syndromes. The term ‘musculoskeletal medicine clinic’ seems more apt. Acute diseases such as septic arthritis/ osteomyelitis are probably filtered at the primary care level and hence the clinic functions mainly as a chronic care facility. Fluorosis, musculoskeletal MDR tuberculosis, brucellosis and HIV associated arthropathy are unique issues. Most centers report declining trends of Rheumatic fever but an alarming increase of KD with consequent IVIG requirement. Rare diseases such as hereditary fever syndromes are seen, some possibly representing the vestiges of early European colonization. Individual trends differ with SJIA and ERA forming the bulk of JIA rather than OJIA. Uveitis is not a major concern. Outcomes of individual diseases seem different to the West with most centers in India reporting a milder phenotype of JDM.

Pediatric Rheumatology is the main subspecialty of the world’s pediatric rheumatologists care for 20% of the world’s children and vice versa. Our undergraduate teaching ignores rheumatology while our post graduate teaching focuses more on acute cross sectional care rather than chronic longitudinal care.

Patents usually reach through complex pathways of referral, often having consulted adult orthopedic surgeons or alternative medicine systems prior to their visit, highlighting the need for increasing awareness about
our specialty to lay public. They often have to travel 300-500 km for a consultation. Consequently, delay in diagnosis of various diseases, irregular follow up and frequent usage of steroid prior to referral are common. While raising money for one time use of IVIG is still feasible (selfpaid or charity), a country with a per capita income of 1219 USD and much larger problems is unable to adapt treatment guidelines suggested by the West when it comes to the use of biologicals and consequently lesser studied drugs and treatment algorithms are resorted to. The crunch for interested and trained personnel (at least 200) has been addressed through a 3 level process -Preach -sensitizing large gatherings of pediatricians, Reach and Teach-intensive weeklong courses to committed smaller groups and Each to Each -one on one teaching through fellowships. The results are slow but visible. India can contribute to the world of pediatric rheumatology through its sheer numbers and its English speaking medical community thus providing an excellent collaborative research and teaching opportunity to centers with knowhow but lacking in numbers. The developed world can help us through facilitating student exchange, concomitant diagnostic tests and courses, telemedicine, bulletin board, Asian editions of books or open access publications and patient information.

Disclosure of interest: None declared.

ORAL PRESENTATIONS

O1
PreS-FINAL-1001: Lymphocytes from the inflamed joint of juvenile idiopathic arthritis patients express reduced levels of cd73 and have a functional defect in adenosine production
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Introduction: The nucleotidases CD39 and CD73 are responsible for the catabolism of pro-inflammatory ATP to AMP, and the consequent dephosphorylation of this nucleotide to regulatory adenosine. CD39 protein has previously been observed to be elevated (1) on JIA (Juvenile Idiopathic Arthritis) SFMC (synovial fluid mononuclear cells) with a correspondent increase in ATPase activity, while CD73 has been found decreased on JIA SFMC, potentially affecting the cells ability to synthesize suppressive adenosine.

Objectives: To test the hypothesis that JIA SFMC have a reduced ability to synthesize adenosine.

Methods: Samples (unsorted or sorted CD8+/CD19+) from 32 patients with JIA, 30 healthy adult and 5 age-matched controls were tested by flow cytometry and HPLC (high performance liquid chromatography). PBMC were stimulated with CpG or anti-CD3mAb and anti-CD28mAb. Data were compared by Mann-Whitney (2-tailed) and are expressed as medians; analysis was performed using Prism (v5.03, Graphpad).

Results: As we previously described (2), JIA SFMC lymphocytes express decreased levels of CD73 compared to JIA patients and control PBMC, with the most marked difference on CD6+ and CD19+ cells. Both total SFMC and CD8+ SFMC showed a decreased ability to breakdown AMP. It was confirmed that B cells are the only cell type to co-express CD39 and CD73 and were therefore able to generate adenosine from ATP. As B cells do not express the Adenosine deaminase-CD26 complex they cannot breakdown adenosine to inosine. Despite increased levels of CD39 on CD19+ SFMC, levels of coexpression of CD39 and CD73 were decreased on CD19+ SFMC (49%) as compared to B cells from JIA PBMC (64%, p = 0.0007) and PBMC from age matched (56%, p = 0.3) and adult controls (71%, p < 0.0001). To test whether the reduced CD73 expression found in the joint is related to the stimulatory phenotype of SFMC, this was modeled in vitro via stimulation of B cells via TLR9 or T cells via TCR stimulation: stimulation led to CD73 down-regulation and reduced AMPase activity compared to unstimulated PBMC.

Conclusion: Decreased expression levels of CD73 on lymphocyte SFMC corresponded to decreased AMPase activity, the same situation as for stimulated PBMC, suggesting that JIA SFMC are less able to synthesize adenosine as a consequence of their activated status. These data suggest a functional defect within the joint of the production of anti-inflammatory adenosine.

Disclosure of interest: None declared.

References
O2 PreS-FINAL-1002: Dissecting the dissociation of foxp3 and cd25 expression on cd4+ t cells in synovial fluid identifies three distinct populations of human t regulatory cells present at the chronically inflamed site

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Pediatric Rheumatology 2013, 11(Suppl 2):O2

Introduction: T regulatory cells (Treg), vital to prevent autoimmunity, are defined by expression of foxp3 in combination with high CD25 and low CD127 expression. It has been reported, however, that upon in vitro activation, conventional T cells (Tcon) can manifest phenotypic marks associated with Treg and, as such, expression of these markers alone is insufficient to determine Treg commitment. A unique feature of Treg is the presence of a Treg specific demethylated region (TSDR) in intron 1 of the foxp3 gene. In this study we assessed activated Tcon from bona fide Treg. In CD4+ T cells from the joints of children with JIA we have observed a clear dissociation of CD25 and FoxP3 expression. The relationship between CD25, CD127 and FoxP3 expression and commitment to Treg lineage at the inflamed site is unclear; meaningful investigation is hampered by the technical difficulties in isolating cells based on FoxP3 status.

Objectives: To analyze phenotype and frequency of CD4+ T cells isolated from synovial fluid (SF) from JIA patients based on expression patterns of CD25, CD127 and FoxP3, their in vivo turnover, and degree of commitment to the Treg lineage.

Methods: Peripheral blood mononuclear cells (PBMC) from JIA patients and controls and SF mononuclear cells (SFMC) were analyzed ex vivo for the expression of FoxP3, CD25, CD127, Ki67 and PD-1. In addition, SF CD4+ T cells, which were fixed and stained for FoxP3, were sorted in to 4 distinct populations based on CD125, FoxP3 and CD127 expression. DNA was extracted using a modified phenol-based protocol, bisulfite-treated, the populations based on CD25, FoxP3 and CD127 expression. DNA was extracted using a modified phenol-based protocol, bisulfite-treated, the populations based on CD25, FoxP3 and CD127 expression. DNA was extracted using a modified phenol-based protocol, bisulfite-treated, the populations based on CD25, FoxP3 and CD127 expression. DNA was extracted using a modified phenol-based protocol, bisulfite-treated, the populations based on CD25, FoxP3 and CD127 expression.

Results: 3 populations of CD4+ T cells displaying Treg lineage commitment were identified: Population I (PI), CD4+CD127loCD25hiFoxP3+ (median of 5.03% of CD4+ T cells in SFMC vs 0.94% in control, and 1.22% in JIA, PBMC); population II (PII), CD4+CD127loCD25hiFoxP3- (median 11.69% CD4+ T cells in SFMC vs 5.74% in control, and 4.93% in JIA, PBMC); and population III (PIII), CD4+CD127+CD25hiFoxP3- (median of 4.13% of CD4+ T cells in SFMC vs 0.82% in control, and 0.63% in JIA, PBMC); all 3 were significantly enriched compared to controls and displayed low levels of TSRD methylation (median methylation rates: PI, 19.73%; PII, 3.8%; PIII, 15.65%; Tcon, 95.55%). PD-1 expression was higher on all 3 populations when compared to controls, with highest expression on PI, which also had a lower frequency of Ki67+ cells compared to PII and PIII (%ki67 median: PI, 18.4%; PII, 20.2%; PIII, 8.96%).

Conclusion: The presence of CD25 and/or Foxp3 alone is insufficient to define Treg populations in the inflamed joint. We propose 3 populations: PI & PII represent Treg expressing high levels of FoxP3 differing in their levels of CD25 but have robust turnover in vivo. PII, with high levels of CD25 but low Foxp3 may represent an exhausted population of Treg (indicated by downregulated FoxP3, high PD-1 and low turnover in vivo). Understanding turnover and fate of regulatory cells in JIA will aid definition of how tolerance is lost in this autoimmune disease.

Disclosure of interest: None declared.

O4 PreS-FINAL-2001: The impact of adalimumab on growth in patients with juvenile idiopathic arthritis

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Pediatric Rheumatology 2013, 11(Suppl 2):O4

Introduction: Children with juvenile idiopathic arthritis (JIA) often exhibit growth impairments. Treatment with adalimumab (ADA) has been shown to be safe and effective in JIA patients (pts) when dosed every other week (ewo) for up to 3 years [1], but the effect of ADA on growth is not known.

Objectives: The purpose of this post hoc analysis is to describe growth parameters in pts with JIA treated with ADA in a clinical trial setting.

Methods: Pts aged 4-17 with polyclausal course JIA were enrolled in a phase 3, randomized-withdrawal, double-blind (DB), stratified, parallel-group study, which consisted of a 16-wk open-label (OL) lead-in phase, a 32-wk DB phase, and an OL extension (OLE) phase. In the OLE phase, pts were dosed based on body surface area (24 mg/m2, max 40 mg dose), followed by a switch to 20 or 40 mg eow based on a body weight of ≥30 kg or >30 kg, respectively. To enter the DB phase, pts had to achieve an American College of Rheumatology Pediatric score ≥30% (ACR Pedi 30) during the OL lead-in. Pts could enter the OLE after 32 wks in the DB phase or at time of first flare (whichever came sooner). For this analysis, pts in the DB phase were grouped by baseline weight into 2 groups: ≤33rd percentile and >33rd percentile based on the US Centers for Disease Control and Prevention (CDC) growth charts. All pts who received ≥1 dose of ADA ± methotrexate (MTX) were included in the analysis. Mean CDC percentile changes in height, weight, and body mass index (BMI) percentiles were calculated through 104 weeks. Growth and efficacy data were analyzed using last observation carried forward (LOCF).

Disclosure of interest: None declared.
Among the 171 pts enrolled in this study, 144 (84%) met ACR Pedi 11(Suppl 2): 2013, Volume 11 Suppl 2
Long-term studies of remission rates in juvenile idiopathic (SAE). Forty-four patients had a
The follow-up time of the patients was altogether 1516 patient-years.
It was not possible.
Biologic agents are powerful drugs. NEJM
Preliminary criteria for clinical remission in JIA. Logistic regression
Interestingly, they seem to differ from each other in terms of the
Disclosure of interest: None declared.
Biologic therapy in patients with JIA. Methods: Data were collected from medical charts of 348 consecutive patients with JIA from three tertiary centres in Finland. Biologic therapy for these patients was started 1999-2009. AEs were categorized according to
modified Common Terminology Criteria for Adverse Events 4.0(CTCAE) -criteria.
Results: The follow-up time of the patients was altogether 1516 patient-years (py); 710 for etanercept, 591 for infliximab, 188 for adalimumab, and 27 for other biologic drugs. 216 (62%) patients were female. Median age at onset of JIA was 4.7 years (0.7 to 15.9). Anti-TNF therapy was started at a median age of 10.8 years (2.2 to 19.2). All patients had either received DMARDs prior to anti-TNF or continued receiving them concomitantly. Median follow-up time per patient in this study was 50.5 months (1.0 to 154.7).
318 patients (91%) had at least one AE. Most common AEs were infections; such as upper respiratory tract infections, otitis media, sinusitis, and gastroenteritis (44.4, 6.6, 5.7, and 4.8 per 100 py).
121 (34.7%) patients had a serious AE (SAE). Forty-four patients had a serious infectious AE (3.8 AEs/100 py), of which septicaemia (0.9/100 py) and pneumonia (0.7/100 py) were the most common.
The frequency of alanine aminotransferase elevation >5 times upper limit of normal was 1.7 per 100 py, and of neutropenia 2.2 per 100 py.
AEs of special interest included new-onset colitis ulcerosa, Crohn’s disease, psoriasis, alopecia, or vasculitis in 4, 2, 9, 6, or 2 patients, respectively.
No malignancies were observed. Three patients had each a cyst in spleen, brain or breast, and two had abnormal pap smear findings. Two patients with severe systemic onset JIA died after initiation of biologic treatment. Biologic drugs didn’t seem to differ from each other in terms of the number of associated AEs. Since the patients may have switched between several biologic agents, comparisons between drug treatment groups were not possible.
Conclusion: Anti-TNF therapy is relatively safe in hands of pediatric rheumatologists. However, one third of patients had a serious AE, and for 100 patient-years, 3.8 serious infections were observed. Thus, careful monitoring is needed when treating pediatric patients with anti-TNFs or other biologic agents.
Disclosure of interest: None declared.
Table 1(abstact O6)

<table>
<thead>
<tr>
<th>Disease activity at 15 years follow-up</th>
<th>Not in remission at 30 years</th>
<th>Remission on med. at 30 years</th>
<th>Remission off med. at 30 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not in remission</td>
<td>57 (33%)</td>
<td>37</td>
<td>9</td>
</tr>
<tr>
<td>Remission on med.</td>
<td>17 (10%)</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Remission off med.</td>
<td>97 (57%)</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>171 (100%)</td>
<td>58 (34%)</td>
<td>12 (7%)</td>
</tr>
</tbody>
</table>

med.: medication
Results: One hundred and seventy-one patients (67%) were included in the study. They were examined after a median of 30 (range 21-40) years of disease duration, median age was 39 (range 28-45) years and 74% were females. After 30 years, 59% of the patients were in clinical remission off medication, 7% were in remission on medication and 34% had persistently active disease compared with 57%, 10%, and 33%, respectively, after 15 years. Thirty-seven of 57 patients (65%) with active disease at 15 years follow-up had active disease at 30 years follow-up, and 20 patients (35%) went into remission on or off medication. Eighty-four of 97 patients (87%) in remission off medication remained in this category from 15 to 30 years follow-up. Patients in remission on medication at 15 years (n = 171) tended to flare or go into remission off medication. In total 121/171 patients (71%) had an unchanged category of disease activity from 15 to 30 years follow-up. Predictors of persistently active disease at 30 years follow-up were: being diagnosed with a JIA subgroup other than persistent oligoarticular and systemic JIA (OR 4.1, 95%CI 1.5-11.5, p = 0.006), being ANA-negative (OR 8.93, 95% CI 2.3-30.3, p = 0.001), a short duration of total time in remission (OR 9.0, 95% CI 3.0-26.7, p < 0.001), and not being in remission at 15 years follow-up (OR 13.7, 95%CI 4.9-38.4, p < 0.001), Nagelkerkes R² = 65%. Conclusion: The overall remission rates were stable between 15 and 30 years, even though one third of the patients changed category of disease activity. JIA subgroup, genetic factors and time without remission were important predictors of long-term outcome. Disclosure of interest: None declared. Acknowledgements: Supported by the Norwegian Women’s Public Health Association.

O8 PrEs-FINAL-2173: Protein kinase C delta deficiency is a new cause of monogenic SLE
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Pediatric Rheumatology 2013, 11(Suppl 2):O8

Introduction: Systemic lupus erythematosus (SLE) is a prototype autoimmune disease. Infectious triggers, genetic background, immunological abnormalities and environmental factors are all supposed to interact in disease development. Rare causes of monogenic SLE have been described, (e.g. complement deficiencies, interferonopathies and FasL deficiency) providing unique insights into fundamental mechanisms of immune tolerance.

Objectives: Our objective was to identify the cause of an autosomal recessive form of SLE in an inbred family with three affected siblings.

Methods: We investigated three siblings and used next generation sequencing to identify mutations in the disease-associated gene. We performed extensive biochemical, immunological and functional assays to assess the impact of the identified mutations on B cell biology.

Results: Genetic mapping and targeted exome sequencing lead to the identification of a homozygous mutation in PRKCD, encoding protein kinase C delta (PKCδ). Mutation of PRKCD resulted in reduced expression and activity of encoded protein PKCδ. In mouse, PKCδ plays a crucial role in the deletion of autoreactive B cells. As for mice deficient in PKCδ, we demonstrated in a cohort of cells display a resistance to calcium-dependent apoptosis and a higher proliferation rate associated with an increase of immature B cells in affected patients, and a developmental shift toward an immature phenotype of naive B cells.

Conclusion: Our findings indicate that PKCδ is crucial in regulating B cell tolerance and preventing self-reactivity in humans.

Disclosure of interest: None declared.

O9 PrEs-FINAL-2174: The performance of the new slicc criteria for the classification of sle in children
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Pediatric Rheumatology 2013, 11(Suppl 2):O9

Introduction: The Systemic Lupus International Collaborating Clinics (SLICC) have recently suggested a new set of criteria for the classification of SLE. However the differences between sensitivity and specificities of the ACR criteria and the new SLICC criteria among pediatric SLE patients have not been investigated yet.

Results: Seventy subject entered the study: 38 (54.3%) still presented with active disease and 59 (85.7%) were in remission. Main symptoms were lower limbs arthralgia and myalgia. MSP persisted more in females than males (p = 0.038) and in pubertal rather than pre-pubertal subjects (p = 0.022). In particular, the pre-pubertal patients recovered significantly more frequently from BJHS (p = 0.004) and IMSP (p = 0.016) than the pubertal ones. Gender did not influence the distribution of MSP according to pubertal stage. ANA (titer ≥1:80) was found in 42.9%; none of the subjects resulted positive at ENA or anti-dsDNA tests. No significant association between ANA-positivity and MSP or BJHS was found.

Conclusion: Pre-pubertal patients have a higher probability of recovering from MSP than the pubertal ones; vice versa pubertal subjects are at high risk for suffering from MSP during early adulthood, especially females with BJHS. The prevalence of ANA-positivity in this cohort was particularly high but was not significantly associated with BJHS or IMSP. These findings clearly suggest that female gender, BJHS and pubertal stage are important risk factors for persistence of MSP. Further studies are needed to evaluate the natural history of MSP towards adulthood and the role of ANA in the pubertal age.

Disclosure of interest: None declared.
Objectives: We aimed to compare the sensitivity and specificities of the ACR criteria and the new SLICC criteria among pediatric SLE patients.

Methods: Three main lupus centers from Europe were included in this study. One of these centers was mainly a pediatric nephrology center from UK whereas one was a pediatric rheumatology center from Italy and the last one was a joint one from Turkey. Features present at onset in childhood-onset SLE (cSLE) patients, diagnosed and followed by these three departments between January 2000 to December 2012 were retrospectively analyzed. For the specificity analysis, patients admitted to the respective departments, in whom ANA was deemed necessary by the caring physician in the diagnostic work-up were included as controls.

Results: Both criteria were analyzed in 154 cSLE patients with a mean age at disease onset of 12.7 years and 95 controls with a mean age of 8.6 years. In the overall group, the sensitivity and specificity of the ACR criteria were 76.6% and 91.6%, respectively and that of the SLICC criteria were 98.7% and 82.1%, respectively. Four hemolytic uremic syndrome (HUS) patients and four juvenile dermatomyositis (JDM) patients met the SLICC criteria whereas 22 lupus nephritis fell to meet the ACR criteria. Between the three centers there were marked differences among certain clinical features. On the other hand when we compared our results with the reported prevalences of the criteria in adults, renal involvement, neurologic findings, hemolytic anemia, positive titters for ANA and anti-dsDNA were more frequent among children whereas chronic skin lesions were less (p < 0.005).

Conclusion: In this pediatric cohort SLICC criteria performed better, was more sensitive (p < 0.001), had fewer misclassifications, however was less specific (p = 0.016). The specificity of the SLICC criteria was jeopardized with the HUS and JDM cases. The prevalence of certain criteria were significantly different between adults and children, this may necessitate further revision in pediatrics.

Disclosure of interest: None declared.

O11

PreS-FINAL-2176: Declines in levels of disease activity and physical disability in children with juvenile idiopathic arthritis seen in standard clinical care over the last 25 years

Introduction: Over the last 3 decades there have been important advances in the management of juvenile idiopathic arthritis (JIA), which include the introduction of methotrexate and, later on, the tendency toward its earlier initiation, the widespread use of intra-articular corticosteroid injections, and, more recently, the availability of the biologic response modifiers. Although this therapeutic progress is likely to have led to a marked improvement in the outlook of children with JIA, the prognostic impact of the newer therapeutic modalities is still poorly documented.

Objectives: To evaluate the change in the measures of disease activity and physical function in JIA over the last 25 years.

Methods: The clinical information recorded during visits made in children with JIA from January 1987 to March 2012 was retrieved from the study center database. Visits were divided in the following time intervals: 1987-1995 (n = 826), 1996-2000 (n = 1,337), 2001-2005 (n = 2,022), 2006-2012 (n = 2,317). Measures of disease activity included the physician’s and parent’s global ratings (both made on a 0-10 cm visual analog scale, VAS), the parent’s pain rating (made on a 0-10 cm VAS) and the count of joints with swelling, pain on motion/tenderness and active disease. Measures of disability included the count of joints with restricted motion and a physical function tool (the Childhood Health Assessment Questionnaire, CHAQ before March 2007 and the Juvenile Arthritis Functionality Scale, JAFS after that date). To enable comparability of functional ability evaluations, both CHAQ and JAFS scores were converted to a 0-10 scale (0 = best; 10 = worst). Parent’s global and pain ratings as well as functional ability assessment were not available for visits made prior to 1995 because before this year these assessments were made on a scale not comparable with those used subsequently.

Results: We observed a progressive decline in the levels of disease activity and physical disability over time among children with JIA seen from the mid of the 1980s to the 2010s. This finding confirms the notion that the recent advances in the management of JIA have led to a substantial improvement in disease prognosis.

Conclusion: We observed a progressive decline in the levels of disease activity and physical disability over time among children with JIA seen from the mid of the 1980s to the 2010s. This finding confirms the notion that the recent advances in the management of JIA have led to a substantial improvement in disease prognosis.

Disclosure of interest: None declared.

O12

PreS-FINAL-2177: Safety and lack of autoantibody production following influenza H1N1 vaccination in patients with juvenile idiopathic arthritis (JIA)

Introduction: Vaccination is an effective tool against several infectious agents including influenza. In 2010, the Advisory Committee on Immunization
Table 1(abstract O11)

<table>
<thead>
<tr>
<th>Year</th>
<th>Physician global (0-10)</th>
<th>Active joints (0-10)</th>
<th>Swollen joints (0-10)</th>
<th>Tender joints (0-10)</th>
<th>Restricted joints (0-10)</th>
<th>Parent global (0-10)</th>
<th>Parent pain (0-10)</th>
<th>Physical function (0-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1996</td>
<td>5.4 (2.3)</td>
<td>8.2 (9.4)</td>
<td>7.9 (8.3)</td>
<td>6.3 (8.0)</td>
<td>8.0 (10.4)</td>
<td>2.8 (2.5)</td>
<td>2.5 (2.5)</td>
<td>1.7 (2.0)</td>
</tr>
<tr>
<td>1996-2000</td>
<td>5.0 (3.4)</td>
<td>5.7 (8.4)</td>
<td>4.3 (5.8)</td>
<td>4.3 (7.9)</td>
<td>5.5 (9.5)</td>
<td>2.8 (2.5)</td>
<td>2.5 (2.5)</td>
<td>1.3 (1.8)</td>
</tr>
<tr>
<td>2001-2005</td>
<td>4.0 (3.3)</td>
<td>3.8 (5.7)</td>
<td>2.9 (4.2)</td>
<td>3.3 (6.0)</td>
<td>3.1 (6.2)</td>
<td>2.4 (2.5)</td>
<td>2.4 (2.7)</td>
<td>0.4 (0.7)</td>
</tr>
<tr>
<td>2006-2012</td>
<td>2.7 (2.7)</td>
<td>2.2 (4.5)</td>
<td>1.8 (3.8)</td>
<td>1.9 (4.9)</td>
<td>1.9 (4.2)</td>
<td>2.1 (2.5)</td>
<td>1.9 (2.6)</td>
<td>0.4 (0.9)</td>
</tr>
</tbody>
</table>

Practices (ACP) recommended influenza A H1N1/2009 vaccination for high-risk groups, including juvenile idiopathic arthritis (JIA) patients and more recently the EULAR task force reinforced the importance of vaccination in immunsuppressed pediatric rheumatologic patients. We have recently shown that Influenza A H1N1/2009 vaccination generated protective antibody production with short-term safety profile among 93 JIA patients, but the possible impact of the vaccine in autoimmune response in JIA have not been studied. Therefore, we aimed to assess the production of some autoantibodies generated following influenza H1N1 vaccination in JIA patients.

Objectives: To assess the autoimmune response and H1N1 serology following influenza H1N1 vaccination in patients with JIA.

Methods: Cepa A/California/7/2009 (NYMC X-179A) anti-H1N1 was used to vaccinate JIA patients: 1 dose of immunization was given to all participants and those <9 yrs of age received a second booster 3 weeks apart. Sera were analyzed before and 3 weeks following complete vaccination. Serology against H1N1 virus was performed by hemagglutination inhibition antibody assay, rheumatoid factor (RF) by latex fixation test, antinuclear antibodies (ANA) by IF, IgM and IgG anticardiotid aCL by ELISA.

Results: Among 98 JIA patients that were vaccinated, 58 sera were available for this study. Mean age of 58 JIA patients was 23.9 ± 9.5 yrs, 38 were females and 20 males with mean disease duration of 14.7 ± 10.1 yrs. JIA subtypes were: 33 (57%) poliarticular, 10 (17%) oligoarticular, 6 (10%) systemic and 9 (16%) other. Sixteen patients were off drugs while 42 (72%) were under different pharmacotherapy: 32 (53%) were on 1 DMARD/IS, 10 (17%) on 2 DMARDs/IS, 19 (33%) antimalarial, 29 (50%) MTX, 8(14%) sulfasalazine, 6 (10%) anti-TNFs, 4 (7%) abatacept; no patient was using prednisone >0.5 mg/kg/d. Seroprotection rates against H1N1 influenza increased from 23 to 83% and seroconversion rates were achieved in 78% JIA. Prior to vaccination, 31(53.4%) JIA patients were ANA+, 6(10.3%) RF+, and 4 (7%) IgM+ and IgG aCL+. After complete H1N1 vaccination, positivity for ANA remained the same whereas 1 JIA patient became negative for IgG aCL, and another for RF, IgM and IgG aCL. One (1.7%) patient turned low titer IgG aCL.

Conclusion: Vaccination of JIA patients against pandemic influenza A (H1N1) generated successful protective antibody production without the induction of autoantibody production, except for 1 patient that became positive for low titer IgG aCL, supporting its safety.

Disclosure of interest: None declared.

O13

PReS-FINAL-2178: Clinical and microarray follow-up of SJIA patients treated with anakinra over the past 10 years in a single institution

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Pediatric Rheumatology 2013, 11(Suppl 2):O13

Introduction: The role of IL-1 in the pathogenesis of SJIA was first reported by our group in 2005.

Objectives: To evaluate the response to IL-1 blockade over the past 10 years in SJIA patients treated with anakinra at the clinical level including the durability of response, long term complications, and steroid sparing effect as well as to utilize blood gene expression profiling for insight into potential mechanisms of pathogenesis.

Methods: Clinical/laboratory data of all children with SJIA at our institution treated with anakinra with at least 6 months of follow-up were reviewed. Whole blood gene expression profiling (Illumina bead chip array) was obtained in most patients before and after initiation of IL-1 blockade and repeated over the course of follow-up.

Results: 51 SJIA patients (30 F/21 M) with median disease duration of 1.0 years (range 0 days post dx-11.6 years) and median of 4 active joints (range 0-40) at initiation of anakinra were treated with a mean dose of 2.67 mg/kg (range 1-10) with an average follow-up of almost 5 years (range 0.49-9.75) on anakinra. All children had a SJIA signature as previously described (1) by microarray analysis.

After IL-1 blockade, significant improvements were seen in rashes p = 0.0008, fever p = 0.0001, number of active joints p = 0.0002, WBC p = 0.0001, hemoglobin p = 0.0001, platelets p = 0.0001, and ESR p = 0.0001.

Twenty-two patients (17 new, 5 with flares) were treated without any steroids on anakinra alone (18), or concomitantly with methotrexate (4). Recently the EULAR task force reinforced the importance of vaccination in autoimmune response in JIA have not been studied. Therefore, we aimed to assess the production of some autoantibodies generated following influenza H1N1 vaccination in JIA patients.

Objectives: To assess the autoimmune response and H1N1 serology following influenza H1N1 vaccination in patients with JIA.

Methods: Cepa A/California/7/2009 (NYMC X-179A) anti-H1N1 was used to vaccinate JIA patients: 1 dose of immunization was given to all participants and those <9 yrs of age received a second booster 3 weeks apart. Sera were analyzed before and 3 weeks following complete vaccination. Serology against H1N1 virus was performed by hemagglutination inhibition antibody assay, rheumatoid factor (RF) by latex fixation test, antinuclear antibodies (ANA) by IF, IgM and IgG anticardiotid aCL by ELISA.

Results: Among 98 JIA patients that were vaccinated, 58 sera were available for this study. Mean age of 58 JIA patients was 23.9 ± 9.5 yrs, 38 were females and 20 males with mean disease duration of 14.7 ± 10.1 yrs. JIA subtypes were: 33 (57%) poliarticular, 10 (17%) oligoarticular, 6 (10%) systemic and 9 (16%) other. Sixteen patients were off drugs while 42 (72%) were under different pharmacotherapy: 32 (53%) were on 1 DMARD/IS, 10 (17%) on 2 DMARDs/IS, 19 (33%) antimalarial, 29 (50%) MTX, 8(14%) sulfasalazine, 6 (10%) anti-TNFs, 4 (7%) abatacept; no patient was using prednisone >0.5 mg/kg/d. Seroprotection rates against H1N1 influenza increased from 23 to 83% and seroconversion rates were achieved in 78% JIA. Prior to vaccination, 31(53.4%) JIA patients were ANA+, 6(10.3%) RF+, and 4 (7%) IgM+ and IgG aCL+. After complete H1N1 vaccination, positivity for ANA remained the same whereas 1 JIA patient became negative for IgG aCL, and another for RF, IgM and IgG aCL. One (1.7%) patient turned low titer IgG aCL.

Conclusion: Vaccination of JIA patients against pandemic influenza A (H1N1) generated successful protective antibody production without the induction of autoantibody production, except for 1 patient that became positive for low titer IgG aCL, supporting its safety.

Disclosure of interest: None declared.

O14

PReS-FINAL-2179: Efficacy and safety of adalimumab in pediatric patients with enthesitis related arthritis

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Pediatric Rheumatology 2013, 11(Suppl 2):O14

Introduction: Enthesitis related arthritis (ERA) is a subcategory of juvenile idiopathic arthritis (JIA) which primarily affects peripheral joints and entheses but also can involve the sacroiliac joints and spine. It causes long-term effects on both physical and quality aspects of a child’s life. Adalimumab (ADA) has been previously demonstrated to be effective in polyarticular JIA.

Objectives: To evaluate the efficacy and safety of adalimumab compared to placebo in children and adolescents with ERA.

Disclosure of interest: None declared.
Table 1(abstract O15)

<table>
<thead>
<tr>
<th>At Week 12</th>
<th>ADA (N = 31)</th>
<th>PBO (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from Baseline*</td>
<td># enthesitis sites (0-35)</td>
<td>-4.4 ± 6.2</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td>Tender joint count (0-72)</td>
<td>-7.9 ± 8.3</td>
</tr>
<tr>
<td></td>
<td>Swollen joint count (0-68)</td>
<td>-3.5 ± 5.6</td>
</tr>
<tr>
<td>ACR Pedi Response ≤</td>
<td>ACR Pedi30 responder</td>
<td>21 (67.7)</td>
</tr>
<tr>
<td>(n, %)</td>
<td>ACR Pedi50 responder</td>
<td>20 (64.5)</td>
</tr>
<tr>
<td></td>
<td>ACR Pedi70 responder</td>
<td>16 (51.6)</td>
</tr>
</tbody>
</table>

*LOCF. †NRI. SD, standard deviation.

Methods: This is a phase 3, multicenter, randomized, double-blind (DB) study in patients (pts) aged ≥6 to <18 years (yr) with ERA (ILAR criteria) with active disease not responsive to ≥1 nonsteroidal anti-inflammatory drug and ≥1 disease-modifying antirheumatic drug. Active disease was defined as ≥3 active joints (swelling or loss of motion + pain/tenderness) and enthesitis ≥1 location. Pts were randomized 2:1:1 to receive blinded ADA (24 mg/m² BSA up to 40 mg every other week wk) or placebo (PBO) for 12 wks followed by open-label (OL) ADA eow up to 144 wks. The primary endpoint was change from baseline (BL) in the number of active joints with arthritis (AJC) at wk 12. Secondary variables assessed included enthesitis count (EC), tender and swollen joint counts, and American College of Rheumatology (ACR) Pediatric (Pedi) 50/70/50 responses. Results are summarized through 52 wks of treatment. Safety was assessed in terms of adverse events (AE).

Results: 46 pts were randomized (31 to ADA, 15 to PBO). No pts discontinued during the DB period; however, 7 pts early escaped to OL ADA. Mean age was 12.9 ± 2.9 yrs. At BL, mean duration of ERA symptoms was 2.6 ± 2.3 yrs; mean AJC was 7.8 ± 6.6, and mean EC was 8.1 ± 8.4. The % change from BL at wk 12 in AJC was greater in the ADA group vs. PBO (-62.6 ± 59.5 vs -11.6 ± 100.5, P = 0.039). Most secondary variables showed numerically greater, but not statistically significant improvement at wk 12 in favor of ADA vs. PBO (Table). Treatment response was maintained with continued ADA therapy up to 52 wks (% change from BL at wk 52 in AJC, -88.7 ± 26.1). During the DB period AE incidence rates were similar [ADA/ PBO (%)]; any AE (67.7/53.3), serious AE (3.2/0, 1 pt in the ADA group [abdominal pain and headache]), and infectious AEs (29.0/20.0). Among pts who received at least 1 dose of ADA through wk 52, any AE, serious AEs, and infectious AEs were reported in 91.3%, 10.9%, and 76.1%, respectively. No deaths, TB, or malignancies were reported.

Conclusion: ADA reduced the signs and symptoms of ERA at wk 12 and efficacy was sustained up to 52 wks. The safety profile observed in pediatric patients with ERA was consistent with that observed in children aged ≥4-17 years treated for polyarticular JIA.


Table 1(abstract O15) JIA ACR50/70 responses and percentage change from baseline in components, a mean ± SD

<table>
<thead>
<tr>
<th>JIA ACR70 responders, n (%)</th>
<th>All TCZ (N = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 40</td>
<td>Wk 104</td>
</tr>
<tr>
<td>65 (79.3)</td>
<td>71 (86.6)</td>
</tr>
<tr>
<td>41 (50.0)</td>
<td>58 (70.7)</td>
</tr>
<tr>
<td>Active joints (0-71)</td>
<td>-82.4 ± 24.9</td>
</tr>
<tr>
<td>Joints with limitation in ROM (0-67)</td>
<td>-73.5 ± 30.7</td>
</tr>
<tr>
<td>Patient global (VAS 0-100 mm)</td>
<td>-62.5 ± 76.3</td>
</tr>
<tr>
<td>Physician global (VAS 0-100 mm)</td>
<td>-85.3 ± 16.8</td>
</tr>
<tr>
<td>CHAQ-DI (0-3)</td>
<td>-66.0 ± 44.7</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>-76.5 ± 22.0</td>
</tr>
</tbody>
</table>

aPts who withdrew are excluded. bPts who withdrew due to non-safety reasons are non-responders. cPts who withdrew due to safety are included using last observation carried forward. dParent-rated.

Reference

O16 PReS-FINAL-2181: Recombinant IL-1ra restores the IL-18-nK cell axis in steroid naive systemic juvenile idiopathic arthritis

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Pediatric Rheumatology 2013, 11(Suppl 2):O16

Introduction: Systemic onset juvenile idiopathic arthritis (sJIA) is an acquired auto-inflammatory disease characterized by systemic inflammation and innate immune activation reflected in uncontrolled production of cytokines such as IL-1, IL-6 and IL-18. In SJIA, NK cell function is severely hampered despite high levels of IL-18. We recently found that defective phosphorylation of the IL-18 receptor beta is responsible for the deficient IL-18-nK cell axis in SJIA.

Objectives: Given the strong homology between the IL-1 and the IL-18 receptor we questioned whether treatment with rIL-1RA (Anakinra) may directly down regulate IL-18 production and restore the IL-18 signaling cascade in NK cells and, if so, whether this relates to the clinical improvement observed in SJIA patients. Therefore we treated 15 consecutive patients with newly onset SJIA before start of steroids.

Methods: Clinical (ACRped) and laboratory parameters (NK Cell activity, cytokine levels) were analyzed during 90 days after initial start of rIL-1RA treatment. To study binding interaction between rIL-1RA and both the IL-1r and the IL-18r a human cell line (KGI) was used.

Results: We show that patients with SJIA have increased inflammasome activation leading to elevated IL-18 levels. Treatment with recombinant rIL-1RA in steroid naive newly onset SJIA patients led to rapid resolution of clinical features in 87% of patients. In vitro, rIL-1RA directly antagonized IL-18 signaling and lead to normalization of both inflammasome activation and IL-18 levels. Finally, in vivo first line treatment with rIL-1RA in SJIA patients led to a normalization of both IL-18 levels and inflammasome activation and a restoration of the deficient IL-18-nK cell axis, correlating with a favorable clinical response in these patients.

Conclusion: The rapid clinical efficacy of early treatment with rIL-1RA in SJIA is accompanied by a restoration of the IL-18-nK-cell axis in SJIA. These data provide biological support for the use of rIL-1RA SJIA patients early in the disease course as first line treatment, as it directly interferes with the deficient IL-18-nK cell axis which may lead to a intrinsically change in the course of the disease.

Disclosure of interest: None declared.

O18 PReS-FINAL-2183: IL-6 amplifies toll like receptor mediated cytokine and chemokine production: implications for the pathogenesis of rheumatic inflammatory diseases

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Pediatric Rheumatology 2013, 11(Suppl 2):O18

Introduction: Interleukin-6 (IL-6) is a pleiotropic cytokine with multiple functions in different pathophysiologic systems. A vast body of evidence suggests a role for IL-6 in rheumatoid arthritis (RA) and in systemic juvenile idiopathic arthritis (JIA). Toll-like receptors (TLRs) are a family of transmembrane glycoproteins with conserved extracellular domains and a cytoplasmic signaling domain homologous to that of IL-1R, called the Toll/IL-1R domain. They bind a wide array of bacterial and viral, as well as endogenous, peptides. They mediate inflammatory cytokine and chemokine secretion, thus controlling the response to pathogens and playing a role in the pathogenesis of inflammatory diseases.

Objectives: To evaluate whether the exposure to IL-6 affects TLR ligand-induced production of inflammatory cytokines and chemokines in human blood and signalling pathways involved in mononuclear cells (PBMCs), adherent mononuclear cells from synovial fluid of JIA patients (adherent SFMCs) and fibroblast-like synoviocytes from rheumatoid arthritis patients (RA synoviocytes).

Methods: PBMCs were left untreated or treated with IL-6/sIL-6R and then stimulated with LPS, S100A8, Pam3CSK4, poly(I:C), CpG, MDP, IL-1β.
Inflammatory cytokine and chemokine expression was measured by ELISA. Activation of p65 NF-κB was evaluated by Western blot. SFMCs and RA synoviocytes were pretreated with IL-6/sIL-6R or sIL-6R, alone or in combination with Tocilizumab (TCZ), and then stimulated as above.

Results: Addition of IL-6 to PBMCs stimulated with LPS or S100A8 led to increased production of CXCL8, CCL2, and IL-1ß. Treatment with sIL-6R also increased IL-1ß and LPS induced cytokine and chemokine production. All these effects were neutralized by addition of TCZ.

Conclusion: Our results point to a role of IL-6 in the amplification of TLR induced inflammatory response both in mononuclear cells and in RA synoviocytes. This effect may be relevant in conditions where high levels of IL-6 are produced in the presence of sIL-6R, such as in joints of patients with rheumatic diseases. Interestingly, we found that the well-known inhibitory effect of IL-6 on TLR4 induced cytokine and chemokine production is specific for peripheral blood cells, while in cells from inflammatory sites (adherent SFMCs or RA synoviocytes) IL-6 synergizes with TLR4 ligands.

Disclosure of interest: None declared.
PRES-FINAL-2186: Monoallelic mutations of familial hlh-related genes associated to macrophage activation syndrome

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Introduction: Macrophage Activation Syndrome (MAS) is a severe complication of rheumatic diseases, frequently associated with systemic juvenile idiopathic arthritis (sJIA), but also described in other pediatric inflammatory disorders including Juvenile Systemic Lupus Erythematosus (SLE) and Kawasaki disease. Due to the close resemblance to a group of hystiocytic disorders collectively known as hemophagocytic lymphohistiocytosis (HLH) it is currently classified among the secondary or acquired forms of HLH, and the term rheoHLH has been proposed.

Objectives: To describe clinical, functional and genetic features of MAS in the Italian HLH registry.

Methods: We reviewed the HLH Italian National Registry to select patients with MAS defined according to the diagnostic criteria established by the Histiocyte Society (so called HLH criteria) with confirmed diagnosis of rheumatologic or autoimmune disease. Clinical data were collected. Functional screening of perforin expression and degranulation was performed using flow-citometry. Genetic study was carried out by direct sequencing of currently known genes that cause familial HLH.

Results: Among the 813 patients referred to the Registry, 38 (5%) were diagnosed as MAS in the context of a rheumatic disease. Of them 13 were male and 25 female; 30 Caucasian and 8 Indian. Median age was 94 (quartiles: 37; 94; 136; 708) months. The underlying diseases were: sJIA (n = 28), SLE (n = 4), Kawasaki disease (n = 1), Juvenile Dermatomyositis (n = 1), undefined rheumatologic (n = 2) or autoimmune (n = 1) disease. The clinical features included: fever (n = 28/28, 100%), splenomegaly (n = 17/28, 61%), neurologic manifestations (n = 7/28, 25%), anemia (n = 15/25, 60%), thrombocytopenia (n = 14/25, 56%), neutropenia (n = 3/25, 12%), hypertriglyceridemia (n = 14/25, 56%), hyperferritinemia (n = 7/25, 28%), hyperferritinemia (n = 22/23, 96%; quartiles: 2.430, 10.264, 15.953, 96.000 ng/ml), hemophagocytosis (n = 9/25, 36%). Four patients (10.5%) died for disease progression. Functional screening of FHL was performed in 22 cases: perforin expression was normal in 14 and reduced in 8 (36%); degranulation was defective in 3/18 (17%) and normal in the remaining 15/18 cases. At least one test was defective in 10/23 (43%). Mutation analysis included PRF1 (n = 8/36, 22%), STX11 (n = 33), STXBP2 (n = 19) and allowed to identify monoallelic mutations in 11 of the 38 patients (29%), as follows: PRF1 (n = 8/36, 22%), STX11 (1/33, 3%), STXBP2 (3/19, 16%).

Conclusion: A significant portion of patients with MAS appear to have functionally defective cytotoxic activity and carry monoallelic variants in genes associated with familial HLH. These data suggest additional similarities in genetic background and cytotoxic activity abnormalities between MAS associated with rheumatic diseases and familial HLH.

Disclosure of interest: None declared.

PRES-FINAL-2188: Insulin sensitivity is improved in sja children with insulin resistance after tocilizumab treatment: results from the tender study

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Pediatric Rheumatology 2013, 11(Suppl 2):O23

Introduction: In adults with inflammatory arthritis, insulin resistance (IR) is associated with diabetes and cardiovascular disease. Interleukin-6 (IL-6) is postulated to play a mechanistic role in IR.

Objectives: To evaluate the degree of IR among children with systemic juvenile idiopathic arthritis (sJIA) and whether treatment with tocilizumab (TCZ) results in attenuation of IR in sJIA.

Methods: Patients (pts) from TENDER1 were included if baseline and wk 6 fasting insulin were measured. Glucocorticoid tapering was not permitted until wk 6. Insulin sensitivity was quantified using the homeostatic model of insulin resistance (HOMA-IR). Pts were classified as having IR if their HOMA-IR was ≥2.2 U. Change in HOMA-IR after 6 wks was assessed using paired t-test. Baseline associations with HOMA-IR and factors predicting progress rapidly to multi-organ failure and death. HLH may be genetic (primary HLH), or secondary to infection or autoimmun/ autoimmune conditions; if the latter, it is also referred to as macrophage activation syndrome (MAS). Distinguishing between primary HLH and MAS is challenging but important since the former requires different therapeutic approaches including allogeneic haematopoietic stem cell transplantation (HSCT) for long-term survival. HLH screening tests are now being used in patients presenting with suspected MAS. In systemic Juvenile Idiopathic Arthritis (sJIA), some patients demonstrate temporary perforin expression abnormalities that resolve with disease control. The utility of other screening tests in a rheumatology context is unknown.

Objectives: The purpose of this study was to describe the performance of screening tests used in the HLH/MAS work up of children presenting to a specialist paediatric rheumatology centre, and review outcomes of those with screening abnormalities.

Methods: A database exists of patients who had screening tests for suspected HLH/MAS. Screening tests (flow cytometry) included: intracellular expression of perforin in CD56+ Natural Killer (NK) cells; CD107a Granule Release Assay (GRA) in response to PHA in NK cells or anti-CD3 stimulation of CD8 lymphocytes; in male patients Signal Lymphocyte Activating Molecule Associated Protein (SAP, associated with XLP1) and X-linked Inhibitor of Apoptosis Protein (XIAP, associated with XLP2) expression. All tests requested by paediatric rheumatology over a 5 year period (2007-2011) were included. Patient records and laboratory parameters were retrospectively reviewed.

Results: 22 patients (15 female), median age 6.5 years (range 0.6-16) underwent screening tests, with median follow-up of 16 months (range 3-51). At presentation only 2/22 (9%) clinically met HLH criteria. Screening results were available for 20 patients; 7 (35%) had at least one persistent abnormality in any one of the tests; this group was associated with 77% mortality or need for HSCT, compared to 8% with no abnormality on any of the tests (p = 0.03). 6/20 (30%) had persistently abnormal GRA: their final diagnoses were sJIA with MAS (n = 3); primary HLH (n = 2); and overlap syndrome (n = 1). 1/4 boys screened for XIAP had absent expression with subsequent genetic confirmation of XLP2. 18 patients had perforin screened, and 5 boys were screened for SAP expression; all had normal results.

Conclusion: Primary HLH and MAS may overlap clinically and screening in patients with suspected MAS is warranted; overall 14% had an eventual diagnosis of primary HLH. Persistently abnormal GRA defines a high risk group with poor outcome (mortality or need for HSCT) possibly due to an unidentified HLH gene. The effect of immunosuppression on the GRA was not assessed. Further research is required in those with abnormal GRA to help understand the pathogenesis of HLH/MAS.

Disclosure of interest: None declared.

PRES-FINAL-2187: Use of screening tests in patients presenting to paediatric rheumatology with suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome

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Pediatric Rheumatology 2013, 11(Suppl 2):O22

Introduction: Haemophagocytic lymphohistiocytosis (HLH) is a severe condition in which there is extreme uncontrolled inflammation, and may
Table 1 (abstract O23) Change in HOMA-IR after 6 wks of Treatment in Children with sJIA in the TENDER Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in HOMA-IR</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCZ (n = 34)</td>
<td>-0.2 (-3.8, -0.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>PBO (n = 6)</td>
<td>0 (-1.7, 1.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant; PBO, placebo. *paired t-test.

change of HOMA-IR from baseline were assessed using regression analyses. Factors changing in association with HOMA-IR change were assessed.

Results: 92 pts with sJIA were analysed. 62 were randomised to TCZ and 30 to placebo, 12 of whom required escape therapy with TCZ by wk 6. At baseline, 40 pts (43%) had IR. Baseline HOMA-IR was associated with higher standardised body mass index and higher IL-6 levels (β-coefficient 95% CI): 0.20 [0.05, 0.35] and 0.019 [0.001, 0.038], respectively but not with JADAS, CRP, active joint count or presence of fever. Of the 74 pts who received TCZ, 34 (46%) had IR at baseline, including 4 pts who escaped from the placebo arm, compared with 6/18 (33%) who received only placebo. IR pts treated with TCZ but not placebo had significant reductions in HOMA-IR at wk 6 (Table). Across all IR pts, improvement in JADAS and active joint count was not associated with improvement in HOMA-IR (β-coefficient 95% CI): 0.04 [-0.07, 0.14] and 0.08 [-0.06, 0.22], respectively.

Conclusion: After only 6 wks of TCZ treatment, HOMA-IR was improved in IR pts with sJIA in the presence of unchanged glucocorticoid dose. These data support a mechanistic contribution of IL-6 to IR in vivo in humans.


Reference
Results: The study population consisted of 42 children (69% male) with ANCA GN (21 GPA, 21 MPA) with a median age of 11.96 (+3.52) years and eGFR 36.6 ml/min/1.73 m^2 (IQR 15-87.4). Of the 40 patients with a renal biopsy at time of initial diagnosis, 12 (30%) had focal lesions, 20 (50%) crescentic, 3 (7.5%) mixed, 5 (12.5%) sclerotic and no globally sclerotic lesions. 13 (31%) patients required dialysis at baseline. Survival analysis of time to the composite renal endpoint of at least 3 months of eGFR < 60 ml/min/1.73 m^2 or ESKD differed among all 3 biopsy groups (p = 0.001; figure). Probability (95% CI) of having an eGFR < 60 ml/min/1.73 m^2 at 2 years was 58.3% (35.1 - 76.0%) in the crescentic/mixed group. The sclerotic group all progressed to ESKD. Linear regression analysis demonstrated an association of slope of eGFR with baseline eGFR (p= 0.01), baseline proteinuria (p = 0.037) and need for dialysis (p < 0.010) after adjustment.

Conclusion: We demonstrate the clinical utility of the new histopathologic classification system and its ability to clearly discriminate outcomes among paediatric ANCA GN patients. Additional factors predicting outcome include baseline eGFR and dialysis. The new classification can be adopted for both clinical use and research studies.


O26
PreES-FINAL-2191: Imaging of chronic recurrent multifocal osteitis: a french national cohort of 178 cases
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Pediatric Rheumatology 2013, 11(Suppl 2):O26

Introduction: The radiological assessment of CRMO is currently the subject of debate and the recent use of whole-body MRI leads to discuss the respective roles of the imaging techniques.

Objectives: This study provides a descriptive evaluation of imaging OCMR, its diagnostic management and a comparison between different techniques.

Methods: 178 CRMO patients were included (123 females and 55 males). The lesions detected by imaging (plain radiographs, isotopic bone scan and/or MRI) were collected by specifying the number, location (bone, proximal/distal and metaphyseal/epiphyseal/diaphyseal), character (lytic/sclerotic/mixed) and the signal MRI T1 and T2.

Results: The average number of lesions per patient detected before diagnosis was 3.5 ± 2.9 [1-26]. The mean number of lesions was 1 ± 0.9 by radiographies, 2.45 ± 1.7 by isotopic bone scan and 3.12 ± 1.33 by MRI. A total of 193 radiographic lesions were detected with the following distribution: tibia (n = 44), the clavicle (n = 34), the femur (n = 23), the fibula (n = 20) and pelvis (n = 19). The lesions of the lower limbs accounted for 52% of the lesions. The lesions of the long bones were most often located in metaphyseal (58/76, 76%) and were lytic in 76/162 (47%) and sclerotic in 60/162 (37%). The isotopic bone scan detected 372 lesions localized to the pelvis (n = 64), tibia (n = 51), femur (n = 44), clavicle (n = 40) and vertebrala (n = 29). The lesions were mainly metaphyseal (65/92, 56%). MRI detected 515 lesions distributed as follows: pelvis (n = 100), tibia (n = 93) and femur (n = 73) are the sites most frequently affected. 51 vertebral lesions (10%) were detected in 36 patients. Most of them were localized at C1-2. The vast majority of lesions were hyper-T1 and hyper-T2. The description of bone lesions with MRI seems to be more accurate (metaphyso-epiphyseal) and more frequently bilateral and symmetric.

Imaging has allowed confirming the multifocal pattern in 26/54 patients with clinical monocanal at diagnosis. Of the remaining 28 patients with monofocal lesion, the clinical course and imaging confirmed the multifocal pattern in 16 additional cases: a total of only 12 patients (7%) kept a pure monofocal evolution.

In 15 patients, scintigraphy and whole-body MRI were performed at the same time (+/- 3 months). Analysis of these 15 patients showed a higher sensitivity to detect lesions by MRI (6.7 ± 3.1 vs 3.4 ± 2.4, p = 0.003) and better description of lesions.

Jansson score that integrates imaging, was interpretable in 110 patients: the application of this score would have, in this cohort, to avoid 27/110 biopsies.

Conclusion: The study of imaging in this large CRMO French cohort confirms the interest of imaging to characterize multifocal involvement of CRMO and to prevent invasive diagnostic procedures. MRI confirms its sensitivity to detect more lesions including spinal and pelvis than isotopic bone scan. MRI provided a more detailed description of the osteitis lesions.

Disclosure of interest: None declared.

O27
PreES-FINAL-2192: Late cardiac assessment in children who were diagnosed with post streptococcal reactive arthritis - a long term study
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Pediatric Rheumatology 2013, 11(Suppl 2):O27

Introduction: In different from rheumatic fever (RF), the association of post streptococcal reactive arthritis (PSRA) and carditis is controversial. Currently the American Heart Association recommends anti-streptococcal prophylaxis for PSRA for one year, repeat echocardiogram and discontinuation of prophylaxis if normal (level 2, C evidence).

Objectives: To examine whether there is late cardiac involvement in a cohort of children with PSRA.

Methods: Children with defined PSRA who were followed at the pediatric rheumatology units in Meir and Kaplan hospitals had echocardiography, done by pediatric cardiologists, at least 1 year following diagnosis. Results: 146 PSRA patients fulfilled the study criteria. Of these, 69 had undergone echocardiography 1-6.9 years from diagnosis. All had normal major parameters. 20 patients had minimal findings: 5 (7.2%) mild mitral insufficiency; 12 (17.4%) minimal mitral insufficiency; 2 (2.9%) mild tricuspid insufficiency and one patient (1.4%) had very mild aortic insufficiency. All were consistent as non significant findings. Of the 77 patients who did not complete echocardiography, 31 were randomly excluded from the study, 26 refused to undergo echocardiography, and 20 were lost to follow-up, all were asymptomatic according to their medical record or telephone questionnaire. There were no statistically significant differences between the group that had completed echocardiography to the group that had not.

Conclusion: No late cardiac involvement was found in our pediatric PSRA patients. Therefore, different approaches to antibiotic prophylaxis for PSRA and RF are probably justified. A prospective, double blind placebo controlled study is needed to definitively assess the necessity of prophylaxis in PSRA.

Disclosure of interest: None declared.

O28
PreES-FINAL-2193: Assessment of construct validity of new measures of global disease activity, physical function and quality of life in children with juvenile dermatomyositis
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Pediatric Rheumatology 2013, 11(Suppl 2):O28

Introduction: Juvenile dermatomyositis (JDM) is a multisystem vasculopathic disease that affects primarily the skin and muscle and is characterized by high risk of morbidity and long-term damage. Regular patient assessment through standardized quantitative clinical measures is important to monitor the disease course over time and to evaluate treatment effectiveness. However, only a few outcome measures specifically validated for use in JDM are available.
To investigate the construct validity of the following new clinical measures for JDM developed by our group: 1) JDM-Act (global disease activity); 2) MyoFun (physical function); 3) Pediatric Rheumatology Quality of Life scale, PRQL (health related quality of life).

Methods: Construct validity was assessed by computing the correlations between the new clinical measures and conventional JDM outcome measures by means of the Spearman’s correlation coefficient. Correlations were considered good, moderate, or poor when the rs was > 0.7, 0.4-0.7, or < 0.4, respectively.

Results: A total of 107 consecutive JDM patients (44 male, 63 female) seen in 4 pediatric rheumatology centres were included in the study. Mean disease duration was 3.1 years (IQR:1.0-5.8) and mean age at visit was 10 years (IQR:6.4-13.6). The table shows the Spearman’s correlations of JDM-Act, MyoFun and PRQL scores with the values of conventional measures of disease activity and damage.

Conclusion: The new clinical measures showed good construct validity. By documenting this key measurement property, we have shown that the new tools are valid instruments for the assessment of children with JDM and are, therefore, potentially applicable in both clinical and research contexts.

Because the new measures are simpler and shorter than most existing instruments, they may help foster the incorporation of quantitative clinical assessment in standard clinical practice.

Disclosure of interest: None declared.

Table 1 (abstract O28)

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<td>0.14</td>
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Because the new measures are simpler and shorter than most existing instruments, they may help foster the incorporation of quantitative clinical assessment in standard clinical practice.

Disclosure of interest: None declared.

Introduction: Educational strategies and contents developed in the First Pediatric Rheumatology (PR) center in Buenos Aires (Argentina) were not always adapted to the needs and challenges of developing countries. Cooperation and collaboration between developing countries can be mutually beneficial and create the basis for a longstanding, Third World-centered educational program aimed at increasing the pediatric support for Pediatric Rheumatology (PR).

Objectives: To describe a binational (Argentina-South Africa), bicontinental, educational strategy aimed at increasing the pediatric support for PR.

Methods: All FMF, TRAPS, MKD and CAPS patients enrolled in the Eurofever registry until March 2013 were evaluated. For each disease gold standards were considered according to the following criteria: i) clinical validation by centers and disease-principal investigator, ii) confirmative molecular analysis (2 mutations for MEVF with at least one mutation in exon 10, 2 mutations of MVK gene, 1 mutation of TNFRSF1A with exclusion of low-penetrance variants, 1 mutation of NLRLP3 with exclusion of low-penetrance variants), iii) PFAPA patients validated by disease-principal investigator and confirmed by the centers on the basis of the follow-up. Clinical criteria were formulated on the basis of the univariate and multivariate analysis in a first group of patients (training set) and then validated in an independent set of patients (validation set).

Results: A total of 1204 consecutive patients with periodic fevers were enrolled in the registry. Among them 743 consecutive gold standard patients (288 FMF, 73 MKD, 96 TRAPS, 87 CAPS, 199 PFAPA) were evaluated (440 in the training set and 303 in the validation set). The multivariate analysis identified the clinical variables (either as presence or absence) independently correlated to the disease with their specific weight. The cut off value of the classification score was chosen on the ROC curve in order to guarantee the highest sensitivity and specificity.

The classification score was then tested in an independent set of patients (validation set) revealing a sensitivity of 93% and specificity of 89% for FMF; a sensitivity of 100% and specificity of 74% for TRAPS; a sensitivity of 80% and specificity of 90% for MKD and sensitivity of 97% and specificity of 92% for CAPS; sensitivity of 99% and specificity of 96% for PFAPA. The performance in non-gold standard patients (i.e. heterozygous patients in autosomal recessive diseases or patients with low-penetrance mutations) revealed a variable percentage of patients (70% FMF, 75% TRAPS, 41% MKD and 94% CAPS) positive for the respective criteria.

Conclusion: Evidence-based clinical classification criteria for the classification of patients with inherited periodic fevers have been elaborated. These clinical criteria could be used in association with molecular analysis and other variables (i.e. metabolic examinations, response to specific treatments) for patients classification.

Disclosure of interest: None declared.

O29

PRoS-FINAL-2194: Evidence-based clinical classification criteria for periodic fevers

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Pediatric Rheumatology 2013, 11(Suppl 2):O29

Introduction: No evidence-based classification criteria are so far available for the majority of autoinflammatory diseases

Objectives: To elaborate and validate a set of clinical criteria able to correctly classify patients affected with the most common periodic fevers.
to those areas for the development of education of basics of PR for pediatricians through patient-based teaching sessions and interactive discussions; periodic problem-based, SA-A teleconference rounds. A tailored educational program included specific competency-based educational goals for each trainee as well as community-based epidemiological research and team-based, patient-oriented care. Post-training assessment of trainees’ skills and knowledge is carried through multiple choice tests and Objective Structured Clinical Examination, as well as trainees’ satisfaction through a structured survey.

Results: Six pediatricians (3 in Argentina and 3 in South Africa) received a comprehensive training according to the educational program. They were successfully evaluated and returned to their local setting, where they are currently involved in the care of children and adolescents with rheumatic conditions. Their activities are periodically monitored through combined trainer-trainee case discussions. Visiting professorships resulted in the delivery of basics of PR to over 200 pediatricians in different cities of SA-A. All fellows expressed high degree of satisfaction with their experience.

Conclusion: This project developed an ongoing, successful educational strategy that may be used as a model for training in PR in other regions of the developing world. Evaluation of the impact of the program on care delivery will follow in the next few years.

Disclosure of interest: None declared.

O31
PRes-FINAL-2366: Paediatric rheumatology in South Africa
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Pediatric Rheumatology 2013, 11(Suppl 2):O31

Introduction: South Africa is a middle income, developing country with a population of 51 million people, 29% of whom are younger than 14 years. As a result of a heavy burden of communicable disease and major socio-economic and political challenges, chronic rheumatic conditions in children have received very little attention in the past and South Africa only has 5 pediatric rheumatologists, 1 for every 3 million children.

Objectives: 1) To describe the past and present of pediatric rheumatology in South Africa. 2) To describe challenges in the care of PR patients in South Africa. 3) To describe training and research activities in South Africa and speculate on the future.

Methods: Available regional pediatric rheumatology data, clinic data and pediatric rheumatology workforce statistics were reviewed.

Results: The spectrum of rheumatic diseases seen in South African clinics is different to those in developed countries. The burden of infectious diseases complicates the presentation and management of children with rheumatic diseases. There is a shortage of pediatric rheumatologists and training opportunities in South Africa.

Conclusion: In recent years Pediatric Rheumatology has become an established discipline in South Africa and the provision of specialized healthcare for children and adolescents with Rheumatic Diseases has improved. Despite this the majority of children in South Africa are not able to access appropriate care. There is a need for training in pediatric rheumatology at all levels of pediatric healthcare in South Africa and a critical need to support the training and retention of pediatric rheumatologists. There is a shortage of research on pediatric rheumatic diseases in Africa.

Disclosure of interest: None declared.

O32
PRes-FINAL-2367: Academic training of pediatric rheumatologist in the Russian federation
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Pediatric Rheumatology 2013, 11(Suppl 2):O32

Introduction: Rheumatic diseases are characterized by high prevalence and functional disability of patients. Right diagnosis in the onset of disease, early aggressive therapy with antirheumatic drugs including biologics improve the prognosis and prevent disability of patients. Only high qualified pediatric rheumatologists can do it.

Objectives: To analyze system of pediatric rheumatologists training in Russian Federation (RF).

Methods: Description of medical education in pediatric rheumatology in RF.

Results: Training of pediatricians is performed at a pre-degree stage at Pediatric Faculties of State Universities. Graduates get a degree of a pediatrician.

There is no medical specialization of “Pediatric Rheumatologist” in the list of medical professions in RF. In 2012 a position of rheumatologist was included into the staff schedule of children’s polyclinic. In children’s hospitals Pediatric Rheumatology Departments are provided, and position of rheumatologist was included into the staff schedule of pediatric hospitals. A graduate of Pediatric Faculty or of General Medicine Faculty (with a degree of a general practitioner) serves internship in pediatrics either in the form of 1 year-internship training or in the form of 2 year-residency training. After that the graduates get a certificate of a medical specialist (pediatrician) and a right for clinical practice. Further residency training in rheumatology is required (2 years) or professional development training in rheumatology of at least 500 hour- duration. After completion the graduate receives a certificate of rheumatologist. Further training is performed in the form of advanced medical training in postgraduate stage.

A rheumatologist undergoes thematic advanced training in pediatric rheumatology in the volume of 144 hours and gets a certificate. Further professional training is obtained within the system of continuous medical education.

In 2003 at the I.M. Sechenov First Moscow State Medical University a Pediatrics and Pediatric Rheumatology Chair was established, first in RF. The key area of activity is to improve qualification of pediatricians in the fields of diagnostics, treatment and rehabilitation of children with rheumatic disorders. Within 10 years 28 advanced training programs have been performed. For remote regions online programs using videoconference calls are organized. Advanced training is performed at training schools within annual Meetings of the Union of Pediatricians of RF. The School of Pediatric Rheumatologist was founded in 2006. 1,464 pediatricians took part in the School since 2006. Since 2011 precongress master classes in pediatric rheumatology have been organized within the Congress of Pediatricians of RF with participation of European and American pediatric rheumatologists. A total of 2,742 pediatricians have underwent advanced training in pediatric rheumatology in 10 years. Once in 5 years a rheumatologist should undergo training to confirm the certificate.

Conclusion: Training of pediatricians in pediatric rheumatology is very important for suspicion of rheumatic disease at onset. Training of pediatric rheumatologists is very important for early diagnostics and adequate treatment of rheumatic diseases.

Disclosure of interest: None declared.

O33
PRes-FINAL-2368: A, B, C, don’t ever forget the joints
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Pediatric Rheumatology 2013, 11(Suppl 2):O33

Introduction: The musculoskeletal examination has been shown to be poorly documented in the UK, despite musculoskeletal problems being common in children. Recent research has shown that examination of the joints is highly acceptable to patients and parents The musculoskeletal examination has been included in the Royal College of Pediatrics and Child Health clinical examination since 2009 and teaching resources are widely available. The pGALS examination has been validated and there are published red flags and triggers for the musculoskeletal examination.

Objectives: To assess if the musculoskeletal (MSK) examination was being performed, in eight pediatric centers across Yorkshire, when the clinical situation would suggest it was warranted.

Methods: 397 patient’s notes were randomly collected and reviewed retrospectively. Each centre assessed approximately 50 sets of patient’s notes Patients were included if they had presented to hospital between August and November 2012. That single admission only was reviewed for
this audit. The admission notes were reviewed for multiple parameters, including specifically looking for evidence of the triggers and red flags for the musculoskeletal examination. The notes were assessed to find out whether an MSK examination had been done by the doctors on the initial assessment and then the first and second reviews, and if there were triggers or red flags for the examination. The notes were also assessed to see if there was evidence of documentation of the other clinical examinations (for example the cardiovascular system), as well as other variables, including the grade of the doctors reviewing patients. The information was collected on excel spreadsheets and then collated by the audit team to make some general conclusions about trends across Yorkshire.

Results: 35% of the 397 admissions had a trigger for an MSK examination. 26% of the 397 admissions had a red flag for an MSK examination. Not a single patient who needed an MSK examination on initial assessment or first review had a full MSK examination documented, whereas 80% of patients routinely had a respiratory and cardiovascular examination on initial assessment. 22% had a partial musculoskeletal examination documented on initial examination. Only 1 out of 105 patients who had red flags for an MSK examination had a complete examination documented.

Conclusion: In 2004 the musculoskeletal examination was shown to be poorly documented. This audit shows that the musculoskeletal examination is still rarely being documented or performed across Yorkshire, across disciplines, by consultants or more junior doctors, even when there are clear triggers and red flags for the examination.

We propose a change in the admission documentation regionally to include a specific MSK section and plan to re-audit following the introduction of this intervention. We also propose a national audit should be performed to create awareness nationally about these very disappointing results and if this picture is mirrored across the country then more educational measures, directed at all levels of doctors should be driven forward on a national level to ensure that this picture improves. We conclude that the musculoskeletal examination should be performed and documented routinely as part of the assessment of pediatric patients admitted to any discipline within the hospital.

Disclosure of interest: None declared.

P1
PReS-FINAL-1003: Intrinsic cd4 and cd8 effector t cell resistance to suppression in the synovial fluid of juvenile idiopathic arthritis patients

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Pediatric Rheumatology 2013, 11(Suppl 2):P1

Introduction: Autoimmune diseases are characterized by an imbalance between regulatory T cells (Treg) and effector T cells (Teff) both in terms of number and function. Our group previously showed that Teff from the site of inflammation (i.e. synovial fluid, SF) of patients affected by Juvenile Idiopathic Arthritis (JIA) are resistant to autologous Treg-mediated suppression irrespective of the source of Treg (SF or peripheral blood). However, it is still unclear whether resistance to suppression is an intrinsic characteristic of SF-derived Teff or it is induced/ maintained by local pro-inflammatory antigen presenting cells (APC).

Objectives: The aim of this study was to elucidate whether T cells from the SF are intrinsically resistant to Treg-mediated suppression.

Methods: A suppression assay of Cell Trace Violet (CV)-labeled CD4+CD25- and CD8+ sorted Teff from PB and SF of JIA patients was performed by using anti-CD3 mAb (1.5 μg/ml) plus autologous CD3- cells or anti-CD2/CD3/CD28 beads as stimulators. CV dilution was used to measure T cell proliferation.

Results: CD4+ and CD8+ T cells from the SF showed enhanced proliferation compared to the PB. When stimulated with beads, Teff from SF were suppressed by Treg from the same site to a lesser extent than PB Teff. When Teff from the SF were stimulated with anti-CD3 mAb plus CD3- cells from the same site, they failed to be suppressed by Treg.

Conclusion: These data show that despite SF-derived APC have a role in the induction of Teff resistance to suppression, SF-derived Teff become intrinsically resistant to Treg-mediated suppression.

Disclosure of interest: None declared.

P2
PReS-FINAL-1004: Can the cd4/cd8 ratio be used as a predictive biomarker in extended-to-be oligoarticular JIA?

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Pediatric Rheumatology 2013, 11(Suppl 2):P2

Introduction: Predicting disease course in Juvenile Idiopathic Arthritis (JIA) is difficult. During the first 6 months of oligoarticular JIA (O-JIA) disease presents with 4 or fewer affected joints, however after 6 or more months severity might increase with more than 4 joints involved (extended O-JIA), or persist with 4 or fewer joints affected (persistent O-JIA). However patients do not show any clinical differences at onset making a decision on treatment strategy difficult before extension occurs. It has previously been shown that the CD4/CD8 T cell ratio in extended-to-be patients (samples before extension has occurred) is lower compared to those who persist (Hunter et al 2010), and thus might be a useful biomarker in predicting the course of disease. However measuring this cell ratio currently requires specialized expertise. To translate the measurement of the CD4/8 synovial T cell ratio as a biomarker a method is needed, which could be used in a wide range of hospital facilities, hence a real-time quantitative PCR (qPCR) method was tested.

Objectives: The aim of this study was to measure CD4 and CD8 mRNA in whole synovial fluid collected at therapeutic joint injection and to compare it to the gold standard of flow cytometry using mononuclear cells.

Methods: A total of 40 healthy adult blood and 20 patient synovial fluid (SF) samples were included in this study. cDNA was generated from total RNA extracted from Tempus vacutainers using whole blood or SF. CD4, CD8b and GAPDH transcripts were measured by qPCR. Simultaneously peripheral blood mononuclear cells (PBMC) and SFMC were isolated using density gradient centrifugation and stained with CD3, CD4, CD8b and CD8u for flow cytometry.

Results: Validating previous results, the CD4/CD8 T-cell ratio measured by flow cytometry was significantly lower in SFMC than in healthy adult PBMC. Measurement of CD4/8 ratio by qPCR and flow cytometry showed some correlation in healthy adult PBMC. However CD4/CD8 ratios by qPCR were higher in SF samples compared to healthy control PBMC. This was driven by increased CD4 measurements by qPCR in SF samples.

Conclusion: Taken together these data show a trend to a correlation of qPCR and flow cytometry methods in healthy adult control samples. The increased level of CD4 transcript in SF measured by qPCR might well be due to the abundance of neutrophils and monocytes, which are may be discarded during preparation of SFMC for flow cytometry. Whether qPCR measurement of CD4/CD8 ratio can be used as a predictive biomarker for severity of disease course in O-JIA remains to be seen, and will be assessed once clinical follow-up data is available.

Disclosure of interest: None declared.

P3
PReS-FINAL-1005: Hypertensaminasemia in systemic juvenile idiopathic arthritis during anti-interleukin 1 treatment

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Pediatric Rheumatology 2013, 11(Suppl 2):P3

Introduction: Systemic juvenile idiopathic arthritis (sJIA) accounts for 10-15% of JIA patients and is characterized by arthritis with fever, plus rash, generalized lymphadenopathy, hepatosplenomegaly and serositis. It is associated with significant morbidity and may be complicated with macrophagic activation syndrome (MAS). The use of anti-interleukin 1 (IL1) therapy results in dramatic improvement in both the systemic and articular disease.

Elevation of liver enzymes can be seen in sJIA patients because of disease activity, MAS, an infection, hepatotoxicity from pharmacologic treatment
or as manifestation of another disease (such as autoimmune hepatitis). Achieving the diagnosis of the hypertransaminasemia in these patients may be difficult for the clinician.

**Objectives:** To report 4 patients with sJIA who presented significative thymus-derived Treg showed more suppressive capacity than 11(Suppl 2):

We investigated the potential role of regulatory T cells (Treg) 2004, presented elevation of liver enzymes during anti-IL1 treatment. In 4 of these 8 patients, hypertransaminasemia was thought to be related with disease activity or secondary MAS. The other 4 cases were more difficult to interpretate.

Patient 1 presented elevated transaminases (ALT 2254 UI/L) when being 11 months on anakinra (initiated at disease onset), while prednisone tapering 40 days after a MAS. ASMA 1/80. IgG elevation. No evidence of disease flare, MAS, infection, nor other systemic diseases with liver involvement. Anakinra was stopped and liver enzymes decreased. Liver biopsy: compatible with autoimmune hepatitis. Good response to zathioprine. Anakinra was re-started 4 months later because of a disease flare without subsequent transaminases elevation. Patients 2 and 3 presented ALT 1924 UI/L and 852 UI/L, respectively after 3 weeks on anakinra. The workup of hepatitis did not identify a cause. Anakinra was stopped with liver enzymes normalization within 2 months. Patient 4 is a persistent activity patient steroid dependent requiring different drugs during her follow-up. She presented liver enzymes elevations after one dose of canakinumab, while being on anakinra, but also after stopping them; maximum ALT 560 UI/L. Liver biopsy: inflammatory infiltrate without fibrosis. ASMA 1/80. IgG elevation. No evidence of infection, nor other disease with liver involvement. Now she is on anakinra, azathioprine and prednisone with normal liver tests.

**Conclusion:** IL1 inhibitors are effective in sJIA. Hypertransaminasemia in sJIA patients may result a challenge for the clinician.

The possibility of being related to anti-IL1 treatment should be taken into account. Three other cases of hypertransaminasemia in sJIA patients during treatment with IL1 antagonist have been reported, suggesting that a close monitoring for hepatic toxicity may be indicated when treating with IL1 blockers.

Autoimmune hepatitis is another diagnostic possibility, as shown in two of our patients.

**Disclosure of interest:** None declared.

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**P4**

**PRes-FINAL-1006: Autologous bone marrow transplantation in autoimmune, experimental arthritis restores immune homeostasis by renewal of the natural tregs compartment**

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**Introduction:** Autologous bone marrow transplantation (aBMT) is a last resort treatment for patients with refractory juvenile idiopathic arthritis (JIA). It can induce disease remission for 80 months after transplantation. Unfortunately, relapses also occur. The underlying working mechanisms remain largely unknown.

**Objectives:** We investigated the potential role of regulatory T cells (Treg) during immune reconstitution and re-establishment of immune tolerance following aBMT.

**Methods:** Arthritis was induced by two intraperitoneal injections of proteoglycan (PG) in synthetic adjuvant dimethyl dioctadecyl ammonium bromide (DDA), two and five weeks before stem cell transplantation. The onset and severity of arthritis were assessed three times a week in a blinded fashion by a visual scoring system. Two weeks after the second PG/DDA injection, a lethal dose of 7.5 Gy total body irradiation was given to arthritic mice. Recipient mice were injected with 2 x 10^6 bone marrow (BM) cells.

GFP+Treg cells were sorted by flow cytometry as TCRb+ CD4+ CD25+ GFP+ T cells. Before infusion, Treg suspensions were added to the bone marrow graft in different amounts.

**Results:** In the PGIA mouse model, lethal irradiation followed by aBMT, reduced arthritis scores and restored the immune balance between pro-inflammatory effector T cells and Treg. Directly following aBMT the majority of Treg present, consisted of Treg that survived the conditioning. Hereafter, the infused stem cell-derived Treg started dominating the Treg pool and these “new” thymus-derived Treg showed more suppressive capacity than the remaining host Treg. A therapeutic approach was initiated by infusing extra Foxp3+Treg together with the stem cell graft. The infused Treg expanded vigorously in the first month after aBMT, followed by a decrease in numbers in the second month. No extra clinical improvement was found in the Treg-infused groups, the highest Treg dosed group even showed an increase in disease relapse. Both Treg treated groups showed delayed induction of ‘new’ stem cell derived Treg.

**Conclusion:** These data indicate that restoration of the immune balance following aBMT depends on renewal of the natural Treg pool derived from the injected stem cells. For now, infusion of extra Treg during aBMT is not recommended as this may delay T cell reconstitution and development of long-term tolerance.

**Disclosure of interest:** None declared.

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**P5**

**PRes-END-1007: Regulatory T cells functional specialization in jia**

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**Introduction:** Regulatory T cells (Treg) are important players in keeping the immune system in balance. In juvenile idiopathic arthritis (JIA), an autoimmune disease characterized by chronic inflammation of the joints, this balance is disturbed. Recently, different functional subsets of regulatory T cells (Treg) have been described in mice and human that mirror the T helper subsets. A lot remains unknown about the function and mechanism of action of Treg (subsets), especially in inflammatory environments.

**Objectives:** In our study we aim to investigate the adaptability of regulatory T cells based on phenotype and function. In particular, our focus is on Treg derived from different inflammatory environments.

**Methods:** Treg will be isolated from peripheral blood and synovial fluid of JIA patients and peripheral blood of healthy controls and analyzed based on the expression of chemokine receptors CCR3, CCR6 and CCR4. Currently, autologous suppression assays, allogenic T cell suppression assays and monocyte suppression assays are performed with these Treg subsets derived from different environments.

**Results:** Treg subsets that mirror Th subsets can be found and discriminated based on their chemokine receptor profile (e.g. CCR3, CCR6 and CCR4) in peripheral blood of healthy control and JIA patients, and in the synovial fluid of JIA patients.

**Conclusion:** Different subsets of Treg can be identified in the synovial fluid of JIA patients. This allows us to further look in to Treg subset function.

**Disclosure of interest:** None declared.

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**P6**

**PRes-END-1008: Areas of psychological assistance to children with severe disease during rehabilitation**

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**Introduction:** Now there is a significant increase in the number of children with rheumatic diseases. That in return raises the question of the necessity of studying the psychological difficulties that has a child suffering from the disease, as well as provide direction for psychological assistance.

**Objectives:** 41 children aged from 7 to 17 years with rheumatic diseases. The first group (grave disease) - 15 persons, the second group (mild illness) - 26 people. We examined emotional sphere, requirement-motivational sphere, features of autoassessment, - relationship with peers.

**Methods:** Modified test “Painting of a man” (autopainting, a sick person and a healthy person painting), the method of “self-assessment”
Dembo-Rubinstein, the test “Three Wishes” and the method of “complete sentences”.

Results: Results of the study of children and adolescents with rheumatic diseases in remission, whose health was assessed by doctors as a condition of the medium severity, showed that their psychological characteristics are broadly consistent with age norms, and they quickly adapted to the conditions of the hospital. They noted emotional stability, good humor, a wide range of diverse desires specific to each age group. Self-evaluation of the majority of children surveyed were positive.

All children with severe rheumatic diseases were for a long time treated in hospital, their psychological state was directly dependent on the physical. Most often emotional difficulties were expressed in the form of reduced background mood, increased emotional lability, acute emotional reactions, in some cases accompanied by suicidal thoughts.

Children from both groups suffered staying at hospital and had an urgent need to unite with the family. Slightly less than half of the children in the first group on health could not leave the ward or get out of bed because of compression fracture of the spine, which greatly reduces the chances of a child to communicate with peers, satisfy his educational interests, carry out any activities. Enforced isolation had a negative impact on the interests of the child. The severity of the physical and psychological status had a negative impact on the image, self-esteem nature and ego.

Conclusion: The direction of psychological help in the process of treatment must be tailored to the nature of the disease, the age and psychological characteristics of the child.

Children with severe disease require individual form of psychological help in the treatment process to reduce emotional stress, and with the wider community needs, switch the child’s attention from the negative experiences to the joint activity with the specialist.

The work in group is good for children with the medium severity of disease. Through communication and collaboration it will learn them to get and to sfy his educational interests, carry out any activities. Enforced isolation had a negative impact on the interests of the child. Self-evaluation of the majority of children surveyed were positive.

Disclosure of interest: None declared.

P8

PReS-FINAL-1010: circulating micromonas in traps
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Introduction: To the best of our knowledge circulating miRNAs in TRAPS, as well as in other monogenic autoinflammatory disorders have never been investigated.

Objectives: To evaluate circulating microRNAs (miRNAs) levels in patients with tumor necrosis factor-receptor associated periodic syndrome (TRAPS), in comparison to healthy controls, and to correlate their levels to parameters of disease activity and/or disease severity.

Methods: Expression levels of circulating miRNAs were measured by Agilent microarrays in 29 serum samples from 15 TRAPS patients carrying mutations known to be associated with high disease penetrance and 8 healthy controls. Differentially expressed and clinically relevant miRNAs were detected using GeneSpring GX software.

Results: We identified a 6 miRNAs signature able to discriminate TRAPS from healthy controls. Moreover, 4 miRNAs were differentially expressed between patients treated with the interleukin (IL)-1 receptor antagonist anakinra and untreated patients. Of these, mir-92a-3p expression was found to be reduced in untreated patients, while its expression levels were similar to healthy controls in samples obtained during anakinra treatment. Mir-92b levels were inversely correlated with the number of fever attacks/ year during the 1st year from the index attack of TRAPS, while mir-377-5p levels were positively correlated with serum amyloid A (SAA) circulating levels.

Conclusion: Serum miRNAs levels show a baseline pattern in TRAPS, and may serve as potential markers of response to therapeutic intervention.

Disclosure of interest: None declared.
(FoxP3) transcription factor. Human conventional T (Tconv) cells stimulated via the T cell receptor (TCR) can also express FoxP3. Although this can confer some intrinsic regulatory effects, controversy exists over whether FoxP3 expression alone gives rise to the Treg cell phenotype. Treg-specific demethylated region (TSDR) demethylation is thought to be a reliable marker of commitment to the Treg cell lineage. In most human studies, analysis of TSDR methylation status has been performed on bulk populations, where only a subpopulation of cells express FoxP3. However, TSDR demethylation may occur selectively in cells expressing the highest levels of FoxP3 protein. Previously, investigation of epigenetic modifications in FoxP3+ human Tconv cells has been hampered by the inability to separate cells based on the basis of FoxP3 expression. Recently, however, a protocol has been published detailing a method for DNA extraction from cells that have been fixed and stained for FoxP3, permitting more informative phenotyping of TSDR methylation status.

**Objectives:** To examine the kinetics and stability of FoxP3 expression in human Tconv cells undergoing repeated TCR stimulation; in addition to analyze the TSDR methylation status on cells separated based on FoxP3 expression.

**Methods:** Cells were separated into CD4+CD25+CD127+ (Treg) and CD4+CD25+CD127 (Tconv) populations and cultured for 3 weeks with anti-CD3, anti-CD28, cytokine combinations and, in some experiments, demethylating agent 5-azacytidine (5-azaC). At regular intervals, cells were analyzed for expression of Treg cell markers. On days 7 and 16, Tconv cells were sorted into CD4+CD25+FoxP3+ and CD4+CD25+FoxP3- populations for DNA extraction and bisulfite sequencing to analyze TSDR methylation status.

**Results:** Activation-induced FoxP3 expression in Tconv cells was augmented by interleukin-2 (IL-2), but was unstable. TSDR became partially demethylated in the day 7 FoxP3+ population in one of two donors. 5-azaC stabilized FoxP3 protein expression and this was associated with a small increase in overall TSDR demethylation.

**Conclusion:** FoxP3 protein expression alone may not be an adequate marker of Treg cells in states of chronic stimulation, where a notable proportion of FoxP3-expressing cells may be recently activated Tconv cells. TSDR demethylation may be a more specific marker of commitment to the Treg cell lineage. However, preliminary results suggest a small subpopulation of FoxP3-expressing Tconv cells may demethylate at the TSDR in response to TCR stimulation, warranting further investigation. This work may contribute towards understanding how induced Treg cells could be stably generated in vitro, with potential applications in adoptive transfer therapies for the treatment of autoimmune disease.

**Disclosure of interest:** None declared.

**P11**

**PrEs-FINAL-1014: Role of MHC class I overexpression on muscle biopsy of patients with juvenile dermatomyositis**

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**Introduction:** Juvenile Dermatomyositis (JDM) is the most common idiopathic inflammatory myopathy in childhood, a systemic vasculopathy that usually affects skin and skeletal muscle but also can affect gastrointestinal tract and other organs. Diagnosis is based on Bohan and Peter’s criteria and the goals of treatment include control of skin and muscle symptoms and prevention of disease complications. Stepwise aggressive treatment decreases JDM activity and improves long-term outcome. Muscle involvement in JDM can be assessed by electromyography (EMG), magnetic resonance imaging (MRI) and/or muscle biopsy. Muscle biopsy assesses the presence of lymphocytic inflammatory infiltrate, perifascicular atrophy, muscle fibers necrosis and it allows studying the overexpression of major histocompatibility complex (MHC) class I in the sarclemma and sarcoplasma of the muscle cell. In healthy muscles, there is no MHC class I expression but in inflammatory myopathies there is a distinctive and generalized overexpression, not limited to the affected areas, it appears before the inflammatory infiltrate occurs and it is not modified by immunosuppressive treatment.

**Objectives:** To assess MHC I overexpression on muscle biopsy of our patients with JDM.

**Methods:** Descriptive retrospective review of our JDM patients with muscle biopsy at diagnosis between January 2000 and December 2011. In all cases, muscle biopsy techniques were performed with hematoyxlin-eosin, trichrome, oxidative enzymes (NADH, SDH, COX and COX-SDH), neonatal myosin and MHC class I.

**Results:** 12 patients were included, 8 of them were girls (66%). All children had cutaneous and muscular clinical features at diagnosis. All MRI were pathological before treatment. EMG was performed in 9 patients, being altered in 8 of them (88%). Childhood Myositis Assessment Scale (CMAS) was done in 6 children with a median score of 30.5/52 (range 12-50/52). We found pathologic muscle biopsy in 8 children (66%). Mild endomysial inflammation was found in 5 (41%) patients and moderate inflammation in 4 (33%). No vasculitis was found, but 7 (58%) patients had necrotic muscle fibers in biopsy. Immunohistochemical staining for MHC class I was positive in all cases, even in those children with normal muscle biopsy.

**Conclusion:** MHC class I overexpression is present in muscle biopsy of all our patients with suspected JDM, even those with negative EMG or MRI.
normal CMAS score. Although it is an invasive technique, muscle biopsy including MHC class I staining should be performed in all patients with suspected JDM in order to achieve more accurate diagnostic and establish an early and aggressive treatment.

Disclosure of interest: None declared.

P12
PReS-FINAL-1015: A systematic literature review on diagnosis and treatment of pediatric rheumatic diseases: a shared initiative

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Pediatric Rheumatology 2013, 11(Suppl 2):P12

Introduction: Pediatric Rheumatic Diseases (PRD) represent a group of rare diseases that can lead to significant morbidity. As is the problem with many rare diseases, evidence-based guidelines are lacking and treatment is mostly based on physician experience. Consequently, treatment regiments differ throughout Europe. This year, a new project called SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) was launched to describe what is needed for optimal diagnosis and treatment for children and young adults with rheumatic disease. This project tackles problems across different fields, ranging from access to resources to ethical consideration to quality and uniformity of health care.

Objectives: As a part of SHARE, a work package has been defined to identify best practices and establish minimal standards of care for the treatment of patients suffering from PRD, in order to improve and standardize care across Europe.

Methods: A systematic review was conducted on specific questions regarding diagnosis, treatment and complications of PRD, i.e. Juvenile Idiopathic Arthritis, childhood-onset Systemic Lupus Erythematosus, Anti Phospholipid Syndrome, vasculitis, scleroderma, juvenile dermatomyositis and Periodic Fever Syndromes. Articles from 1970 onwards were included. Related articles on MEDLINE, EMBASE and Cochran were selected using systematically built and validated search strings, yielding more than 30,000 hits. Reviews, case-reports and case-series smaller than three cases were excluded. After screening, this number of papers will be reduced to several thousands and a review process will be executed according to EULAR guidelines by groups of experts from PReS workgroups.

Results: The results from the systematic reviews will form the basis of guidelines on minimal standard of care. Consensus meetings will finalize these guidelines by filling in the shortcomings of existing evidence with expert opinion, using the Delphi method. The final result of this work package will be the formulation of minimum standards of care per individual PRD.

Conclusion: It is essential to formulate well-founded standards of care for these rare pediatric diseases; doing so will most importantly benefit patients themselves, but also increase uniformity of care within the European Union. All in all, SHARE will thus facilitate improved and more uniform care within Europe.

Disclosure of interest: None declared.

P14
PReS-FINAL-1017: Antioxidant superoxide dismutase activity is elevated in JIA but not associated with disease activity

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Pediatric Rheumatology 2013, 11(Suppl 2):P14

Introduction: Oxidative stress has been implicated in the pathogenesis of a number of autoimmune diseases including rheumatoid arthritis. The antioxidant superoxide dismutase (SOD) is one of the most important enzymes involved in combating oxidative stress. It exerts its protective effect by neutralizing free radicals to form oxygen and hydrogen peroxide.

Objectives: The aim of the present study was to measure SOD activity in juvenile idiopathic arthritis (JIA) patients and to assess whether these levels are influenced by disease activity or JIA subtype.

Methods: Serum SOD activity was measured in 166 pediatric and adolescent JIA patients attending Rheumatology clinics at Great Ormond Street Hospital and University College London Hospital and in 17 healthy controls (HC) using a commercial colorimetric assay. Median age at sampling was 16.37 [IQR 10.41-18.04] years for JIA patients and 14.78 [IQR 10.22-23.03] years for HC. Median age of JIA onset was 5.68 years [IQR 2.30-11.23] for JIA patients and 11.5 [64.7%] female in HC. Similar numbers of patients for each subtype were included. Between JIA patients and HC there was no statistical difference in SOD activity between subtypes. No difference in SOD activity was observed between patients with active disease and those with inactive disease and SOD activity did not change depending on drug treatment. However, SOD activity did change with anti-nuclear antigen (ANA) status, with ANA positive patients having elevated SOD levels (median = 5.95 U/ml [IQR 4.63-7.98]) compared to those who were ANA negative (median = 5.95 U/ml [IQR 4.63-7.98]) (p = 0.022).

Disclosure of interest: None declared.

P13
PReS-FINAL-1016: Micro vesicles as a magnifying glass; uncovering potential biomarkers in juvenile idiopathic arthritis

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Pediatric Rheumatology 2013, 11(Suppl 2):P13

Introduction: Juvenile idiopathic arthritis (JIA) is a common chronic inflammatory diseases in childhood. Despite remission as a result of a plethora of treatment techniques, the chronic and relapsing nature of the disease requires continuous treatment which causes adverse side effects. It is important to uncover a biomarker that can efficiently predict patient responses to therapy as well as determine if patients will progress or regress as a result of treatment. Micro vesicles are key messengers containing many immune signaling molecules including cytokines, molecules known to play a major role in JIA.

Objectives: Due to the localized inflammation seen in JIA, we aim to analyze if micro vesicles isolated from patients can provide a source of biomarkers, giving specific information on molecules that can be targeted for treatment and allow the disease state to be monitored.

Methods: Micro vesicles where isolated from the blood and synovial fluid of patients with various subtypes of JIA. Vescular protein profiles where then compared using Luminex technology.

Results: Pilot data showed that whole JIA patient plasma and synovial fluid has an inflammatory phenotype expressing high levels of TNF-R1, S100 A12, CXC9 and CXC10. This phenotype is also seen in exoquik isolated plasma micro vesicles however, when micro vesicles are isolated by ultra-centrifugation, this phenomenon disappears. Ultra-centrifugation isolated vesicles express lower levels of IL-6, MIF, TNF-R1, CXC9 and S100 A12 when compared to whole plasma and healthy control vesicles. An analysis of exoquik background activity on Luminex MIA technology reveals a high level of interference.

Conclusion: Preliminary data indicates that micro vesicles isolated from JIA patient plasma by ultracentrifugation have low amounts of inflammatory cytokines. In addition, a more in depth investigation into exoquik activity shows that this product interferes with Luminex MIA technology. As a whole data seems to suggest that micro vesicle cytokine levels from individuals with JIA do not reflect the inflammatory process.

Disclosure of interest: None declared.
Conclusion: In conclusion, elevated activity of the antioxidant SOD may be a response to increased oxidative stress in JIA. However, it does not seemingly represent a useful biomarker of disease activity. The association with ANA is interesting and we are currently investigating whether SOD levels correlate with uveitis.

Disclosure of interest: None declared.

P15
PRes-FINAL-1018: Can the CD4/CD8b ratio be used as a predictive biomarker in extended-to-oligoarticular JIA?

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Pediatric Rheumatology 2013, 11(Suppl 2):P15

Introduction: Predicting disease course in Juvenile Idiopathic Arthritis (JIA) is difficult. During the first 6 months of oligoarticular JIA (O-JIA) disease presents with 4 or fewer affected joints, however after 6 or more months severity might increase with more than 4 joints involved (extended O-JIA), or persist with 4 or fewer joints affected (persistent O-JIA). However patients do not show any clinical differences at onset making a decision on treatment strategy difficult before extension occurs. It has previously been shown that the CD4/CD8 T cell ratio in extended-to-be patients (samples before extension has occurred) is lower compared to those who persist (Hunter et al 2010), and thus might be a useful biomarker in predicting the course of disease. However measuring this cell ratio currently requires specialized expertise. To translate the measurement of the CD4/8 synovial T cell ratio as a biomarker a method is needed, which could be used in a wide range of hospital facilities, hence a real-time quantitative PCR (qPCR) method was tested.

Objectives: The aim of this study was to measure CD4 and CD8 mRNA in whole synovial fluid collected at therapeutic joint injection and to compare it to the gold standard of flow cytometry using mononuclear cells.

Methods: A total of 40 healthy adult blood and 20 patient synovial fluid (SF) samples were included in this study. cDNA was generated from total RNA extracted from Tempus vacutainers using whole blood or SF. CD4, CD8b and GAPDH transcripts were measured by qPCR. Simultaneously peripheral blood mononuclear cells (PBMC) and SFMC were isolated using density gradient centrifugation and stained with CD3, CD4, CD8 and CD8a for flow cytometry.

Results: Validating previous results, the CD4/CD8 T cell ratio measured by flow cytometry was significantly lower in SFMC than in healthy adult PBMC. Measurement of CD4/8 ratio by qPCR and flow cytometry showed some correlation. Healthy adult PBMC showed higher CD4/CD8 ratios by qPCR were higher in SF samples compared to healthy control PBMC. This was driven by increased CD4 measurements by qPCR in SF samples.

Conclusion: Taken together these data show a trend to a correlation of qPCR and flow cytometry methods in healthy adult control samples. The increased level of CD4 transcript in SF measured by qPCR might well be due to the abundance of neutrophils and monocytes, which are/may be discarded during preparation of SFMC for flow cytometry. Whether qPCR measurement of CD4/CD8 ratio can be used as a predictive biomarker for severity of disease course in O-JIA remains to be seen, and will be assessed once clinical follow-up data is available.

Disclosure of interest: None declared.

P16
PRes-FINAL-1019: Inflammatory monocytes induce resistance of effector T cells to suppression

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Pediatric Rheumatology 2013, 11(Suppl 2):P16

Introduction: Ever since their discovery research has focused on whether deficiencies in FOXP3+ regulatory T cells (Treg) underlie human autoimmune pathology. Very recently however, the topic of Treg extrinsic factors as the cause of regulatory defects in chronic autoimmune inflammation has become more prominent in the discussion. It has become clear that resistance of effector cells (Teff) to suppression contributes to disturbed immune regulation in autoimmune inflammation, especially at the site of inflammation. Therefore, targeting this unresponsiveness to suppression could be a promising treatment option for patients with autoimmune disease. It remains unknown how resistance of T cells to suppression is induced.

Objectives: To investigate how resistance of Teff cells to suppression is induced, and what the role is of antigen-presenting cells (APC) in this.

Methods: We phenotypically characterized APC present at the site of autoimmune inflammation in patients with juvenile idiopathic arthriti (JIA) by means of flow cytometry and LumineX technology. Furthermore, we co-incubated APC with Teff and Treg, and subsequently measured Teff proliferation and cytokine production to investigate the role of APC in inducing Teff resistance to suppression.

Results: We observed a clear difference in the composition of APC in synovial fluid (SF), obtained from inflamed joints, compared to peripheral blood. Moreover. SF monocytes displayed strong pro-inflammatory characteristics with especially high TNFa and IL-6 production directly ex vivo. Upon co-culture with Teff, these SF monocytes and not dendritic cells (DCs) induced unresponsiveness of Teff to suppression, resulting in impaired Treg-mediated control of cell proliferation and cytokine production. By blocking IL-6, TNF-a or both, control of Teff proliferation and cytokine production by Treg was (partially) restored in these co-cultures.

Conclusion: These data shed new light on the role of monocytes in autoimmune pathology, indicating that monocytes actively contribute to the ongoing inflammation by interfering with T cell regulation. Moreover, our results identify inflammatory monocytes and their ability to induce resistance to suppression as a new target to treat autoimmune inflammation.

Disclosure of interest: None declared.
to their CD161- counterparts. Among JIA SFMC, the expression of CXCR3 was increased compared to the levels within HC PMBC. The percentage of CD161+ Treg expressing CTLA4 on the cell surface was increased compared to CD161- Treg in HC PMBC and JIA SFMC. Total CTLA4 expression was enhanced on both CD161+ and CD161- Treg in JIA SFMC. Expression of GITR by CD161+ Treg was increased compared to CD161- Treg among HC PMBC and JIA SFMC. Also, CD161+ Treg expressed higher levels of GARP compared to CD161- Treg among HC PMBC. 

Conclusion: The selected markers are all involved in mechanisms by which Treg exert their immune regulatory function. Therefore, the observed phenotypic differences between CD161+ and CD161- Treg may indicate differences in functional mechanisms used by these two different Treg populations in health and disease. Divergent functional capacity between CD161+ and CD161- Treg could explain the dual function of CD161 Treg in health and disease. These data might contribute towards development of new and/or optimized treatment strategies for JIA.

Disclosure of interest: None declared.

P18
PreSe-FINAL-2005: Prevalence of antinuclear antibodies in schoolchildren across puberty and possible relationship with musculoskeletal pain. A longitudinal study
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Pediatric Rheumatology 2013, 11(Suppl 2):P18

Introduction: Antinuclear antibodies (ANA) are frequently found in children with connective tissue diseases but can be also found in healthy individuals even in absence of autoimmune conditions, with a prevalence ranging from 13.3% (titer ≥1:80) to 5.0% (titer ≥1:160). Puberty is a period of important changing in immune system because of the sexual and adrenohypophyseal hormones modulation; in fact many autoimmune and connective tissue diseases have their onset in this period. To date, a few studies have evaluated the role of ANA in healthy subjects but no one has explored their meaning and frequency across the puberty switch.

Objectives: To evaluate prevalence and persistence of ANA in subjects without any evident autoimmune disease followed for 3 years, and their possible relationship with chronic non-inflammatory musculoskeletal pain (MSP).

Methods: Each subject underwent a general and rheumatologic examination focusing on presence of chronic non-inflammatory MSP and including the evaluation of the pubertal stage. Chronic MSP was defined as continuous or recurrent pain lasting more than 3 months and heavily interfering with daily activities, according to the International Association for the Study of Pain. Subjects with past or present sign of any neurological, skeletal, metabolic or autoimmune conditions were excluded. Family history for autoimmune diseases in first degree relatives was also investigated. Finally, each subject underwent laboratory tests to determine the presence of ANA, ENA and anti-dsDNA, following the international guidelines. Subjects with ANA positivity (titer ≥1:80) and/or MSP have been re-evaluated with the same methods 3 years later.

Results: 261 subjects, aged 8-13 years, entered the study. 32 (12.3%) resulted ANA+, equally distributed as far as gender and pubertal status. None of the ANA+ subjects resulted positive at ENA or anti-dsDNA testing. A positive family history for autoimmune conditions was reported in 6.5% of the subjects.

Three years later, in the group of patients followed for MSP (no. 67) ANA-positivity significantly increased from 13.4% to 44.8% (p < 0.001) showing a trend to involve more pre-pubertal subjects than pubertal ones and more females than males, without statistical significance. Particularly, ANA positivity involved more pubertal females than pubertal males (50.0% vs 28.0). In the cohort followed for ANA-positivity (no. 28) 92.9% of subjects confirmed the ANA-positivity 3 years later, showing a significant increase of autoantibodies titer during time (p = 0.002). The prevalence of positive family history did not significantly changed during the study period. None of the ANA+ subjects resulted positive at ENA or anti-dsDNA testing. Overall, no significant association between ANA-positivity and MSP was found.

Conclusion: Prevalence and titer of ANA increase across puberty, especially in females, but have no relationship with MSP. This phenomenon could be explained by the complex hormonal changing of the puberty switch period. Further long-term prospective studies are needed to clarify the potential role of ANA as marker of autoimmune-rheumatic conditions, particularly in this period.

Disclosure of interest: None declared.

P19
PreSe-FINAL-2006: Resilience and coping in adolescents with rheumatic illness
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Pediatric Rheumatology 2013, 11(Suppl 2):P19

Introduction: The adolescents with rheumatic disease are not only suffering physically, but they are also in the midst of an intense emotional experience, for that is important to help patients to bounce back from the double challenge, illness and adolescence.

Objectives: In this study, we aim to assess resilience and to analyze the resilience styles and the coping skills of the subjects within the care pathway trying to obtain the helpful feedback.

Methods: The reported studies involved rheumatic patients (n = 22 out of them 8 males) aged 15.68 ± 1.08 years at 4 years from the onset of their illness.

The applied tools included the Coping Inventory for Stressful Situations (CISS) which measures coping with stress style understood as a trait of personality and the Italian version of the (RPQ) Resilience Process Questionnaire.

Results: Among these adolescents with rheumatic disease, resilience was significantly related to the avoidance-oriented coping (P < 0.05). See table 1.

Conclusion: The results of this study shows that our patients have the ability to withstand stressful events, but their strategies do not lead to a positive resolution, since the resilience appears to be low and they have avoidance coping strategies.

The results of the presented study may become a stimulus to creating prevention.

Disclosure of interest: None declared.

Table 1 (abstract P19)

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<td>Dysfunctional Reintegration</td>
<td>3.81 ± 1.56</td>
<td>NV &gt; 8</td>
<td></td>
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<tr>
<td>Resilient Reintegration</td>
<td>5.0 ± 1.77</td>
<td>NV &gt; 8</td>
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<tr>
<td>Return to baseline/Homeostasis</td>
<td>7.36 ± 1.43</td>
<td>NV &gt; 8</td>
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<tr>
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<tr>
<td></td>
<td>51.13 ± 8.19</td>
<td>NV 45-55</td>
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<tr>
<td>Emotion coping</td>
<td>46.56 ± 9.0</td>
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<td>Avoidance coping</td>
<td>78.73 ± 19.5</td>
<td>NV 45-55</td>
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Also the parents will slowly hand over the responsibility to the acrolecent.

**Methods:** An adolescent clinic for patients aged 12-15 years will be established.

**Results:** The adolescents are expected to gain a greater understanding of their disease. The adolescents will gradually be introduced to take over the responsibility for their treatment through learning about the disease, the treatment, the impact of the disease on their everyday life and the future. Concurrently, the parents will be supported in handing over the responsibility to their adolescent.

**Conclusion:** The transfer from pediatric to adult department will occur smoothly and the experience of transition will improve. The young patients will experience a more youth-oriented approach to their disease and treatment. Which will benefit the transition from childhood to adulthood with JIA.

**Disclosure of interest:** None declared.

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**P21**

**Abstract:** Juvenile dermatomyositis: a report of 22 cases

**Methods:** Patients diagnosed of Juvenile dermatomyositis in La Fe Hospital (Valencia, Spain) since June 1992 to March 2013. Dates are shown in median and interquartile range for non-parametric variables, and for parametric variables is given as mean and standard deviation.

**Results:** We included 22 patients, 45.5% women, age at diagnosis 7.6 (3.7-10.8) years and evolution time 2.75 (1-5) months.

The most frequent initial manifestation were muscle weakness (40%) and skin alterations (40%). Also constitutional symptoms (15%) and myalgia (5%). They presented muscle weakness (100%), heliotrope rash (100%), Gottron papules (90.9%), calcinosis (27.3%), other skin lesions such as telangiectasias, oral ulcers, livedo reticularis and purpura (55.5%), mialgia (55.5%), arthralgia (55.5%), arthritis (50%), constitutional symptoms (50%), esophageal involvement (28.6%), gastrointestinal (18.2%), fever (27.3%), anasarca (18.2%), dysphonia (18.2%), and lung disease (18.2%).

Patients were treated with corticosteroids, immunoglobulins and immunosuppressants such as methotrexate, tacrolimus, cyclosporine and antimalarial, alone or in combination, with significant improvement.

**Conclusion:** The dermatomyositis is a chronic inflammatory muscular disease that affects every year 1.5-3 children per million and also produces systemic, skin, joint, digestive and respiratory manifestations.

**Disclosure of interest:** None declared.

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**P22**

**Abstract:** Pres-FINAL-2009: Pediatric rheumatology practitioners experience with biologics in juvenile dermatomyositis: survey results

**Methods:** A Pediatric Arthritis Childhood Arthritis Research Alliance (PACARA) biologics survey was conducted in 2009 to gauge the practitioner's experiences with biologics in JDM. The survey was distributed to members of the child rheumatology community, with the objective of obtaining experience of practitioners who had used biologics in JDM.

**Results:** Seventy-three percent of respondents that used biologics noted disease. Seventy-three percent of respondents that used biologics noted improvement, while 10% reported worsening disease. Over half (53%) of respondents that used biologics noted improvement in calcinosis, while 64% reported side effects (common and uncommon). Among the respondents that had not used biologics (39%) in JDM, 88% would use this therapy if the opportunity arose; nearly half (47%) of these respondents had not used biologics because of uncertainty regarding effectiveness in JDM. Seventy percent of practitioners recommended that biologics be formally studied in patients with JDM; 24% of respondents were unsure and 6% felt biologics should not be studied in patients with JDM.

**Conclusion:** Several PR have used biologics in the management of pediatric patients with JDM. Among respondents that have not used biologics in this patient population, most would be interested in prescribing biologics. This survey supports the rationale for considering clinical trials and consensus protocols to elucidate the safety and effectiveness of biologics in children with JDM. Further information will be gathered by the CARRA JDM Subcommittee on Biologics through second survey to prioritize specific medications for investigation.

**Disclosure of interest:** None declared.

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**P23**

**Abstract:** Pres-FINAL-2010: Predictive value of whole-body MRI in juvenile dermatomyositis

**Methods:** A 1.5 T whole-body MRI study was performed on 32 juvenile dermatomyositis patients, 13 male and 19 female, aged 6-18 years (mean age 13.7 ± 2.6 years). The study included a comprehensive examination of musculoskeletal, visceral and cutaneous disease. The predictive value of MRI findings for disease activity was assessed using logistic regression analysis.

**Results:** The study showed that MRI findings were significantly associated with disease activity. The most predictive MRI findings included muscle edema, subcutaneous fat atrophy, and skin thickening. The area under the ROC curve for disease activity was 0.78 (p < 0.001).

**Conclusion:** MRI is a valuable tool for the assessment of disease activity in juvenile dermatomyositis and can help in the optimization of therapeutic strategies.

**Disclosure of interest:** None declared.
magnitude of inflammatory process throughout the entire body. By providing an accurate estimation of the total disease activity load, this technique could be useful to tailor treatment according to disease severity. 

**Objectives:** To explore the potential value of WB-MRI in predicting treatment efficacy in JDM.

**Methods:** WB-MRI was performed on a 1.5 T MRI scanner (using STIR sequences) to all consecutive JDM patients with disease duration ≤ 2 months, seen at the study Department between March 2010 and February 2013. Muscle signal abnormalities and subcutaneous tissue/myofascial involvement were assessed using a recently validated WB-MRI scoring system. Treatment efficacy was assessed at 3-months follow-up visit using the PRINTO criteria for the evaluation of response to therapy in JDM.

**Results:** 21 patients (9 boys, 12 girls, median age 6,6 years) were included. Four patients were treated with prednisone alone, while the others received prednisone in different combinations with methotrexate (N = 15) or cyclosporine (N = 2). Eleven patients (52.4%) met the PRINTO criteria for improvement at 3-months follow-up visit. WB-MRI muscular score was significantly higher in non-responders (median value 61.2; IQR 53.5-65.5) compared to the responders (34.5; IQR 18-55 p = 0.001). A WB-MRI muscle score ≥ 57 was predictive of a poor response to treatment, as evaluated by ROC curve analysis (AUC0.9; IC95%: 0.70-0.99; sensitivity: 100%, specificity: 70% + LR 3.33 - LR 0.00). Non-responders showed also a significant higher myofascial score (median value 1.5; IQR 0-3.5) compared to the improved patients (0; IQR 0-1.5 p = 0.04); no significant difference in subcutaneous involvement was found between responders (0.5; IQR 0-1.5) and non-responders (2.5; IQR 0.5-7; p = 0.08). Seven out of 8 patients (87.5%) with diffuse and homogeneous pattern of distribution of muscle inflammation were not improved at 3 months follow-up visit; vice versa 10 out of 13 patients with the typical patchy distribution of muscle signal abnormalities were improved (p = 0.02).

**Conclusion:** High WB-MRI muscular and myofascial scores and the diffuse and homogeneous pattern of muscle inflammation were associated with a more severe disease course. WB-MRI represents a promising tool to identify patients who could benefit from a more aggressive therapeutic regimen since the early stages of the disease.

**Disclosure of interest:** None declared.

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**Table 1 (abstract P24)**

<table>
<thead>
<tr>
<th>MYOACT HMC (VAS)</th>
<th>CK (VAS)</th>
<th>CHAQ</th>
<th>MDI glob VAS</th>
<th>MDI Extent VAS</th>
<th>MDI Severity VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMC -0.54</td>
<td>-0.35</td>
<td>-0.58</td>
<td>-0.47</td>
<td>-0.68</td>
<td>-0.23</td>
</tr>
<tr>
<td>MMT -0.58</td>
<td>-0.35</td>
<td>-0.58</td>
<td>-0.47</td>
<td>-0.69</td>
<td>-0.21</td>
</tr>
<tr>
<td>CMAS -0.42</td>
<td>-0.28</td>
<td>-0.50</td>
<td>-0.40</td>
<td>-0.61</td>
<td>-0.27</td>
</tr>
</tbody>
</table>

The SRM HMC, MMT, CMAS was, respectively, 0.90, 0.80 and 0.89.
Results: A total of 107 consecutive JDM patients (44 male, 63 female) seen in 4 pediatric rheumatology centers (2 in Italy, 1 in UK and 1 in Croatia) were included in the study. Median disease duration was 3.1 years (IQR:1.0-5.8) and median age at visit was 10 years (IQR:6.4-13.6). All parents and children reported that the questionnaire was simple and easy to understand. Completion and scoring appeared to be quick, requiring 5-10 minutes. The proportion of parents who reported normal scores on the various JDMAR scales are summarized in the table.

Conclusion: Development of the JDMAR provides a promising approach to quantitative measurement in standard pediatric rheumatology care. Availability of this new instrument may foster regular use of parent/patient questionnaires in routine practice and contribute to improved quality of care of children with JDMAR.

Disclosure of interest: None declared.

Table 1(abstract P25)

<table>
<thead>
<tr>
<th>JDMAR assessments On a 10-cm VAS</th>
<th>Pts assessed</th>
<th>No. Positive (%)</th>
<th>Others JDMAR assessments</th>
<th>Pts assessed</th>
<th>No. Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal well-being</td>
<td>98</td>
<td>39 (39.8)</td>
<td>Normal functional ability</td>
<td>97</td>
<td>53 (54.6)</td>
</tr>
<tr>
<td>No pain</td>
<td>99</td>
<td>52 (53.6)</td>
<td>Normal HRQL - Total score</td>
<td>94</td>
<td>27 (28.7)</td>
</tr>
<tr>
<td>No fatigue</td>
<td>73</td>
<td>24 (32.9)</td>
<td>Remission</td>
<td>92</td>
<td>50 (54.3)</td>
</tr>
<tr>
<td>No disease activity</td>
<td>67</td>
<td>31 (46.3)</td>
<td>Satisfied with illness outcome</td>
<td>93</td>
<td>66 (71.0)</td>
</tr>
</tbody>
</table>

P26

Introduction: Juvenile Dermatomyositis (JDM) is an inflammatory myopathy with a predilection for proximal muscles and skin. Current treatment of JDM includes early aggressive use of corticosteroids coupled with immunosuppressive drugs such as methotrexate, cyclosporine and intravenous immune globulins (IVIG). Delay to diagnosis and inadequate treatment increase the risk of developing calcinosis. However, once established, this complication is difficult to treat.

Objectives: We describe a case of JDM with severe skin manifestations including ulcerations and diffuse calcinosis, poorly responsive to conventional therapy.

Methods: Case report. A Caucasian boy presented at the age of 3 years and 10 months with malaise, fatigue, arthralgia, heliotrope rash, Gottron’s papules on PIP joints, elbows and knees, shrill sign, and periangual telangectasia. There was weakness of proximal muscles, elevation of aldolase (11.0 U/L, normal < 7.3 U/L), normal serum lactate dehydrogenase (LDH) and creatine kinase (CK), and negative anti-nuclear antibody. Magnetic resonance imaging (MRI) demonstrated diffuse muscle edema of proximal muscles and electromyography showed a myopathic pattern. Despite treatment with steroids pulses, followed by daily oral steroids and hydroxychloroquine, his illness was complicated by skin ulcerations of the upper and lower extremities and widespread calcinosis. X-ray of extremities showed superficial diffuse nodules and plaques. The patient still had elevation of aldolase (193 U/L) and a Childhood Myositis Assessment Scale (CMAS) score of 35 out of 52, with a Manual Muscle Testing (MMT8) score of 50 out 80. So a treatment with Methotrexate was added, but his areas of calcinosis and ulcerations continued to spread, so alendronate was introduced (two years from disease onset), but without benefit. On the basis of a published report (Arabshahi B, et al. J Pediatr 2012) treatment with topical sodium thiosulfate was initiated. Thiosulfate was used initially at 3% concentration, and subsequently increased to 10% concentration, applied to calcification of upper and lower extremities daily under occlusive dressing.

Results: After 9 months of therapy, a significant improvement of calcinosis and ulcerations was noted, together with lack of progression. Photos, with the family consent, were taken before and after treatment.

Conclusion: Treatment of calcinosis in JDM is very difficult. Several agents have been used, such as calcium channel blockers, probenecid, colchicine, tumor necrosis factors inhibitors, bisphosphonates, and intra-lesional corticosteroids. None of these however has shown to be consistently effective and no controlled trial exist. Sodium thiosulfate is a potent antioxidant and vasodilator that also chelates and dissolves calcium deposits. Topical use has been described for ulcerations associated with lupus calcinosis and uremic calciphylaxis. However, the use of this agent for treatment of calcinosis associated to dermatomyositis has been reported only once in literature. We hypothesize that sodium thiosulfate may have a role in stabilizing or improving calcinosis, and in diminishing pain and promoting revascularization of cutaneous ulcerations. A controlled study in order to determine the safety and efficacy of this treatment in JDM is currently planned.

Disclosure of interest: None declared.

P27

Introduction: Juvenile dermatomyositis (JDM) is a rare rheumatic disorder, often associated with poor functional outcome because of the high incidence of diffuse calcinosis in skeletal muscles, especially in case of late diagnosis.

Objectives: To present the case report of the late-diagnosed JDM with severe calcinosis in a child with disease onset at 9 months.

Methods: We have observed a female patient suffering from JDM since 9 months.

Results: The disease started after revaccination against diphtheria and pertussis from symptoms of fever and muscle involvement (thickness and weakness) following a series of scheduled vaccinations (mumps, measles and rubella). Clinical symptoms worsened, there were the typical skin changes, muscle weakness progressed, there were sporadic calcifications (8 months after disease onset), but the diagnosis was not established as a child experienced in primary care clinics. She was examined in our clinic after 3 years of disease onset when JDM was first diagnosed. The patient had fever, proximal muscle weakness, gait disturbance, typical cutaneous lesions (erythematous rash, discrete heliotrope of upper eyelids, Gottron’s papules), slight enzymes elevation, nail fold changes by capillaroscopy and extensive diffuse calcinosis with significant muscle atrophy and lipodystrophy. The patient received oral prednisolone 1 mg/kg/day with slow dose tapering and full cancellation after 4 years, methotrexate 10 mg/m²/week till presence time, IVIG 1.5 g/kg monthly during the first 6 months and quarterly next two year. The treatment provided excellent results with rapid normalization of muscle strength, regression of skin and vascular lesions. The physical activity of the child and a relief of an inflammation led to the good development of muscle mass and displacement of calcifications to the surface of the skin with their localization in the larger conglomerates with its occasional spontaneous emptying.

Conclusion: Unusual onset of JDM at a very early age, probably triggered by numerous vaccinations and lack of awareness about the disease general pediatricians contributes a significant delay in the diagnosis. But on the other hand there is an opportunity of good outcome of myopathy and calcinosis in infants with JDM.

Disclosure of interest: None declared.
We reviewed medical records of all patients aged 18 years or younger according to the WHO-criteria: Juvenile dermatomyositis (JDM) is a rare autoimmune disease with the onset in childhood involving chronic inflammation of striated muscle and skin. The disease is often leading to severe disability, prolonged decreased physical activity, which together with chronic inflammatory activity, and long-term medical treatment with glucocorticoids, contributes to the well-known risk factors for developing osteopenia or osteoporosis. Only a few studies have followed JDM patients into adulthood.

Objectives: The objective of the present study was to investigate the long-term outcome on bone mineral status in a Danish cohort of patients with JDM.

Methods: A total of 49 patients with JDM diagnosed between 1976 and 2005 were investigated. The female/male ratio was 2.5. The mean age at disease onset was 7 years (range 1.5-16 years) and the mean disease duration was 3.7 years (range 0.7-9 years). The follow-up time ranged from 2 years to 36 years (mean 7 years). Bone mass density (BMD) (g/cm2) was determined by dual X-ray absorptiometry (DXA).

Conclusion: Early diagnosis as well as early aggressive therapy (including anti-TNF) were the key of favourable outcomes in most patients enrolled in our study. In this respect, to our opinion, anti-TNF therapy should be considered as a part of an early treatment, especially in cases with severe, progressive forms of JDM.

Disclosure of interest: None declared.

Table 1 (abstract P29) Bone Mineral Density Standard Deviation scores in 49 patients with JDM

<table>
<thead>
<tr>
<th>Score</th>
<th>N</th>
<th>Patients</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>P-value*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T-score</strong></td>
<td>23</td>
<td>Adults &gt; 20 years:</td>
<td>0.43 ± 1.1</td>
<td>-1.6 - 2.6</td>
<td>0.08</td>
<td>-0.05-0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Whole body scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Children &lt; 20 years:</td>
<td>-0.02 ± 0.8</td>
<td>-2.0 - 2.0</td>
<td>0.9</td>
<td>-1.1(-0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Lumbar spine scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Z-score</strong></td>
<td>23</td>
<td>Adults &gt; 20 years:</td>
<td>0.26 ± 1.1</td>
<td>-1.3 - 2.1</td>
<td>0.29</td>
<td>-0.24-0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Whole body scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Children &lt; 20 years:</td>
<td>-0.57 ± 1.1</td>
<td>-2.7 - 1.6</td>
<td>0.04</td>
<td>-0.3 - 0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Lumbar spine scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table presents the mean T- and Z-scores with SDs and range.

*P-values were calculated from the scores with One-Sample T-test.
Introduction: Systemic onset Juvenile Idiopathic Arthritis (SJIA) is rare pediatric disease, it accounts for 10% of children with Juvenile Idiopathic Arthritis. The onset of disease can be vary nonspecific and may suggest bacterial or viral infection, malignancy or other rheumatic disease. It is highly characterised by its extra-articular systemic illness features and, in some ways, it resembles a fever of unknown origin. Diagnosis is mostly clinical by using ILAR criteria (International League of Associations for Rheumatology).

Objectives: To assess the frequency of presenting symptoms and laboratory findings in SJIA patients over 5 years period.

Methods: This is retrospective study on all SJIA patients diagnosed in department of pediatric rheumatology from January 2008 until January 2013 using ILAR criteria. The medical records were reviewed. In each case age, gender, presenting symptoms and laboratory data were reviewed.

Results: During the study period 12 patients were diagnosed, mean age at diagnosis was 8.9 years (14 month to 15 years). There were an equal distribution of genders. Mean duration of fever at the time of diagnosis was 22.4 days. At the presentation all 12 children had fever longer than 2 weeks (100%), 8 children had salmon rash (66%), 9 had arthritis (75%, 100% developed arthritis in the first year of disease), 8 had splenomegaly (66%), only 2 hepatomegaly (16%), 10 children had generalised lymphadenopathy (83%), 5 had serositis (40%). Mild anaemia was present in 75% of patients, leucocytosis in 92%, thrombocytosis in 58%. Elevated sedimentation rate and C reactive protein (CRP) were found in 100% patient. Antinuclear antibody (ANA) was positive in 4 patients (30%).

Conclusion: Data from our study were consistent with clinical and laboratory findings in SJIA patients over 5 years period. Antinuclear antibody (ANA) was positive in 4 patients (30%). This is probably false positive result.

Disclosure of interest: None declared.
Introduction: Enthesitis Related Arthritis Category of Juvenile Idiopathic Arthritis (JIA-EAR) is the most common category of JIA seen in Asian Indians. Transcriptome analysis is a useful tool to analyse pathways involved in disease pathogenesis. Peripheral blood mononuclear cells (PBMC) and SFMC analysis showed involvement of innate immune cells in JIA-EAR. However PBMC/SFMC have variable number of different cells and that can affect interpretation. No data is available on cell type specific transcriptome analysis of blood and synovial fluid in children with JIA-EAR.

Objectives: To study the cell type specific transcriptome analysis of blood and synovial fluid in children with JIA-EAR.

Methods: Six samples each of peripheral blood and synovial fluid were collected from patients with ERA-JIA. Blood from 6 healthy controls was also collected. Mononuclear cells were separated by density gradient centrifugation. B cells, T cells and monocytes were separated using MACS columns and purity assessed by flow cytometry. After RNA extraction and checking the quality of RNA (RIN > 8) microarray was done using Illumina chips WG 12 for whole PBMC/SFMC population, T cells, B cells and monocytes. Some of the significant genes were validated by qRT-PCR.

Results: Unsupervised hierarchical clustering revealed that cell sets could be distinguished based on their gene expression profile. No significant differences were observed between PBMC of patients and healthy controls. Comparison of SFMC and PBMC reconfirmed the results seen earlier. Among T cells and B cells the differential athways identified were related to inflammation like Cell adhesion, antigen processing, cytokine and chemokine signaling, BCR signaling and leukocyte migration. Results obtained with monocytes are summarized below in table 1.

Conclusion: Monocyte probably play a major role in pathogenesis of JIA-EAR and TLR signaling may be the pathway involved.

Disclosure of interest: None declared.

### Table 1 (abstract P33)

<table>
<thead>
<tr>
<th>Groups compared</th>
<th>Genes up regulated</th>
<th>Genes down regulated</th>
<th>Number of dysregulated pathways [total (significant)]</th>
<th>Pathways of immunological relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB vs EF</td>
<td>776</td>
<td>189</td>
<td>19 (12)</td>
<td>Cell adhesion, IgA production, antigen processing, lysosomal processing</td>
</tr>
<tr>
<td>CBMO vs EBMO</td>
<td>821</td>
<td>1251</td>
<td>21 (12)</td>
<td>Cytokine signaling, TLR signaling, antigen presentation, chemokines signaling</td>
</tr>
<tr>
<td>EBMO vs EFMO</td>
<td>595</td>
<td>512</td>
<td>17 (9)</td>
<td>Complement cascade, cytokine signaling, antigen presentation</td>
</tr>
</tbody>
</table>

EB: ERA blood mononuclear cells; CB: control blood mononuclear cells; EF: ERA Synovial fluid mononuclear cells; MCD14+ monocytes. The major differences were found in monocyte subset. TLR pathway was one of the major pathway identified besides antigen presentation, cytokine and chemokine signaling.

### P34

PReS-FINAL-2021: JADAS-CRP instead of JADAS-ESR...results from Reuma.PT

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**Introduction:** Recently, Juvenile Arthritis Disease Activity Score (JADAS) was found to be a valid instrument for assessment of disease activity. JADAS was developed with erythrocyte sedimentation rate (ESR) because C-reactive protein (CRP) values were not available in all databases used to validate the tool. Nordal et al compared recently in a Nordic population the JADAS based on CRP with JADAS based on ESR and concluded that these instruments correlated closely, indicating that both scores can be recommended for assessing disease activity in JIA.

**Objectives:** Determine JADAS-CRP and compare its performance to the JADAS-ESR and to test the agreement of both scores on each disease activity category, in a Portuguese population with JIA.

**Methods:** A National cohort of patients with JIA, registered in Rheumatic Diseases Portuguese Register, was selected. Patients were included in the study when all disease activity measures were available for JADAS-ESR and CRP calculation and one visit per patient was randomly selected. JADAS-CRP was adapted by replacing ESR with CRP as the inflammatory marker. CRP was truncated at a 0-10 scale, similar to the truncated ESR used in JADAS. JADAS 27-CRP was calculated similarly to JADAS 27-ESR as the simple linear sum of its four components. Pearson correlations and K statistics were used in analyses.

**Results:** 358 children included, 65.4% were female, mean disease duration 11.75 ± 9.03 years. 37.5% were persistent oligoarticular, 14.8% had extended oligoarticular, 14.2% were polyarticular rheumatoid factor negative, 8.4% polyarticular RF positive, 10.9% systemic, 9.8% enthesitis-related arthritis, 3.1% psoriatic arthritis and in 1.4% patients we could not have access to the subtype of JIA. The correlation coefficient was 0.967 (p < 0.0001), though the correlation coefficient between CRP and ESR was only 0.335 (p < 0.0001). When comparing the JADAS-ESR and JADAS-CRP within each subtype of JIA, the strong correlation was maintained (all values of correlation > 0.9 and all p-values < 0.0001). The agreement between JADAS-ESR and CRP across the 4 activity states (inactive disease, minimal disease activity, parent's acceptable symptom state and active disease) assessed by K statistics was very good, showing 91.1% of the observations in agreement, K = 0.867 (95% CI 0.824-0.91).

**Conclusion:** In our study the JADAS27 based on CRP and ESR correlated closely, indicating that both measures can be used in clinical practice.

**Disclosure of interest:** None declared.

### P35

PReS-FINAL-2022: Juvenile idiopathic arthritis after allogeneic bone marrow transplantation: a case report

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**Pediatric Rheumatology, 2013, 11(Suppl 2):P35**

**Introduction:** The allogeneic bone marrow transplantation is a therapeutic weapon for treating severe and drug-resistant autoimmune diseases determining the resolution and improvement in the quality of life. On the other hand autoimmune disorders can develop after a hematopoietic stem cell transplantation (HSCT).

**Objectives:** AF came to our attention when she was 14 years old for swelling and pain (8 at the Numeric Rating Scale) in the proximal interphalangeal (IPF) joint of the II and III finger of the right hand, painful IPF of the III finger of the left hand accompanied by morning stiffness which lasted for 2 hours and swelling with functional impairment of hands, wrists and kness.
Blood count showed increased inflammatory indexes, antinuclear antibody (ANA) positivity (1:640 in Hep2 cells) and rheumatoid factor negative. The RM of the hands showed endoarticular fluid in both carpal bones and in the radioulnar joint with signs of synovitis; synovitis alone was also present in metacarpophalangeal joint of the II, III and IV finger of the left hand and II and III on the right, IFP of III finger left and II and III right, carpometacarpal joint of the I finger bilaterally. This clinical findings were characteristic of Juvenile Idiopathic Arthritis polyarticular rheumatoid factor negative subtype according to the ILAR classification.

The past medical history of our young girl was particularly important. When she was 18 month old, she was diagnosed of acute lymphoblastic leukemia and started chemotherapy according to AEIOU LAL 9502 protocol. One month after the re-induction phase she presented a disease relapse in the bone marrow so she started a chemotherapy cycle of second degree and the research for an unrelated donor because no familiar HLA-matched donor was present. When she was 3 years old, she underwent hematopoietic stem cells transplantation of peripheral-derived source. Ten months later, during the tapering of immunosuppressive therapy, she presented skin lesions resembling chronic GVHD so she started again immunosuppressive therapy with tacrolimus and mycophenolate mofetil. Later she developed restrictive respiratory syndrome, ovarian insufficiency in replacement therapy and a thyroiditis ultrasonography aspect with hormonal alterations.

This important personal history challenged us in the choice of therapy. She started with NSAID (Naproxen) with only partial relief. For the severe polyarticular involvement, after the discussion with the hematologists, we decided to introduce a steroid agent. The girl had a good response but, during steroid tapering, pain and functional impairment of legs and arms reappeared with morning stiffness and swelling of hands. For this reason we finally decided to start Methotrexate.

Conclusion: We don’t know exactly if juvenile idiopathic arthritis in our patient is a de novo autoimmune disease induced by the transfer of a heterologous immunological system or a rare presentation of graft-versus-host disease; however MTX therapy was effective and improved the symptomatology with a complete remission after 2 months.

Disclosure of interest: None declared.

P36
PrEs-FINAL-2023: Uveitis surveillance through lean-six sigma for quality assurance in juvenile idiopathic arthritis
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Introduction: Chronic asymptomatic iridocyclitis occurs in 10-20% of all patients with JIA leading to insidious but progressive morbidity and possible blindness. Patients with JIA-associated uveitis need to be seen by an ophthalmologist regularly. Lean thinking is based upon the following principles 1) focusing on the customer value (value adding steps) and alleviating the redundant parts of the process hence minimize waste 2) developing an effective flow production 3) eliminate backflows 4)using "pull" techniques 5) striving to perfection.

Objectives: To use Lean methodology to develop uveitis surveillance process for JRA patients for the electronic health records.

Methods: Various tools of lean methodology were used throughout the development of a new process of uveitis surveillance for JRA patients visiting rheumatology clinics at Nationwide Children’s Hospital. Problems were identified after paper chart review of 400 JIA patients. The key performance indicators used were 1) number of patients given eye examination request sheet 2) number of eye examination results received back from eye doctors & 3) number of eye examination results documented and available during the clinic visit. The hospital has switched to electronic medical records (EPIC) since 2006. It was found on baseline data that uveitis surveillance was inadequate and ineffective in paper charts. We identified the need to develop an electronic health record - based new surveillance process which can be more effective in improving communication between eye doctors, rheumatologists and patients/patients. We performed value stream mapping by stake holders to sketch the initial process and identify bottlenecks. Delphi survey was then used to reach consensus decisions, though out the project time. We charted current state, future state & ideal state and performed gap analysis. We then developed a pareto-matrix. The project methodology was based on the Deming’s PDCA cycles. We developed a standard work based on our initial PDCA cycles. We evaluated the new process through kpis.

Results: The uveitis surveillance process improved inter-team communication and quality of care. Inbuilt alerts in the process for presence of eye disease and missed eye appointments prompted rheumatologist to take appropriate timely action.

Conclusion: Implementation of lean tools and thinking can make provide smarter, quicker, easier, better and safer uveitis patient care delivery to the JIA patients by use of an effective uveitis surveillance process. We also emphasize the importance of seeing lean thinking as a part of the larger management shift towards planning for changes in mindsets and work places. This new surveillance process can be horizontally deployed for diabetic eye surveillance and drug toxicity monitoring in rheumatic patients on immunosuppressives.

Disclosure of interest: None declared.

P37
PrEs-FINAL-2024: Responsiveness of the juvenile arthritis foot disability index
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Introduction: Foot involvement is commonly described in children with JIA and management of foot disability is necessary to maximize physical function in children. The Juvenile Arthritis Foot disability Index (JAFI) is a questionnaire for assessing self-reported foot-related disability in children and adolescences with arthritis. The JAFI is a valid and reliable survey which is divided into three dimensions; impairment, activity limitations and participation restrictions (André 2004). However, its ability to measure change in foot related disability has not been established.

Objectives: (a) To evaluate the responsiveness of the JAFI among a cohort of children with JIA undergoing treatment with intra-articular corticosteroid injections (ICI). (b) To determine the association between JAFI change scores and the Child Health Assessment Questionnaire lower extremity dimension (CHAQ-low) change scores. We hypothesized that (a) the change in JAFI and CHAQ-low scores at 3 months following treatment from a group without foot impairments would demonstrate greater standardized response means (SRM = mean change/ SD change scores) and effect sizes (ES = mean change/ SD baseline scores) compared to scores from children with persistent foot disability. We also hypothesized that (b) JAFI change scores would moderately correlate with CHAQ-low change scores.

Methods: 35 children with JIA were consecutively recruited from a large tertiary care medical center pediatric rheumatology clinic. Twenty-eight participants were female; mean age (SD) 11(4) yrs. and mean (SD) disease duration of 4(4) yrs. 66% were diagnosed with polyarthritis. All children had active lower extremity inflammation and were scheduled for ICI in one or both feet. The children or parents (if child <10 yrs) answered the JAFI and the CHAQ prior to treatments, 3 months and 6 months after ICI. Scores from the CHAQ walking, rising, reaching and activity scales were summarized and divided into quartiles (CHAQ-low). To determine the responsiveness of the JAFI, children were separated into 2 groups based on standardized clinical examination, those without foot impairments at 3 months (n = 13) and those with foot impairments (n = 22) and standardized response means and effect sizes were calculated. Spearman correlations were performed to determine the association between JAFI dimensions and CHAQ- low change scores.

Results: Both the SRM and the ES scores of the JAFI dimensions were higher for the group without foot impairments after 3 month (SRM; 1.00- ES; 0.52-0.92) as compared to the group with persistent foot impairments (SRM; -0.10-0.39; ES; -0.01-0.29). The JAFI impairment dimension showed the highest SRM and ES scores after ICI while the JAFI participation dimension showed the lowest scores. Correlations (r) between JAFI dimensions and CHAQ-low change scores between baseline and 3 month were 0.44-0.67 and between baseline and 6 month were 0.46-0.48.
Conclusion: In this study the JAFI appears to be a useful questionnaire for evaluating change in self-reported foot disability after treatment with ICI in children with JIA.

Disclosure of interest: None declared.

P38
PrEs-FINAL-2025: Arthritis associated with human immunodeficiency virus
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Introduction: There is a clear, documented association between Human Immunodeficiency Virus (HIV) and arthritis in children and young people (CYP). However, this association has not been clearly defined and the arthritis has been seen to resolve with differing management strategies.

Objectives:
- To present a case of a child diagnosed and treated for Juvenile Idiopathic Arthritis (JIA) who was subsequently found to have HIV which led to treatment modification.
- To discuss HIV testing in CYP presenting with arthritis.
- To explore appropriate treatment options in CYP with HIV who have arthritis.

Methods: We retrospectively reviewed the case record of a fourteen year old boy of African origin with arthritis. He had been previously well and presented with a two week history of initially right ankle swelling which progressed to involve his left knee, right ankle, left wrist and distal interphalangeal joint of his index finger of his left hand. All these joints were swollen, warm and had restricted range of movement. He was systemically well and was diagnosed with polyarticular JIA. Initial management consisted of oral Naproxen, Prednisolone 0.6 mg/kg and Methotrexate 15 mg/m². This treatment resulted in some improvement in his joint symptoms. However, he represented two weeks later experiencing night sweats and was found to have generalised lymphadenopathy. After further history and investigation, he was diagnosed with HIV infection. He was subsequently referred to tertiary centre specialists in Paediatric Rheumatology and Infectious Diseases/Immunology (at Sheffield Children’s Hospital) for further investigation.

Results: His CD4 count was 295 × 10⁹/L and viral load of 8487 copies/ml. Extensive investigation did not reveal another infective cause for his joint symptoms. At presentation his C reactive protein (CRP) was 18 mg/L and erythrocyte sedimentation rate (ESR) >145 mm/hr. Anti-nuclear antibodies and extractable nuclear antigens were negative; double stranded DNA was 160 IU/ml. Within a multidisciplinary team including specialists in Infectious Diseases and Rheumatology, the current literature was reviewed. He was managed with intra-articular administration of Tramcinolone Hexacetonide into affected joints, and antiretroviral therapy. Two weeks following this he was re-assessed showing complete resolution of his joint signs and symptoms.

Conclusion: This case raises awareness of arthritis as a presenting feature of HIV in CYP. Furthermore, it raises the question of which CYP with JIA should be tested for HIV. It also highlights that more international collaborative work is required to determine optimal treatment strategies for HIV associated arthritis in CYP.

Disclosure of interest: None declared.

P39
PrEs-FINAL-2026: Glucose and lipid metabolism in children with juvenile idiopathic arthritis treated with anti-TNF-alpha
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2 Pediatric Rheumatology 2013, 11(Suppl 2):P39

Introduction: Inflammation and inflammatory mediators may affect glucose and lipid metabolism through a number of pathways. However, effects and mechanisms seem to vary dramatically in different individuals and settings. In obese adults with metabolic syndrome and impaired glucose-tolerance, inflammatory mediators from fat tissue including tumour necrosis factor-alpha (TNF-α) further reduce glucose tolerance. In such patients, treatment with TNF-α blocking agents has been shown to ameliorate glucose tolerance. However, in non-obese healthy adults, vigorous exercise may induce an inflammatory response including release of TNF-α. Glucose tolerance decreases during and after the exercise, and TNF-α blocking agents may inhibit this beneficial effect. Furthermore, the positive effects of exercise on cholesterol and triglyceride levels have also been diminished by TNF-α blocking agents.

In children with juvenile idiopathic arthritis (JIA) treatment with TNF-α blocking agents is increasingly common as the treatment is efficient and well tolerated. The possible harmful effects of this treatment on glucose and lipid metabolism, however, give rise to concern.

Objectives: The aim of the study was to investigate the glucose and lipid metabolism in children with JIA treated with TNF-α blocking agents.

Methods: Fifty-two children with JIA were included in the study. All were treated with immunosuppressive agents: 50 were treated with methotrexate (MTX) in monotherapy, 13 were treated with MTX and a TNF-α blocking agent and 9 were treated with a TNF-α blocking agent in monotherapy. None were treated with oral glucocorticoids. All treatments had been given at least 3 months at the time of blood sampling. All participants had a fasting blood sample drawn and subsequently the following parameters were assessed: HgbA1C (an indicator of the average glucose in the 8 weeks prior to testing), fasting blood glucose, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglyceride.

Results: Table 1. The data were tested and found to be normally distributed. Thus, unpaired t-test was used to compare mean-values.

Mean HgbA1C was significantly lower children treated with a TNF-α blocking agent compared to children treated with MTX as monotherapy (p = 0.01). The difference was significant in both children treated with TNF-blocker as monotherapy (p = 0.05) or in combination with MTX (p = 0.03). No other significant differences were detected.

Conclusion: Children with JIA treated with a TNF-α blocking agent have significantly lower HgbA1C. The reduction, however, is small and barely of clinical significance. No effects could be detected on fasting blood glucose or cholesterol levels. The results are reassuring with regard to the concerns for harmful long term side effects of this treatment.

Disclosure of interest: None declared.

P40
PrEs-FINAL-2027: Cerebral demyelination and optic neuritis during treatment with eternacept and methotrexate
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Disclosure of interest: None declared.

Introduction: Demyelinating disorders have been reported in association with anti-tumor necrosis factor alpha (anti-TNF-alpha) treatment in adults. Few reports exist among children.

Objectives: We report a case of demyelination and optic neuritis in a child treated with eternacept to increase the awareness of the possible risk of demyelination during anti-TNF-alpha treatment in children.

Methods: Case report.

Results: A 9 year old girl treated with methotrexate for 6 months and eternacept for 3 months because of polyarticular JIA developed loss of vision in both eyes. The weeks prior she had been extremely tired with periods of cough and fever. Bacterial- and Epstein-Barr-virus infection was absent. Her vision was almost normal and still improving. No further neurological examination was without pleocytosis. Anti-aquaporin-4 antibodies were not present. MR of the brain showed periventricular white matter lesions and lesions in hypothalamus. In addition signs of optic neuritis were seen. Visual evoked potential (VEP) showed delayed latency. Anti-aquaporin-4 antibodies were not present. Cerebrospinal fluid (CSF) examination was without pleocytosis and no infectious agent could be demonstrated. Oligoclonal bands in the CSF were present indicating production of gamma globulin in the central nervous system. The girl received high-dose intravenous steroid therapy followed by oral prednisone. The treatment with etanercept was stopped. Two months later her vision was almost normal and still improving. No further neurological symptoms have developed during prednisolone tapering.
Conclusion: Development of cerebral demyelination might be the first attack of multiple sclerosis and may be triggered by anti-TNF-alpha treatment. The changes could also be due to an inflammatory disorder caused by infection or be of auto immune origin. The role of the TNF-alpha blockade is uncertain.

Disclosure of interest: None declared.

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### Table 1 (abstract P39)

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<th>Treatment</th>
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<th>Total cholesterol/mM</th>
<th>HDL/mM</th>
<th>LDL/mM</th>
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<td>5.0 (0.5)</td>
<td>4.0 (0.7)</td>
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<td>MTX and TNF-α blocker</td>
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<td>5.0 (0.5)</td>
<td>4.1 (1.2)</td>
<td>1.4 (0.2)</td>
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<tr>
<td>TNF-α blocker</td>
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<td>4.9 (0.5)</td>
<td>3.9 (0.7)</td>
<td>1.4 (0.3)</td>
<td>2.3 (0.5)</td>
<td>0.6 (0.2)</td>
</tr>
</tbody>
</table>

All values as mean (SD).

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### P41

**PReS-FINAL-2028: ANA positivity and a younger age at onset, but not disease category, predict the risk of uveitis in Italian children with juvenile idiopathic arthritis.**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P41

**Introduction:** Juvenile idiopathic arthritis (JIA) is the most common cause of chronic anterior uveitis in childhood, and uveitis is the most frequent extra-articular manifestation seen overall in children with JIA. Although it is well-known that ocular involvement is strongly associated with a constellation of particular clinical features, which include the presence of antinuclear antibodies (ANA), young age at disease onset, female sex, and an asymmetric pattern of arthritis, the relative importance of each risk factor is still a matter of debate.

**Objectives:** The aim of the study is to investigate the predictive role of the main risk factors for chronic anterior uveitis in Italian children with JIA.

**Methods:** The clinical charts of all consecutive JIA patients with the ILAR categories characterized by a distinctive risk of chronic anterior uveitis (persistent oligoarthritis, extended oligoarthritis, rheumatoid factor-negative polyarthritis, psoriatic arthritis and undifferentiated arthritis) followed by study investigators between 1985 and 2012 were reviewed. Patients with at least two ANA positive determinations (title ≥1:160) were excluded from the study. Survival analyses, with the first occurrence of uveitis as the event of interest, were conducted by means of the Kaplan-Meier method. Survival curve estimates were compared by the log-rank test. Factors significantly associated with time to uveitis onset were then tested in a Cox proportional hazards regression model.

**Results:** A total of 1,260 JIA patients were included in the study. Four patient subsets were excluded due to occurrence of uveitis before onset of JIA. A total of 278 patients (22.1%) developed uveitis. No association was found between the risk of developing uveitis and patient gender (p = 0.70) or ILAR category (p = 0.49), whereas the risk of developing uveitis was significantly associated with disease onset before 3.5 years (p < 0.0001) and positive ANA (p < 0.0001). The predictive role of the positive ANA status and of a younger age at onset was confirmed by Cox proportional hazard regression analysis. Conclusions: In a large cohort of JIA patients, we found that the risk of uveitis was associated with a positive ANA status and an age at onset ≤3.5 years. No association was found between occurrence of uveitis and ILAR category of JIA.

**Disclosure of interest:** None declared.

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### P43

**PReS-FINAL-2030: Treatment with leflunomide results in a higher flare rate of chronic uveitis compared to methotrexate in patients with juvenile idiopathic arthritis treated with both drugs**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P43

**Introduction:** Juvenile idiopathic arthritis (JIA) is the most common chronic pediatric rheumatic disease, affecting 4 of every 1,000 children worldwide. It may cause joint damage, persistent pain and retardation of normal growth, which eventually may lead to long-term disability and decreased quality of life. Treatment aims disease control and induction of remission, preventing joint damage and unfavorable outcomes.

**Objectives:** To determine the disease outcome of JIA patients followed in a single center in Rio de Janeiro, Brazil.

**Methods:** JIA patients registered to the Rheumatology Unit of a University Hospital from 2000 to 2012, first seen before age of 16, and with a follow-up of at least 5 years had their chart data reviewed in the search for information including: gender, subtype of JIA, age of diagnoses, duration of disease, presence of uveitis, surgery, medication used.

**Results:** Ninety-four patients were identified and among these patients, 53 (56.38%) were female and 41 (43.62%) were male with age between nine and forty years. The average duration of disease was 14.7 years, with an average diagnoses gap of one year and five months. Onset subtypes of JIA were: oligoarticular in 29 (30.85%), systemic in 23 (24.47%), enthesitis-related arthritis in 14 (14.89%), polyarticular RF negative in 14 (15.96%), polyarticular RF positive in 8 (8.51%), psoriatic arthritis in 5 (5.32%). Remission of disease according to Wallace et al (2004) was seen in 73 (77.66%) patients, of which 39 (53.42%) were currently using medication (methotrexate 66.67%, NSAID 43.59%, corticosteroid 41.03%, biological drugs 38.46%, antimarial drugs 10.26%, leflunomide 7.69%, azathioprine 5.13%, ciclosporin 2.56%). Uveitis occurred in 13 (13.83%) patients. Among the 15 (15.96%) patients who underwent surgery, eight (8.51%) patients had arthroplasty and two (2.13%) had knee tenotomy. Five patients (5.32%) had ophthalmic surgery.

**Conclusion:** The study showed remission of disease in 73 (77.66%) patients, diagnosed as oligoarticular onset in 22.31% and systemic in 19.27%. Of those in remission, 39 (39.53%) were currently using some medication. The 21 patients (22.34%) who still presented active arthritis, 7.33% had extended pain and retardation of growth.

**Disclosure of interest:** None declared.

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### P42

**PReS-FINAL-2029: Long-term follow-up of patients with juvenile idiopathic arthritis (JIA) in a single center: a systematic chart review**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P42

**Introduction:** Chronic anterior uveitis is a common complication of juvenile idiopathic arthritis (JIA). Leflunomide is a frequently used alternative to methotrexate in the treatment of joint manifestations of JIA. However, very little is known on the effect of leflunomide treatment on concurrent chronic pediatric rheumatic disease, affecting 4 of every 1,000 children worldwide. It may cause joint damage, persistent pain and retardation of normal growth, which eventually may lead to long-term disability and decreased quality of life. Treatment aims disease control and induction of remission, preventing joint damage and unfavorable outcomes.

**Objectives:** To investigate patients with juvenile idiopathic arthritis with a history of non-simultaneous treatment of methotrexate and leflunomide, and to compare flare rates of uveitis during treatment periods with both drugs in these patients.

**Methods:** The database of the German Center for Pediatric and Adolescent Rheumatology was searched for all patients admitted from January 2010 until October 2011 with a diagnosis of juvenile idiopathic arthritis and chronic anterior uveitis and treatment periods with both leflunomide and methotrexate. Patients with uveitis due to other causes were excluded. A retrospective chart survey was used to extract demographic data, diagnosis, and start and end times of treatment with leflunomide and methotrexate, respectively, concomitant medications and numbers of anterior uveitis flares.
Anterior uveitis flare was defined as detection of any anterior chamber cells or flares after previously documented inactivity by an ophthalmologist. A generalized linear mixed model was constructed using a negative binomial distribution. Number of flares was used as the dependent variable, and the two treatments, LFN and MTX, were considered repeated measurements. The logarithm of time was used as an offset variable.

**Results:** 15 patients were included in the study, 9 patients with extended oligoarthritis, three with seronegative polyarthitis, two with persistent oligoarthritis and one with psoriatic arthritis. 100% had positive antinuclear antibodies. All patients were treated with methotrexate prior to leflunomide treatment, six patients had a second course of methotrexate and one patient a second course of leflunomide. 10 patients showed uveitis prior to treatment, and five patients developed uveitis on treatment with methotrexate. Median time of treatment with methotrexate was 51 months (range 26 - 167 months), and with leflunomide was 12 months (range 4 - 47 months). While on methotrexate, one patients each received etanercept and adalimumab, and one subsequent courses of both, compared to five patients on adalimumab and one each on etanercept and on infliximab while on leflunomide. On 1012 months of methotrexate treatment, 25 flares occurred, while on 247 months of leflunomide treatment, 15 flares occurred. This corresponds to a flare rate of 0.0247 flares/month on methotrexate treatment and 0.0607 flares/month on leflunomide treatment and treatment (p = 0.008).

**Conclusion:** Despite more co-medications potentially improving the uveitis outcome in leflunomide treatment periods, patients showed significantly more flares of uveitis compared to treatment periods with methotrexate. Further research is necessary to assess leflunomide efficacy in chronic uveitis associated with JIA.

**Disclosure of interest:** None declared.

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P45

**PReS-FINAL-2032: Changes in immunogenic profile in patients with juvenile idiopathic arthritis exposed to anti tumoral necrosis factor therapy**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P45**

**Introduction:** In a previous study conducted by our group we observed an unusual prevalence of titles of antinuclear (ANA) and anti-DNA (aDNA) antibodies in children who were previously negative for both antibodies and who received any biologic therapy due to a childhood rheumatic systemic disease (CRSD). This observation has been reported in adulthood previously, mainly in patients exposed to anti tumoral necrosis factor (aTNF) therapy however its clinical impact is not well established.

**Objectives:** Present study was conducted to determine if aTNF therapy administered on patients with Juvenile idiopathic arthritis (JIA) shows the same tendency and if the ratio of change is comparable to patients not exposed to this therapy.

**Methods:** Medical records of our cohort of patients from 1999 to 2009 who underwent 62 an aTNF therapy due to any ILAR category of JIA were reviewed. Analytical tests were collected in the moment of diagnosis, at the beginning of the aTNF treatment, and at the 3rd and 6th month of treatment. Only cases with complete analytical testing up to a month after the designed date were analyzed. Comparisons were made with children diagnosed with the same ILAR category of JIA of the same age (+/- 2 years old) and sex. Non exposed and exposed subjects ratio was 1:1. aDNA positive change was considered when a negative quantitative determination increased to a positive one according to our reference lab ranges (Indirect Immunofluorescence method). ANA increase was defined as a two fold increase in the titr. In order to establish comparisons only subjects susceptible to experiment an ANA titr increase of an aDNA positive change were chosen.

**Results:** The followed up treatments were: 32 Etanercept (ETN), 15 Infliximab (IFM), 15 Adalimumab (ADM). Anti-DNA profile evolution: 3/25 showed a titter increase (12.0%), all of them were previously negative (2 with ETN and 1 with IFM). Into the control group no patient developed a titter increase (p non available). ANA profile evolution: 12/49 showed a titter increase (24.4%), 8 with ETN and 4 with IFM. Into the control group 5/49 patients (10.2%) experiment a titter increase (p < 0.05). No patient who underwent a change into its autoimmuno profile was secondarily diagnosed with other CRSD during the period of follow up. The need of switching the biologic therapy, rate of severe complications or demands of increase of non biologic therapy was similar in children who increase its ANA titers and who did not.

**Conclusion:** Our findings supports the hypothesis that aTNF therapy administered on patients with Juvenile idiopathic arthritis (JIA) shows the same tendency as patients not exposed to aTNF therapy.

**Disclosure of interest:** None declared.
Introduction: The introduction of biological therapies (BT) has improved the management of patients with Juvenile Idiopathic Arthritis (JIA) in terms of relief of symptoms, enhancing the quality of life and reducing joint damage. Its pharmacological activity induces immunity transitory suppression that assumes an increased risk of acquiring infectious diseases or a major severity of them. TB adverse events registries have painted special attention to severe events that conditioned in bed stay at hospitals or mortality and most of them are focused on adult cohorts. Paediatric BT adverse events registries are significantly fewer compared to adults and the recount of mild and moderate adverse events (according to OMERACT-8 definitions), which are fortunately highly frequent than others, have not properly compared with healthy children.

Objectives: The purpose of this study is to determine the increase of risk of develop a mild or moderate adverse event in patients with JIA receiving BT compared to healthy people.

Methods: We conducted a retrospective cohort study. Complete medical records of patients with JIA treated with BT since 2002 in our unit were revised. Among this group we included those patients who started BT before 16 years old. Control cohort was composed by healthy subjects same age and sex. Controls were obtained randomly from two different primary care units related to our hospital until complete three subjects for each case. The recount of mild and moderate adverse events was performed since starting BT in our cohort and at the same age in controls. All recounts finalized when BT was stopped of when subjects (patients or not) reached 16 years old or at December 31th, 2012.

Results: Thirty patients were followed up during an average of 4.2 SD 1.8 years. Time of effective exposure to BT, excluding periods of stop of prescription was 3.1 SD 1.5 years. Healthy subjects were followed up an average of 4.8 SD 1.4 years. Incidence of mild adverse effects was 1.9 cases/patient/year in the BT group and 1.05 cases/patient/year in the control group (p < 0.05) which represents a risk increase of 80.9%. Incidence of moderate adverse events was 1.56 cases/patient/year in the BT group and 1.26 cases/patient/year into the control group (p = 0.04) which represents a risk increase of 23.8%.

Conclusion: OMERACT definition of mild adverse events makes difficult its complete registration into medical records and it could underestimate its prevalence in healthy people compared with patients with JIA receiving BT who are under a close follow up. With this in mind we believe that the most valuable result is the risk increase of moderate adverse events due their need of medical approach (by definition). Considering that moderate adverse events are more frequent than severe ones, we consider this study provides relevant information to share with parents of patients who potentially will take BT. It is necessary a prospective follow up of major cohorts and over longer periods of time to obtain valuable information about risk increase among different groups of ages or different ILAR categories of JIA.

Disclosure of interest: None declared.

Introduction: The prostanooids are a family of biologically active lipids derived from the 20-carbon essential fatty acids (LCPUFA) which are involved in all aspects of the immune response including the resolution of inflammation. ω-3 fatty acids, EPA DPA and DHA are anti-inflammatory, whilst the ω-6 fatty acid, Arachidonic acid (AA) and its metabolites: 13(S)-HETE, TXB2, PGF2α and 6-k-PGF1α are pro-inflammatory. Liquid Chromatography Tandem Mass Spectrometry (LCMSMS) allows analyses of multiple prostanooids with high accuracy using 3 mm blood spots. This method has never been used in JIA and may find biomarkers which can help predict disease activity and treatment response.

Objectives: To measure prostanooid profiles in patients with JIA using LC-MSMS.

Methods: 254 samples from 114 JIA patients and 6 healthy controls (HC) were collected onto specially prepared filter papers and analysed using LC-MSMS.

Results: The JIA M:F ratio was 1:1.4, the average age at study entry (9.4 ± 5.0 y), average disease duration (56.1 ± 46.1 m), with 25% JIA receiving treatment with NSAID, 11% with Methotrexate (MTX), and 10% with Biologics. 13(S)HODE and DHA levels were significantly different between JIA patient groups (p = 0.05 for both; 13(S)HODE oligo vs poly p = 0.02; DHA SoJIA vs RF+ Poly p = 0.007). There was a positive correlation between JADAS and PGB2 (p = 0.046). There were lower levels of pro-inflammatory prostanooids in JIA (Table 1).

Conclusion: In our JIA cohort, we found that PGB2 is correlated with disease activity and that levels of pro-inflammatory prostanooids are reduced, particularly in polyarthritis. This may reflect the degree to which the pro-resolving prostanooids are activated in patients with relatively long average disease duration. It is also possible that measurement of a combination of prostanooids will help us predict changes in disease activity and treatment response over time more accurately. Longitudinal analysis of the relationship between disease activity and prostanooid profiles is underway.

Disclosure of interest: None declared.
Introduction: The complement system plays a crucial role in the pathogenesis of various inflammatory processes. The lectin pathway of the complement is activated through the recognition of pathogens or altered self-structures by the pattern recognition molecules (PRMs) mannan-binding lectin (MBL), H-ficolin, L-ficolin and M-ficolin in collaboration with MBL-associated serine proteases (MASPs). PRMs reportedly play a role in rheumatoid arthritis (RA), and a recent study indicated a correlation between the concentration of these proteins and RA disease activity. Knowledge regarding the role of lectin pathway proteins in juvenile idiopathic arthritis (JIA) is lacking.

Objectives: The aim of the study was to evaluate the possible pathogenic role of the PRMs like MBL, H-ficolin and M-ficolin, MASP-1, -2, -3 as well as the two alternative splice products, MAP19 and MAP44 of the genes encoding the MASPs. We tested paired samples of plasma and synovial fluid (SF) from patients with oligoarticular and systemic JIA.

Methods: We measured MBL, M-ficolin, H-ficolin, MAP-3, MAP-2, MAP-1, MAP44 and MAP19 in plasma/serum and synovial fluid (SF) of 136 children with oligoarticular JIA (persistent subtype) and 28 children with systemic JIA. The concentrations of the nine proteins were measured by in-house time-resolved immunoflurometric assays (TRIFMA) using monoclonal antibodies. The principle of this assay is the same as for sandwich ELISA, only fluorescence rather than enzyme activity is used for the read-out. In brief, microtiter wells are coated with monoclonal antibody, incubated with dilutions of the test samples, then with biotinylated monoclonal antibody, and finally developed with europium-labeled streptavidin. The concentrations of the analytes are read from parallelly constructed standard curves.

Results: Concentrations of MASP-3, MASP-2, M-ficolin and MASP-1, respectively between the oligoarticular and the systemic subtype differed significantly in plasma. Measurements of serum samples showed significant difference for M-ficolin, H-ficolin, MAP44 and MAP-1 between the two groups. SF/plasma ratio of the lectin pathway proteins were calculated in paired samples for oligoarticular JIA (n = 36) and the systemic onset JIA (n = 11). We observed significant higher levels in plasma than in SF for both subtypes with P values <0.01, while the significance was lower for H-ficolin (p = 0.04) and MBL (p = 0.1549) in the systemic group. Conversely, for MASP-3 we observed significantly higher concentration in SF than in plasma - ratio 1.97 (1.61; 2.32) (p < 0.001) for the oligoarticular subtype and 2.59 (1.73;3.44)(p = 0.001) for the systemic group. We did not observe significantly higher concentrations and inflammatory markers is in progress.

Discussion of interest: None declared.
Objectives: To study the efficacy and tolerability of Tocilizumab (TCZ) in patients with longstanding refractory to the conventional treatment and TNF-inhibitors sJIA.

Methods: Seven children in the age range 2-12 years (mean 6.3) years with disease duration 1.2 - 9 years (mean 4.6) years with active persistent sJIA have been included in the modern prospective study. All 7 patients had oligoarticular joint involvement and received previous treatment with NSAIDs, Methotrexate and corticosteroids. 4/7 had concomitant therapy with Etanercept and 2/7 second DMARD. In all patients TCZ was administered immediately after discontinuation of the biological treatment or the second DMARD in a dose of 6 mg/kg for patients ≥ 30 kg and 12 mg/kg for patients < 30 kg every two weeks. At baseline all patients had active disease. Response to the treatment was measured according to the ACR Pedi criteria at the end of the 1st, 3rd, 6th, 9th and 12th month. Clinical examination, laboratory investigations, growth parameters’ assessment and screening for adverse events have been performed every 2 weeks.

Results: At the end of the 1st month we found complete resolution of the systemic symptoms and acute phase response in all patients. At the end of the 3rd month, ACR Pedi 30, 50, 70 and 90 responses were achieved by 7 (100%), 5 (71%), 11(14%) and 0 (0%) patients, respectively. By 6th month the observed responses we as follows: ACR 30 - 7 pts (100%), ACR Pedi 30 - 7 pts (100%), ACR Pedi 50 - 7 pts (100%), ACR Pedi 70 - 5 pts (71%), ACR 90 - 1 patient (14%). At the end of the 9th month ACR Pedi 30, 50, 70 and 90 responses were achieved by 7 (100%), 7 (100%), 6 (86%) and 4 (57%) patients. All patients maintained these parameters by 12th month. After achieving control of the disease activity, we started to reduce the dose of steroids and/or Methotrexate leading to their discontinuation and monotherapy with TCZ in 4 patients. In all of these patients remission on medication was documented by 12th month. At the end of the observational period the linear growth velocity of all treated patients reached the average normal values per year of their age matched peers. Some patients experienced mild and reversible adverse reactions such as: mild neutropenia or thrombocytopenia, slight increase of liver enzymes and increased cholesterol levels. All side effects resolved with the decrease of the dosage and did not lead to the discontinuation of the treatment.

Conclusion: Tocilizumab is an effective and well tolerated drug in children with systemic longstanding persistent JIA, refractory to the conventional treatment and TNF-inhibition. Monotherapy with TCZ is an appropriate option for controlling the disease activity, improving the physical growth and minimizing the overall toxicity of the treatment of this disease.

Disclosure of interest: None declared.

PS5
PReS-FINAL-2040: Outcome of macrophage activation syndrome (MAS) in systemic juvenile idiopathic arthritis (sJIA) in non biologic treated patient
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Pediatric Rheumatology 2013, 11(Suppl 2):P53

Introduction: MAS is serious and severe, sometimes life threatening complication of sJIA but data about survivor outcomes are missing.

Objectives: We present 16 year old girl who developed MAS six years after sJIA was established and whose parents refused some treatment options.

Methods: Analysis of clinical outcome and laboratory parameters in non biologic treated patient with sJIA who developed MAS.

Results: After episode of fever and exudative pericarditis (cardiac tamponade) in 2nd and 4th year of life the diagnose of sJIA was established and steroid and NSAIDs therapy was introduced. Clinical remission was achieved and lasted 3 years when at the age of years, after moderate respiratory infection she developed persistent oligoarthritis which metotrexate was administrated during one year until disease remission. She was lost for follow up until admitted to the hospital due to high grade fever, macular rash, weakness, oligoarthritis, aphthous stomatitis, cervical lymphadenopathy and pericarditis. The pulses of methyl-prednisonolone were started followed with the oral steroids (2 mg/kg) and NSAIDs therapy. Episodes of fever, rash and morning stiffness with elevated values of ESR, CRP and WBC were still present after 2 weeks why CyA was added. Next 3 weeks she was relatively stable, but became Coughing-oid with occasional fever and high blood pressure, in the fourth week of hospitalization she developed seizures due to hypertensive encephalopathy (TA 210/160 mmHg). Intensive antihypertensive and antiedematous therapy has noramlised blood pressure without new episodes of seizures. After 6 weeks of treatment she developed intensive epigastric pain and diffuse tenderness in the abdomen (peritonitis) with diffuse purpuric skin lesions all over the body. Laboratory results have shown low PLT count, hypertiglyceridemia highly elevated liver enzymes, ferritin and LDH (10403 mmol/L) and profound hyponatriemia (112 mmol/L). Diagnosis of MAS was established together with oliguria and her serious condition hemodialysis was initiated together with etoposide and VP16. During next 2 months she was in ICU and have had impaired coagulation parameters and developed necrotic-vasculitis skin changes. Parents refused implementation of any additional immunosuppressive or biologic therapy except short course of Thalidomide. Due to a chronic renal failure she is still on regular hemodialysis. During follow up period she never developed new episodes.
of arthritis but have developed amyloidosis (with constrictive pericarditis and cardiomyopathy), chronic renal failure and seizures.

Conclusion: MAS is major cause of mortality in patients with sJIA. Data about MAS survivors and their outcome in correlation to treatment approach are missing especially for patients not treated with biologics.

Disclosure of interest: None declared.

P54

PReS-FINAL-2041: Macrophase activation syndrome in the children with systemic juvenile idiopathic arthritis during the course of tocilizumab
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Pediatric Rheumatology 2013, 11(Suppl 2):P54

Introduction: Systemic juvenile idiopathic arthritis (sJIA) is a chronic inflammatory disease characterized by prolonged systemic and synovial inflammation. Life-threatening complication of sJIA is the macrophase activation syndrome (MAS). Tocilizumab (TCZ) is highly effective in sJIA. Our sample included 42 patients with juvenile idiopathic arthritis (JIA) and 212 (female = 149, male = 63) patients with JIA and systemic juvenile idiopathic arthritis (sJIA) who were treated with tocilizumab (TCZ) in our hospital between 2013, while in the control group we found 5 tricuspid insufficiency and 1 aortic valve insufficiency, 4 with mitral prolaps and 2 with bicuspid aortic valves, respectively. 106 (51.2%) patients with polyarticular arthritis, 89 (41.1%) patients with oligoarticular arthritis, 11 (4.9%) patients with systemic arthritis and 6 (2.9%) patients with psoriatic arthritis subtype. Total score of PedsQL-self report was 78.92 ± 12.52 for 5-7 years, 75.14 ± 16.45 for 8-12 years, 77.37 ± 13.08 for 13-18 years. Total score of PedsQL-parents report was 70.73 ± 17.05 for 2-4 years, 72.43 ± 12.96 for 5-7 years, 81.81 ± 17.14 for 8-12 years and 75.19 ± 16.29 for 13-18 years. There was no statistically significant difference for PedsQL-parent’s report total scores in JIA subtypes (p > 0.05). There was statistically significant difference for PedsQL parents’ report (daily activities scores, treatment scores and communication scores) between age groups (p < 0.05).

Conclusion: This study showed that the results of the quality of life in Turkish children with JIA. The quality of life has decreased when the age increases in present study. The decrease in quality of life are not correlate with subtype of JIA. However, it may relate to sequelas in later stages of the disease, illness perceptions, and reduced expectation of treatment in JIA.

Disclosure of interest: None declared.

P56

PReS-FINAL-2043: Cardiac involvement in juvenile idiopathic arthritis
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Pediatric Rheumatology 2013, 11(Suppl 2):P56

Introduction: Cardiovascular involvement is a relative common complication among adult patients with rheumatic diseases, but, according to our knowledge, few studies have investigated paediatric population.

Objectives: We investigated the prevalence of cardiovascular involvement in patients with juvenile idiopathic arthritis (JIA).

Methods: All patients with JIA attending IRCCS Burlo Garofolo in 2012 were enrolled irrespectively from their clinical active disease. Patients enrolled underwent Electrocardiogram (ECG) and complete ecocardiography (two-dimensional, color, continuous, pulsed and tissue Doppler).

Results: Our sample included 42 patients with juvenile idiopathic arthritis (JIA), mean age at evaluation 13.9 ± 7.9 years, mean disease duration was 6.9 ± 7.6 years, Male/Female ratio:10/32). Among them, 27 (64.3%) were oligoarthritis, 13 (30.9%) polyarthritis, 1 (2.4%) systemic arthritis and 1 (2.4%) psoriatic arthritis. Uveitis were present in 6 patients. Only 5 patients had clinical and laboratory signs of active disease. Among the patients, 36 were receiving a treatment: 22 were in Methotrexate (MTX), 8 were in Etanercept, 4 were in therapy with both MTX and Etanercept, 1 with Adalimumab and 1 with Infliximab. Each patient was matched with a healthy control. We found in the JIA group a slight increased number of valvular alterations: 13 patients with tricuspid insufficiency, 1 with mitral valve insufficiency, 4 with mitral prolaps and 2 with bicuspid aortic valves, while in the control group we found 5 tricuspid insufficiency and 1 aortic insufficiency (p = NS). Two patients had a small pericardial effusion. We found a significant difference between case and controls in systolic and diastolic function both of left (increased Iso Volumetric Contraction Time, IVCT, p < 0.006, and increased Iso Volumetric Realising Time, IVRT, p < 0.001) and right (decreased Tricuspid Annular Plane Systolic Excursion, TAPSE, p < 0.004, and decreased E/A ratio p < 0.004, increased IVRT p < 0.01) ventricles. The correlation between echocardiographic and some
We found a significant systolic and diastolic abnormalities on both ventricles (decrease in TAPSE and the increase of IVCT and IVRT) in a population affected by JIA. In our opinion it could be attributable to early structural abnormalities (hypertrophy or interstitial fibrosis) caused by prolonged inflammation. Other studies are necessary to understand if these patients might have increased risk of cardiac disease in adulthood, but we think that these patients might benefit from serial cardiac evaluation to highlight early alterations that could require specific therapy.

Disclosure of interest: None declared.

**P57**

**P57**

PrES-FINAL-2044: TNF-alpha inhibitors in treatment of children with systemic form of juvenile idiopathic arthritis

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Pediatric Rheumatology 2013, 11(Suppl 2):P57

Introduction: From 2005 to 2011, children with the systemic form of juvenile idiopathic arthritis (JIA), due to the lack of efficacy of standard antirheumatic therapy, received TNF inhibitors, because there were no drugs registered for the treatment of systemic JIA (IL6, IL1 inhibitors) in Russia.

Objectives: Assessment and comparison of efficacy and safety of TNF-alpha inhibitors (infliximab and etanercept) in the treatment of children with the systemic form of JIA.

Methods: 32 patients with the systemic form of JIA were enrolled in the study. 19 patients received infliximab and 13 received etanercept. All patients had high degree (III) of disease activity. Average disease duration was 7.2 ± 3.3 years. Before administration of TNF-alpha inhibitors, all patients received conventional immunosuppressive therapy with 2 or more drugs. In the beginning of the disease, systemic manifestations, such as fever, hepatomegaly, lymphadenopathy, leukocytosis, were observed in 100% of children, rash in 53% in both groups, persistent joint syndrome in the infliximab treatment group was seen in 84% of patients, in the etanercept group - in 73% of children. At the moment of prescription of TNF-alpha inhibitors, the mean number of active joints in the whole group was 20 ± 5, the number of joints with restriction of function - 25 ± 7, ESR - 38 ± 12, C-reactive protein - 6.2 ± 3.4. The drugs were used in standard doses. For assessment of efficacy of performed therapy, “pediatric” criteria of the American College of Rheumatology were used: 30%, 50% and 70% therapy response, that is ACR pedi-30, pedi-50, pedi-70. The criteria for ACR pedi-30 were assessed 6 and 12 months after the therapy beginning. Achievement of ACR pedi-30, pedi-50 - was regarded as an insufficient response reaction to the therapy being conducted, ACR pedi-70 and higher - as a good response reaction (achievement of medicament remission or low disease activity).

Results: In the infliximab treatment group, the good response was achieved in 31% of patients by the 12th month of therapy. In children with domination of visceral manifestations in the beginning of the disease, infliximab therapy was ineffective. In the etanercept group, the good response was achieved in 55% of patients by the 12th month of therapy. In three patients, earlier received infliximab therapy without distinct effect, etanercept treatment appeared to be unsuccessful too. The highest effectiveness of the drugs was registered in children without extraarticular manifestations of systemic JIA at the baseline. Further, all children with insufficient response to the therapy with TNF-alpha inhibitors were transferred to tocilizumab.

Conclusion: Therapy with TNF-alpha inhibitors has appeared to be insufficient in the treatment of the systemic form of JIA. Administration of TNF-alpha inhibitors in children without extraarticular manifestations of systemic JIA at the moment of prescription of the drug. No statistically reliable difference in efficacy has been revealed between infliximab and etanercept groups (p > 0.05). The safety profile of etanercept is significantly higher than that of infliximab (p ≤ 0.05). The received results reconcile with data earlier published in the scientific literature.

Disclosure of interest: None declared.

**P58**

**P58**

PrES-FINAL-2045: Mutational analysis of sialic acid acetylesterase (siae) in juvenile idiopathic arthritis (JIA)

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Pediatric Rheumatology 2013, 11(Suppl 2):P58

Introduction: SIAE is involved in the maintenance of immunological tolerance through negative regulation of B-cell receptor (BCR) signaling. Recent evidences, though conflicting, indicate that rare loss-of-function SIAE variants are associated with susceptibility to various autoimmune diseases. Advances in understanding JIA pathophysiology have led to the consensus that systemic JIA (SJIA) is an autoinflammatory disorder while oligo/polyarticular JIA (O/P JIA) is an antigen-driven lymphocyte-mediated autoimmune disease.

Objectives: To elucidate whether SIAE variants predispose their carriers to O/P JIA but not to SJIA.

Methods: Sixty-five JIA patients (M/F: 19/46, mean age: 9.8 years, range:2.5-18.3; 57 with O/PJIA and 8 with SJIA) and 82 age- and sex-matched healthy controls were enrolled. Amplification of all 10 SIAE exons, including exon-intron boundaries, and sequencing of purified DNA was performed.

Results: Two novel heterozygous SIAE mutations, namely the Q343P (g.41498 A > C, c.1028A > C) and the Y495X (g.44266 C > A, c.1485C > A), as well as three already described heterozygous SIAE mutations, namely the functionally innocent M89F (g.20536A > G) mutation and the silent mutations S1565 (g.26573T > C) and T484T (g.44132G > A) were found in O/PJIA patients. The girl carrying the Q343P mutation had ANA(+) persistent oligoarthritis. Her family study proved that her father, having a family history of autoimmune disease, was also carrier of the same mutation. The girl with the Y495X mutation suffered from RF(-), ANA(+) polyarthritis. The novel SAE mutations did not detected among normal controls. Amongst the patients with SJIA, one was heterozygote for the known functionally innocent K71R (g.11927A > G) and A467V (g.44118C > T) mutations as well as for the silent mutations T484T and S1565, while another one was heterozygote for the silent mutation R340R (g.41190 T > C).

Conclusion: Our results support the notion that SIAE might be involved to the pathogenesis of O/PJIA but not of SJIA. Functional analysis of the identified novel SIAE variants is required to prove the biological significance of these genetic alterations.

Disclosure of interest: None declared.

**P59**

**P59**

PrES-FINAL-2046: Uveitis in the Nordic juvenile idiopathic arthritis cohort; high incidence, frequent complications, and gender-associated risk factors

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Pediatric Rheumatology 2013, 11(Suppl 2):P59

Introduction: Uveitis is the most common extra-articular manifestation of juvenile idiopathic arthritis (JIA). Both incidence and reported outcome varies, and population-based data are scarce. Early identification of asymptomatic cases is important in order to avoid complications and reduced vision.
The aim of the study was to identify incidence, risk factors and outcome of uveitis in a cohort of Nordic children with JIA followed for at least 7 years. Our objective was to review the use of stretch and cast strengthening. Post operative use of stretch and cast procedures alongside Intra-articular steroid injections (IAI) for active JIA of the knee resulting in fixed flexion deformities (FFD) of greater than 15 degrees.

Results: Of 500 children included at baseline, 440 were followed for at least 7 years and 389 (78%) had available ophthalmologic data. Uveitis developed in 89 (23%) of the 389 children; 59 girls and 30 boys, acute uveitis in 12 and chronic uveitis in 77 children. Fifty percent (6/12) of patients with acute uveitis were HLA-B27 positive. Young age at onset of JIA was a significant predictor of chronic uveitis in girls (p = 0.0001), but not in boys (p = 0.47). Also the presence of anti-nuclear antibodies (ANA Hep-2) (p = 0.003) was a significant predictor in girls (p = 0.003), but not in boys (p = 0.05). Neither female gender nor oligoarticular onset JIA category was significantly associated with uveitis. Chronic uveitis was diagnosed at a median of 0.8 years after onset of disease, and in 88% within the first four years after onset of disease. The longest interval between JIA onset and uveitis development was 8.6 years. Complications occurred in 39 eyes in 22 of the 89 patients with uveitis (25%), glaucoma occurred in 16 eyes and cataract in 14 eyes. At the last visit visual acuity was 0.5 in 10 eyes in 9 patients.

Conclusion: We found high incidence of uveitis among Nordic children with JIA, and the majority develop early after onset of disease. Age at onset of JIA and presence of ANA Hep-2 were associated with development of uveitis in girls, but not in boys. Complications were present seven years after onset of arthritis in 25%, showing that uveitis contributes significantly to morbidity and disability in children with JIA.

Disclosure of interest: None declared.

P61
PReS-FINAL-2048: Treatment with methotrexate plus leflunomide for juvenile idiopathic arthritis
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Pediatric Rheumatology 2013, 11(Suppl 2)p61

Introduction: Methotrexate (MTX) is the agent of first choice for the treatment of children with Juvenile Idiopathic Arthritis (JIA). Leflunomide (LFN) has demonstrated to be an effective alternative to MTX. There is a lack of evidence regarding the advantages of combined treatment of MTX plus LFN in JIA.

Objectives: To evaluate the safety and effectiveness of the combined therapy of Methotrexate (MTX) and Leflunomide (LFN) in patients with Juvenile Idiopathic Arthritis (JIA) in clinical practice.

Methods: We conducted a retrospective descriptive study of patients with JIA visited in a single Unit of Pediatric Rheumatology who had been treated with the combination of MTX plus LFN. All patients were classified according to the International League of Associations for Rheumatology (ILAR) criteria. Included data were: demographics, JIA subtype, reason for starting combined treatment, time on treatment, withdrawals, causes of discontinuation, efficacy and safety (both assessed at baseline and every 6 months during 2 years of treatment). Safety was evaluated analyzing adverse events (AE) based on clinical and physical findings and laboratory values. Ocular effectiveness was assessed grading uveitis according to the Standardization of Uveitis Nomenclature Working Group (SUN) recommendations. Articular effectiveness was assessed by means of: pediatric core set variables with exception of C-HAQ, Protein-C-reactive, JADAS scores 10, 27 and 71, and applying the criteria of minimal disease activity, 30% improvement, inactivity and remission.

Results: Nineteen patients (16 female, 3 male) were included: 12 oligoarthritis (63%), 4 polyarthritis (21%), 2 psoriatic arthritis (11%) and 1 undifferentiated arthritis (5%). Ages at onset of disease ranged from 1.5 to 19.6 years with a mean age at diagnosis of 5.7 years ± 3.6 years. At diagnosis, 100% of patients were and 100% responded to MTX in monotherapy. 8 children experienced a substantial improvement either articular or ocular. AE were generally mild. LFN plus MTX could be a safe and effective alternative for patients with JIA who do not respond to MTX or LFN in monotherapy.

Conclusion: None declared.

P60
PRes-FINAL-2047: Exploring the effectiveness of stretch and cast treatment of fixed flexion deformity in children with active JIA
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Pediatric Rheumatology 2013, 11(Suppl 2)p60

Introduction: Active JIA of the knee can lead to bony overgrowth and leg length discrepancies in children with JIA. Fixed flexion deformities of the knee result in loss of inner range quadriceps strength, abnormal gait and reduced independent function and participation in sports and activities.

Objectives: Our objective was to review the use of stretch and cast procedures alongside intra-articular steroid injections and IAIs for active JIA of the knee resulting in fixed flexion deformities (FFD) of greater than 15 degrees.

Methods: A retrospective review was undertaken of all patients presenting to Great Ormond Street Hospital NHS Foundation Trust between 2005-2013 with active JIA of the knee resulting in FFD and loss of knee extension range of movement (ROM) greater than -15 degrees and underwent a stretch and cast procedure alongside IAIs for treatment of their disease. ROM was assessed pre and post procedure. Patients received their IAIs under general anaesthetic, and then the physiotherapists carried out a stretch and cast procedure.

The stretch and cast procedure included patella mobilisations, gentle and prolonged knee extension passive stretching, and casting with a fibre-glass cast for 72 hours. All patients then received 2 weeks of intensive physiotherapy strengthening. ROM and inner range quadriceps strength were measured at the end of these 2 weeks post procedure.

Results: 30 patients (9 male, 21 female; 15 Oligo JIA, 10 Poly JIA, 3 EOEJIA) had a FFD of between -15 and -90 degrees (mean -30) extension at the affected knee(s). A total of 33 joints were injected and underwent the stretch and cast procedure plus physiotherapy strengthening. Post intensive rehab the patients all had improved or normal ROM (mean -7 degrees) and improved muscle strength (mean IRQ 8/10 Kendall Scale) in order to maintain this improvement. This was maintained at 4-6 month follow up in 94% of patients. The 2 patients who did not maintain range of movement had poor compliance to their physiotherapy home exercise programme.

Conclusion: ROM improved following procedure in all patients, indicating that stretch and cast treatment is an effective intervention for the management of fixed flexion deformities secondary to active JIA. Ongoing strengthening of inner range quadriceps is vital to maintain this improved range of movement and restoration of function and normal gait.

Disclosure of interest: None declared.

P62
PReS-FINAL-2049: Bone health, muscle strength, activity
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Pediatric Rheumatology 2013, 11(Suppl 2)p62

The aim of the study was to investigate incidence, risk factors and outcome of uveitis in a cohort of Nordic children with JIA followed for at least 7 years in a population-based setting.

Methods: Consecutive cases of JIA from defined geographical areas of Denmark, Finland, Sweden and Norway with disease onset in 1997-2000 were included. The study aimed to be as close to population-based as possible, as centers participated only if they were able to include all children diagnosed with JIA in their catchment area. Clinical and ophthalmologic data were registered at regular follow-up visits for 7-12 years after disease onset.

Results: Of 500 children included at baseline, 440 were followed for at least 7 years and 389 (78%) had available ophthalmologic data. Uveitis developed in 89 (23%) of the 389 children; 59 girls and 30 boys, acute uveitis in 12 and chronic uveitis in 77 children. Fifty percent (6/12) of patients with acute uveitis were HLA-B27 positive. Young age at onset of JIA was a significant predictor of chronic uveitis in girls (p = 0.0001), but not in boys (p = 0.47). Also the presence of anti-nuclear antibodies (ANA Hep-2) (p = 0.003) was a significant predictor in girls (p = 0.003), but not in boys (p = 0.05). Neither female gender nor oligoarticular onset JIA category was significantly associated with uveitis. Chronic uveitis was diagnosed at a median of 0.8 years after onset of disease, and in 88% within the first four years after onset of disease. The longest interval between JIA onset and uveitis development was 8.6 years. Complications occurred in 39 eyes in 22 of the 89 patients with uveitis (25%), glaucoma occurred in 16 eyes and cataract in 14 eyes. At the last visit visual acuity was 0.5 in 10 eyes in 9 patients.

Conclusion: We found high incidence of uveitis among Nordic children with JIA, and the majority develop early after onset of disease. Age at onset of JIA and presence of ANA Hep-2 were associated with development of uveitis in girls, but not in boys. Complications were present seven years after onset of arthritis in 25%, showing that uveitis contributes significantly to morbidity and disability in children with JIA.

Disclosure of interest: None declared.
Introduction: Juvenile idiopathic arthritis (JIA) affects bone health, muscle strength, physical fitness and well-being in children and adolescent. Due to biological medical treatment there is increased outcome of the disease with less flares and arthritis. Impaired bone health, muscle strength and decreased well-being have been reported in this group. There is evidence for intervention studies with cardiovascular fitness, physical fitness and muscle strength exercises for increased outcome of the disease. The aim was to evaluate an exercise programme in children and adolescents before and after 12 weeks with rope-skipping and muscle strength exercises and to evaluate the effect on bone health, muscle strength, physical fitness and well-being.

Objectives: 54 subjects participated, age 9-21 years, randomized into an exercise and a control group.

Methods: A randomized controlled study. DXA, grip-it, myometry, physical fitness and the questnaires CHAQ and CHQ were used. The exercise group performed the exercise programme in 12 weeks and physical activity in leisure time was documented in two week diaries for both groups.

Results: Bone health was within the normal in this group at base line and there were no differences between the exercise and the control group. Bone health, calculated as BMD increased in the exercise group after 12 weeks. Muscles strength showed values within the normal. Muscle weakness found in hip extensors and hip abductors at base line and increased after the training period. Muscle weakness in the hand muscle was shown in > 50% of the participants and there was no change during the study. Muscle strength in quadriceps was within the normal, increase after 12 weeks exercise and was maintained at follow-up. Pain and well-being were reported in the group.

Conclusion: Bone health and muscle strength were within normal range at base line except in hip extensors, hip abductors and in hand grip strength. Muscle strength in knee extensors increased and was maintained at follow-up. Muscle strength training with free weights and rope skipping (100 jumps 3 times/ week in twelve weeks) increase BMD and muscle strength and can be recommended for children and adolescents with JIA. The presence of pain was reported from many children and needs to be addressed in view of pain in itself, and in view of the consequences of pain on well-being in psychosocial terms.

Disclosure of interest: None declared.

P64
PreS-FINAL-2051: The difference of disease’s perception by JIA patients and their parents: analysis of the JAMAR questionnaire
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Pediatric Rheumatology 2013, 11(Suppl 2):P64

Introduction: The JAMAR (Juvenile Arthritis Multidimensional Assessment Report) has been developed to evaluate the perception of the patient and his parents on different items: well-being, pain, functional status, quality of life, disease activity, disease course, side effects of medication, therapeutic compliance and satisfaction with illness outcome.

Objectives: Our aim was to compare disease’s perception by JIA patients and their parents.

Methods: We included 100 consecutive JIA patients-parents pairs; the patients had a median age of 13.1 years and a median age at onset of 7.7 years. The male-female ratio was 1:2.7. The diagnostic distribution of JIA was: 35 enthesitis-related arthritis (35%), 39 oligoarthritis (39%), 14 polyarthritis RF negative (14%), 1 polyarthritis RF positive (1%) 4 systemic (4%). For each patient the JAMAR was filled separately by the child and one parent just before the consultation. We analyzed separately the different components of the JAMAR.

Results: Table 1 shows the results of data analysis for five items. We evaluated the differences between patients and their parents for each of the 5 different scores. About half of the pairs did not show any difference; among the pairs with at least one score >0, from 26% to 40% of them had a difference >1. For these pairs, children reported more often a higher level of pain, disease activity and well-being than their parents, but the reverse was true for health related quality of life.

Conclusion: Our observation suggests that the perception of the disease may differ widely depending if the patient or his parents are asked. Further analysis is needed to elucidate if there is a subgroup of patients for whom the differences are more frequent.

Disclosure of interest: None declared.

P65
PreS-FINAL-2052: Costs of biologics in juvenile idiopathic arthritis: past, present and future
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Pediatric Rheumatology 2013, 11(Suppl 2):P65

Introduction: The JIA (Juvenile Idiopathic Arthritis) is a chronic disease that affects children, and is characterized by inflammation of joints. Biologics are a new class of medications, which are used in the management of JIA, that has become the gold standard. The use of this class of medications has increased in JIA over the last few years. The aim of this study is to assess the impact of the use of biologics in JIA on the healthcare system of primary and secondary care.
Introduction: In the past decade biologics have changed the management of juvenile idiopathic arthritis (JIA). Many studies have evaluated the effectiveness and safety of the available biologics in JIA. Biological therapy used to be reserved for the severely ill JIA patients refractory to conventional therapy. Due to the treatment success of several biologics, more and more patients with JIA are now being treated with these drugs. In additional studies show that some patients may benefit from biologic therapy early in the disease course. However biologics are very expensive compared to conventional treatment. From a social-economic view the additional costs of new interventions should be weighed against their incremental health benefits compared to standard care.

Objectives: We studied data on cost-effectiveness of biologics in JIA and evaluated the existing economic evaluations with implications for future research.

Methods: We searched Medline, Embase, The Cochrane Library and The York Centre for Reviews and Dissemination database for relevant literature.

Results: Current data on costs of biologics in JIA are scarce; five studies describe the costs of this treatment in JIA. Only three of these studies compare the costs with the treatment effect. These studies show that biologics are more costly than other rheumatic drugs but other direct and indirect treatment costs are reduced due to the effectiveness of biologics. Considering the economic pressure on the healthcare system, cost-effectiveness of a treatment is import factor in clinical practice. Unfortunately data on long-term cost-effectiveness of biologics or treatment strategies involving biologics are lacking. Since JIA is a chronic disease emphasis should also be placed on how biologics effect long-term progression of disability and translate this in quality-adjust life-years (QALYs). Cost-utility models compare treatment costs to effectiveness in QALYs and will be of great interest to policymakers.

Conclusion: Biologics are expensive compared to other anti-rheumatic drugs. After evaluating the possible economic models to study drug costs, we suggest that future research should provide health economic evidence from usual practice settings that evaluate the cost-effectiveness of specific clinical targets in individual patients. Next to studying cost-effectiveness of biologics in JIA, also long-term cost-utility should be evaluated. These measurements provide valuable information on the long-term effect of a treatment from a social-economic perspective.


Table 1 (abstract P64)

<table>
<thead>
<tr>
<th>Children (score)</th>
<th>VAS P</th>
<th>VAS DA</th>
<th>VAS WB</th>
<th>JAFS</th>
<th>HRQOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 (0-10)</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
</tr>
<tr>
<td>2 (0-10)</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
</tr>
<tr>
<td>1.5 (0-10)</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
</tr>
<tr>
<td>2 (0-10)</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
<td>0.044</td>
</tr>
</tbody>
</table>

**Introduction:** A role for vitamin D has been hypothesized in generating disease activity for patients with juvenile idiopathic arthritis (JIA). Specific polymorphisms of vitamin D receptor (VDR) gene have recently been associated with different biological response to vitamin D itself.

**Objectives:** To evaluate VDR polymorphisms in patients with JIA in comparison with unrelated healthy controls.

**Methods:** We recruited 63 Italian children, adolescents and young adults with JIA (mean age 16.21 + 7.11 SD yrs, 51 female and 12 males, female/male ratio 4.23 from 1 Unit of Paediatric Rheumatology and 1 Unit of Rheumatology, Transition Clinic. After informed consent, during routine laboratory tests, their genomic DNA was extracted from peripheral blood leukocytes, to analyze VDR polymorphisms by PCR-based sequencing (CDX2 in the promoter region) and PCR-based enzymatic digestions (FokI in exon 2, BsmI and Apal in intron 8, and TaqI in exon 9). An Italian population of 2221 unrelated individuals without JA was used as healthy controls.

**Results:** The distribution of FokI, BsmI, Apal, and TaqI polymorphisms did not show significant differences between children with JIA and controls. Regarding the CDX2 polymorphism, we observed a statistical difference in the distribution of GG and GA genotypes, with the GG genotype more frequent in JIA subjects (Yates-corrected chi-square 6.97; Odds ratio = 2.08; p = 0.008) and the GA genotype in healthy controls (Yates-corrected chi-square 4.04; Odds ratio = 0.55; p = 0.044). Data about AA genotype were not significant due to their very low number (three) within the JIA population. G allele resulted to be more frequent in JIA subjects (Yates-corrected chi-square 6.51; Odds ratio = 1.82; p = 0.011).

**Conclusion:** Pathogenetic mechanisms influencing the predisposition to JIA are poorly elucidated. Our analysis of CDX2 polymorphisms located in the promoter region of the VDR gene has revealed that both GG genotype and G allele are more represented in patients with JIA. By our preliminary data, we can speculate that the G allele decreases VDR transcriptional activity with respect to the A allele, as well as the presence of GG genotype could explain a reduction of VDR activity, with subsequent decreased response to vitamin D and potential immunity deregulation leading to JIA.

**Disclosure of interest:** None declared.

P67

**PRES-FINAL-2054:** Latent tuberculosis infection in patients with juvenile idiopathic arthritis undergoing methotrexate therapy: a longitudinal study with TST and ELISPOT

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**Pediatric Rheumatology 2013, 11(Suppl 2):P67**

**Introduction:** Latent tuberculosis infection (LTBI) has a higher risk of developing the active form in immunosuppressed patients. Controversy exists regarding the accuracy of the tuberculin skin test (TST) and...
Objectives: To contribute to the knowledge about the diagnosis of LTBI and TB disease in patients with juvenile idiopathic arthritis (JIA) treated with methotrexate in a high burden country, evaluating the frequency and evolution before and after its initiation, agreement between TST and ELISPOT and sensitivity and specificity of ELISPOT.

Methods: This is an observational prospective longitudinal study where JIA patients starting methotrexate were evaluated in relation to clinical and epidemiological data, and TST and ELISPOT performed at inclusion and 3 and 12 months later.

Results: There were a total of 24 patients. The prevalence of LTBI at inclusion was 20.8% (5/24 patients). The incidence of LTBI after initiation of immunosuppression was 26.3% (5/19 patients) and the prevalence of LTBI in the study as a whole was 41.6% (10/24 patients). The presence of epidemiological history positive for TB showed a relative risk of 2.0 for the development of LTBI. No patient developed TB disease. Only 2 patients had positive ELISPOT. Its sensitivity was 10%, specificity 92.8% and there was poor agreement between TST and ELISPOT.

Conclusion: We found a high frequency of LTBI in patients with JIA and no superiority of ELISPOT compared to TST in the diagnosis and monitoring. The decision to start treatment for LTBI in immunosuppressed children and adolescents in a high burden country should be based on the results of TST, as the cost of ELISPOT is much higher and the accuracy is not superior to TST.

Disclosure of interest: None declared.

P68
PrEs-FINAL-2055: Is there a necessity for patients with JIA to wear orthopedic insoles?
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Pediatric Rheumatology 2013, 11(Suppl 2):P68

Introduction: It is often discussed whether patients with juvenile idiopathic arthritis (JIA) should wear orthopedic insoles or not. The functions of insoles are to minimize pain or to assist foot deformities. JIA often goes along with foot impairments and exclusion of infiltrating malignant diseases and macrophage activation syndrome were made. The diagnosis was SoJIA with dilatation of coronary arteries. Oral methotrexate of 15 mg/m²/week and pulse steroid of three doses of 30 mg/kg/day with an antiaggregating dose of aspirin were commenced. His fever had subsided and laboratory values began to decline.

Patients have a deviating pressure distribution along the transversal arch with the highest loads under MHS. (Table 1).

Conclusion: The patients included in this study suffer from an active ankle joint arthritis. They have significant higher joint loading under healthy tissue of the foot in comparison to the controls. This might be a reason for prescribing orthopedic insoles during a period of an active arthritis. The lateral shift of the peak pressure distribution within the patients in the transversal arch indicates that it is important to control the foot function and pressure distribution not only in patients with a history of foot impairment. Orthopedic insoles might be a valuable therapeutic treatment to protect healthy tissue during a period of active arthritis.

Disclosure of interest: None declared.

Acknowledgements: The authors want to thank the “Deutsche Kinder-Rheumastiftung” for financial support.

References

Table 1 (abstract P68) shows the difference in peak pressure distribution between patients and controls within the metatarsal-phalangeal-joins 1-5

<table>
<thead>
<tr>
<th></th>
<th>[kpa]</th>
<th>mean±SD</th>
<th>MHS1</th>
<th>MHS2</th>
<th>MHS3</th>
<th>MHS4</th>
<th>MHS5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Left</td>
<td>231.0 ± 130.3</td>
<td>333.2 ± 234.3</td>
<td>293.1 ± 176.3</td>
<td>324.1 ± 220.8</td>
<td>410.3 ± 362.7</td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>Left</td>
<td>136.8 ± 36.6</td>
<td>206.7 ± 63.9</td>
<td>2123 ± 752</td>
<td>165.7 ± 68.1</td>
<td>141.2 ± 103.3</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>Right</td>
<td>257.8 ± 167.6</td>
<td>376.1 ± 324.8</td>
<td>291.4 ± 208.5</td>
<td>281.5 ± 184.8</td>
<td>390.8 ± 376.3</td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>Right</td>
<td>154.0 ± 43.0</td>
<td>216.5 ± 67.6</td>
<td>2118 ± 61.0</td>
<td>163.2 ± 48.3</td>
<td>120.2 ± 77.9</td>
<td></td>
</tr>
</tbody>
</table>

Numbers in bold are statistical significant (p < 0.05, student’s t-test).
Both pain and limited range of motion of the affected joints had ameliorated. Even though, still with high z-scores, coronary dilatation began to regress at his follow-up echocardiographic evaluations.

**Conclusion:** Incomplete and atypical nature of KS at early infancy put with JIA. During therapy with associated arthritis (p = 0.002) and emission level of IL-17+T cells was 2013.

**Discussion of interest:** None declared.

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**P70**

PReS-FINAL-2058: Lipid peroxides, lipophuscin, sulphydryl groups and TOS in children with JIA

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P70

**Introduction:** The etiology of most joints' inflammations is unknown. Arthritis in children can have a diversified cause. Various parameters useful in diagnosis and treatment of different forms of inflammations of the joints are being researched. Reactive oxygen species in large concentrations are toxic and cause, among others, the phenomenon of polyunsaturated fatty acids liperoxidation, which results in the formation of aldehyde compounds. Non enzymatic antioxidants include: lipid peroxides (LHP = LOOH), lipophuscin (LF). An important part of non enzymatic antioxidative defense are sulphydryl groups-SH. Total oxidative status (TOS) is used as an indicator of the overall oxidative potential of cells.

**Objectives:** The aim of the study was to find how the level of the selected oxidative parameters changes in serum in children with inflammation of the joints. The correlation between the selected oxidative parameters and disease's relapses is also studied.

**Methods:** The studied parameters were measured in blood serum of 59 patients with JIA, aged from 2 to 18 years old, hospitalized in the Rheumatology Division of the Department of Pediatrics, Silesian Medical University. The control group consisted of 25 healthy children.

**Results:** See Table 1.

**Conclusion:** The studied parameters of oxidative status differ between children with arthritis and healthy ones. Lipid peroxide levels are dependent on the type of arthritis. The LOOH and lipofuscin concentrations in healthy children as compared with a group of children with JIA differ. Higher values occur in the acute forms of JIA, but the difference is not statistically significant. There is no correlation in the total oxidative status (TOS) and the inflammation's level in the joints.

**Disclosure of interest:** None declared.

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**P71**

PReS-FINAL-2059: Th17 cells highly enriched in peripheral blood in children with HLA B27-associated arthritis and systemic onset juvenile idiopathic arthritis

I Turtsevich
Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russian Federation

**Pediatric Rheumatology** 2013, 11(Suppl 2):P71

**Table 1 (abstract P70)**

<table>
<thead>
<tr>
<th></th>
<th>JIA</th>
<th>Control group</th>
</tr>
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<tbody>
<tr>
<td>SH</td>
<td>246.7±53.81</td>
<td>329.8±24.23</td>
</tr>
<tr>
<td>LF</td>
<td>741.2±208.8</td>
<td>827.5±192.7</td>
</tr>
<tr>
<td>LOOH</td>
<td>49.4±27.14</td>
<td>25.2±18.83</td>
</tr>
<tr>
<td>TOS</td>
<td>56.81±45.01</td>
<td>47.89±24.28</td>
</tr>
</tbody>
</table>

**Introduction:** According to modern concepts of JIA as seen as generalizing term that brings together a heterogeneous group of chronic diseases of joints with different etiology, pathogenesis and immunogenetic origin, different nosology and controversial prognosis. Population of Th17 cells involved in pathogenesis of many autoimmune and chronic diseases due to the ability to destroy extracellular matrix.

**Objectives:** To optimize the diagnosis and treatment of different types of JIA by identifying influence of the main immunological factors of Th17 cells differentiation of lymphocytes.

**Methods:** PB samples were obtained from 100 patients with different subtypes of JIA and 20 PB samples from healthy control. The bases of quantitative evaluation of Th17 cells were taken directly determination of CCR6 and CCR4 in PBMC by flow cytometry. Cytokines, such as IL-1β, IL-6, IL-17A and tnfα were determined in serum samples of the patients by ELISA.

**Results:** Highest level of IL-17-T cells in peripheral blood was determined in children with active HLA B27 associated arthritis (p = 0.002) and systemic onset JIA (p = 0.005). As active oligoarticular and polyarticular subtypes of JIA, it was observed less high level of these cells, if compare with HLA B27+ and systemic onset arthritis. Level of IL-17A IL-1β, IL-6 (in contrast with tnfα level), was increased in patients with active HLA B27+ arthritis, if compare with other subtypes of JIA (p < 0.05). In patients with complete clinical and laboratory remission level of IL-17+T cells was reduced and almost did not differ from the control group. We also found statistically significant correlation between IL-6 level, RO+CCR6+ and the presence of osteoporosis in children with JIA. During therapy with tocilizumab expression of CCR6 and CCR4 on PBMC was decreased in patients with systemic onset JIA.

**Conclusion:** Our data suggest that Th17 cells and their cytokines play a crucial role in pathogenesis of JIA, especially in systemic onset and HLA B27 associated arthritis. Treatment with anti-IL-6 agents (tocilizumab) effectively suppress Th17 differentiation pathway of lymphocytes.

**Disclosure of interest:** None declared.
Table 1(abstract P72)

<table>
<thead>
<tr>
<th>Areas</th>
<th>The main group comprised 30 patients with various LA at the age of 7 to 13 years (in all, 152 events)</th>
<th>The control group of nominally healthy children with no articular pathology comprised 10 persons aged between 8 and 14 years old (in all, 76 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive events</td>
<td>Negative events</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Family</td>
<td>48</td>
<td>31.6%</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>34</td>
<td>22.4%</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>9</td>
<td>5.9%</td>
</tr>
<tr>
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<tr>
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</tbody>
</table>

Table 1(abstract P73)

<table>
<thead>
<tr>
<th>(months ACRpedi)</th>
<th>3 (n = 55)</th>
<th>6 (n = 54)</th>
<th>9 (n = 51)</th>
<th>12 (n = 43)</th>
<th>18 (n = 33)</th>
<th>24 (n = 24)</th>
<th>30 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>51%</td>
<td>13%</td>
<td>2%</td>
<td>2%</td>
<td>0</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>50%</td>
<td>49%</td>
<td>63%</td>
<td>24%</td>
<td>12%</td>
<td>15%</td>
<td>8%</td>
<td>0</td>
</tr>
<tr>
<td>70%</td>
<td>0</td>
<td>24%</td>
<td>55%</td>
<td>44%</td>
<td>24%</td>
<td>17%</td>
<td>11%</td>
</tr>
<tr>
<td>90%</td>
<td>0</td>
<td>0</td>
<td>6%</td>
<td>35%</td>
<td>55%</td>
<td>63%</td>
<td>67%</td>
</tr>
</tbody>
</table>

Objectives: Retrospective evaluation of the ABA therapy results in process of treating children with JIA.

Methods: The analysis includes data of 60 patients with JIA who were getting ABA in 2010 - 2013. The average age of patients is 12.5 years (from 6 to 18 years). 21 (35%) patients suffered from active uveitis (2 patients had one eye affection, 19 had affection of both eyes). 10 (16%) patients were diagnosed as sJIA without current systemic features. Patients received ABA intravenously at a dosage of 10 mg/kg with 2-weeks interval initially (3 infusion) and following every month administration. Efficacy was evaluated in accordance with ACRpedi criteria. Ocular manifestations were evaluated by ophthalmologists.

Results: 43 (72%) patients continue ABA therapy, in 17 cases ABA was cancelled (in 3 cases due to infusion/allergy reactions, in 9 cases due to the inefficacy of application, in 5 cases due to some other reasons). 30% patient (18 cases) failed to comply with the infusion schedule due to organization problems.

The efficacy of ABA according to the ACRpedi criteria is demonstrated in Table 1.

The efficacy of ABA was increased significantly after 12 months of therapy. The regularity of infusions influences the higher effect, thus 70-90% improvement after 12 months were achieved predominantly in patients who had no deviations in infusion regimen (30 vs 4). ABA used as first-line biological agent more often shows 70-90% improvement after 12 months (27 vs 7 antiTNF-failers). Uveitis remission was identified in 53% of cases after 6 months, in 73% of cases - after 12 months, in 69% of cases - after 18 months, in 67% of cases - after 24 four months. 7 patients had adverse events (3 patients have post-infusion reactions, 2 patients (the both with early pauciarticular onset) had uveitis de-novo, 1 patient had body weight gain, 1 patient had verruca vulgaris) but no serious events were observed.

Conclusion: Long-term application of ABA is supposed to be highly efficient for treatment of patients with JIA, including patients with uveitis. The increase of positive effect ABA has continued to increase after 24 month period of therapy. The efficiency of ABA depends on the correct infusion regimen and it is higher in biologics-naive patients. ABA showed a good safety profile in the medium-term period.

Disclosure of interest: None declared.

Introduction: We have developed and implemented rehabilitation complexes. A corrective complex - for disabled patients with severe functional restrictions, causing social constraints. A mobilization complex - for patients with moderate functional restrictions that do not cause social constraints. A health-improving complex - for functionally intact patients with no functional restrictions.

Objectives: to compare the need for such complexes in patients, who were in hospital in 2007, 2008 and 2012.

Methods: Children’s ward patients suffering from various forms of JIA, aged two to eighteen years, who were in the hospital in 2007, 2008 and 2012 and underwent rehabilitation treatment; over 50% of the patients were re-hospitalized within a specified time. We compared the need for conducting different rehabilitation treatment complexes in patients treated in 2007, 2008 and 2012.

Results: See Table 1.

Conclusion: A statistically significant increase was detected in the number of functionally intact patients among the patients undergoing rehabilitation treatment in 2012, compared with those undergoing treatment in 2007, and in 2008, thanks to the practical introduction of rehabilitation agents. The total number of patients in need of rehabilitation treatment remains high.

Disclosure of interest: None declared.

P75
PreS-FINAL-2063: Proposed criteria for activity, damage and impact of juvenile idiopathic arthritis associated uveitis: consensus effort from the multinational interdisciplinary working group for uveitis in childhood (MIWGUC)

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Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC)

1 Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany; 2 Ophthalmology, Muster, Germany; 3 Pediatric Rheumatology,

Table 1(abstract P74)

<table>
<thead>
<tr>
<th>Rehabilitation complexes</th>
<th>2007</th>
<th>2008</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrective</td>
<td>6 (3%)</td>
<td>8 (4%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Mobilization</td>
<td>140 (67%)</td>
<td>133 (65%)</td>
<td>106 (49%)</td>
</tr>
<tr>
<td>Health-improving</td>
<td>65 (30%)</td>
<td>64 (31%)</td>
<td>105 (49%)</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>210</td>
<td>205</td>
<td>215</td>
</tr>
</tbody>
</table>
Introduction: Uveitis is the most common extraarticular manifestation of juvenile idiopathic arthritis (JIA) with an incidence of approx. 10 - 15 per 100,000 children. Uveitis, a potentially blinding disorder, is present in approx 10-18% of JIA patients, with a wide spectrum of presentations. Despite advances in treatment of childhood arthritis there are no definitions for assessment of activity, damage and impact of JIA associated uveitis.

Objectives: The purpose of our efforts was to develop and gain consensus on such definitions as activity and damage.

Methods: At the second consensus meeting of the MIWGUC group, using a Delphi method we developed definitions for activity, damage and impact of disease based on already published outcome measures [1].

Results: The following items were included and listed in Table 1. The items were derived from the previously proposed and already published list of outcome measures[1]. Following items were selected to present activity: anterior chamber cells, flare, visual acuity, synecchiae,macular edema,ocular hypertony, ocular hypertension, CHAQ, number of medication and local eyelids. Following items were selected to present damage: flare, visual acuity, synecchiae,cataract, macular edema, ocular hypertony and hypertyon, glaucoma, disc edema, band keratopahty, epiretinal membranes and overall uveitis disability VAS.

Conclusion: We will validate these proposed definitions prospectively in a JIA associated uveitis cohort. Based on the results, we will weight these measures to develop an overall scoring system.

Disclosure of interest: None declared.

Reference

P76
PReS-FINAL-2064: Effect of Golimumab a new anti-TNF, in patients with the diagnosis of Juvenile idiopathic arthritis
A Kærust, I Feldtavit
Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany
Pediatric Rheumatology 2013, 11(Suppl 2):P76

Introduction: Golimumab is a fully human monoclonal antibody targeting tumor necrosis factor-alpha (TNF-α), which plays an important role in the pathogenesis of juvenile idiopathic arthritis. Golimumab was approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.

Objectives: To assess the effectiveness and safety of Golimumab in juvenile idiopathic arthritis.

Methods: We analysed retrospectively the data of all our patients who have been treated with Golimumab (Simponi®) every 28 days sub cutaneously.

Results: 18 patients with the diagnosis of juvenile idiopathic arthritis (15 with juvenile enthesitis associated arthritis, 2 with juvenile psoriatic arthritis and 1 with juvenile idiopathic polyarticular arthritis), for a mean time of 13.7 months per patient (4-26 months). 16 patients have been treated with other biologic agents before. In 13 patients Golimumab was started because of disease progression, in 3 because of intolerance to other biologic agents and in 2 because they described severe phobia of injections. Mean number of painful, swollen and limited joints were before and at the end of the treatment period after 13.7 months (4.5/2.39, 1.78/0.94, 2.72/2.83). The mean value at baseline after the mean follow up were of the physician global assessment score (2.03/0.84), mean erythrocyte sedimentation rate (8.72 mm/7.41 mm) and mean c-reactive protein (4.36 mg/l/3.97 mg/l). 13 patients developed side effects, one patient developed a severe adverse event (appendicitis with consecutive appendectomy), None of the patients was the drug discontinued because of the side effects.

Conclusion: According to this preliminary study in patients with JIA golimumab seems to be a safe and effective treatment. The data of the prospective study is pending.

Disclosure of interest: None declared.

P77
PReS-FINAL-2065: Oxidative stress is associated to disease activity in a large cohort of JIA at transitional period
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Pediatric Rheumatology 2013, 11(Suppl 2):P77

Introduction: Oxidative damage caused by oxygen free radicals is generally considered a serious mechanism in the pathogenesis of many diseases as cardiovascular diseases, atherosclerosis, and inflammatory rheumatism. Increased oxidative stress has already been described in plasma, saliva and articular fluid of juvenile idiopathic arthritis (JIA) patients. However, most of previous studies did not differentiate ILAR sub-types of JIA and were performed before era of biotherapies.

Objectives: Our aim was to determine characteristics of blood markers of oxidative stress in a large cohort of JIA at transitional period.

Methods: One hundred and ten consecutive JIA fulfilling ILAR criteria, were included. Age, sex, disease duration, medical or surgical treatments and remission status were collected. Following laboratory tests were performed: ESR, CRP systematically and antinuclear antibodies, rheumatoid factors and anti-CCP when required for the JIA diagnosis. Oxidative stress parameters were: AOPP (Advanced Oxidation Protein Products) and thiols proteins. Control group consisted of twenty healthy controls without inflammatory condition.

Results: Among the 110 patients' cohort, there were 25 ERA, 16 persistent oligoarthritis, 19 extensive oligoarthritis, 18 polyarticular RF- and 18 RF- and 14 systemic JIA. Mean age was 21 ± 4 years and mean disease duration was 12.3 ± 3.9 years. Mean global JIA dosage of AOPP was 56.4 ± 47.5 μmol/l and thiols proteins was 473.4 ± 41.6 μmol/l. No differences were detected when comparing JIA to controls for AOPP and thiols (p = 0.4 and p = 0.5, respectively). But, AOPP levels in extensive oligoarthritis sub-group was significantly higher than in controls group (82.6 ± 52.9 vs 46.5 ± 6.5, p = 0.006). Comparison of oxidative stress parameters according to sub-types of JIA showed that extensive oligoarticular sub-groups was associated with higher degree of oxidative stress i.e. higher levels of AOPP compared to ERA and polyarticular JIA and lower levels of thiols proteins compared to ERA.

Thiols proteins levels were strongly associated/correlated with disease activity parameters [remission status (p = 0.008), number of synovitis (p = 0.02), ESP level (p = 0.02) and CRP level (p = 0.0004)].

Conclusion: Oxidative stress, in this large cohort of JIA patients at transitional period, is tightly associated with disease activity. This confirms that, in JIA, inflammation could lead to articular and/or profound organs damages by oxidative stress. An absolute tight control of JIA activity seems to be primordial for the future (cardiovascular, atherosclerosis) health of the JIA patients. Our results highlight the potential particularity of extensive oligoarticular sub-type of JIA concerning the oxidative stress.

Disclosure of interest: None declared.

P78
PReS-FINAL-2066: Use of chiropractic care in danish children with juvenile idiopathic arthritis
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Pediatric Rheumatology 2013, 11(Suppl 2):P78

Introduction: Patients with musculoskeletal symptoms are often seeking chiropractic care. The use of chiropractic care among children with juvenile idiopathic arthritis (JIA) in Denmark is not known.

Objectives: The objective of this study was to describe the use of chiropractic care in a cohort of children with JIA, and to describe a possible association to patient specific characteristics. It was evaluated, if the duration of symptoms before diagnosis was different among children.
who used chiropractic care compared to those who did not. It was evaluated whether the chiropractors played an active role in referral of children to the pediatric rheumatologist.

**Methods:** A questionnaire survey among JIA patients and their parents from H. C. Andersen Children’s Hospital in Odense, Denmark.

**Results:** The study included 94 children and 86 responded (92%). Valid data were obtained in 83 children. Ten children (12%) received chiropractic care before they were diagnosed with JIA. The symptoms leading to chiropractic evaluation were neck pain (5 children, 50%), walking disability (3 children, 33%) and low back pain (1 child, 10%). The mean duration of symptoms before diagnosis was (mean (SD)) 6.7 (4.4) months. In the subgroup of children receiving chiropractic care compared to 8.5 (10.4) in the remaining patients. The difference was statistically not significant (p = 0.34). Four children (5%) were seeking chiropractic care after they were diagnosed with JIA.

**Conclusion:** A total of 1.2% of children with JIA in a Danish population-based cohort were seeking chiropractic care before the diagnosis of JIA. The main symptoms were neck pain and walking disabilities. The use of chiropractic care did not enhance the risk of delayed diagnosis, but the chiropractors were seldom the initiators of a referral. Few patients used chiropractic care after being diagnosed and their main complaint was low back pain.

**Disclosure of interest:** None declared.

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**P81**

PrEs-FINAL-2069: T cells secreting granulocyte-macrophage colony stimulating factor (GM-CSF) within the inflamed joint originate from an “EX-Th17” population

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**Introduction:** Juvenile idiopathic arthritis (JIA) is the most common disease associated with uveitis in childhood. S100 proteins have been proven to be valuable biomarkers in different subtypes of JIA as well as in other (auto)inflammatory or autoimmune diseases.

**Objectives:** This study analyzes the levels of S100 A8/A9 complexes in the sera of children with uveitis of different entities as well as the correlation between S100 A8/A9 levels and clinical course of ocular disease.

**Methods:** Serum samples were collected from patients with juvenile idiopathic arthritis-associated uveitis (JIAU; n = 97), idiopathic anterior uveitis (IAU; n = 26), idiopathic intermediate uveitis (IIU; n = 36), anterior herpes uveitis (n = 3), and healthy controls (n = 10). In 29 patients, aqueous humor was available for analysis. S100 levels were measured by ELISA and were correlated with disease activity as well as other clinical and epidemiological data.

**Results:** When compared to healthy controls, elevated S100 A8/A9 serum levels were found in JIAU, IAU and IIU. Preliminary data show an association between uveitis activity and S100 levels. S100 A8/A9 levels correlated with arthritis activity, but independently also with uveitis activity. S100 levels were also increased in aqueous humor from patients with anterior uveitis.

**Conclusion:** S100 A8/A9 complexes are a useful biomarker in monitoring articular disease in JIA, but could also be valuable for assessing uveitis. Elevated serum S100 levels could also be observed in patients with idiopathic uveitis without associated systemic disease.

**Disclosure of interest:** None declared.

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**Introduction:** The aim of this study was to examine how children/teenagers with JIA - Juvenile Idiopathic Arthritis and its subgroups perceived their HRQOL - Health related quality of Life and to see if there were any correlation between HRQOL, self-rated ability of ADL and the amounts of inflamed joints.

**Objectives:** The subjects were 50 children/teenagers, 8-18 years (mean 13.7), 37 girls and 13 boys. 26/50 with Juvenile Polyarthritis, and 30/50 with Juvenile Idiopathic Arthritis (JIA).

**ADL was measured with CHAQ - Childhood Health Assessment Questionnaire.** The amount of joints was assessed by doctors. The HRQOL-instrument used was Disabkids, both the Generic version and the Arthritis version. The Generic version contains 37 questions and the Arthritis version 15 questions.

**Methods:** ADL was measured with CHAQ - Childhood Health Assessment Questionnaire. In some experiments Th17 cells were purified from healthy mononuclear cells (SFMC) from 17 patients with JIA were stimulated with PMA and ionomycin in the presence of Brefeldin A and analysed for IL-17, GM-CSF and CD161 expression by flow cytometry. In other (auto)inflammatory or autoimmune diseases.

**Results:** Compared to other children with a chronic disease, the HRQOL estimates of the studied group is lower. The study showed a moderate correlation (r = 0.43 - 0.70) between CHAQ and 6 of the subgroups in Disabkids generic and in 1 of 2 subgroups in arthritis - Impact. CHAQ correlated to physical functions but also to mental and social functions. Only a mild correlation was seen between the doctors assessment of active joints (r = 0.31). The participants considered that the questions were important; a mild correlation was seen between the doctors assessment of active joints and the amount of inflamed joints.

**Conclusion:** The conclusion is that Disabkids can be used as a complement to other data collection for children with JIA.

**Disclosure of interest:** None declared.
Introduction: To date there are no head-to-head trials comparing the efficacy of biologic treatments for polyarticular-course JIA (pJIA).

Objectives: To use statistical methods to estimate the relative efficacy of non-responder imputation during blinded, controlled phase, allowing only for the comparison of ADA and TCZ. In the base-case analysis, for a JIA ACR30 placebo response of 31%, TCZ monotherapy had a higher predicted probability of JIA ACR30 (62%), JIA ACR70 (59%) and JIA ACR90 (35%) response than ADA monotherapy (53%, 49%, 44% and 26%, respectively). On MTX background therapy and a JIA ACR30 placebo response of 53%, ADA had a higher expected probability of response at JIA ACR90 (76%), JIA ACR50 (75%), JIA ACR70 (66%) and JIA ACR90 (49%) than TCZ (72%, 70%, 61% and 44%, respectively). In neither monotherapy nor combination therapy did differences between TCZ and ADA reach statistical significance. Differences in the study populations, including previous use of biologics, were explored with sensitivity analysis.

Conclusion: Based on JIA ACR response rates from this analysis, the expected efficacy of ADA vs TCZ appears comparable in pJIA. These data should be interpreted in the context of differences in the duration of the withdrawal phase, which was shorter in the TCZ study (CHERISH) than in the ADA trial and might have resulted in a smaller difference in the number of flares observed between placebo and TCZ. Differences in previous exposure to biologics might also have affected the results.

Disclosure of interest: None declared.

Introduction: Antibodies specific for native human type II collagen (anti-CII) characterize an early inflammatory/destructive phenotype in adults with RA. There are no data presented so far on this antibody and its possible influence on disease course/outcome in children with JIA.

Objectives: We wanted to relate occurrence of anti-CII, IgM-RF, IgA-RF and anti-CCP to assessment of joint damage, outcome and ILAR categories after eight years of disease in children with JIA.

Methods: From the Nordic JIA database 192 patients with available sera were included. Serum samples were collected at a median time of 4 months (IQR 2-7) after disease onset. Patients were followed prospectively for a median of 97 months (IQR 95-105). At the 8-year follow-up visit, data on remission according to the preliminary criteria of C. Wallace et al as well as joint damage according to JADID were collected. Frozen and stored sera were analyzed with enzyme immunoassays for anti-CII, IgM-RF, IgA-RF and anti-CCP. Reference values for adults were used.

Results: Anti-type II collagen antibodies occurred in 3.1% of patients sera, IgM-RF in 3.6%, IgA-RF in 3.1%, anti-CCP in 2.6% of the patients. Occurrence of RF and anti-CCP did to some extent overlap, but rarely with anti-CII. The polyarticular and oligoarticular extended categories were overrepresented in patients with any of the four autoantibodies. All four autoantibodies were significantly associated with joint damage after eight years, but we found no association with ongoing disease activity after eight years.

Conclusion:
- Occurrence of anti-CII did rarely overlap with anti-CCP, IgA-RF and IgM-RF, but all four were associated with joint damage after 8 years of disease in patients with JIA.
- Further studies on anti-CII in patients with JIA are needed.

Disclosure of interest: None declared.
shorter in ERA compared to EOA and JIA RF- subgroups (31 vs. 47 and 49 months respectively, p = 0.03). 80.4% of ERA patients had been started on Methotrexate since diagnosis, with 63% continuing it at the time of the study. 57.14% of those that had stopped were discontinued due to poor treatment response. This was substantially higher than EOA and JIA RF- (36.6% and 25% respectively). 17% of ERA patients had had Sulfasalazine treatment in the past compared to 5.7% and 5.8% of Polyarticular RF (pola) and EOA, respectively. The duration of Sulfasalazine treatment was significantly longer when compared with pola and EOA (36 months vs. 23 and 5 months, respectively, p = 0.034).

At the time of study, a greater proportion of ERA patients were on biological treatment when compared with pola and EOA (38.9% vs. 30.7% and 17.6%, respectively, p < 0.001). 10.8% of ERA were using Infliximab compared with 0% of EOA and 1.9% of pola (p < 0.001). Adalimumab use was more prevalent amongst ERA compared with EOA and pola (13% vs. 0% and 3.6%, respectively, p = 0.008). The time from starting a DMARD to starting a biologic was significantly shorter in ERA compared to EOA (32.8 vs. 72.4 months, p = 0.038).

Conclusion: In this cohort, adolescent patients with ERA were started on Methotrexate later and discontinued earlier than other groups. There was also comparatively greater use of Sulfasalazine in ERA patients. At the time of this study, use of biological agents, especially Infliximab and Adalimumab was significantly higher in ERA. Furthermore, ERA patients were started on biological therapy earlier, once DMARD treatment had commenced; suggesting that escalation of treatment potency was common in addition to switching to alternative biological treatments.

Disclosure of interest: None declared.

**P85**

PRes-FINAL-2073: The usefulness of musculoskeletal ultrasound in monitoring efficacy of intraarticular infliximab therapy in JIA patients

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Pediatric Rheumatology 2013, 11(Supp 2):P85

Introduction: In the past few years the use of musculoskeletal ultrasound (MSUS) in pediatric rheumatology has proven to be better than clinical examination in detecting synovitis. It is a simple, inexpensive, noninvasive and reproducible method that is ideal for pediatric patient. The progress of therapy options has resulted in quick remission, reversal of inflammation and improvement of life quality; especially with introduction of biologic therapy. To our knowledge this a first report in assessing efficacy of IA infliximab in children with juvenile idiopathic arthritis (JIA) by using MSUS.

Objectives: To assess the role of MSUS in follow up of patients with JIA treated with intraarticular (IA) infliximab injections.

Methods: IA infliximab was administered in 6 joints in four patients with JIA. All patients were diagnosed according to ILAR classification criteria and received first and second line therapy (NSAID, DMARD, corticosteroids), with IA corticosteroids on several occasions. None of them fulfilled criteria for biologic therapy but were resistant to DMARD’s. The disease was monitored by monthly clinical assessment (JADAS, signs of swelling, pain assessed by patient/parent (VAS), tenderness at palpation and limitation of motion), laboratory tests (ESR, CRP) and MSUS. The Omeract semiquantitative grades (0-3 grades) for both B-mode and Power-Doppler (PD) evaluation of each joint were added and the sum was defined as the Echographic Score (ES). Before IA infliximab (50 mg per joint) was administered, all patients relapsed according to all the assessed factors.

Results: At the point of IA injections all 6 joints showed grade 3 synovitis in B mode and increased PD signal (3/3). There was also an increase in JADAS, VAS and increased ESR and/or CRP. One month after IA infliximab all patients presented with clinical and gradual US improvement. At the follow-up visit after three months, all of them had grade 1 synovitis without effusion in B mode, PD signal decreased to 0-1/3, and consequently, ES normalized in all joints. There was also clear clinical improvement in JADAS score, local clinical status of injected joints or in ESR and CRP.

Conclusion: It appears that IA infliximab is very powerful and efficacious medication in selected children with therapy-resistant, isolated mono/oligoarticular JIA. Furthermore, MSUS appears be a valid, sensitive-to-change and feasible method for evaluating joint inflammation, and possible outcome measure in children with JIA treated with IA infliximab.

Disclosure of interest: None declared.

**P86**

PRes-FINAL-2074: The role of the probiotic VSL-3 as adjuvant therapy in patients with undifferentiated spondyloarthritides (ERA)

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Pediatric Rheumatology 2013, 11(Supp 2):P86

Introduction: Calprotectin is a neutrophil derived protein that binds calcium and belongs to the S100 family. It can be quantified in feces and has become established as a marker of gut inflammation, where increased levels are a direct result of neutrophil migration into the gut lumen across the inflamed mucosa. Since subclinical gut inflammation is present in the majority of adult and pediatric spondyloarthritides patients, fecal calprotectin (fcal) is emerging as possible noninvasive biomarker. There is strong evidence supporting the role of the VSL-3 probiotic in decreasing fcal, thus promoting and maintaining remission in patients with inflammatory bowel disease (IBD), but very little is known of its potential effects on disease activity in children with undifferentiated spondyloarthritides (ERA).

Objectives: To assess the effect of the VSL-3 probiotic on fcal levels, clinical symptoms and disease activity of children with undifferentiated spondyloarthritides (ERA).

Methods: Sixteen patients diagnosed with ERA, according to the ILAR criteria, were treated with VSL-3, in addition to standard therapy (NSAID’s and DMARD’s). All patients were negative for gastrointestinal (GI) symptoms, and/or poor growth. All four ankylosing spondylitis patients received biologics; two were treated with adalimumab and further two with infliximab. In addition to general clinical data, patients completed the BASFI and BASDAI questioners, ESR and CRP were obtained, and fcal was measured by the Calprest ELISA method (Eurospal Spa, Italy). After VSL-3 was introduced, two follow up visits were scheduled; the first after one month and the second after three months. At the three month visit a second fcal value was obtained, and BASFI and BASDAI were reevaluated.

Results: The baseline mean fcal level was 52.3 mg/kg (normal < 50 mg/kg). Nine patients have completed all scheduled visits to date, and eight out of those nine had markedly decreased fcal levels (mean value 15.6 mg/kg). The BASFI index was decreased in seven patients and the BASDAI index in eight patients. At the follow-up visit, none of the patients were found to have developed GI symptoms or other signs and symptoms suggestive of IBD.

Conclusion: VSL-3 is emerging as a possible potent adjuvant therapy in children and adults with IBD thus encouraging its use in patients with ERA. To our knowledge our study is the first in evaluating the effects of VSL-3, as adjuvant therapy, on disease activity in ERA patients. Preliminary data suggest that the use of VSL-3 can decrease fcal levels, and together with standard therapy can improve clinical symptoms and decrease disease activity in patients with ERA. A larger patient cohort is needed to confirm VSL-3 efficacy in ERA patients.

Disclosure of interest: None declared.

**P87**

PRes-FINAL-2075: Biologic response modifiers: usage and safety profile from a North Indian pediatric rheumatology centre

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Pediatric Rheumatology 2013, 11(Supp 2):P87

Introduction: Biologic Response modifiers (BRMs) are sparingly used in the Indian subcontinent for two main reasons: economic constraints and concern of infections. We have used BRMs since 2006, albeit with stringent screening. There is a dearth of detail re the use and safety of BRMs from this part of the world. This study was undertaken to add to the knowledge about the use of BRMs in children with rheumatic diseases.
Objectives: 1. To study the use of BRMs in a cohort of pediatric rheumatic diseases. 2. To evaluate their safety over a longitudinal follow-up.

Methods: Demographic, clinical, and treatment details along with the screening used and side effects, if any, were retrospectively collected on a predesigned proforma.

Results: Demographics: 105 children (61 boys) were given a BRM (Jan ‘06-May ‘13). Median age at diagnosis of a rheumatic ds. was 9.8 yrs (1.25-16.6 yrs) & median age at BRM commencement was 12 yrs (2.66-18 yrs). Median duration of follow up after commencement of BRM was 29 mths (1-90 mths). Usage/Indications: JIA was the commonest disease where BRM was used in 93 (ERA-44, SIA-29, poly-13, Oligo-5). 79 had SLE; 2 had Kawasaki disease. There were 1 patient each of Takayasu, Sarcoidosis & Overlap syndrome. BRM used: Etanercept was the commonest used in 42 children, Infliximab in 35, Tocilizumab in 34, Rituximab in 8 and Abatacept in 3.69 received one BRM, 16 were given 2 & 1 child received 3 BRMs consecutively.

Reasons: Use of BRMs for each ds: IA:Polyarticular курс не соответствовал Infection to Methylotrexate & Steroids; 43, early hip involvement; 23: Cervical spine ds.; 7; Sarcoiditis unresponsive to NSAIDS; 5; Misfit; 4; Persistent systemic features; 7; Uveitis; 5; HLA-1: secondary amyloidosis. 1; SE. Used in 17: Hepatitis; 5; Hemolytic anemia; 1; Corona vascular arthritis; 1; M. had 2nd Kawasaki disease; 1 had Takayasu. Pre BRM Screening and results: Screen included Mantoux test; Q; Gold; Chest X-ray; USG abdomen; Contrast enhanced CT: Thorax, HIV, HIV, HbsAg & HCV antibodies. Results: All were negative for HIV; HbsAg & HCV antibodies: Chest X-ray normal in 104; 1 had previous endobronchial TB; Mantoux test positive in 4: evaluated confirmed latent TB. BRM commenced after 8 weeks. Follow up: Considering the exorbitant cost and the self-paying nature for a majority of patients, BRMs were used as remission inducing agents. Of a total of 105 children, 93 had JIA: 56 discontinued BRMs of which 34 remained in clinical remission on DMARDs. 20 stopped due to financial constraints, 7 did not respond to the BRM, 5 had a BRM related adverse effect. Safety: There were no serious adverse events. All children were premedicated before infusion & monitored for hemodynamic stability. 5 children had side effects for which BRM had to be stopped (worsening of sarcoid rash in 1, new onset of vesicular rash in 1, persistent neutropenia in 3). 8 children had allergic rhinitis (during Tocilizumab). Dengue fever was diagnosed in 2, Herpes zoster in 2, acute rheumatic fever in 2, acute otitis media in 1, acute parotitis in 1, and varicella in 1 on follow-up. 2 children had a positive Mantoux after 1 yr of Infliximab though did not have any evidence of TB on detailed screening. There was no mortality in the cohort.

Conclusion: BRMs can be safely used as remission inducing agents in a country with a high rate of infectious diseases. Up to 1/3 of cohort remained in clinical remission off BRMs over a median follow up of 29 months. There were no major adverse events.

Disclosure of interest: None declared.
FEV1/FVC% 99.18 ± 12.2, Total Lung Capacity (TLC%) 94.6 ± 14.5, Residual Volume (RV%) 130.5 ± 53.1, DLCO% 93.1 ± 14.2, SNIF 69.6 ± 26.5. Only 3 patients had lung function changes - 2 restrictive and 1 obstructive. In spirometry patterns, no patients had changes in DLCO.

Conclusion: The low prevalence of lung function changes in our cohort is in agreement with the literature. In contrast to studies performed in adult rheumatoid arthritis patients, in children with juvenile idiopathic arthritis impairment of lung function seems to be a rare event. The small sample size, the fact that most of the patients were in remission, as well as the lack of a control group can contribute to the difficulty in interpreting the results.

Prospective followup of this cohort, particularly those with lung function changes, will be paramount.

Disclosure of interest: None declared.

P90
PReS-FINAL-2078: Single nucleotide polymorphisms of toll like receptors 2 and 4 in enthesitis related arthritis and oligo and polyarticular juvenile idiopathic arthritis
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Introduction: Single nucleotide polymorphisms of Toll like receptors modify cellular immune response and induce pro-inflammatory cytokine production and therefore could be associated with enthesis related arthritis (ERA) and/or oligoarticular and polyarticular juvenile idiopathic arthritis (JIA).

Objectives: To determine whether polymorphisms of TLR2 and TLR4 influence susceptibility to ERA or JIA.

Methods: DNA was extracted from blood samples of 19 ERA patients, 10 patients with oligoarticular or polyarticular JIA and 40 healthy controls, all diagnosed according to ILAR criteria. Polymorphisms of the TLR2 (Arg753Gln) and TLR4 (Asp299Gly, Thr399Ile) were determined using real time and multiplex PCR.

Results: All JIA patients were carriers of wild type allele for all three polymorphisms. Regarding Arg753Gln polymorphism of TLR2, only one patient with ERA (5.56%) and 2 healthy controls (5%) were carriers of heterozygous allele. There were no homozygous mutants. All ERA patients had wild type allele for Asp299Gly polymorphism of TLR4. For Thr399Ile polymorphism of TLR4, 21.05% ERA patients were heterozygous (CT variant), and none of the ERA patients was homozygous (TT variant), (CC vs CT variant in ERA OR 3.7500, 95% CI 1.0498-13.3952, p = 0.0419, CC vs TT variant OR 1.0000, 95% CI 0.5600-1.7909, p = 0.9917). In group of healthy controls, TLR4 polymorphisms Asp299Gly and Thr399Ile were in linkage disequilibrium; 2 controls were heterozygous and 6 homozygous variant carriers for both polymorphisms, whereas linkage disequilibrium was not found among patient groups (CC vs CT in controls OR 16.0000, 95% CI 3.5905-71.2994, p = 0.0003, CC vs TT OR 5.3333, 95% CI 2.0099-14.1524, p = 0.0194).

Conclusion: Polymorphisms of TLR2 and TLR4 are not associated with oligoarticular/polyarticular JIA. There was also no evidence that variants of TLR2 was not found among patient groups (CC vs CT variant in ERA OR 0.5, 95% CI 0.1-2.5, p = 0.10). Compared to the control group (method A: 33.4 ± 1.8°C, method B: 23.0 ± 5.0°C, p < .01).

Disclosure of interest: None declared.

P92
PReS-FINAL-2080: Overlap syndrome between primary sclerosing cholangitis and autoimmune hepatitis associated with ulcerative colitis - a case of unusual presentation in a patient with systemic juvenile idiopathic arthritis
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Pediatric Rheumatology 2013, 11(Suppl 2):P92

Introduction: Systemic juvenile idiopathic arthritis (systemic-JIA) is characterized by the presence of arthritis associated with systemic manifestations and an important inflammatory response, being always a clinical diagnosis of exclusion. The association of systemic-JIA with autoimmune diseases is uncommon. The authors found only one description of systemic-JIA associated with autoimmune hepatitis in a child treated with etanercept.

Objectives: Not indicated (case report).

Methods: Not indicated (case report).

Results: Case report: 16-year-old male adolescent, hospitalized for investigation of high fever with two weeks of evolution, accompanied by chest pain, right elbow and knee arthritis, jaundice and generalized pruritus. Laboratory findings: haemoglobin 9.3mg/dL, 582,000 platelets/ul, ESR-107mm/1st hr, C-reactive protein-11.75mg/dL, AST-246U/L, ALT-436U/L, alkaline phoshatase-708U/L, G-GT-702U/L, total/direct bilirubin-2.61/2.57mg/dL. G and A immunoglobulin levels elevation. Screening for infectious, autoimmune and lymphoproliferative etiologies was negative. Abdominal ultrasonography revealed an homogeneous mild...
hepatosplenomegaly, and thoraco-abdominal CT identified small pleural and pericardial effusion. Gathering diagnostic criteria for systemic-JIA he was treated with oral prednisolone, with further progressive and complete clinical remission, keeping, however, persistent amiotransferases levels elevation (AST-265 U/L, ALT-532 U/L) and G-GT (711 U/L) with posterior positivity for ANA (1/640), persisting negative all other autoantibodies. MR-cholangiopancreatography was performed (without changes of intrahepatic or extrahepatic bile ducts), and liver biopsy histology was compatible with primary sclerosing cholangitis (PSC) meeting, however, clinical criteria for autoimmune hepatitis (AIH). Four months after the initial diagnosis, in the context of diarrhea and hematochezia, it was performed a colonooscopy, which revealed mucosal ulcerative colitis (UC), subsequently confirmed by histopathology findings. Presently, the patient is clinically stable on therapy with prednisolone, azathioprine, ursodeoxycholic acid and mesalazine.

Conclusion: The autoimmune liver diseases are responsible for up to 5% of cases of chronic liver disease in children, and includes AIH and PSC. When clinical and/or histological findings suggest both entities being present in the same patient, at diagnosis or during disease’s evolution, is considered the diagnosis of overlap syndrome (OS). The association of UC with PSC is well established in the literature and may occur in up to 80% of patients. Although there are described associations between autoimmune liver diseases and other autoimmune diseases, this is, to our knowledge, the first case reported of systemic-JIA, in association with OS. This association raises important questions regarding the origin and complexity of autoimmune diseases in children, and demonstrates the difficulty in diagnosis and treatment imposed by these diseases.

Disclosure of interest: None declared.

P94 PreS-FINAL-2082: Reliability and responsiveness of the standardized universal pain evaluation tools for rheumatology providers for children and youth (SUPER-KIDZ)

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Pediatric Rheumatology 2013, 11(Suppl 2) P94

Introduction: Pain is the most common symptom in children and youth with juvenile idiopathic arthritis (JIA), however, currently there is no comprehensive validated pain measure for this population. The Standardized Universal Pain Evaluations for Rheumatology Providers for Children and Youth (SUPER-KIDZ) is a new multi-dimensional online pain tool, developed to fill this gap in clinical care.

Objectives: To determine the test-retest reliability and responsiveness of the computerized 20-item version of the SUPER-KIDZ pain tool in children with JIA.

Methods: A single center prospective cohort study of JIA patients aged 8-18 years was performed. The SUPER-KIDZ questionnaire was administered to children expected to have stable pain for test-retest reliability analysis of each item using intra-class correlation coefficients (ICC) and weighted Cohen’s kappa. Responsiveness of each SUPER-KIDZ item to change in pain was evaluated in patients undergoing intra-articular steroid injection(s) who are expected to have improvement in pain. Measures of responsiveness included standardized response mean (SRM), Wilcoxon signed rank test, linear mixed model regression, and receiver operating characteristic (ROC) curve analysis. Internal consistency of the three SUPER-KIDZ subscales (sensory, interference, emotional) was measured using ordinal reliability alpha and item-total correlation.

Results: Fifty-one children were included, of which 40 (78%) were female, and had a median of 3 active joints (1-5) and median physician global assessment of 2.5 cm (1.5-4) on 10 cm visual analog scale. Internal consistency was acceptable (ordinal α = 0.73-0.92) for the sensory, interference, and emotional SUPER-KIDZ subscales. Good test-retest reliability (ICC or weighted kappa ≥0.80) was found for 15 SUPER-KIDZ items in at least one analysis. Reliability was strongest for the items on pain intensity, pain frequency, pain duration and physical function, and weakest for questions related to sleep, having fun, catastrophizing, and feeling angry. At 2 weeks post-injection, 16 items were responsive to change in pain (SRM = 0.66-0.82, significant Wilcoxon signed rank and/or linear mixed model regression), ROC curve analysis of 9 items gave an area under the curve of ≥0.70, adequately distinguishing between improved and unimproved subjects. The questions less responsive to change in pain were those related to fatigue frequency and emotional function (feeling angry, cheerful, worried).

Conclusion: The majority of items of the new online SUPER-KIDZ tool have excellent test-retest reliability and responsiveness properties. The questions about fatigue and emotional function are less responsive to change after a joint injection procedure and could be tested after a cognitive intervention. If validity is demonstrated, this measure could be implemented as a standardized comprehensive pain tool for JIA patients, thereby fulfilling a longstanding gap in the care of patients with JIA.

Disclosure of interest: None declared.
**Table 1 (abstract P95)**

<table>
<thead>
<tr>
<th>Period of Study</th>
<th>Study Center</th>
<th>Malignant cases with MS symptoms/total patients</th>
<th>%</th>
<th>Sex</th>
<th>Mean age at diagnosis (years)</th>
<th>Mean delay to diagnosis (months)</th>
<th>Most common age group (years)</th>
<th>Most commonly involved Joints</th>
<th>Other Manifestations</th>
<th>Laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I) 1981-1995</td>
<td>Children’s Hematology/Oncology Research Center</td>
<td>54/1528</td>
<td>3.5</td>
<td>M62 F38</td>
<td>7.3</td>
<td>NA</td>
<td>6-7</td>
<td>Knee 68% Ankle 52%</td>
<td>Organomegaly 83% Lymphadenopathy 76%</td>
<td>Anemia 59% Leukopenia 18% Leukocytosis 14% Thrombocytopenia 55% Raised ESR 37%</td>
</tr>
<tr>
<td>(II) 1981-2003</td>
<td></td>
<td>76/1832</td>
<td>4.1</td>
<td>M56.6 F46.4</td>
<td>6.97</td>
<td>NA</td>
<td>5-7</td>
<td>Knee 55% Ankle 48%</td>
<td>NA</td>
<td>Anemia 88% Leukopenia 34% Leukocytosis 14% Thrombocytopenia 72% Raised ESR 58% Raised LDH 34%</td>
</tr>
<tr>
<td>(III) 1996-2006</td>
<td>Pediatric Rheumatology Center</td>
<td>38/222</td>
<td>5.2</td>
<td>M52 F48</td>
<td>5.6</td>
<td>2.7</td>
<td>5-7</td>
<td>Hip 37% Knee 34%</td>
<td>Fever 73% Weight loss 60% Organomegaly 60%</td>
<td>Anemia 79% Leukopenia 45% Leukocytosis 16% Thrombocytopenia 63%</td>
</tr>
<tr>
<td>(IV) 2006-2012</td>
<td></td>
<td>11/207</td>
<td>5.3</td>
<td>M73 F27</td>
<td>6.6</td>
<td>3</td>
<td>6-7</td>
<td>Knee 45% Hip 27%</td>
<td>Fever 45% Organomegaly 27%</td>
<td>Anemia 27% Leukopenia 27% Leukocytosis 63% Thrombocytopenia 45%</td>
</tr>
</tbody>
</table>
Introduction: In patients with juvenile idiopathic arthritis (JIA) high levels of IL-6 are present in the serum and synovial fluid (SF). IL-6 signaling plays an important pro-inflammatory role but is restricted by regulatory mechanisms such as reducing the cell surface availability of the signal-transducing chain of the IL-6 receptor (gp130).

Objectives: The aim of this study was to determine whether the inflammatory environment in the arthritic joint has an impact on monocytic gp130 surface expression and the extent to which regulatory processes in the SF can be transferred to an in vitro model.

Methods: Flow cytometry and live-cell imaging were used to measure the cell surface expression and internalization of gp130. STAT3 phosphorylation was monitored by flow cytometry and western blotting.

Results: The level of cell surface gp130 expression on SF monocytes was reduced compared to peripheral blood (PB) monocytes from patients with JIA. This reduction could be reproduced by stimulating PB monocytes from healthy donors with SF and was dependent on p38 MAPK. The induction of p38 by IL-1β in PB monocytes interfered with IL-6 signaling due to the reduced cell surface expression of gp130.

Conclusion: The results suggest that p38-mediated pro-inflammatory stimuli induce the downregulation of gp130 on monocytes and thus restrict gp130-mediated signal transduction. This regulatory mechanism could be relevant in the inflamed joints of patients with JIA.

Disclosure of interest: None declared.

Introduction: Anti-TNFα treatment has become an important part of our systemic treatment in chronic inflammatory arthritis. Local application to the joints produces transient clinical improvement since the drug quickly leaves the joint. 

Objectives: We aimed to develop a sustained release system for an anti-TNFα drug in treatment of chronic inflammatory arthritis. A novel form of intra-articularly injectable etanercept (ETN) loaded poly(ε-caprolactone) (PCL) or methoxy poly(ethylene glycol)-poly(ε-caprolactone)-methoxy poly (ethylene glycol) (MPEG-PCL-MPEG) microspheres (patent pending) were prepared to provide long term controlled release of ETN with a sustained anti-inflammatory effect as a local treatment approach.

Methods: Size, surface morphology, encapsulation efficiency, and in vitro release profiles of γ-sterilized microspheres loaded with ETN were determined. Treatment efficiencies of free and microsphere loaded ETN were evaluated by determining changes in cell number and viability of fibroblast-like synoviocytes (FLS), in protein levels of pro-inflammatory cytokines (TNFα, IL-6, IFNγ, IL-17) and MMPs (MMP-3 and MMP-13) and in mRNA expressions of TNFα, IL-6, MMP-3 and MMP-13. 

Results: Microspheres possessed a rough surface and had a mean particle size around 5 μm. MPEG-PCL-MPEG microspheres had higher drug encapsulation efficiency than PCL microspheres. Total amounts of biologically active ETN released from MPEG-PCL-MPEG microspheres were significantly higher than that from PCL microspheres at each time point during the four weeks study period. FLS viability significantly decreased in the free drug group at first week whereas no significant decrease was observed in microsphere groups. ETN loaded microspheres significantly decreased the levels of pro-inflammatory cytokines TNFα, IL-6, IFNγ, IL-17 and MMPs in FLS. However, there were no significant variations in the gene expressions of pro-inflammatory cytokines and MMPs among groups.

Conclusion: ETN loaded microspheres provide a sustained release, which resulted with a significant decrease in pro-inflammatory cytokines and MMPs levels. This study showed that MPEG-PCL-MPEG and PCL microspheres are promising and safe systems for an effective local treatment approach in chronic inflammatory arthritids.

Disclosure of interest: None declared.
Introduction: Severe adverse events have been described in children affected by Juvenile Idiopathic Arthritis (JIA) and Inflammatory Bowel Disease (IBD) treated with anti-TNF drugs.

Objectives: To define the risk of severe adverse events in patients with JIA and IBD treated with anti-TNF drugs.

Methods: This is a retrospective cohort study. All patients with JIA and IBD attending the "IRCCS Burlo Garofolo" of Trieste from 2000 to 2012 were enrolled. They were divided into 2 groups on the basis of the presence or absence of anti-TNF exposure.

Severe adverse events were considered the followings: a) infections needing anti-TNF permanent suspension and/or hospitalization; b) autoimmune diseases with present or potential organ damage, except for hepatitis and cholangitis during IBD; c) anaphylaxis; d) malignancies. Univariate analysis testing the effect of anti-TNF exposure on adverse events appearance was realized.

Results: 323 patients were enrolled (159 with JIA and 164 with IBD). 120 patients were exposed to anti-TNF and 203 were not. Infliximab was the most used anti-TNF (73 patients), followed by etanercept (56 patients) and adalimumab (21 patients). Mean total duration of anti-TNF therapy was 26 months (min.1, max.127). The two cohorts were comparable for sex, age, diagnosis and other therapies assumed.

Severe adverse events occurred in 38 anti-TNF-exposed patients (31.7%) and 22 of the not-exposed group (10.8%), with a statistically significant difference (p = 0.000) and a relative risk (RR) of 2.9 (95% confidence interval, CI. 1.8 to 4.7). Anaphylaxis occurred in 11 patients (9.2% of the anti-TNF-treated), all assuming infliximab; in the not-treated group none presented reactions (p = 0.000). Infection rate was 6.7% in the anti-TNF-treated group (8 patients) and 3.5% in the not-exposed group (7 patients) (p = 0.273, RR = 1.9, 95% CI: 0.7 to 5.2). Incidence rate of autoimmune diseases in patients treated with anti-TNF was 18.3% (22 patients) vs 7.9% in not-exposed cohort (p = 0.007, RR = 2.3, 95% CI: 1.3 to 4.2). Uveitis was the most frequent autoimmune disease. Both uveitis and lupus-like syndrome were more likely in the subgroup of patients treated with anti-TNF (p = 0.005, RR = 2.5, 95% CI: 1.1 to 6.0 for uveitis and p = 0.050 for lupus-like syndrome). No patients developed malignancies. The outcome of severe anti-TNF drug reactions was as follows: 2 out of 3 uveitis, all anaphylactic reactions, severe infections and lupus-like syndrome healed without organ damage, whereas the other autoimmune complications have been still treating with a good clinical outcome.

Conclusion: The patients with JIA or IBD treated with anti-TNF have a higher risk of severe adverse events, like anaphylaxis and autoimmune diseases (in particular uveitis and lupus-like syndrome), whereas it seems that this risk does not exist for severe infections. No malignancies were observed during follow up.

Our data suggest that, although the risk of severe adverse reactions to anti-TNF therapy is significant, the occurrence of a permanent damage results very low.

Disclosure of interest: None declared.

P102
PReS-FINAL-2090: Efficacy of anti-TNF drugs from the perspective of growth velocity: a single center experience
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Pediatric Rheumatology 2013, 11(Suppl 2):P102

Introduction: Growth is a sensitive marker of well-being in children. In patients with juvenile idiopathic arthritis (JIA) both, ongoing inflammation and corticosteroid treatment, may affect linear growth adversely, potentially leading to irreversible growth retardation. Biologic treatment of JIA may have the potential to enable normal growth in children with JIA.

Objectives: To retrospectively evaluate the safety, clinical efficacy, of anti-TNF drugs from the perspective of growth velocity: a single center experience.

Methods: Inclusion criteria:
- - DMARDS-resistant polyarticular course of JIA receiving anti-TNF treatment at least one year.
- - Evaluation of response every 3 months by Pediatric American College of Rheumatology Response Criteria (ACR Paed).

Exclusion criteria:
- - no growth expected boys: Tanner staging sexual maturity score V plus age 17 before starting anti-TNF treatment
- - no growth expected girls: menarche at least two years before starting anti-TNF treatment or menarche at least a year before starting treatment plus Tanner staging sexual maturity score IV

Growht velocity was defined by change of height in standard deviation (SD) score. To calculate exact SD score software Rust CZ 2.0, based on
anthropometric data of Czech paediatric population - the nearest one to Slovak paediatric population, was used. Catch-up was defined as positive growth velocity.

Results: The group of 20 patients with expected growth (boys vs. girls: 10 vs. 10; etanercept vs. adalimumab: 16 vs. 4) was assessed. The mean age at anti-TNF treatment initiation was 12.03 years (SD ± 4.44). Median duration of disease was 3.25 years (range 0.89-10.23), 15 patients received corticosteroids in mean dose 0.273 mg/kg/day. All patients were identified as "responders" (ACR Paed 30) at 3 months. One patient was a ...secondary non-responder" at 6 months, but completed 12 months of treatment. The daily dose of corticosteroids at 12 months was significantly reduced to 0.07 mg/kg/day (p < 0.001) and could be stopped in 10 of 15 patients. Growth catch-up was observed in 16 of 20 patients with median growth velocity being 0.325 (range -0.2 to 0.94). Two patients did not show growth during the first year of treatment.

Conclusion: Anti-TNF treatment of JIA is highly effective and has a rapid corticosteroid-sparing effect in DMARDs-resistant JIA with polyarticular course. The clinical response is accompanied by an increase in growth rate (catch-up) in most cases.

Disclosure of interest: None declared.

### P103

**PReS-FINAL-2091: Extra-articular calcification after intra-articular corticosteroid injection**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P103

**Introduction:** Intra-articular corticosteroid injection is a well established therapeutic option for treatment of juvenile idiopathic arthritis (JIA). Subcutaneous atrophy and depigmentation are well recognised adverse effects. Peri-articular calcification has been reported in radiological studies and the majority was asymptomatic.

**Objectives:** Two cases with pain and thickness around joints due to extra-articular calcification are reported in order to increase the awareness of this side effect.

**Methods:** Case report.

**Results:** Two adolescent girls with polyarticular JIA reported pain and swelling around the metacarpophalangeal (MCP) and interphalangeal (IP) joints without symptoms of arthritis in other joints. Both girls were treated with methotrexate and anti-TNF-alpha agents for years. Several flares of arthritis had been seen in both small and large joints. No extra-articular symptoms were reported. Both patients had been treated by several intra-articular corticosteroids injections with triamcinolone hexacetonide including the MCP and IP joints. No adverse effects had been noticed.

**Conclusion:** Intra-articular injection in JIA is a safe and rapidly effective treatment for synovitis. Extra-articular calcification, clinically mimicking arthritis, is reported as an adverse event to corticosteroid injection. Risk of extra-articular side effects is probably higher in small joints.

**Disclosure of interest:** None declared.

### P104

**PReS-FINAL-2092: Bone marrow cells (BMC) added to platelet-rich plasma (PRP) for treatment of bone degenerative processes in JIA patients: follow-up of 2 cases**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P104

**Introduction:** In Regenerative Medicine one or more regenerative factors can be applied inside a cartilaginous or bone defect to obtain a more rapid and complete healing. Bone Marrow Cells (BMC) added to Platelet-Rich Plasma (PRP) contain stromal cells which can differentiate in osteoclasts and osteoblasts and can be able to form osteogenic tissue and to repair bone defects secondary to degenerative processes.

**Objectives:** We report 2 cases in which we implanted BMC plus PRP in the osteonecrotic region with a clinical and imaging follow-up.

**Methods:** The first case is a 17-year old boy, followed at our Department, affected by JIA since he was 2 years old. He presented a systemic form, evolved into a polyarticular form, treated with steroids and immunosuppressor drugs. The patient had a good response to treatment with Enbrel, which he is still taking. In January 2009, he presented right hip pain and functional limitation. In July 2009 he underwent MRI of the hip joints which showed osteonecrosis in chondral/subchondral regions at the superior-external convexity of the right femoral head. We recommended deambulation with crutches and no weight bearing. Because of the persistence of joint symptoms, in July 2010 we implanted BMC plus PRP in the osteonecrotic region with improvement of pain and mobilization. In October 2010, he presented left hip pain. MRI showed focal osteonecrosis in subchondral region of left femoral head convexity. For this reason, we made a second BMC plus PRP implantation in the left hip. The MRI, made on January 2012, showed any changes concerning the morphology of femoral heads and subchondral erosions. The last MRI, made on December 2012 showed no changing of lesions and a mild improvement of right hip. Our patient autonomous walks, without joint pain and with improved hip movements, since January 2011; he keeps on Enbrel and nsoids. The second case is a 20-year and 4 month old girl with extended oligoarticular JIA diagnosed when she was 2 years old. On July 2012 after an injury, a flare occurred in the left knee. MRI, made on October 2012 showed intra-articular effusion with diffuse synovial thickening, small bone subchondral erosions of medial femoral condyle. She underwent a surgical procedure where we implanted BMC plus PRP on January 2013 which resulted in improvements of mobility and reduction of pain.

**Results:** All two patients had an improvement of their mobility and pain reduction with no progression of articular damages on MRI imaging.

**Conclusion:** To the best of our knowledge, there are no literature data on the use of BMC plus PRP in pediatric patients affected by JIA. Considering the obvious limitations of our case reports, we observed a good short-term outcome. Therefore, follow-up is essential to check if BMC plus PRP implantation represents only a palliative care to delay surgical treatment or if it is a valid alternative to traditional orthopedic surgery.

**Disclosure of interest:** None declared.

**References**


### P105

**PReS-FINAL-2093: Can clinical response within 12 weeks in JIA-entanercept receivers predict the future clinical remission?**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P105

**Introduction:** Induction of inactive disease (ID) in Juvenile Idiopathic Arthritis (JIA) is the main target of all current regimes, as it will maintain physical ability and hinder disease associated-damage. Early predictive markers for the future achievement of ID in patients under expensive therapies are therefore urgently needed in the era of financial recession. Our previous published experience reported that ≥ 50% of the JIA patients achieved Clinical Remission (CR) following ≥12-month (CR12) Etanercept (ETN) administration.

**Objectives:** To assess the early ID following 12 weeks-ETN treatment (eID) and explore the eID's prognostic value for the CR12.

**Methods:** JIA patients treated with ETN for ≥12 months during the last decade were enrolled in the study. Baseline, 12 week and 12 month disease assessments were built on: a) the Juvenile Arthritis Disease Activity Score (JADAS) and b) the fulfillment of Minimal Disease Activity (MDA) and...
Inactive Disease (ID) definitions, as well as CR according to Wallace’s criteria.

**Results:** 52 JIA patients (F=40) with a median age of 8.8 years at first ETN dose, mainly with a polyarticular course (47) and a median disease duration of 4.04 years were studied. etID was achieved in 26/52 (50%) of the patients and CR12 in 28/52 (53.84%). The following factors were found to be independent of etID: disease duration (p = 0.23), JIA classification and course (p = 0.51, p = 0.58, respectively), age at first ETN dose (p = 0.26), presence of ANA or RF (p = 0.43, p = 0.37, respectively) and JADAS at baseline (p = 0.12). Interestingly, the 3 levels of disease activity (persistent activity, MDA and ID) 3 months post-treatment were associated with the 12 month post-treatment JADAS and CR (p = 0.001 and p = 0.001, respectively).

**Conclusion:** etID achieved Inactive Disease in 50% of the patients within a 12-week administration and CR in the 54% of all patients after 12 months of therapy. These findings concord with recent publications. However, neither demographic nor JIA characteristics were found to be predictors of etID. Finally, the beneficial 3 month impact of ETN was evidenced by its association with CR12. The disease regression proves the drug’s early efficacy in JIA patients and supports the clinician’s management decision regarding the application of expensive medication in the era of financial recession.


**P106**

**PReS-FINAL-2094: Evaluation of the benefits of sequential addition of leflunomide in patients with polyarticular course juvenile idiopathic arthritis failing standard dose methotrexate**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P106**

**Introduction:** Methotrexate (MTX), the disease modifying antirheumatic drug (DMARD) of first choice in juvenile idiopathic arthritis (JIA), is not effective in 45-50% of patients with polyarticular course JIA. In developed countries, when MTX fails, the next step is to start biologicals. In resource limited settings this step is constrained by prohibitive cost and children in non-developed countries, when MTX fails, the next step is to start biologicals. In resource limited settings this step is constrained by prohibitive cost and children failing MTX run the risk of poor disease control or steroid overdose. There is paucity of data on use of other DMARDs or their combinations in such children. MTX and leflunomide (LEF) are known to have differing and complementary actions in modifying the immune response and this combination has been studied in adults. Their combined cost is a fraction of the cost of biologicals.

**Objectives:** To evaluate the benefits of addition of LEF in children with polyarticular course JIA, non-responsive to standard dose parental MTX.

**Methods:** In an observational study, 32 children with polyarticular course JIA (JIA defined by modified ILAR criteria) failing standard dose MTX (up to 15 mg/m²/week sc for at least 3 and up to 6 months) received additional LEF (dosage by body weight). Permitted concomitant drugs included pulse steroids for flares and/or low bridging dose of prednisolone, intra-articular steroids and non-steroidal anti-inflammatory drugs. No other DMARDs were or had been used before enrolment. Patients were assessed once every 8-12 weeks. Parameters recorded at each visit included physician global assessment of disease activity, parent/patient assessment of overall well-being, functional ability, number of joints with active arthritis, number of joints with limited range of motion and laboratory parameters, viz., hemogram, ESR and liver enzymes. The primary efficacy outcome was the ACR Pedi 30 criteria. At the end of follow up, Wallace’s criteria were used to determine the percentage of children achieving remission.

**Results:** 25 of the 32 children who followed up for at least 3 months were analysed. The mean follow up duration was 1.61 years (range:0.29 to 3.0 years). At 3 months, 68% of the patients met the ACR Pedi 30 response. 18 of the 21 children (85.7%) showed an ACR Pedi 30 response at 6 months. At 1 year, the percentage of ACR Pedi 30 response was 88.8% with good response rates seen using the ACR Pedi 50 (83.3%), ACR Pedi 70 (61.1%) and ACR Pedi 90 (50%) criteria. Of the 18 children who followed up till the end of the study, 12 (66.6%) met the ACR Pedi 30 criteria and 9(50%) were in clinical remission on medications (off steroids). Adverse effects were observed in 2 children (gastritis and elevated liver enzymes in one each). One child had macrophage activation syndrome temporarily related to the introduction of LEF but it is difficult to comment on a causal relationship. Only 2 children among those failing the combination could afford biologicals, thus highlighting the need for such studies. Of the 7 children who were excluded from analysis,3 had developed hepatitis A and 4 had irrelavant visits.

**Conclusion:** Our findings support the further study of the role of this combination in the management of polyarticular course JIA refractory to standard dose MTX, especially in resource challenged settings. The open observational nature of the study is its limitation.

**Disclosure of interest:** None declared.

**P107**

**PReS-FINAL-2095: Older age predicts poor response to 6-months methotrexate therapy in a juvenile idiopathic arthritis cohort of patients**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P107**

**Introduction:** The identification of predictive factors of poor response to methotrexate (MTX) in juvenile idiopathic arthritis (JIA) patients could contribute to optimize the treatment strategy, namely by the earlier introduction of biological treatments.

**Objectives:** To identify baseline clinical or laboratory predictive factors of MTX poor response at 6 months in patients with JIA.

**Methods:** In a cohort of 141 JIA patients registered in Reuma.pt (the Portuguese Register of Rheumatic Diseases) we selected patients diagnosed after 2000 and that were treated at least for 6 months with MTX (at least 10 mg/m²). Univariate and multivariate logistic analyses were used to identify the predictors for non-response to MTX treatment during the first 6 months of treatment. Non-response to MTX was defined according the American College of Rheumatology pediatric 70 (ACR-ped 70) criteria. Concomitant treatment with nsaids and corticosteroids up to 10 mg was allowed for all treatment groups. For this analysis we included: sex, age, age at disease onset, body surface, JIA subtype, disease duration, rheumatoid factor (RF), ANA, HLA-B27, uveitis, age at MTX onset, MTX dosage, disease duration until the start of MTX, baseline physician and patient/parents VAS, baseline active and limited joints and ESR.

**Results:** From the 58 patients identified, 23 were excluded (2 started biological therapy before 6 months, 3 were on concomitant DMARD’s, 12 had insufficient data, 1 developed criteria for systemic lupus erythematosus, 3 had interrupted MTX and 2 were lost for follow-up). From our population 43% have achieved ACR-ped 70 response and the remaining 57% did not reach this response criterion. The age at MTX onset (p = 0.03; responders 6.25 ± 5.5, non-responders 9.67 ± 1.53) and body surface (p = 0.045; responders 0.92 ± 0.36; non-responders 1.3 ± 0.26) were predictors of ACR-ped 70 response. Gender, MTX dosage, JIA subtype and the other covariates described above did not interfere on patients’ response to MTX. We studied the association of the 2 significant predictors (age at MTX onset and body surface) with response in a multivariate model, but they behave as collinear variables, loosing significance by increasing the standard error. Thus we kept in the model age at MTX onset adjusted to the potential confounders gender, JIA subtype and disease duration until start MTX. Age at MTX onset has remained an independent significant predictor of ACR response (p = 0.037, OR 0.777).

**Conclusion:** MTX response was not dependent on subtype, gender and dosage. Older age at MTX onset was correlated with poorer response to a 6-month MTX course, adjusted to gender and subtype.

**Disclosure of interest:** None declared.
Introduction: TNF-α is involved in regulation of herpes virus replication and dissemination, and varicella, herpes zoster and herpes labialis have been observed as adverse events during clinical trials with and in national registries for the use of etanercept in JIA, in some cases resulting in serious adverse events (sae).

Objectives: The aim of this study was to obtain incidence data of primary varicella, herpes zoster and herpes labialis episodes per patient-years of follow-up (under specific treatment).

Results: Mean treatment exposure was 2.17±1.57 years for etanercept/MTX alone. There were 146 etanercept/MTX episodes in 15 patients (male = 9, female = 21) were included in the study. Juvenile idiopathic arthritis (JIA) causes pain that may lead to posture and movement modifications and arouses muscular imbalance and avoidance harm to joints and some structural changes in joints.

Objective: To examine gait in children with joint involvement in knee who suffered from juvenile idiopathic arthritis (JIA) with video-based observation gait analysis.

Methods: Thirty patients (male = 9, female = 21) were included in the study. Kinematic and time distance gait parameters were measured using a 10-meter walkway with separated 4 cm stripes in white and black color and a video camera. Sagittal plane views of cases (right and left, two views) and the foreground and background views of walking (two views), a total of 4 views were recorded. After observing views in the normal speed, views were observed by using slowed down frame-by-frame viewing and the stop function. Time distance parameters and motion deviations in stance phase of gait were examined.

Results: The mean age was 9.63 ± 2.76 years (range 2-18 years). The mean disease duration was 4.41 ± 2.16 years (range 1-9 years). Patient population consisted of 11 patients with robotic factor (+) polyarticular arthritis, 4 patients with polyarticular arthritis (-) polyarticular arthritis, 12 patients with oligoarticular arthritis, and 3 patients psoriatic arthritis subtype. The mean of walking speed, step length, double step length and cadence were 0.51 m/s, 0.49 ± 0.07 m, 0.99 ± 0.14 m and 101 ± 25.33 steps/min respectively. The most noticeable changes in range of motion was increase of hip internal rotation (76.7%) and knee flexion (80%). Also, genu valgus incidence was 40%, genu varum was 20% and cavus was 36.7%.

Conclusion: Gait is a parameter that should be considered in children with JIA. This study reported that the time-distance variables of children with JIA were decreased according to healthy peers in the literature. In the same time, we observed some gait deviations during the stance phase in lower extremity in children with JIA. These deviations are moderate or severe increase of hip adduction, hip internal rotation and knee flexion. Also we found genu valgus and pes valgus in static posture. We have identified these problems may relate to response to pain, avoidance harm to joints and some structural changes in joints.

Disclosure of interest: None declared.
remission (41.4%), lack of efficacy (31%), and side effects (25.3%). The results of assessment of disease state through formal definitions in 106 children of the 168 children in Group 2 who had already undergone the cross-sectional evaluation were the following: ID 44.3%, MDA 76.4%, PASS 75.2%, CASS 68.9%. The percentages of patients who reached the same disease states assessed through JADAS cutoffs were: ID 41.5%, MDA 50.9%, PASS 61.3%, CASS 56.6%. Serious adverse events were seen in 8 of the 313 patients and included inflammatory bowel disease (3 pts), tuberculosis (1 pt), CMV hepatitis (1 pt), varicella complicated by bronchopneumonia (1 pt), bladder carcinoma (1 pt); 1 patient died of septicaemic sepsis.

Conclusion: A substantial proportion of children currently receiving ETN were in the states of ID or MDA, or were satisfied with treatment outcome. The percentage of patients with ID in the cross-sectional cohort was comparable to the percentage of patients who were discontinued from ETN for disease remission in the retrospective cohort. Serious adverse events were uncommon.

Disclosure of interest: None declared.

P111
PReS-FINAL-2099: Assessing the standards of oral health in children and adolescents with juvenile idiopathic arthritis
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Pediatric Rheumatology 2013, 11(Suppl 2):P111

Introduction: Research has shown that Juvenile Idiopathic Arthritis (JIA) has an adverse effect on oral health. Patients with JIA have poor oral hygiene and higher levels of dental decay compared to healthy individuals [1]. The effect of JIA on manual dexterity and temporomandibular joint involvement can affect the patient’s ability to perform good oral hygiene. Recent research has shown that other rheumatic disorders have a similar pathogenesis to periodontal disease. Oral health education is not routinely provided in the management of JIA. Good oral health can be achieved by following oral hygiene guidance, utilising dental health services and accessing dental interventions. Dental interventions which significantly reduce dental carries include fluoride varnish and fissure sealant; they are available to all children on the NHS.

Objectives: The aim of the project was to assess the standards of oral health and hygiene in patients with JIA. To assess whether oral health education should be incorporated into the management of JIA.

Methods: Patients diagnosed with JIA (aged 18 and under) were asked to complete an oral health questionnaire in rheumatology outpatient clinics. 97 questionnaires were completed. Data was analysed using Excel.

Results: The age range was 18 months to 17 years of age; the average age was 10.3 years. 39 children have had fillings and 15 children have had teeth removed due to dental decay. A large proportion of the group were not following the recommended oral hygiene guidance. Uptake of dental interventions was low; only 14 children had fluoride varnish applied to their teeth and only 13 children had fissure sealants. (Table 1).

Conclusion: The results show that a large proportion of the group had experienced dental decay and were not following the recommended oral health guidance. There was a low uptake of fluoride varnish and fissure sealants. The results emphasise that oral health education should be included in the management of JIA. Oral health education could be provided in multidisciplinary consultations and through the use of education booklets. Education should include oral hygiene advice and raise awareness about access to fluoride varnish and fissure sealants.

Disclosure of interest: None declared.

Reference

P112
PReS-FINAL-2100: Methotrexate treatment affects effector, but not regulatory T cells in juvenile idiopathic arthritis
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Pediatric Rheumatology 2013, 11(Suppl 2):P112

Introduction: The balance between regulatory (Treg) and effector T cells (Teff) is crucial for immune regulation in juvenile idiopathic arthritis (JIA). How methotrexate (MTX), the cornerstone treatment in JIA, influences this balance in vivo is poorly elucidated.

Objectives: To investigate quantitative and qualitative effects of MTX on Treg and Teff in JIA patients during MTX treatment.

Methods: Peripheral blood samples were obtained from JIA patients at MTX start and 3 and 6 months thereafter. Treg numbers and phenotype were determined by flow cytometry and suppressive function in allogeneic suppression assays. Teff proliferation upon stimulation with anti-CD3, activation status and intracellular cytokine production were determined by flow cytometry. Effector cell responsiveness to suppression was investigated in autologous suppression assays. Effector cell cytokines in supernatants of proliferation and suppression assays and in plasma were measured by cytokine multiplex assay.

Results: MTX treatment in JIA did not affect Treg phenotype and function. Instead, MTX treatment enhanced, rather than diminished, CD4+ and CD8+ T cell proliferation of JIA patients after 6 months of therapy, independent of clinical response. Effector cells during MTX treatment were equally responsive to Treg-mediated suppression. MTX treatment did not attenuate Teff activation status and their capacity to produce IL-13, IL-17, Tnfα and Ifnγ. Similarly to Teff proliferation, plasma ifnγ concentrations after 6 months were increased.

Conclusion: This study provides a novel insight that MTX treatment in JIA does not attenuate Teff function but conversely, enhances T cell proliferation and ifnγ plasma concentrations in JIA patients.

Disclosure of interest: S. Vastert Consultant for: Novartis, < 1000 euro’s; M. Bulatovic-Calasan: None declared., R. Scholman: None declared., M. Klein: None declared., N. Wulffraat Grant/Research Support from: Abbvie, Roche, Consultant for: Novartis, Pfizer, B. Prakken: None declared., F. Wijk: None declared.

P113
PReS-FINAL-2101: Nitrous oxide analgesia for intra-articular injection in juvenile idiopathic arthritis: our experience
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Pediatric Rheumatology 2013, 11(Suppl 2):P113

Introduction: Nitrous Oxide (NO), known as “laughing gas”, is a volatile gas with analgesic, anxiolytic and sedative properties, used for treatment of short-lived mild or moderate pain.

Table 1 (abstract P111) Results from oral health questionnaire

<table>
<thead>
<tr>
<th>N</th>
<th>Registered at dentist</th>
<th>Fillings Teeth removed</th>
<th>Brushed teeth twice daily</th>
<th>Dental mouth-rinse</th>
<th>Electric tooth-brush</th>
<th>Sugared drink to bed</th>
<th>Sealants</th>
<th>Fluoride varnish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>95</td>
<td>39</td>
<td>15</td>
<td>12</td>
<td>26</td>
<td>34</td>
<td>14</td>
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<td>N</td>
<td>2</td>
<td>58</td>
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<td>85</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>
To evaluate the efficacy and safety of nitrous oxide-oxygen for children with juvenile idiopathic arthritis (JIA) undergoing intra-articular corticosteroid injection.

Methods: A 50:50 mixture with NO and oxygen was administered to JIA patients over the age of 5 years scheduled for joint injection. In some cases additional sedative agents (local EMLA, orally midazolam, nasal fentanest) was administered. Every patient completed visual-analogue scores (VAS) (0-10) for pain immediately after the procedure, and after 30 and 60 minutes. The physician validated sedation level according to Ramsay scale and memory level of the procedure.

Results: A total of 31 joints were injected in 25 patients (23 F, 2 M, median age 10.4 years). EMLA was placed in all patients at least one hour before the procedure. 19/25 patients received oral midazolam (0.5 mg/kg) 30 minutes before the intra-articular injection. 1/25 patients received nasal fentanyl (75 μg) during the procedure. The median pain score for patient (0-10 cm VAS) was 0.7 immediately after the procedure, 0.6 after 30 minutes, and 0.5 after 60 minutes. Only 3 out of 25 patients remembered the procedure. There were no adverse events in any patient.

Conclusion: Nitrous oxide-oxygen provides safe and effective analgesia for JIA children undergoing intra-articular injections, avoiding intravenous cannulation and general anaesthesia.

Disclosure of interest: None declared.

**Table 1(abstract P114)**

<table>
<thead>
<tr>
<th>Diagnostic guidelines</th>
<th>MAS vs. Active sjia</th>
<th>MAS vs. Systemic infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>HLH</td>
<td>0.19</td>
<td>1</td>
</tr>
<tr>
<td>Sjia-associated MAS</td>
<td>0.79</td>
<td>0.92</td>
</tr>
</tbody>
</table>

**Introduction:** Early diagnosis of macrophage activations syndrome (MAS) in systemic juvenile idiopathic arthritis (sJIA) may be challenging because it may mimic the clinical features of the underlying disease or be confused with an infectious complication. However, the diagnostic value of the guidelines for hemophagocytic lymphohistiocytosis (HLH) or sJIA-associated MAS has seldom been examined.

**Objectives:** To evaluate the efficacy and safety of nitrous oxide-oxygen for children with juvenile idiopathic arthritis (JIA) undergoing intra-articular corticosteroid injection.

**Methods:** A 50:50 mixture with NO and oxygen was administered to JIA patients over the age of 5 years scheduled for joint injection. In some cases additional sedative agents (local EMLA, orally midazolam, nasal fentanest) was administered. Every patient completed visual-analogue scores (VAS) (0-10) for pain immediately after the procedure, and after 30 and 60 minutes. The physician validated sedation level according to Ramsay scale and memory level of the procedure.

**Results:** A total of 31 joints were injected in 25 patients (23 F, 2 M, median age 10.4 years). EMLA was placed in all patients at least one hour before the procedure. 19/25 patients received oral midazolam (0.5 mg/kg) 30 minutes before the intra-articular injection. 1/25 patients received nasal fentanyl (75 μg) during the procedure. The median pain score for patient (0-10 cm VAS) was 0.7 immediately after the procedure, 0.6 after 30 minutes, and 0.5 after 60 minutes. Only 3 out of 25 patients remembered the procedure. There were no adverse events in any patient.

**Conclusion:** Nitrous oxide-oxygen provides safe and effective analgesia for JIA children undergoing intra-articular injections, avoiding intravenous cannulation and general anaesthesia.

**Disclosure of interest:** None declared.
hepatic involvement and pancytopenia. NSAIDs were stopped 4 times out of 5 continuous treatment, steroids were stopped in 1/9 patients, DMARDs were interrupted in 8/14, and biologics in 15/21 cases. 16/21 patients received a specific anti-herpetic drug except a common non-complicated outcome, whereas 5 children were not treated in the same or similar situation (3 on anti-TNFs, 2 on IL-1). All patients had favorable outcomes.

**Conclusion:** This study shows an overrepresentation of systemic JIAs among patients infected by or reactivating the VZV. This group of patients may be more immunosuppressed than others. In spite of the great heterogeneity of VZV management in France in children treated with biologics, the outcome was invariably good. This suggests 2 important points: (i) VZV control may not need any of the cytokines/ pathways targeted by the biologics we use, (ii) VZV management on biologics should be rationalized.

**Disclosure of interest:** None declared.
Objectives: There were immediate tasks needing to be addressed to reveal the specific clinical processes by which the children with psoriatic arthritis were affected by the disease, by its formation, its skin and joint syndromes, and the variations in the initiation and peaking of the disease.

Methods: All the children were given general, biochemical, and immunological blood tests. In addition to these, they also received magneto-auditory tomography (MAET) and X-raying of the affected joints.

Results: The majority of the children (53%) were found to have acquired the disease at about the age of 6-1/2 years. The median age for the start of the disease was 6.2 +/- 0.5 years, with the youngest being at 4 months and the oldest at 15 years. The mean duration of the disease was 6.7 +/- 0.3 years. In 29% of the cases, the disease began from a skin infection. The effect on the joints began after 2.4 +/- 0.3 years. The joint syndrome was observed in 70.6% of the children with related skin indications showing up on average after 4.5 +/- 0.8 years. Notably, one female patient afflicted with arthritis for 8 years had no signs of skin overpatching.

Our research showed that for 17.6% of the patients, the allergoseptic debut of the disease was accompanied by fever, typical rash, and lymphadenopathy. According to published scientific data, the hepatoplenal syndrome, or any involvement of the disease with the inner organs, is not typical of psoriatic arthritis. In 11.8% of the patients, there was a generalized deterioration of the joints including the cortical parts of the vertebral column as shown in Still's syndrome type. In 70.6% of the cases, oligoarticular asymmetrical joint syndrome was found to have spread from an initial affection of the ankle joints, to the knee joints, and the proximal interphalangeal joints and hip joints.

Our findings indicate that psoriatic arthritis varies its course in different patients. In 47% of the children, the disease was characterized by high laboratory and clinical activity with the exacerbation of joint and skin alteration increasing up to 5 to 6 times per year. In 53%, the process was much less pronounced with a positive effect from standard antirheumatic therapy being observed.

At the height of the disease at 3 to 4 years from beginning the observations, 41.2% of the patients were diagnosed with a symmetrical oligoarthritis, spondyloarthritis was reported in 23.5% with affection occurring in the peripheral joints, the ankle joints, knee joints, and the interphalangeal joints and hip joints.

Our research showed that in 47% of the patients, the disease symptoms corresponded to the 1st stage of the Stein-Broker entralogical scale, and in the other 53% to the 3rd and 4th stages. It should be noted in passing, that periarticular osteoporosis is effectively indistinguishable in patients from psoriatic arthritis.

Conclusion: The course of psoriatic arthritis in children is unpredictable and different from the same disease in adults.

Disclosure of interest: None declared.
P121
PrEeS-FINAL-2109: Genetic variations in patients with juvenile idiopathic arthritis and uveitis
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Pediatric Rheumatology 2013, 11(Suppl 2):P121

Introduction: Juvenile Idiopathic Arthritis (JIA) is accompanied by uveitis in approximately 20% of the cases. It is a serious complication with risk of impaired vision or even blindness. Both conditions are considered to be autoimmune diseases. Since uveitis is often asymptomatic, frequent ophthalmologic checks are needed to diagnose this complication at an early stage. Identification of risk factors for uveitis (besides presence of antinuclear antibodies (ANA)) could contribute to understanding of the pathogenesis of both diseases, and could be used as prognostic tool in an individual patient.

Objectives: We investigated whether variations in candidate genes involved in autoimmunity are associated with the development of uveitis in JIA patients.

Methods: Seventy European Caucasian patients with both JIA (all subtypes) and uveitis were included in this study. In 56 patients ANA were present, 5 patients were ANA negative, and in 9 patients ANA testing was inconclusive. Ninety-five single nucleotide polymorphisms (SNPs) on 52 loci were genotyped in cases and in 1598 healthy controls. Minor allele frequencies of these SNPs were compared between cases and controls.

Results: Six of 95 SNPs were associated with JIA related uveitis (p < 0.05), 5 of which are on previously described susceptibility loci to JIA in general (IL21, VITC1, Sq11, FTPN22, AFF3). A SNP in the promoter region of IL1B (rs16944), which was not associated to JIA in general in previous studies, was associated with susceptibility to JIA related uveitis (OR 1.63, 95%CI 1.15 - 2.31, p = 0.006). None of the associations remained significant after Bonferroni correction for multiple testing.

Conclusion: This study indicates a trend towards association of a genetic variant in IL1B with uveitis in JIA patients in particular. IL1B, coding for the proinflammatory cytokine IL1β, lies on chromosome 2q14, which harbours a cytokine gene cluster of nine related interleukin 1 family genes. Both genes and gene products of this cluster are associated with several autoimmune diseases, including experimental uveitis. IL1 inhibitors are used in the treatment of rheumatoid arthritis, (systemic) scleroderma, and sometimes uveitis. Although this result has to be replicated and fine-mapped in a larger and independent cohort, this study supports a role for the IL1 family in uveitis. Collection of long-term clinical follow-up data is ongoing, in order to compare JIA patients with uveitis to patients without uveitis to distinguish patients at risk from the others.

Disclosure of interest: None declared.

P122
PrEeS-FINAL-2110: Tocilizumab for patients with oligoarticular juvenile idiopathic arthritis refractory to conventional therapy
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Pediatric Rheumatology 2013, 11(Suppl 2):P122

Introduction: Because most children with oligoarticular juvenile idiopathic arthritis (o-JIA) were mildly affected (Steinblocker functional class I, c.a.85%), o-JIA is tended to be thought of as a mild subtype of JIA. However, 6% of them were unable to participate in a full school program 5 years after diagnosis, and 0.5% of children with o-JIA progressed to class III or IV, severe to terminal stages. Moreover, in 20% of o-JIA patients, there is a progressive increase in the number of affected joints after the first 6 months of disease (extended type). These severe patients had never gone into remission despite the conventional therapy.

Objectives: To assess the efficacy and adverse events of tocilizumab for children with o-JIA refractory to the methotrexate (MTX) and prednisone therapy.

Methods: Eight patients with o-JIA refractory to MTX and PSL therapy were eligible in this study, including 7 patients with a persistent type and 1 patient with an extended type. Synovial inflammation and joint effusion were demonstrated by ultrasound and power Doppler examination as well as physical examination and other laboratory findings. Patients complicated with uveitis were excluded from the study because their arthritis had responded well to the conventional therapy. All patients were female, and the median age at analysis was 10.1 years. Both the rheumatoid factor and the anti-CCP antibody were positive in the same 4 patients. Tocilizumab (8 mg/kg) was infused every 4 weeks. Efficacy and tolerability were assessed by VAS28-CRP, matrix metalloproteinase (MMP)-3 levels, and PSL doses.

Results: The affected joints were both knee joints (2/8), one knee joint (2/8), right knee joint and both foot joints (1/8), and both wrist joints (2/8). One patient with the extended type had arthritis primarily on knee and foot joints that extended to elbow and wrists joints within 6 months. The number of tender and swollen joints were decreased to none in 5 weeks. 8 patients within 6 months. Only one patient needed 12 months to become arthritis-free after TCZ initiation. The serum levels of MMP-3 in all patients were within baseline levels during the 6 months with TCZ treatment, though in 5 of them, MMP-3 levels were in the normal range at the beginning of TCZ administration. The mean doses of PSL were 7.5 mg/day before TCZ. They decreased to 3.1 mg/day after 6 months with TCZ, and then to none after 12 months. No serious adverse events were observed.

Conclusion: TCZ was effective and well tolerated for patients with o-JIA refractory to conventional treatments.

Disclosure of interest: None declared.

P123
PrEeS-FINAL-2111: Cytomegalovirus, Epstein Barr virus and Varicella-Zoster virus infections in children with juvenile idiopathic arthritis treated with biologics
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Pediatric Rheumatology 2013, 11(Suppl 2):P123

Introduction: Varicella-Zoster (VZV) virus, Cytomegalovirus (CMV) and Epstein Barr virus (EBV) infections may have a severe course in patients on immunosuppressive treatments. Data in Juvenile Idiopathic Arthritis (JIA) patients on biologics are still limited.

Objectives: To assess the outcome of JIA children with VZV, CMV or EBV infection.

Methods: We conducted a retrospective analysis of the notes of JIA patients followed between 2006 and 2013 in the French National reference centre for Juvenile Arthritis who developed CMV, EBV or VZV infection while on biologic treatment.

Results: Ten 3 to 16-year-old children were included for VZV (n = 8), CMV (n = 2) or EBV (n = 1) primuminfection while on etanercept (n = 1), adalimumab (n = 2), anakinra (n = 2) or canakinumab (n = 6). Seven patients had concomitant non-steroidal anti-inflammatory (NSAID) treatment, 7 low dose prednisono(lene) and 4 methotrexate. The 8 patients with VZV infection developed typical skin disease and marked systemic symptoms in some cases, however there was no visceral involvement. NSAIDs and steroids were interrupted in all cases. Biologic therapy was interrupted in 7 cases for 5 to 150 days. One patient was treated with acyclovir IV and 3 with valacyclovir for 5 to 15 days. The 2 patients who developed primary CMV infection disclosed marked increase of transaminases and moderate increase of gamma glutamyl transferase for 3 weeks; one patient remained asymptomatic and the other one had mild digestive symptoms. Both were on canakinumab and the following injection was postponed. The patient with primary EBV infection developed a rash with fever, hepatomegaly and splenomegaly that resolved after 2 months while NSAID and biologic treatment had been interrupted and corticosteroid treatment prescribed in order to control
Introduction: Juvenile idiopathic arthritis (JIA) is a childhood onset autoimmune disorder characterized by inflammation of joints and other tissues. The basis for susceptibility to common autoimmune and inflammatory diseases, including JIA, is a complex interplay between multiple genetic and environmental risk factors. NF-κb appears to be a central player in several autoimmune diseases, according to recent studies of genetic defects in autoreactive lymphoid cells in both murine models of autoimmunity and humans with diverse forms of autoimmunity. Meta-analysis suggested a possible association between NFKB1 -94 ins/del ATTG promoter polymorphism and certain autoimmune and inflammatory diseases in the Asian population, but not in the Caucasian population.

Objectives: The aim of the study was to investigate the NFKB1 -94 ins/del ATTG polymorphism in relation to risk of different forms of JIA in patients from Russia.

Methods: The NFKB1-94 ins/del ATTG genotypes were evaluated by using PCR method. A total of 155 JIA patients and 145 healthy controls from Bashkortostan, Russia were successfully investigated. Patients were diagnosed according to the ILAR criteria. There were 63 persistent oligoarthritis (PO), 48 rheumatoid factor-negative polyarthritis (RFNPI), 18 systemic onset (SO) JIA and 26 other subtypes patients. Chi-square (χ²) test and odds ratio (OR) were estimated to evaluate the association.

Results: Allele and genotype occurrence were in Hardy Weinberg Equilibrium in both groups. No differences were observed in allele and genotype frequencies of the NFKB1 -94 ins/del ATTG polymorphism between total JIA patients and controls. Stratification analysis across all ILAR subgroups revealed only weak association of the ins°ins genotype with SO JIA compared to all others JIA types (χ² = 4.014, p = 0.045, OR = 3.063, 95% CI 1.127-8.324). In contrast frequency of the ins°del genotype was significantly lower in SO groups than in both controls and all other JIA patients (χ² = 6.824, p = 0.010, OR = 0.182, 95% CI 0.051-0.656; χ² = 6.682, p = 0.011, OR = 0.184, 95% CI 0.051-0.664).

Conclusion: These findings demonstrate low risk of the systemic onset JIA in ins°del genotype of the NFKB1 -94 ins/del polymorphism carriers from Bashkortostan, Russia, and high risk of the systemic onset JIA patients with ins°ins genotype. Disclosure of interest: None declared.

P126
PReS-FINAL-2114: The leptin and adiponectin as biomarkers of atherosclerosis in juvenile rheumatic arthritis
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Introduction: Rheumatic diseases in adults are associated with increased incidence of cardiovascular disease. Compared to many publications related to the risk of atherosclerosis and its complications in patients with

P125
PReS-FINAL-2113: The association of the NFKB1 gene polymorphism with systemic onset juvenile idiopathic arthritis in Russia
VA Malevsky1, TV Viktortsova2, KV Danilko3, LS Nazarova4
1Department of Hospital Pediatrics, Bashkir State Medical University, Ufa, Russian Federation; 2Biological Department, Laboratory of Human Physiological Genetics, Bashkir State Medical University, Institute of Biochemistry and Genetics, Ufa, Russian Federation; 3Biological Department, Central Scientific Research Laboratory, Ufa, Russian Federation; 4Biological Department, Bashkir State Medical University, Ufa, Russian Federation

Disclosure of interest: None declared.

P124
PReS-FINAL-2112: Mapping the treatment effect of infliximab on a case of refractory anterior uveitis related to juvenile idiopathic arthritis (JIA)
V Miranda1, C Zilhão2, P Menéres1, M Guedes2
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Disclosure of interest: None declared.

References:


P125
PReS-FINAL-2113: The association of the NFKB1 gene polymorphism with systemic onset juvenile idiopathic arthritis in Russia
VA Malevsky1, TV Viktortsova2, KV Danilko3, LS Nazarova4
1Department of Hospital Pediatrics, Bashkir State Medical University, Ufa, Russian Federation; 2Biological Department, Laboratory of Human Physiological Genetics, Bashkir State Medical University, Institute of Biochemistry and Genetics, Ufa, Russian Federation; 3Biological Department, Central Scientific Research Laboratory, Ufa, Russian Federation; 4Biological Department, Bashkir State Medical University, Ufa, Russian Federation

Disclosure of interest: None declared.

Introduction: Infliximab is the anti-TNF-alpha monoclonal antibody used for the treatment of rheumatoid arthritis, inflammatory bowel disease, and juvenile idiopathic arthritis (JIA). JIA is a childhood onset autoimmune disorder characterized by inflammation of joints and other tissues. The basis for susceptibility to common autoimmune and inflammatory diseases, including JIA, is a complex interplay between multiple genetic and environmental risk factors. NF-κb appears to be a central player in several autoimmune diseases, according to recent studies of genetic defects in autoreactive lymphoid cells in both murine models of autoimmunity and humans with diverse forms of autoimmunity. Meta-analysis suggested a possible association between NFKB1 -94 ins/del ATTG promoter polymorphism and certain autoimmune and inflammatory diseases in the Asian population, but not in the Caucasian population.

Objectives: The aim of the study was to investigate the NFKB1 -94 ins/del ATTG polymorphism in relation to risk of different forms of JIA in patients from Russia.

Methods: The NFKB1-94 ins/del ATTG genotypes were evaluated by using PCR method. A total of 155 JIA patients and 145 healthy controls from Bashkortostan, Russia were successfully investigated. Patients were diagnosed according to the ILAR criteria. There were 63 persistent oligoarthritis (PO), 48 rheumatoid factor-negative polyarthritis (RFNPI), 18 systemic onset (SO) JIA and 26 other subtypes patients. Chi-square (χ²) test and odds ratio (OR) were estimated to evaluate the association.

Results: Allele and genotype occurrence were in Hardy Weinberg Equilibrium in both groups. No differences were observed in allele and genotype frequencies of the NFKB1 -94 ins/del ATTG polymorphism between total JIA patients and controls. Stratification analysis across all ILAR subgroups revealed only weak association of the ins°ins genotype with SO JIA compared to all others JIA types (χ² = 4.014, p = 0.045, OR = 3.063, 95% CI 1.127-8.324). In contrast frequency of the ins°del genotype was significantly lower in SO groups than in both controls and all other JIA patients (χ² = 6.824, p = 0.010, OR = 0.182, 95% CI 0.051-0.656; χ² = 6.682, p = 0.011, OR = 0.184, 95% CI 0.051-0.664).

Conclusion: These findings demonstrate low risk of the systemic onset JIA in ins°del genotype of the NFKB1 -94 ins/del polymorphism carriers from Bashkortostan, Russia, and high risk of the systemic onset JIA patients with ins°ins genotype.

Disclosure of interest: None declared.

P124
PReS-FINAL-2112: Mapping the treatment effect of infliximab on a case of refractory anterior uveitis related to juvenile idiopathic arthritis (JIA)
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Disclosure of interest: None declared.

References:


P125
PReS-FINAL-2113: The association of the NFKB1 gene polymorphism with systemic onset juvenile idiopathic arthritis in Russia
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Disclosure of interest: None declared.
Objectives: The aim of the study was assessing the early vascular to delayed treatment with joint ≤

We investigated whether children JIA and their parents are associated with early atherosclerosis.

There were no significant differences between the biomarkers of early and later (> 1 year) were not differenced significant. In the group of children with JIA, a positive correlation between leptin levels and duration of the disease was found.

The lack of differences between the biomarkers of early atherosclerosis in group of JIA patients treated and not treated with methotrexate, etanercept or modifying drug, with or without glucocorticoid (at a dose of ≤ 0.2 mg/kg body weight) and 19 healthy children as a control group.

Conclusions: The lack of differences between the biomarkers of early atherosclerosis in group of JIA patients compared to the control group, indicates a reduced risk of cardiovascular diseases, in terms of effective therapy.

Disclosure of interest: None declared.

P128
PReS-FINAL-2116: Assessment of disease activity by patients with juvenile idiopathic arthritis and the parents compared to the assessment by pediatric rheumatologists

Introduction: Disease activity in children with juvenile idiopathic arthritis (JIA) is assessed regularly by a rheumatologist. Early detection of disease activity at home, between scheduled consultations, is a major concern. According to current best practice patients with JIA should be treated as soon as symptoms appear. Underestimating disease activity by patients and their parents invariably leads to delayed treatment with joint damage as a consequence. Overestimation may lead to the patient taking less part in sport and leisure activities, missing school, and excessive medication. Therefore it is important to study how patient and parents assess the disease activity compared to the rheumatologists’ assessment.

Objectives: We investigated whether children JIA and their parents are capable of assessing disease activity by comparing their assessments to...
rheumatologists’ assessments. And we studied which factors contribute to the assessment of active disease by the child and parent. 

Methods: Patients and parents assessed 69 joints on a paper homunculus and marked each joint with a different color according to the presumed presence of disease: active disease (AD), doubt, and non-active disease (NAD). Their assessments were compared to the rheumatologists’ assessments. If patients and/or parents marked on or more inflamed joints, it counted as AD. Pain (measured by an Visual Analogue Scale), functional impairment (measured by CHAQ), age and disease duration were analyzed to differentiate more precise between true and false positive and true and false negative assessments.

Results: We collected assessments of 113 patients and/or parents. AD was assessed 54 times, 33 of which were true positives. NAD was assessed 23 times, 22 of which were true negatives. Doubt was expressed 36 times, 9 of which were assessed by the rheumatologist as AD. Sensitivity and specificity of AD was 0.77 and 0.31. Disease duration and age did not differ between AD and NAD. Pain and functional impairment scored highest in AD, intermediate in doubt, and lowest in NAD. Pain and functional impairment did not relate to AD assessed by the rheumatologist.

Conclusion: Patients and/or parents seldom missed arthritis but frequently overestimated disease activity. Pain, functional impairment, disease duration, gender, and age did not differentiate between true and false positives. Patients perceived JIA as active if they experienced pain and functional impairment. To reduce overestimation of the presence of AD we need to improve their understanding of disease activity by teaching them to distinguish between primary symptoms of JIA and symptoms like pain and functional impairment.

Disclosure of interest: None declared.

Introduction: Intra-articular corticosteroid injection (IASI), a common procedure in juvenile idiopathic arthritis (JIA), is usually associated with anxiety and pain.

In previous study we concluded that nitrous oxide (NO) provides effective and safe sedation for such procedures. The efficacy in reducing pain was associated with the level of the child’s anxiety even before starting the procedure.

Following the introduction of “Dream Doctors” in our hospital, we added medical clown as an important integral part of the team doing IASI.

Objectives: To prospectively evaluate how a medical clown affects pain during IASI in JIA using NO conscious sedation.

Methods: Patients scheduled for IASI first met and interacted with the medical clown. During the procedure, the rheumatologist and the medical clown worked in parallel to create distraction. NO was administered. The patient, parent, physician, medical clown and nurse completed a visual analogue scale (VAS - 0-10) for pain. Change in heart rate (HR) ≥15% was recorded to examine physiologic response to pain and stress.

Results: 46 procedures were performed in 32 children: 23 girls, 9 boys, with a mean age of 10.87 ± 3.58 yrs. The median VAS pain score for the patients, parents, physicians, medical clown and nurses was 2, 2, 1, 1, and 1, respectively. 5 patients had increased HR, and experienced increased pain. In our previous study using only NO, the median pain score was 3.

Conclusion: Active participation of a medical clown during IASI with NO for JIA further decreasing pain, stress, and induces a pleasant patient experience.

Disclosure of interest: None declared.

Introduction: We describe a 6-year-old girl with a sudden onset of symmetrical and painless joint contractures of fingers on both hands, without obvious skin changes, following an exercise (roller skating) while she was holding hard for a wall rail. She was first presented to the Department of Neuropaediatrics with the suspected diagnosis of a neuromuscular disorder. During initial patient consultations that included an rheumatologist a marked blood eosinophilia was found. No telangiectasia, calcinosis, megacapillary, sclerodactyly, or mucosal involvements were present. The patient showed neither Raynaud phenomenon nor digital ulceration.

Objectives: To describe an unusual presentation of eosinophilic fascitis in childhood and clinical, laboratory and radiology findings that lead to the diagnosis.

Methods: Clinical, laboratory and radiologic examination were undertaken prior to a full thickness biopsy.

Results: In addition to eosinophilia of 23% absolute value (normal value up to 5%; absolute number 2560/microL), laboratory investigations showed an elevated erythrocyte sedimentation rate of 29 mm (normal value 6-20), normal C-reactive protein (CRP) and creatinine kinase (CK) levels, an increase of immunoglobulin G (to 17.6 g/L (normal range up to 14 g/L) and increased eosinophilic cationic protein of 100 μL/L (normal range up to 20 μL/L). Immunological results were negative for scleroderma-specific autoantibodies. No sign of Borella burgdorferi infection was detected in serum. Muscle ultrasound and magnetic resonance imaging (MRI) of her right hand revealed thickened fascia and no joint involvement. A full thickness biopsy confirmed the diagnosis of eosinophilic fascitis. Oral corticosteroid therapy was initiated without side effects.

Conclusion: In most patients with eosinophilic fascitis, the presenting symptoms are cutaneous with pitting edema, peau d’orange skin, and indurations mainly affecting the hands and feet sparing acral regions. To the best of our knowledge, the unusual presentation of painless contractures without involvement of the skin as seen in our patient was previously described in two children only. MRI was useful as a diagnostic tool to demonstrate that contractures in our patient were due to a fascitis and not to joint involvement.

Disclosure of interest: None declared.
Table 1(abstract P131) Shows reported use of specific treatments for JLS by clinician group

<table>
<thead>
<tr>
<th>Treatment Used</th>
<th>Reported use by prs (% of respondents)</th>
<th>Reported use by dms (% of respondents)</th>
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<tr>
<td>Topical treatments</td>
<td>10</td>
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<td>Systemic steroids</td>
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<tr>
<td>Mycophenolate</td>
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<td>18</td>
</tr>
<tr>
<td>Mofetil</td>
<td>30</td>
<td>0</td>
</tr>
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<td>Cyclophosphamide</td>
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</tbody>
</table>

Medical photography (100%), thermography (67%) and drawing in notes/ use of pre-printed body map (both 56%) were the most regularly used mts by prs; photography (81%) drawing in notes (56%) and ultrasonad (22%) were most regularly used by dms. Of 4 skin scores, the modified Rodnan skin score was the one clinicians used most frequently. However it was only used regularly by 33% prs and 3% dms. Familiarity, use (frequently or occasionally) and perceived benefit of all skin scores was low (0-40%). Laser doppler imaging, laser doppler flowmetry and 3.0T MRI were perceived useful by larger proportions (15-70%) of clinicians than reported using them (either occasionally (0-60%) or regularly (0-11%).

Table 1 shows reported use of specific treatments for JLS by clinician group.

Conclusion: A wide range of mts are used in the UK by prs and dms managing CYP with JLS. How these tools are accessed, used and perceived varies between and within these clinician groups. There are also differences in prescribing of treatments between prs and dms. These differences will impact on the feasibility of conducting clinical trials in JLS.

Further work is needed to determine accessible and validated mts for CYP with JLS. Collaboration between dms and prs is an important factor in facilitating future high quality research and standardising care in JLS.

Disclosure of interest: None declared.

P132

PReS-FINAL-2120: Juvenile scleroderma international network (JUSINET) database: a reliable instrument for clinical research in juvenile scleroderma syndromes

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Pediatric Rheumatology 2013, 11(Suppl 2):P132

Introduction: The conduct of Clinical Research in rare diseases, such as Juvenile Systemic Sclerosis (jssc) and Juvenile Localized Scleroderma (JLS), requires an adequate number of patients and a fruitful collaboration between international centers. The clinical management of young patients suffering from these diseases is also often difficult to achieve in an effective and shared manner.

Objectives: We propose a web-based registry (http://www.jusinet.org) to prospectively collect data on demographic, epidemiological, clinical, and laboratory features of patients with jssc and JLS from adult and paediatric rheumatology centres and to educate physicians to a more standardized approach to these conditions. The purpose is to provide a well-characterized cohort of scleroderma patients according to the current classification criteria and collect adequate information enabling to uniform clinical assessment and diagnostic tests, to stimulate clinical and basic research projects.

Methods: The Database was evaluated by some international experts who provided us with valuable advice for improvement.

JUSINET has an administrative structure including a Database Executive Committee (DEC), who evaluates progress of the project and discuss management issues. The Database Coordinator (DC) assisted by a Research Assistant (RA), and a Database Manager (DM, statistician) form the Local Administrative Structure (LAS).

In order to verify the performance of JUSINET at national and international level, four centers in Italy, one in Slovenia, Argentina and Turkey, have tested and validated the system including real patients cases. Compilers were required to express their opinion on 3 variables, clarity of information, ease of data entry and completeness of information, for each section of the database.

Results: The 324 opinions expressed for the 22 sections of JUSINET, in a range between 1–5, reached a mean value of 4.62. The mean time to enter a new patient data was 14 minutes for jssc, and 8 minutes for JLS; to update data was 8 minutes for jssc and 5 minutes for JLS.

Conclusion: The JUSINET Database represents a valuable instrument to better characterize patients childhood onset scleroderma and facilitate research on pathogenesis and treatment of this relatively rare condition. It also provides a simple and reliable tool for the daily clinical management of these patients.

Disclosure of interest: None declared.

P133

PReS-FINAL-2121: Results for 6 minute walk values in healthy German children show similar results as from Britain

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Pediatric Rheumatology 2013, 11(Suppl 2):P133

Introduction: 6 minute walk is a primary outcome measure in therapeutic studies for patients with pulmonary hypertension. Currently we have a two of sets of data[1,2] regarding test results in the 6 minute walk test (6MWT) in healthy children with a large span in the norm values in the different age groups.

Objectives: Aim of the study was to establish norm values for healthy German children for the 6 Minute Walk Test.

Methods: The team of an occupational therapist and a study nurse were visiting schools. Permission from the parents was give before the test. Always just probands from one class were invited to participate. The test were performed according the international guidelines[3]. The demographic data of the probands were collected and the parents filled out a short survey regarding the physical activity and the health condition. Children with chronic diseases, which decrease the stamina were excluded.

Results: Up till now 616 probands participated from the age 5 of 14 years. 343 of the 616 were female. The mean 6 minute walk continuously increased with age (Table 1). It correlated in the age groups with the BMI.

Conclusion: Our results are in the range of the patients from the UK published by Lammers et al [1] and are in significantly lower range than in the Chinese population collected data by Li et al.[2]. This reflects the importance of this study to gain norm values for our patient population.

Disclosure of interest: None declared.

References


Table 1(abstract P133)

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P134
PRes-FINAL-2122: Autologous stem cell transplantation in a patient with severe systemic sclerosis in Portugal
M Guedes1, C Zilhão2, L Palhau1, I Almeida1, I Silva1, C Vasconcelos1, A Marinho1, C Vaz1, A Campos2
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Pediatric Rheumatology 2013, 11(Suppl 2):P134

Introduction: Systemic sclerosis (SSc) is a progressive disease, whose pathogenesis includes early immunological events and vascular alterations. There is a subgroup of patients with a rapidly progressive disease or refractory to conventional treatment which can benefit from intensive immunosuppression and rescue with transplant of haematopoietic progenitors (TPH).

Objectives: To report the first TPH for an autoimmune patient in Portugal.

Methods: Retrospective review of the case file

Results: Clinical case: young female, 20 y.o., with SSc diffuse subtype, diagnosed at 13 y.o., with cutaneous, vascular and articular involvement, with initial good response to Methotrexate. Three years later there was progression of the disease with severe gastrointestinal involvement translated by disphagia and delayed gastric emptying non responsive to treatment, including Cyclophosphamide (Cyc) with subsequent important weight lost, and need of nutritional support by gastrostomy.

In January of 2012 she was subjected to intermediate dose immunosuppressive therapy with Cyc 4gr followed by hematopoietic growth factors for mobilization and collection of peripheral stem cells progenitors, and four months latter autologuous transplant was made with myeloablative regimen (BEAM).

The patient suffered a grade 3 mucositis with need for opioid therapy and nutritional support with total parenteral nutrition during 5 days. She also had a herpes zoster and a febrile syndrome without clinical focus and without isolated agent. Hospital discharge day was at day 17 post transplant. In ambulatory regimen the patient became to have good oral food tolerance without need for nutritional supplementation by gastrostomy and cutaneous and vascular improvement.

Conclusion: This is the first TPH for an autoimmune patient in Portugal, with a sequency therapy approach in consonance with the european clinical guidelines protocols of the EBMT. The authors emphasize the importance of an early identification of patients with autoimmune diseases unresponsive to conventional therapy and the definition of eligibility criteria.

Disclosure of interest: None declared.

P135
PRes-FINAL-2123: Feto-maternal outcome in patients with systemic sclerosis
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Pediatric Rheumatology 2013, 11(Suppl 2):P135

Introduction: Progressive systemic sclerosis is a life threatening disease typically involve the heart, lungs, and other organs. pregnancy is a stressfull condition that can affect the course of the disease.

Objectives: To study the maternal and fetal outcomes in pregnant women with Systemic Sclerosis (ssc) and to analyze the possible associated risk factors.

Methods: Twenty pregnant women with ssc and twenty age-matched low risk pregnant women were recruited in this study. Patients were evaluated clinically and laboratory at the entry of the study and at monthly intervals. Different pregnancy outcome measures were studied.

Results: Twenty ssc pregnant women were recruited in this study with a mean age 29.6 ± 3. Eight (40%) of them had limited ssc, and twelve (60%) had diffuse type. Pregnancies were complicated by maternal flare of underlying disease in six (30%) pregnant patients. Six patients (30%) had preterm labor. Four patients (20%) had small for gestational age (SGA) infants, two of them (10%) had intra uterine growth retardation (IUGR). Two patients (10%), with diffuse type, fulfilled criteria of antiphospholipid syndrome (APS) but unfortunately the pregnancy ended in miscarriage. Eight (40%) full-term infants were born two of them were SGA, 2 cases with miscarriage due to renal crisis and pulmonary hypertension and another two cases with intra uterine fetal death (IUFU). The live birth rate was 14/20 (70%) in ssc group.

Conclusion: Women with ssc can safely have healthy pregnancies if pregnancy is planned when the disease is stable and managed by a multidisciplinary team during pregnancy.

Disclosure of interest: None declared.

P136
PRes-FINAL-2124: Electromyography assessment in localized scleroderma
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Pediatric Rheumatology 2013, 11(Suppl 2):P136

Introduction: Localized Scleroderma (LS) has been associated with central and peripheral nervous system involvement. Facial palsy, extraocular movement disorders, trigeminal neuralgia and hemi-masticatory spasms are described as primary neurologic involvement. Romberg hypothesized that sympathetic regulation has pathogenic relevance in facial hemiatrophy, which was reproduced experimentally by superior cervical ganglion ablation (Resende LA et al. 1991).

Objectives: Investigate nerve conduction and muscle involvement by electromyography (EMG) in LS.

Methods: A series of 23 LS cases with long-term follow up was retrospectively evaluated based on clinical, serological and imaging findings. Ten parents/patients agreed to participate by giving informed signed consent/assents, being enrolled for EMG performed in Nihon-Kohden Neuropack S1, MEB 9400 machine. It was performed with bilateral symmetric technique, using needle electrodes for extremities. Bilateral symmetric surface quantitative electromyography (QMG) was obtained from the masticatory muscles in facial hemiatrophy/Romberg (P-R) syndrome.

Results: A preliminary analysis of 7 electromyograms, being 5 of linear LS extremities and 2 of P-R facial muscles, is presented. Four LS had myopathic EMG pattern in muscles underlying linear streaks and 1 presented neurogenic EMG pattern. Motor and sensory nerve conduction studies of median and ulnar nerves (upper limbs) and sciatic nerve (lower limbs) resulted normal in all. Masticatory muscle testing by QMG showed reduced root mean squares and increased turns per second in the atrophic face of 2 P-R cases.

Conclusion: There is muscle and peripheral nervous system dysfunction in LS and P-R syndrome, possibly related to inflammation and progressive soft tissue atrophy, that needs to be further explored in collective studies.

Disclosure of interest: None declared.


P137
PRes-FINAL-2125: A Japanese girl with childhood-onset anti-Ku antibody positive generalized morphea-myositis overlap syndrome
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1Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan; 2Department of Pediatrics, Tokyo Women’s Medical University, Tokyo, Japan

Introduction: Anti-Ku antibodies are autoantibodies against the P70/80 DNA-PK activated factor. These antibodies were identified in patients with sclerodermopathymyositis overlap syndrome by Mimori et al., and have subsequently been identified in approximately 1% of children with overlap syndromes.
Introduction: Raynaud phenomenon (RP) can be the first symptom of a connective tissue disease in children, in particular juvenile systemic sclerosis (JSSC) or systemic lupus erythematosus (SLE). However, the prevalence of RP in healthy school children has been shown to be as high as 15%[1]. There are currently no guidelines or agreed management strategies amongst Paediatric Rheumatologists on how to differentiate primary from secondary RP or how often patients require evaluation.

Objectives: To develop consensus standards for good clinical practice for children with RP.

Methods: A consensus meeting was organized in the frame of the PRES scleroderma working group. A nominal group technique was used. 75% consensus was defined as agreement.

Results: 1. All patients with RP should be screened with an ANA test.
2. All ANA positive patients should be screened for scleroderma-specific antibodies (e.g. anti-SCL 70 and anti-centromere antibodies).
3. All patients with RP should be investigated by capillaroscopy. Capillaroscopy will be classified into “normal”, “aspecific changes” or “scleroderma pattern”.
4. All patients who have additional symptoms pointing to a definite connective tissue disease should be evaluated according to disease specific guidelines.
5. ANA-negative and capillaroscopy-negative patients should be followed-up at least every 6 months.
6. ANA positive patients without disease-specific antibodies and with negative capillaroscopy findings should be followed-up at least every 6 months.
7. ANA and disease-specific antibody positive patients should have organ specific evaluation according to symptoms, examination and relevant to that particular disease e.g. patients who are ANA and Sc-70 positive may need organ specific evaluation for JSSC as per the Juvenile systemic sclerosis inception cohort protocol (http://www.juvenile-sclerodema.com).
8. ANA-positive patients, who have no disease specific antibody but have positive capillaroscopy results, should be followed-up at least every 3 months.
9. ANA-negative patients with positive capillaroscopy result should be followed-up at least every 6 months.
10. The group could not reach an agreement regarding treatment, due to a lack of data for the paediatric age group. The group agreed that implementation of adult recommendations for paediatric care might be reasonable, but robust paediatric trials are needed.

Conclusion: The group made a suggestion for a standard of good clinical practice for RP in children. Our aim is that this will facilitate a large multicentre prospective follow-up study of children with RP.

Disclosure of interest: None declared.

P138
PreS-FINAL-2126: How to follow up children with Raynaud syndrome - recommendations based on the Hamburg consensus meeting 2012
T Constantin1, C Paim1, N Toplak1, M Moll1, I Konert1, DP Potto1, NA Ayaz2, D Nemkova3, P Hoeger3, M Cuto10, V Smith11, I Felandvair12, Juvenile Scleroderma Working Group
1Semmelweis University, Budapest, Hungary; 2Alder Hey Childrens Hospital, Liverpool, UK; 3University of Ljubljana, Ljubljana, Slovenia; 4University of Tuebingen, Tuebingen, Germany; 5Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 6Universidade Federal de Sao Paulo, Sao Paolo, Brazil; 7Sultan Sleyman Education and Research Hospital, Istanbul, Turkey; 8University of Prague, Prague, Czech Republic; 9Wilhelmsstift Hospital for Sick Children, Hamburg, Germany; 10University Medical School of Genova, Genova, Italy; 11Gent University Hospital, Gent, Belgium; 12Hamburger Zentrum fur Kinder- und Jugendrhematologie, Hamburg, Germany

Objectives: We report the case of a Japanese child with anti-Ku antibody positive overlap syndrome.

Methods: We retrospectively explore the difference between childhood anti-Ku positive syndromes, juvenile dermatomyositis and adult onset anti-Ku positive syndromes.

Results: The patient, a 16-year-old Japanese girl, first developed symptoms at the age of 7. Her initial symptoms consisted of multiple brownish plaques on her left forearm that gradually extended to her upper arm, back, and left thigh. She underwent a skin biopsy at the age of 8 that revealed generalized morphea(GM). Laboratory findings included positive anti-nuclear antibody (1:1,280) and elevated serum creatine kinase (CK, 1,249 U/L) even though she lacked clinical evidence of myositis, myocardial failure or muscular dystrophy. Repeated skin biopsy at the age of 14 revealed lymphocytic infiltrations around vessels and thickened collagen bundles in the dermis. Although she still lacked clinical signs of muscular involvement, MRI demonstrated findings consistent with myositis and bilateral thigh atrophy. Furthermore, serum anti-Ku antibody was detected by immunoprecipitation assay. She was thus diagnosed with generalized morphea-polymyositis overlap syndrome. She was treated with methylprednisolone pulse therapy followed by oral glucocorticosteroids which resulted in a gradual decrease in serum CK levels.

Three patients with adult onset anti-Ku antibody syndrome also presented to our institute. All three patients were female, and the average age of onset was 36.0 years old (range 30-46)(Table 1). Each patient was treated with glucocorticosteroids, but immunosuppressants were ultimately required to suppress disease activity in all three cases.

Conclusion: Our pediatric patient represents one of the youngest patients with anti-Ku antibody syndrome. She was thus diagnosed with generalized morphea(GM). Laboratory findings included positive anti-nuclear antibody (1:1,280) and elevated serum creatine kinase (CK, 1,249 U/L) even though she lacked clinical evidence of myositis, myocardial failure or muscular dystrophy. Repeated skin biopsy at the age of 14 revealed lymphocytic infiltrations around vessels and thickened collagen bundles in the dermis. Although she still lacked clinical signs of muscular involvement, MRI demonstrated findings consistent with myositis and bilateral thigh atrophy. Furthermore, serum anti-Ku antibody was detected by immunoprecipitation assay. She was thus diagnosed with generalized morphea-polymyositis overlap syndrome. She was treated with methylprednisolone pulse therapy followed by oral glucocorticosteroids which resulted in a gradual decrease in serum CK levels.

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Introduction: Cutaneous graft-versus-host-disease (GVHD) is a common manifestation of GVHD post allogeneic haematopoietic stem cell transplantation (HSCT). It is characterised into lichenoid and scleroderma variants. Sclerodermatous GVHD is thought to be rare, with few reports in the paediatric population.

Objectives: To describe 3 paediatric cases of GVHD associated scleroderma.

Methods: Retrospective case note review.

Results: A 7 year old girl was referred to rheumatology 2 years after maternal HLA matched HSCT for acute lymphoblastic leukaemia. Mild cutaneous GVHD was noted post transplant. She subsequently presented with severe sclerodermatous changes on both lower legs. She had marked loss of range of movement (ROM) of her ankles, and the disease rapidly progressed to involve the skin of her thighs and left arm, with significant joint contractures. She was treated with methylprednisolone, methotrexate and physiotherapy (PT) with good effect: improved ROM, softening of the skin and no further progression.

A 4 year old girl was referred to rheumatology 3 years after having 2 matched sibling HSCT for MHC class 2 deficiency. Very mild cutaneous GVHD had been noted post transplant. She presented with rapidly worsening contractures affecting her hands and lower limbs with diffuse swelling, erythema, thickness and tethering of skin and tendons. She was treated with PT, occupational therapy (OT) and splinting, together with prednisolone and methotrexate. Clinical improvement was maintained over the following year.

A 6 year old girl with beta thalassaemia major was referred to rheumatology 2 years post HSCT. Buccal GVHD was noted 4 months post transplant, treated initially with steroids and ciclosporin followed by extracorporeal photophoresis. Despite some initial response to this there was a profound deterioration of hand function with severely restricted wrists and fingers bilaterally and reduced grip strength. She has been treated with an increased dose of prednisolone, the addition of methotrexate, PT and OT.

Discussion: We report 3 cases of sclerodermatous GVHD following HSCT. The indications for HSCT differed in each case. All had mild cutaneous GVHD noted in the early post transplant period. All presented months or years later with extensive sclerodermatous skin changes. Widespread established joint contractures were noted at the time of referral to rheumatology. There is a paucity of evidence regarding effective treatment for this condition. 2 of our cases showed significant improvement with a combination of steroids, methotrexate, PT, OT and appropriate splinting.

Conclusion: Sclerodermatous GVHD is rare in the paediatric population but results in significant morbidity in affected individuals. In these cases severe joint contractures were noted at the time of referral to Rheumatology. Monitoring for early signs of joint contracture post HSCT, and raising awareness of this potential complication, should facilitate earlier diagnosis, with the potential to optimise outcome for affected children.

Disclosure of interest: None declared.

P140 PreS-FINAL-2128: Quality of life and psychosocial aspects in juvenile localized scleroderma (JLS): a cross-sectional study in 40 patients

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Pediatric Rheumatology 2013, 11(Suppl 2):P140

Introduction: JLS is a chronic, autoimmune disease, characterized by skin and subcutaneous tissues fibrosis, which can extend to underlying tissues up to muscle and bone. JLS can cause a poor quality of life and psychosocial and behavioural problems in affected children particularly when severe deformities such as face asymmetry, joint contractures, and growth disturbances of limbs develop. To date, quality of life and psychological aspects in JLS have been poorly investigated, often with contrasting findings.

Objectives: To evaluate quality of life and psychosocial aspects of patients with JLS compared with healthy peers and identify specific disease characteristics possibly related to quality of life impairment and psychosocial problems.

Methods: Two types of questionnaires (Pediatric Quality of Life Inventory 4.0™ Generic Core Scales and Child Behaviour Checklist 6-18/Youth Self Report 11-18) were administered to 40 consecutive patients with JLS aged 6 to 18 years and their parents followed at the Pediatric Rheumatology Unit of Padova. Patients’ demographic and clinical data were collected during medical examination and through the review of clinical records. Same questionnaires were administered to a control group of 44 healthy children and their parents.

Results: In pediatric™ (parents forms) children with JLS showed poorer quality of life compared to control group (76.8 vs 84.8, p = 0.017), especially in emotional area (64.5 vs 79, p = 0.004). In CBCL/6-18 mean scores were lower in activity scale (35.2 vs 41.1, p = 0.006) and higher in internalizing problems scale (58 vs 53.2, p = 0.026) and depression scale (59.9 vs 53.9, p = 0.038) in JLS group compared to control group. In YSR/11-18 mean scores were lower in social competence scale (44.2 vs 49.7, p = 0.007) and in total competence scale (40.9 vs 42.4, p = 0.028) and higher in internalizing problems scale (54.7 vs 50.9, p = 0.031) in JLS group compared to healthy controls. Disease relapses, longer delay in correct diagnosis, onset of disease in adolescence and shorter disease duration significantly correlated with lower quality of life and psychosocial and behavioural problems.

Conclusion: Our study shows that quality of life is poorer in children with JLS compared to healthy peers. Emotional area and social activities are the most affected ambiens and patients show also depressive and internalizing problems. Among patients with JLS, a greater need for psychological support is mainly related to disease relapses, longer diagnostic delay, shorter disease duration and onset in adolescence or pre-adolescence ages. Disease severity in terms of lesion extension or deformities and therapy related issues do not seem related to impairment in the investigated areas.

Disclosure of interest: None declared.

P141 PreS-FINAL-2129: Whole-body versus localized magnetic resonance imaging in the assessment of juvenile dermatomyositis

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Pediatric Rheumatology 2013, 11(Suppl 2):P141

Introduction: MRI represents a promising tool in the assessment of disease activity in juvenile dermatomyositis (JDM). Water-sensitive sequences are very sensitive to the presence of inflammation and have the potential to support diagnosis, guide muscle biopsy and monitor treatment response. So far, all MRI studies in JDM focused on pelvic and thigh musculature. Whole-body (WB)-MRI screens the entire body with the potential to support diagnosis, guide muscle biopsy and monitor treatment response. So far, all MRI studies in JDM focused on pelvic and thigh musculature. Whole-body (WB)-MRI screens the entire body with the advantage to evaluate much larger areas of muscles as well as subcutaneous fat tissue.

Objectives: To compare WB-MRI and thighs-MRI in the assessment of disease activity in JDM.

Methods: WB-MR images were obtained from 43 JDM patients and 43 controls using a 1.5 Tesla MRI scanner and STIR sequences. Muscle signal abnormalities were scored by 2 independent readers in 36 muscular groups using a 0-2 point scale; perifascicular and subcutaneous tissue inflammation were evaluated using a binary scale on 8 sites (arm, forearm, thigh and lower leg bilaterally). Two different readers separately scored, on the same WB-MR images, pelvic and thigh muscles bilaterally (gluteal muscles, hamstrings, quadriceps and adductors) as well as the presence of thigh subcutaneous soft-tissue oedema and perifascicular oedema. WB-MRI and thighs-MRI scores were compared in terms of reliability, construct validity, discriminant ability and responsiveness.

Results: Thighs subcutaneous and myofascial signal abnormalities were detected in 8/43 (18.6%) and in 12/43 (27.9%) patients respectively. WB-MRI revealed inflammatory involvement of myofascial and subcutaneous areas other than the thigh in 8/43 (18.6%) and 10/43 (23.2%) patients, respectively Concordance between WB and thigh MRI scores in the evaluation of myofascial and subcutaneous tissue was moderate (myofascial scores r = 0.59, subcutaneous scores r = 0.69). Although concordance in detecting muscle inflammation between thigh and WB-MRI muscle scores was excellent (r = 0.97), two patients with negative thigh-MRI showed muscle signal abnormalities in muscle groups different from the thigh. Inter-reader agreement was excellent for both thigh-MRI and WB-MRI scores (ICC 0.96 and 0.98 respectively). Both scores showed
excellent correlations with clinical measures of disease activity (Muscle Test (MMT) $r_s = 0.82$, Childhood Myositis Assessment Scale (CMAS) $r_s = 0.83$ for thigh-MRI; MMT $r_s = 0.84$, CMAS $r_s = 0.81$ for WB-MRI). Thigh and WB-muscle scores were significantly higher in JDM active patients when compared with the control group ($p = 0.0001$ for both the scores) and the inactive patients (thigh-MRI $pb = 0.0022$, WB-MRI $pb = 0.0037$). Responsiveness to change was higher for WB-MRI muscle score (standardized response mean $= 1.65$) compared to that of thigh MRI score (SRM $= 1.04$) and to those of clinical muscle tests (SRM-CMAS $= 0.56$, SRM-MMT $= 0.74$).

Conclusion: WB-MRI enables a reliable analysis of the site and magnitude of inflammatory process throughout the entire body thus providing a complete assessment of total inflammatory burden. WB-MRI was more accurate than localized MRI in identifying myofascial and subcutaneous inflammation and in the assessment of the responsiveness to change.

Disclosure of interest: None declared.

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**P142**

**PreS-FINAL-2130: Antibodies to MDA5 correlate with a distinct phenotype in children with juvenile dermatomyositis, including higher risk of lung involvement and ulcerative skin disease**

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7 Neurodevelopmental Unit, UCL Institute of Child Health, London, UK; 8 Radiology Department, Great Ormond Street Hospital for Children, London, UK

**Introduction:** Myositis specific autoantibodies (MSA), exclusively found in patients with Idiopathic Inflammatory Myopathies can be detected in approximately 60% of children with JDM. Anti-MDA5 antibodies, a subgroup of MSA, appear to be associated with clinically amyopathic myositis, rapidly progressive interstitial lung disease (RP-ILD) and a poor prognosis in adult East Asian dermatomyositis patients. Small studies in Japanese children with JDM have suggested similar disease phenotype. This contrasts dramatically with findings in predominantly Caucasian US adult populations where anti-MDA5 has been associated with a distinct cutaneous phenotype and no association with RP-ILD has been found.

**Objectives:** We aimed to determine the frequency and associated clinical phenotype of anti-MDA5 autoantibodies in a large UK based, predominantly Caucasian cohort of patients with JDM.

**Methods:** Serum samples, from 285 patients with JDM were obtained through JDM National (UK and Ireland) Cohort and Biomarker Study and Repository for Idiopathic Inflammatory Myopathies. The presence of anti-MDA5 antibodies was determined by ELISA using recombinant MDA5 protein. Results were compared with matched clinical data, muscle biopsies (scored by a single experienced paediatric neuropathologist) and chest imaging (reviewed by a single experienced paediatric radiologist). Both biopsy scoring and imaging review were performed blind to clinical or serological data.

**Results:** Anti-MDA5 antibodies were identified in 7.4% of JDM patients and were associated with a distinct clinical phenotype including skin ulceration ($p = 0.025$), oral ulceration ($p = 0.013$), arthritis ($p = 0.002$) and milder muscle disease both clinically (as determined by a lower ever Childhood Myositis Activity Score ($p = 0.0241$) and histologically (as determined by a lower JDM muscle biopsy score). Five out of 14 children had radiological evidence of interstitial lung disease (ILD) but none had RP-ILD. Despite these associations children with anti-MDA5 had an improved prognosis and a greater proportion achieved disease remission at 2 years post diagnosis according to PRINTO criteria ($p = 0.023$).

**Conclusion:** Anti-MDA5 antibodies can be identified in a small but significant proportion of UK children with JDM. They identify a distinctive subgroup with an increased risk of skin and oral ulceration, arthritis, ILD and milder muscle disease, both clinically and histologically. Screening for anti-MDA5 autoantibodies at diagnosis would be useful to guide further investigation for possible lung disease, inform on prognosis and potentially to confirm the diagnosis, as subtle biopsy changes could otherwise be missed.

Disclosure of interest: None declared.

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**P143**

**PreS-FINAL-2130-A: Effectiveness of intravenous cyclophosphamide in severe or refractory juvenile dermatomyositis - a national cohort study UK and Ireland**

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**Introduction:** Evidence suggests that early and aggressive treatment in Juvenile Dermatomyositis (JDM) improves outcome and prevents complications. Cyclophosphamide has been used as a second-line agent in the treatment of severe or refractory JDM. Published data on the effectiveness of cyclophosphamide in JDM are limited to a previous small case series and case reports.

**Objectives:** To describe the response to, and evaluate the effectiveness of intravenous-cyclophosphamide in the patients with JDM from the UK JDM National (UK and Ireland) Cohort and Biomarker Study and Repository for Idiopathic Inflammatory Myopathies.

**Methods:** The JDM National (UK and Ireland) Cohort and Biomarker Study and Repository for Idiopathic Inflammatory Myopathies (n = 410) prospectively collects clinical and laboratory data and samples on all children recruited to the study, using standardised protocols. 56 patients in the cohort were treated with cyclophosphamide between 2000-2011. Eight patients were excluded due to incomplete data or short follow up. The remaining 48 had a diagnosis of definite JDM, probable JDM or JDM overlap (Bohan and Peter criteria), with a minimum of 12 months follow up after the first dose of the cyclophosphamide. Demographic data, core set measures of disease activity, skin data, laboratory measures, treatment data were analysed at baseline, 6, 12, 18, 24 months and last follow up.

**Results:** Indicators for starting the cyclophosphamide were ulcerative or severe skin disease, profound muscle weakness, lung disease, gastrointestinal vasculopathy or refractory disease. All patients starting with muscle weakness (n = 44) significantly improved at 12 months, and the gains were maintained at follow up. Physician VAS was available at baseline for 32 patients and these all improved by 12 and 24 months, and for 31 remained stable at follow up. At last follow up, 26/46 (56%) had no rash, 32/46 (69%) had normal nailfolds, 37/45 (82%) had no Gottron’s, and calcinosis has resolved in 9/41 (46%). The steroid dose was decreased by 65.8% at 6 months, and the majority of patients were off steroids or on very low doses at 24 months. Patients receiving cyclophosphamide had a significant decrease in steroid dose by 6 months, with most of the patients coming off steroids between 18 and 24 months.

**Conclusion:** These data suggest that cyclophosphamide provides clinical benefit in JDM patients with severe or refractory disease, improving both muscle and skin domains.

Disclosure of interest: None declared.
Objectives: To identify a panel of mediators specially related to the inflammatory process in JDM, which might help in clinical assessment and in guiding treatment.

Methods: We performed a multiplex immunoassay and measured plasma levels of 45 inflammation related proteins in patients with four different disease stages determined by their clinical activity and their treatment. Peripheral blood and clinical data were collected in a prospective way from 25 patients diagnosed with JDM. 15 healthy children and 8 patients with non-autoimmune muscle disease served as controls.

Results: Patients with JDM at time of diagnosis had significantly higher levels of three proteins compared to patients in remission, patients with non-autoimmune muscle disease and healthy-age-matched controls.

Conclusion: Our results show that these three proteins (which are currently not named due to a pending patent application) correspond to the activation status during inflammation in JDM and might be instrumental in monitoring disease activity and treatment guiding.

Disclosure of interest: None declared.

Introduction: Since the development of the first biological agents, ongoing clinical trials and National marketing authorizations have led to the availability of several biologic agents, ongoing clinical trials and National marketing authorizations.

Methods: We performed a multiplex immunoassay and measured plasma levels of 45 inflammation related proteins in patients with four different disease stages determined by their clinical activity and their treatment. Peripheral blood and clinical data were collected in a prospective way from 25 patients diagnosed with JDM. 15 healthy children and 8 patients with non-autoimmune muscle disease served as controls.

Results: Patients with JDM at time of diagnosis had significantly higher levels of three proteins compared to patients in remission, patients with non-autoimmune muscle disease and healthy-age-matched controls.

Conclusion: Our results show that these three proteins (which are currently not named due to a pending patent application) correspond to the activation status during inflammation in JDM and might be instrumental in monitoring disease activity and treatment guiding.

Disclosure of interest: None declared.

Introduction: Assessment of disease activity is a fundamental component of the clinical evaluation of children with juvenile idiopathic arthritis (JIA) because persistently active disease plays a major role in causing joint damage and physical functional disability. Furthermore, measurement of the level of disease activity over time is important in monitoring the disease course and in assessing the effectiveness of therapeutic interventions.

Objectives: To determine cutoff values for defining the state of high disease activity (HDA) in juvenile idiopathic arthritis (JIA) using the Juvenile Arthritis Disease Activity Score (JADAS).

Methods: For the selection of cutoff values, data from a clinical database including 609 patients were used. Optimal cutoffs were determined against external criteria by calculating the 25th percentile of cumulative score distribution and through receiver operating characteristic curve analysis. External criteria were based on the therapeutic decision made by the attending physician at the time of the visit. The choice of cutoffs was made based on clinical and statistical grounds. Cross-validation was performed using 5 JIA patient samples that included a total of 1,421 patients, and was based on assessment of construct, discriminant, and predictive validity.

Results: The best performance in selecting the cutoffs was provided by the 25th percentile approach. The final JADAS cutoff values were the following: 7 and 11 for JADAS27 in oligoarthritis and polyarthritis, respectively; 8 and 12 for both JADAS10 and JADAS71 in oligoarthritis and polyarthritis, respectively. In cross-validation analyses, the cutoff values revealed strong ability to discriminate between different levels of ACR Pedi response in 2 clinical trials and revealed good concordance with the subjective evaluations of the physicians and the parents. Furthermore, they proved able to predict a worse functional and radiographic outcome.

Conclusion: Cutoff values for classifying HDA in JIA using the JADAS were developed. In cross-validation analyses, they proved to have good construct and discriminant validity and ability to predict disease outcome.

Disclosure of interest: None declared.

Introduction: Several biologic agents have become available for the treatment of systemic juvenile idiopathic arthritis (SJIA) over the last two decades. Prescription strategies may depend on disease course, which is heterogeneous and other factors including the availability of biological agents, ongoing clinical trials and National marketing authorizations.

Methods: A retrospective observational study was conducted on SJIA patients treated in a French pediatric rheumatology reference center using the CEMARA register, a nation-wide information system for rare diseases. We included patients who started bioterapy between 2005 and 2012 with a follow-up of at least 6 months after treatment initiation. Factors for switching or discontinuation of a biological agent were assessed.

Results: 74 SJIA patients were included, with 41 female and 33 male subjects and a median age of 4.1 years at diagnosis (range 9 months to 15.1 years). Median disease duration before starting the first biological agent was 17.3 months [range 1.7 to 107]. The cumulative follow up on biologics represented 266.5 patient-years. Concomitant treatment included non-steroidal anti-inflammatory drugs in 94%, systemic steroids in 84% and disease modifying anti-rheumatic drugs (7 methotrexate, 1 hydroxychloroquine, 1 leflunomide) in 12% at onset of biological treatment. First line biological agents were anakinra (ANA) in 45 patients, canakinumab (CAN) in 13, tocilizumab (TCZ) in 3, etanercept (ETA) in 12 and adalimumab (ADA) in 1 patient. At 3 months, drug survival for ANA versus CAN versus TCZ versus ETA as first-line biological therapy was 82% versus 100% versus 100% versus 67% percent, respectively. At 12/24 months, drug survival for ANA was 55/55%, for CAN 76/69%, for TCZ 67/67% and for ETA 58/58%, respectively. With first-line treatment, clinical remission was obtained in 55/69/67/9% of ANA/CAN/TCZ/ETA treated patients, respectively.

Conclusion: Switching to a second or third biological agent is an appropriate approach for treatment of SJIA. Median drug survival was comparable for ANA, CAN and TCZ when used as a first line biologic.

Disclosure of interest: A. Woerner Grant/Research Support from: Abbott/Abbvie, BMS, Chugai-Roche, Novartis, Pfizer, Servier, SOBI, R. Mouy Grant/Research Support from: Abbvie, Chugai-Roche, Novartis, Pfizer, Consultant for: Novartis, Consultant for: Roche, F. Uettwiller: None declared., B. Bader-Meunier Grant/Research Support from: Abbvie, Novartis, Consultant for: Roche, F. Uettwiller: None declared., I. Melki: None declared., D. Stern-Sordi: None declared., A. Dalmau: None declared., F. De Benedetti: None declared., E. Palmisani: None declared., S. Pederzoli: None declared., A. Pistorio: None declared., J. Wang: None declared., C. Wouters: None declared., P. Quartier Grant/Research Support from: Abbvie, Chugai-Roche, Novartis, Pfizer, Consultant for: Abbott/Abbvie, BMS, Chugai-Roche, Novartis, Pfizer, Servier, SOBI, R. Mouy Grant/Research Support from: Abbvie, Chugai-Roche, Novartis, Pfizer, Consultant for: Abbott/Abbvie, BMS, Chugai-Roche, Novartis, Pfizer, Servier, SOBI, C. Wouters: None declared., P. Quartier Grant/Research Support from: Abbvie, Chugai-Roche, Novartis, Pfizer, Consultant for: Abbott/Abbvie, BMS, Chugai-Roche, Novartis, Pfizer, Servier, SOBI, Speakers Bureau: Chugai-Roche, Novartis, Pfizer.

Disclosure of interest: None declared.
Table 1 (abstract P147)

<table>
<thead>
<tr>
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<th>Wk 52</th>
<th>Wk 104</th>
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</thead>
<tbody>
<tr>
<td>Ash score (n = 47), median (IQR)</td>
<td>0.00 (8.70: -4.00)</td>
<td>0.50 (-7.50: 12.00)</td>
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<tr>
<td>Poznanski score (n = 33), median (IQR)</td>
<td>0.30 (0.02: 1.03)</td>
<td>0.17 (0.01: 1.04)</td>
</tr>
<tr>
<td>ACR Pedi 70 (n = 112), n/N (%)</td>
<td>92/106 (86.8)</td>
<td>57/65 (87.7)</td>
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<tr>
<td>ACR Pedi 90 (n = 112), n/N (%)</td>
<td>67/106 (63.2)</td>
<td>46/65 (70.8)</td>
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</table>

Introduction: A phase 3 trial (TENDER) demonstrated the efficacy of the interleukin-6 receptor inhibitor TCZ in pts with sJIA [1,2].

Objectives: To investigate progression of radiographic joint damage in pts with sJIA treated with TCZ for up to 2 years in TENDER.

Methods: 112 pts 2-17 yrs old with active, refractory sJIA of ≥6 months’ duration and inadequate response to previous non-steroidal anti-inflammatory drugs and oral corticosteroids were enrolled in TENDER. Pts were randomised 2:1 to receive TCZ according to body weight (12 mg/kg <30 kg or 8 mg/kg ≥30 kg) or placebo IV every 2 wks for 12 wks. Pts then received open-label TCZ in the ongoing long-term extension. Radiographic progression was calculated as change in adapted Sharp/van der Heijde score (ash) score and/or Poznanski score, assessed on hand and wrist radiographs, from baseline to wks 52 and 104. Radiographic progression was indicated by a positive ash score change or negative Poznanski score change. Clinical efficacy endpoints included American College of Rheumatology (ACR) Paediatric (Pedi) 70/90 responses.

Results: Baseline and ≥1 postbaseline ash and Poznanski scores were available for 47 and 33 pts, respectively (reasons for missing x-rays: early withdrawal, no consent, unreadable x-rays). Baseline characteristics for pts with radiographic data were similar to the whole TCZ population [1]. Pts with assessable ash/Poznanski scores had 5.2/4.6-yr disease duration, 21.3/19.2 active joints, 20.0/18.2 joints with limitation of movement and erythrocyte sedimentation rates of 53.9/59.2 mm/h. At wks 52 and 104, 20 and 19 pts, respectively, had ash progression, and 8 and 6 pts, respectively, had Poznanski score progression. Median change in ash score from baseline to wks 52 and 104 were 0 and 0.5, respectively (Table). Median change in Poznanski score from baseline to wks 52 and 104 were 0.3 and 0.17, respectively (Table 1).

Conclusion: Though changes in radiographic scores over time were seen in many pts, on average, pts with sJIA did not experience noticeable progression of radiographic damage over 2 yrs of treatment with TCZ.

Disclosure of interest: C. Malattia: None declared., N. Ruperto: Grant/Research Support from: Abbott, Pfizer, BMS, Roche, Novimmune, Novartis, SOBI. A. Raveli: None declared.

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Reference:

P148

PRÈS-FINAL-2135: Analysis of the HLA region in a large cohort of juvenile idiopathic arthritis cases identifies independent effects at HLA-DRB1

Introduction: Juvenile idiopathic arthritis (JIA) is the most common arthritic disease of childhood and is caused by a combination of genes and environment. In the last few years great advances have been made in dissecting the genetic basis of JIA with now 17 confirmed susceptibility loci identified. One of these loci, the MHC region, has been established for many years but the complexity and the broad linkage disequilibrium (LD) across the region has rendered fine-mapping associations challenging. Novel imputation strategies can now be utilized to impute HLA classical alleles and amino acids across the region.

Objectives: The aim of this work was to gain a greater understanding of the associations across the HLA region in the 2 most common subtypes of JIA, oligoarthritis and rheumatoid factor-negative polyarthritis.

Methods: Using the dense genotype data obtained from the analysis of the custom-designed Illumina immunochip in 2816 JIA cases and 13056 controls, we imputed HLA classical alleles (2-digit and 4-digit resolution) and amino acids across the MHC region (Chr6:29-34 Mb) using the SNP2HLA algorithm and a large reference panel of 5225 individuals from the T1DGC consortium. We performed logistic regression for all markers across the region and tested all amino acids in HLA-DRB1 performing an omnibus test of amino acid residues for each position. Conditional analysis to identify potential independent effects was performed.

Results: We observed high correlation (0.99) between imputed and classically typed actual allele frequencies for HLA-DRB1 2-digit and 4-digit alleles for a subset of JIA cases (n = 394). The most significant association across the HLA region was for the phenylalanine residue at amino acid 67 of HLA-DRB1 OR = 3.03, p = 1 x 10^-79. The omnibus test for all amino acids across HLA-DRB1 showed most significant association at HLA-DRB1 amino acid 13 and conditioning on all residues at amino acid 13 found significant association remaining at HLA-DRB1 amino acid 67, suggesting two independent effects in HLA-DRB1.

Conclusion: Analysis of the MHC region in the largest cohort of JIA cases and controls studied to date has found the strongest association with the HLA-DRB1 region. Two independent effects have been identified, amino acid 67 and 13. Interestingly, amino acid 13 has previously been associated with adult rheumatoid arthritis (RA) whereas amino acid 67 has not. Further analysis to look for independent effects across the rest of the HLA region is now underway.

Disclosure of interest: None declared.

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P149
PreS-FINAL-2137: Adalimumab monotherapy results in clinical and radiological improvement in newly diagnosed patients with juvenile spondylarthristis (JSPA)/enthesitis related arthritis (ERA)

Introduction: Enthesitis related arthritis (ERA) is a chronic inflammatory disorder primarily affecting the axial skeleton as well as peripheral joints and entheses. DMARD’s are successful in controlling peripheral disease; however their effect is diminished when axial inflammation is present. The use of anti-TNF medications in adult patients with ankylosing spondylitis is well documented. Nevertheless, data regarding their use in children with the juvenile spondylarthristis (Jspa) are missing.

Objectives: To assess the efficacy and safety of adalimumab, if a fully humanized anti-TNF monoclonal antibody, as monotherapy in Jspa/ERA.

Methods: 16 patients (9 females, 7 males; mean age: 10 years) who met the EULAR criteria for ERA and the ASAS criteria for AS were enrolled. Following NSAID treatment failure, the patients received 24 mg/m2 of adalimumab subcutaneously every 4 days for 12 months. Patients had MRI proven sacroiliitis, inflammatory lumbar pain (ILP) and were HLA-B27 positive. Outcome measures were presence of morning stiffness, duration of morning stiffness, CRP measurement, pain assessment (based on 10 cm Visual Analog Scale-VAS) and physician assessment (based on 10 cm VAS). Mean time from diagnosis to initiation of treatment was 4 months (range 3-7 months), while from the onset of symptoms till the beginning treatment mean time was 12 months (range 5-28 months). Patients were reviewed at 3, 6, 9 and 12 months following initiation of treatment and had repeat MRI scans at 3 and 9 months.

Results: At the beginning of the study all patients had ILP (mean pain VAS 6.8 cm), morning stiffness with a mean duration of 75 min and positive MRI findings. Mean physician VAS was 4.6 cm and mean CRP 69 mg/dl (range: 25-102 mg/dl). At three months the mean CRP was 18 mg/dl, physician VAS was 1.9 cm, pain VAS 1.6 cm; morning stiffness improved by 80% and 57% of patients showed improved MRI findings. Reassessment at 6 months showed improvement of morning stiffness (18%) and its duration (9 min) as well as further improvement in mean physician VAS (1.2 cm) and pain VAS (1 cm). At 9 months mild further reduction in the prevalence (13%) and duration of morning stiffness (7 min) and improvement in physician VAS (0.5 cm) and pain VAS (0.7 cm) was recorded. Mean CRP was 9 mg/dl. 19% of patients showed persistent although improved MRI findings. The majority of these children had bilateral sacroiliitis in the beginning of the study. At 12 months 8% had morning stiffness, and its mean duration was unchanged (7 min). Mean pain and physician VAS values were similar to those at nine months (physician VAS 0.3 cm, pain VAS 0.5 cm). Mild-moderate adverse reactions were seen in 37%.

Conclusion: This is a novel study in the pediatric population showing that adalimumab monotherapy in early stages of Jspa/ERA is effective and safe. Adalimumab leads to early remission as defined by reduction of pain and stiffness. Overall, patient improvement is gradual and sustained. No further improvement was noted beyond 9 months of treatment. MRI findings show slower improvement; however 19% of patients had radiological evidence of inflammation at nine months. More studies are required to prove its long-term benefit and safety.

Disclosure of interest: None declared.

P151
PreS-FINAL-2139: Tapering and withdrawal of tocilizumab in patients with systemic JIA in inactive disease: results from an alternative dosing regimen in the tender study

Introduction: Tocilizumab (TCZ) is an anti-IL-6 receptor monoclonal antibody that has demonstrated efficacy in the treatment of juvenile idiopathic arthritis (JIA). TCZ is approved for the treatment of systemic JIA and polyarticular JIA, and is given subcutaneously at a dose of 8 mg/kg every 4 weeks. However, the optimal duration of treatment and the best strategy for tapering and withdrawal of TCZ in patients with systemic JIA in inactive disease is not yet clear.

Objectives: The primary objective of this study was to evaluate the safety and tolerability of tapering and withdrawal of TCZ in patients with systemic JIA in inactive disease. The secondary objectives were to evaluate the efficacy and clinical benefit of tapering and withdrawal of TCZ in patients with systemic JIA in inactive disease.

Methods: This was a multi-center, open-label, non-interventional study conducted in Europe and the United States. Patients aged 2-17 years with systemic JIA in inactive disease were enrolled. Patients were treated with TCZ at a dose of 8 mg/kg every 4 weeks for 12 months. After 12 months, patients were tapered to a dose of 4 mg/kg every 4 weeks for 4 weeks, followed by a dose of 2 mg/kg every 4 weeks for 4 weeks. Finally, patients were tapered to a dose of 1 mg/kg every 4 weeks for 4 weeks, and then the treatment was withdrawn. The primary endpoint was the occurrence of any adverse event during the tapering and withdrawal phase.

Results: A total of 24 patients were enrolled in the study. The mean duration of treatment was 12 months. At the end of the tapering and withdrawal phase, 22 patients remained in the study. The most common adverse events were upper respiratory tract infections (12 patients), infusion-related reactions (8 patients), and injection-site reactions (7 patients). No serious adverse events were reported. The efficacy and clinical benefit of tapering and withdrawal of TCZ were similar to the findings from previous studies.

Conclusion: This study demonstrates that tapering and withdrawal of TCZ in patients with systemic JIA in inactive disease is safe and effective. This information is important for clinicians when deciding on the optimal duration of treatment and the best strategy for tapering and withdrawal of TCZ in patients with systemic JIA in inactive disease.

Disclosure of interest: None declared.
prolongation of the time interval between TCZ infusions from 2 weeks (standard interval) to 3 weeks, then 4 weeks, with the option of prolongation of the time interval between TCZ infusions from 2 weeks to 3 weeks, then 4 weeks, with the option of

Results: 23 male and 16 female patients entered the OADS. Their mean baseline characteristics were 14.2 active joints, 15.4 joints with limitation of motion (LOM), physician global VAS score of 58.5, CHAQ-DI score of 1.62 and ESR of 56.8; 15 had fever. Of these 39 patients, 13 patients lost clinically inactive disease status while on the OADS. In these 13 patients, the time to loss of inactive disease status ranged from 1.4 to 16.8 months from initiation of the OADS (n = 4 on 3 weekly dosing, n = 6 on 4 weekly dosing, n = 3 on e-TZ). Risk of losing inactive disease status on OADS was similar in patients treated with MTX (6/16, 37.5% flared) and in those not receiving MTX (7/23, 30% flared). Inactive disease status was maintained in 26 of the 39 patients entering the OADS. Present dosing intervals were every 3 weeks in 3 pts and every 4 weeks in 14 pts; 9 pts have been able to discontinue TCZ (range of time since discontinuation: 3.6-13.4 months). At baseline, 9 pts were clinically similar to other pts entering the OADS (mean characteristics: age 9.1 years, 10.9 active joints, 10.9 joints with LOM, physician global VAS score of 45.4, CHAQ-DI score of 1.42, ESR of 47.2; 4 pts with fever at baseline).

Conclusion: Patients with sJIA who maintain clinically inactive disease status may progressively space TCZ infusions, with one-fourth of them able to discontinue treatments, including TCZ.


P152
PreS-FINAL-2140: Neutropenia with Tocilizumab (TCZ) treatment is not associated with increased infection risk in patients with systemic juvenile idiopathic arthritis (sJIA)
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Pediatric Rheumatology 2013, 11(Suppl 2):P152

Introduction: In the phase 3 TENDER trial of TCZ treatment in patients with sJIA, decreases in neutrophil count were commonly observed.

Objective: To determine if neutropenia was associated with increased risk of infections in patients treated with TCZ for up to 2 years in TENDER.

Methods: 112 children with active, persistent sJIA were randomised 2:1 to receive TCZ by body weight (12 mg/kg <30 kg or 8 mg/kg ≥30 kg) or placebo IV every 2 weeks for 12 weeks and continued in an ongoing, TCZ open-label extension. [1]. Worst common toxicity criteria (CTC) neutropenia grade (grade 1, ≤1.5 and <2.0 × 109/L; grade 2, ≥1.0 and <1.5 × 109/L; grade 3, ≥0.5 and <1.0 × 109/L; grade 4, <0.5 × 109/L) and lowest observed neutrophil count (107/L) were identified for each patient. Univariate linear regression analysis was performed to investigate association of patient characteristics with lowest observed neutrophil count. Rates of infections and serious infections (per 100 patient years [PY]) in periods ±15 days around grade 1-2 neutropenia (22.9 PY) and around grade 3-4 neutropenia (5.5 PY) were compared to corresponding rates in periods with normal neutrophil count (173.6 PY).

Results: Up to 1004, 64/112 patients (57.1%) had at least 1 episode of grade 1-4 neutropenia; worst grade: 1 (n = 2), 2 (n = 34), 3 (n = 26) and 4 (n = 2). Rates of infections and serious infections during period of normal neutrophil counts (276.5/100PY [95% CI 252.3, 302.3] and 11.5/ 100PY [95% CI 7.0, 17.8], respectively) were comparable to those observed ±15 days around grade 1-2 neutropenia (226.7/100PY [95% CI 169.3, 297.3]; 8.7/100PY [95% CI 1.1, 31.5]) and grade 3-4 neutropenia (292.5/100PY [95% CI 167.2, 475.0]; 0/100PY), with no trend towards increased risk with higher grade neutropenia. Methotrexate (MTX) use (Yes/No) was significantly associated with lowest observed neutrophil count (difference: -0.575 [95% CI: -1.02, -0.13], p = 0.012), with 62% of 77 patients receiving MTX vs 46% of 35 patients not receiving MTX having grade 1-4 neutropenia. Younger age was borderline associated with lowest observed neutrophil count (β = 0.04661, p = 0.047). Concurrent use of glucocorticoids (GC) and TCZ exposure were not associated with lowest observed neutrophil count (p<0.3).

Conclusion: No trend for association between neutropenia and increased risk of infections was observed in the TENDER trial. Background MTX, and somewhat younger age, was associated with increased risk for neutropenia, while TCZ exposure and concurrent GC use were not.


Reference

P153
PreS-FINAL-2141: Clinical features, therapeutic interventions and outcome of 362 patients with macrophage activation syndrome enrolled in a multinational observational study-
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**Introduction:** A multinational collaborative effort aimed to develop a new set of criteria for macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (sJIA) is ongoing. The data-collection phase of the project has been recently completed.

**Objectives:** To describe the demographic, clinical, laboratory, and histopathologic features, therapeutic interventions and outcome of 362 children with MAS collected in the study.

**Methods:** Patient data were collected retrospectively in a web-based database, developed and handled at the coordinating centre (Istituto G. Gaslini, Genoa, Italy).

**Results:** 362 patients with sJIA-associated MAS were entered in the study website by 95 investigators (78.2% paediatric rheumatologists, 21.8% paediatric hematol- oncologists) from 33 countries. 208 patients (57.5%) were females. Median age at onset of sJIA was 5.3 years (IQR 2.7-10.1 years) and median disease duration at onset of MAS was 3.5 months (IQR 0.1-2.6 years); MAS occurred at onset of sJIA in 77 patients (22.2%). The most frequently observed clinical features were fever (96%), liver enlargement (70%) and spleen enlargement (58%); CNS involvement was reported in 122 patients (35%) and haemorrhagic manifestations in 71 patients (20%).

The main laboratory abnormalities were: hyperferritinemia, increased D-dimer and liver enzymes, falling platelet count, hypertriglyceridemia and increased LDH. The most frequently reported trigger of MAS was sJIA flare (53.8%), followed by infections (37.8%) and medication toxicity (4.3%).

**Conclusion:** Fever and hepatosplenomegaly were the most frequently reported clinical features. Hyperferritinemia, increased liver enzymes, LDH, triglycerides and D-dimer and falling platelet count were the sole laboratory abnormalities that showed a percentage change greater than 50% between pre-MAS visit and onset of MAS. Hemophagocytosis was seen in 2/3 of patients who underwent bone marrow aspirate. Therapeutic interventions included corticosteroids (97.7%), cyclosporine (61.2%), Ig IV (36.3%), biologic medications (15.2%), etoposide (11.8%), other immunosuppressants (7.1%) and plasma exchange (4.1%). ICU admission was required in 34.9% of patients; the mortality rate was 8.1%.

**Disclosure of interest:** None declared.

**P154**

**PrEs-FINAL-2142: Predictors of persistent remission following etanercept (ETN) withdrawal in patients with juvenile idiopathic arthritis (JIA)**

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**Introduction:** At present, no guidelines on the appropriate withdrawal of ETN in JIA patients in clinical remission exist. The identification of predictors of clinical remission off medication (CROM) in these patients represents a key step in their development.

**Objectives:** To evaluate the rate of CROM in JIA patients after ETN withdrawal; to identify predictors of CROM in these patients.

**Methods:** Retrospective data of polyarticular JIA patients who discontinued ETN due to clinical remission on therapy and had a follow-up period after ETN withdrawal of at least 12 months were collected, including: age, number and type of active joints at disease onset, sex, ANA status, disease duration before ETN start, number and type of active joints, ESR, and CRP at the time of ETN start, duration of clinical remission on medication and off-medication. Based on their clinical course after ETN withdrawal, patients were divided into 2 groups: 1) with CROM 2) with disease flare. Demographic, clinical and laboratory features were compared between the two groups.

**Results:** A total of 49 patients were included in the study. 11 patients (22.4%) achieved CROM, while 77.6% experienced a disease flare after a median of 4.8 months (IQ 2.9-9.2). Patients with CROM showed a significantly lower frequency of ANA positivity, ESR values < 20 mm/1 h and ankle involvement at the beginning of ETN treatment than those who relapsed (respectively, p = 0.034, 0.044 and 0.008). None of the other parameters showed any difference in the two groups.

**Conclusion:** Only 1/5 of JIA patients in our cohort achieved CROM. Children with ANA negativity, ESR < 20 mm/1 h and without ankle involvement have had a greater likelihood of achieving CROM. Further prospective studies with longer follow-up are needed to confirm these results.

**Disclosure of interest:** None declared.

**P155**

**PReS-FINAL-2143: Treat-to-target strategy in juvenile idiopathic arthritis: experience in 175 newly-diagnosed patients**

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**Introduction:** The recent advances in the management of juvenile idiopathic arthritis (JIA) have increased considerably the potential to achieve disease remission or, at least, low levels of disease activity, and have consequently moved the therapeutic aims towards the attainment of inactive disease (ID). Complete disease quiescence is regarded as the ideal therapeutic target because its achievement helps preventing further joint damage and disability and may enhance physical function and quality of life.

**Objectives:** These issues have led to suggest that a tight control approach should be adopted in the management of JIA. We describe our experience with treat-to-target strategy.

**Methods:** Starting in March 2007, a treat-to-target approach to the management of all children with JIA first seen in the senior author's clinic was implemented, setting achievement of ID as primary goal and of minimal disease activity (MDA) or parent-acceptable symptom state (PASS) as secondary goals. In case primary goal was not reached, treatment was intensified as deemed necessary. Patient records were reviewed to evaluate the frequency of achievement of the therapeutic goals at 6, 12, 18 and 24 months following initial evaluation. ID, MDA and PASS were defined according to both established criteria and Juvenile Arthritis Disease Activity Score (JADAS) cutoffs. The outcome of patients who achieved or did not achieve ID at last follow-up visit was compared by means of the Juvenile Arthritis Functionality Scale (JAFS) and the Pediatric Rheumatology Quality of Life scale (PReQoL).

**Results:** A total of 175 patients (77.7% females) were enrolled. The most common ILAR subtypes were persistent oligoarthritis (53.1%), extended oligoarthritis (14.9%), and RF-negative polyarthritis (14.3%). 3.4% of patients had systemic arthritis. The median age at disease onset was 2.8 years. At baseline visit, the median age was 3.5 years and the median disease duration was 0.2 years. Initial therapeutic interventions included intra-articular corticosteroid injection (84%), methotrexate (28%), systemic corticosteroids (5.7%), and biologic medications (1.1%). The frequency of achievement of treatment goals at study endpoints is shown in the table. At last follow-up visit, patients who had achieved ID had better functional ability (p = 0.007) and physical well-being (p = 0.007) than those who did not. The frequency of clinical remission on medication was 29.2% (Table 1).

**Conclusion:** At 2 years after initial visit, a substantial percentage of patients had reached the states of ID or MDA or were in PASS. Patients who achieved ID had better physical function and well-being than those who did not. These findings suggest that the implementation of a treat-to-target approach may help improve patient outcomes.

**Disclosure of interest:** None declared.
Table 1 (abstract P155)

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<td>Minimal disease activity (MDA)</td>
<td>Parent-acceptable symptom state (PASS)</td>
<td>JADAS10 ≤ 1 (ID)</td>
<td>JADAS10 ≤ 2/3.8 (MDA)</td>
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**P156**

**PRES-FINAL-214: Bone mineral status in patients with juvenile idiopathic arthritis after 12 months of treatment with etanercept**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P156**

**Introduction:** Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease of childhood. It is associated with decreased bone mineral density (BMD), as result of disturbance of bone metabolism which develops gradually and progressively influenced by many factors, presumably by disease severity.

**Objectives:** To examine bone mineral status in patients with JIA after 12 months of treatment with etanercept (ETN).

**Methods:** In prospective study of 63 polyarticular JIA pts (46 F, 17 M), median age 15 yrs. Treated with ETN 0.4 mg/kg/2x week. BMD and bone mineral content (BMC) by dual x-ray absorptiometry on the lumbar spine (L2-L4) were assessed. For statistical analysis Z score and bmdval were taken as well. ACR pedi 50 criteria (physician global assessment-PGA, parent’s/ patient’s global assessment, No of joints with limited range of motion-LOM, No of joints with active arthritis, functional ability assessment using CHAQ-Serbian version and ESR) were done at the baseline and one year later.

**Results:** We found significant improvement in all six variables represented disease activity, after 12 mo of treatment with ETN (PGA 80%, parent’s/ patient’s global assessment 56%, No of LOM joints 68%, No joints with active arthritis 89%, functional ability 66%, ESR 37% (p < 0.001). At the last visit 54 (85.7%) pts met the ACR pedi 50 criteria, assigned as responders (Group I), while 9 (14.3%) were non-responders (Group II). After one year of treatment with ETN it was shown high statistically significant increment in all osteodensitometry variables (p < 0.001). Annual enhancement for BMC was 11.7%, for BMD 6.1%, for bmdval 3.4% for whole group. Z score improved from -1.03 to -0.81 SD at the last visit. Comparing annually difference of BMD between responders and non-responders we found statistically significant improvement in the first group (6.78% vs. -2.23%, p < 0.02) as well bmdval (4.31% vs. -0.87%, p < 0.013).

**Conclusion:** Our results confirmed significant suppression of disease activity and improvement of bone mineral status in children with JIA after 12 months of treatment with ETN. Thus reasonable therapeutic approach in preventing osteoporosis in the later life are the new therapeutic options as ETN that could have protective role at structural bone damage.

**Disclosure of interest:** None declared.

**P157**

**PRES-FINAL-2145: MRBP/14 serum complexes as predictor of response to etanercept treatment in juvenile idiopathic arthritis**

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Introduction: Treatment of juvenile idiopathic arthritis (JIA) has changed dramatically since the introduction of biologicals in 1999. Because of more insight in the cytokines involved in JIA the number of available biologic agents increased. Together with the introduction of these new drugs, new insights in the optimal treatment of JIA indicate that earlier and more aggressive therapy is associated with better outcomes. Whether these developments with regard to biologic treatment have resulted in better patients' outcomes in daily practice is not yet reported. 

Objectives: To evaluate trends in prescription of biologics and influence on outcomes of Dutch JIA patients that started their first biologic between 1999 and 2010.

Methods: The Arthritis and Biologicals in Children register (a multicenter prospective observational study) aims to include all JIA patients in the Netherlands who use or used biologic agents since 1999. Patients were divided in time periods according to the year of introduction of first biologic agent. Trends in characteristics of patients before introduction of first biologic and effectiveness of the first biologic were analyzed over a 12 year period.

Results: 343 non-systemic and 86 systemic JIA patients started at least 1 biologic agent between 1999 and 2010. Etanercept remained biologic of first choice for non-systemic JIA and anakinra has become first choice for systemic JIA. The use of systemic prednisone and synthetic disease-modifying anti-rheumatic drugs (besides methotrexate) prior to biologics decreased. During these 12 years of observation, biologics were prescribed after shorter disease duration; the proportion of patients with less than 1.5 years of disease duration before start of the first biologic agent increased from zero in the years 1999-2001 to 31% in 2008-2010. Disease activity and acquired sequelae at baseline decreased with regard to number of joints with arthritis (median of 18 in 1999-2001 decreased to 5 in 2008-2010), number of joints with limited motion (median of 12 in 1999-2001 decreased to 3 in 2008-2010) and functional disability (CHAQ) scores (median score of 1.8 in 1999-2001 decreased to 1.1 in 2008-2010). In systemic biologics are now being introduced in patients with higher ESR values. These changes resulted in more patients with inactive disease and less joints with limited motion after 3 and 15 months of treatment in all JIA categories.

Conclusion: Biologics are prescribed increasingly, are introduced earlier during the disease course and in JIA patients with lower disease activity. These changes are accompanied by better short-term disease outcomes. Etanercept remains biologic of first choice for non-systemic JIA and anakinra has become first choice for systemic JIA.

Disclosure of interest: None declared.
PA levels in children with JIA an internet-based program has been developed. A pilot showed to be effective in improving PA and exercise capacity in children with JIA.

Objectives: The aim of this multicenter study is to explore the efficacy of an internet based cognitive behavioural intervention Rheumat@work on PA and exercise capacity.

Methods: We performed a randomized controlled trial. Patients with JIA aged 8-12 year, with access to internet were selected for this study. PA was measured with a 7-day activity diary and an Actical accelerometer. PA level was categorized by time spend on moderate to vigorous PA and the number of days with 1 hour of moderate to vigorous PA. Aerobic exercise capacity was assessed by the Bruce treadmill test expressed by walking time. Disease activity was assessed by using the JIA core set. Adherence was electronically monitored. Patients with low physical activity defined as equal to or less than three days of one hour of moderate to vigorous PA or with a low exercise capacity defined as less than 50% on the Bruce treadmill test were included.

Results: Out of 83 selected patients, 49 eligible patients were included and randomized in the intervention (n = 28) and control waiting list group (n = 21). Adherence was good 26 out of 28 patients (93%) completed the program. The intervention group improved significantly in exercise capacity (p<0.01), and in number of minutes spend on vigorous activity (p<0.001). The control group did not improve significant. Disease activity did not increase in both groups.

Conclusion: Preliminary results show that the internet based cognitive behavioural program rheumat@work was effective in improving exercise capacity and stimulated the patients to be more vigorously active. Rheumat@work is safe to administer.

Disclosure of interest: None declared.

P162
PreS-FINAL-2150: Anticocular autoantibodies in children with juvenile idiopathic arthritis-associated uveitis
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Introduction: Juvenile idiopathic arthritis (JIA) is the most common disease associated with uveitis of childhood. The pathogenesis of JIA-associated uveitis (JIAU) is undefined, although there is evidence for a B-cell-mediated autoimmune process with a probably pathogenetic role for autoantibodies.

Objectives: This study intended to analyze the anticocular autoantibodies in serum and their correlation with disease course.

Methods: Serum samples from children with JIAU (n = 47), JIA without uveitis (n = 67), idiopathic anterior uveitis (IAU, n = 12) and healthy controls (n = 52) were collected. The binding patterns of serum antibodies to ocular cyrossections from swine eyes were analyzed by indirect immunohistochemistry, and were correlated to epidemiological, clinical and laboratory test results.

Results: The patient groups differed with respect to their presence of antibody-binding to the sections: JIAU (94%), JIA (75%), IAU (75%), and healthy controls (29%) to uveal and/or retinal structures. Serum antibodies of JIAU patients predominantly bound at iris (74%) and ciliary body (cb, 79%). Iris/cb positive staining correlated with the presence of uveitis complications (p < 0.005) in JIAU patients, but not with positivity for serum anti-nuclear antibodies (ANA), rheumatoid factor (RF) or HLA-B27, and was independent from uveitis activity or type of anti-inflammatory treatment.

Conclusion: In JIAU patients, anti-ocular serum antibodies can be detected more frequently than in control groups. Binding patterns to ocular tissue correlate with complicated uveitis course but not with uveitis activity and anti-inflammatory treatment. Antibody-binding is not specific for this uveitis entity, and does not correlate with ANA-positivity.

Disclosure of interest: None declared.

P163
PreS-FINAL-2151: The shared genetic master-key genes leading to development of undifferentiated spondyloarthitis/era in children
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Introduction: Undifferentiated spondyloarthitis/era in children (undifferentiated spondyloarthitis/era in children (USPEN)). The genetic basis of USPEN is not clear.

Objectives: The USPEN project is focused on the genetic architecture of USPEN. To date, the analyses focused on the genome-wide association analysis (GWAA) of USPEN.

Methods: GWAA using a mini-genotyping array containing 300 markers was performed in cohort of Caucasian children recruited to CLARIETY. The SNPs were genotyped in two independent Caucasian cohorts.

Results: Two SNPs were found to be associated with USPEN. The first SNP rs1155563 was associated with USPEN in all cohorts (odds ratio = 1.71; 95% CI: 1.25–2.32; p = 0.001). The second SNP rs254151 was associated with USPEN in all cohorts (odds ratio = 1.59; 95% CI: 1.12–2.24; p = 0.01). A meta-analysis of the GWAA results in both cohorts showed that the genotypes of the SNP rs1155563 were associated with USPEN in Caucasian children (odds ratio = 1.71; 95% CI: 1.25–2.32; p = 0.001). The genotypes of the SNP rs254151 were associated with USPEN in Caucasian children (odds ratio = 1.59; 95% CI: 1.12–2.24; p = 0.01).

Conclusion: The GWAA results suggest that the SNPs rs1155563 and rs254151 are associated with USPEN in Caucasian children. Further studies are needed to confirm these findings.
Introduction: Enthesis related arthritis (era) represent an undifferentiated form of spondyloarthritis (spa), distinguishing it from other subtypes of JIA for optimum treatment and outcome, as well as for studies aimed at understanding genetic predisposition and pathogenesis. Majority of these studies focused on genome associations within MHC, only few searched for connections outside of this region and only some analyzed transcriptome of era patients. Our preliminary results of gene expression profiling in PBMC of 11 new onset and untreated patients diagnosed with era, identified 744 differently expressed genes.

Objectives: To validate results of gene expression analysis in groups of patients diagnosed with era and other subtypes of JIA.

Methods: Based on extensive and diligent statistical analysis, ten genes (CXC4R, NLRP3, PTPRN2, TLR4, DUSP6, MAP2K2, MAPKBP1, MYST3, PTPN12, TNFSF4) were selected for further RT-PCR analysis in four groups of era patients selected according to ILAR criteria (N = 56): untreated era patients with obtained expression profile (P1 = 11; B7, 2 B27), untreated era patients (P2 = 10; 2 B7, 6 B27), treated era patients (P3 = 24; 5 B7, 12 B27, 1 B7/B27) and treated JIA patients (P4 = 11). All groups were compared to healthy controls (N = 12). For all era patients HLA typing was performed.

Results: Statistically significant (p < 0.05) fold change (FC) was found for CXC4R (FC 1.89), TLR4 (FC 4.36), MAPKBP1 (FC -3.13) and PTPN12 (FC -3.70) in P1 group, CXC4R (FC 1.87), NLRP3 (FC -5), PTPRN2 (FC -5.55), TLR4 (FC 3.91) and PTPN12 (FC -2.63) in P2 group, CXC4R (FC 1.37), NLRP3 (FC -3.71), MAPKBP1 (FC -1.82), PTPN12 (FC -2.44) and TNFSF4 (FC -1.52) in P3 group and PTPN12 (FC -5) in P4 group.

Conclusion: Majority of genes with significant FC had a role in NF-kb and MAPK pathways, which are important for regulation of immune response. TLR-4 is known activator of inflammatory cascade that involves NLRP3, and is responsible for secretion of proinflammatory cytokines, while PTPN12 negatively regulates TLR-triggered innate response and lymphocyte activation. Hence, lower expression of PTPN12 can boost immune response. CXC4R triggers MAPK signaling in response to LPS, and recruits inflammatory cells. CXC4R showed higher expression in all groups of era patients, regardless of treatment, and PTPN12 showed lower expression even in group of other JIA patients, which could indicate an important role of these genes in pathogenesis of era and other JIA subtypes. TLR4 showed higher expression in untreated era patients, suggesting that standard treatment could influence this gene expression. Interestingly, NLRP3 showed lower expression in group of treated and untreated patients with era. Polymorphisms of NLRP3 that causes decreased gene expression and IL-1β production were linked with increased susceptibility to Chron’s disease, while polymorphisms of PTPN12 gene were identified in autoinflammatory diseases. Further on, oncology studies showed PTPN12 gene could be silenced by methylation. Precise mechanism responsible for lower expression of these genes in era and other JIA patients still needs to be clarified.

Disclosure of interest: None declared.

P165
PReS-FINAL-2153: Intestinal gamma/delta- T cells are upregulated in children with active uveitis

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Introduction: In experimental uveitis, activated γδ-T lymphocytes produce cytokines, which contribute to differentiation of pathogenic effector T-cells. In addition mucosal tolerance in experimental uveitis can be induced by introducing uveitogenic retinal soluble antigen orally and this phenomenon is dependent on γδ T cells. The major reservoir for γδ T cells is intestinal mucosa, where they function in safeguarding the integrity of the epithelial barrier. Abnormal activation of these intraepithelial γδ-T-cells may contribute to immunopathological responses which can even present themselves as extraintestinal manifestations. ANA-positive in JIA is associated both with uveitis and accumulation of γδ- T cells with gut-associated subtype in synovium.

Objectives: Our objective was to assess the potential association of intestinal mucosal γδ-T-cell subsets with uveitis in patients with JIA and gastrointestinal symptoms.

Methods: Duodenal mucosal samples were taken from patients with JIA and gastrointestinal symptoms (n = 13). γδ-T- cells and γδ- T cells were immunohistochemically stained in frozen sections. Intestinal mucosal γδ/ and α/β- intraepithelial cells were quantitated from duodenal mucosal samples by an assessor blinded for all clinical data.

Results: Patients with active uveitis (n = 4) during endoscopy had higher α/β- T cell (19, 14-23) and γδ- T cell counts (2.7, 2.1-3.4) in duodenal biopsies compared with patients without uveitis (n = 9) (13, 4-22; p = 0.05; 0.7, 0- 4.9; p = 0.034; Mann-Whitney U-test).

Conclusion: Our finding suggests, that intestinal immune activation involving the increase of γδ lymphocytes contributes to the pathogenesis of uveitis in children with JIA. Although both the factors inducing the intestinal mucosal immune activation in JIA and the mechanism linking intestinal activation and uveitis remain speculative, we suspect that pathological entry of the gut originating lymphocytes into the iris is possible because intensive distribution of the adhesion molecules on the endothelium of the vessels in the iris in patients with uveitis. Our finding encourages to study the potential role of gastrointestinal factors in the pathogenesis of uveitis associated with JIA. Our finding together with
reports of experimental autoimmune uveitis models support the hypothesis of gut mucosa, gut lymphocyte homing receptors in the uvea, and the role of gut originating lymphocytes in the development of uveitis.

**Disclosure of interest:** None declared.

**P166**

**PReS-FINAL-2154: The early predictors of fatal outcome of macrophage activation syndrome in pediatric rheumatic diseases**

**Introduction:** Macrophage activation syndrome (MAS) - is a severe life-threatening hematological condition, complicated different rheumatic diseases. MAS is characterized by uncontrolled proliferation of T cells and macrophages, associated with decreased natural killer (NK) cells and cytotoxic T cell function due to mutations in perforin gene.

**Objectives:** The aim of our study was to evaluate early predictors associated with fatal outcomes in pediatric rheumatic disease. These clinical and biomarkers can be useful in the measurement of severity MAS.

**Methods:** We have performed retrospective study. Medical charts of children with definite MAS were admitted to our rheumatology department in 2005-2013 were reviewed. We utilized the A.Ravelli criteria (2002) for detecting MAS. We used the main characteristic clinical and laboratorial markers of MAS only at the moment of MAS confirmation (± 3 days). The patients who developed MAS in the terminal stage (irreversible polyorgan damage) were excluded. We evaluated demographic data, data related to MAS. Also we calculated cutoff points for fatal outcomes (ROC-analysis), performed analysis of sensitivity and specificity and identified predictors with Log-Rank analysis and Kaplan-Meier survival curves.

**Results:** 23 patients (9 boys and 14 girls) with SLE (n = 2), AAV (n = 2), SJIA (n = 17) and virus-associated HLH (n = 2) were included. Median age of MAS was 7.4 years (range:1.5 mo-16.8 y), median time between disease onset and MAS onset 11.4 mo (range:0.4-93.6 mo) and median duration of MAS episode 68 days (range:11-336 days). Fatal outcome was in 4 patients (2 SLE, 1 AAV, 1 SJIA). The main predictors of fatal outcomes were: onset of disease>10.15 years (OR = 42.4, p = 0.004) ongoing glucocorticoid treatment at the time of MAS onset (OR = 63.0, p = 0.008), flare or active course of background rheumatic disease (p = 0.015), low sodium Nasc123 mmol/l (OR = 93.0, p = 0.001), no splenomegaly (p = 0.023), no lymphadenopathy (OR = 16.0, p = 0.04), hemorrhagic syndrome (OR = 31.0, p = 0.015), central nervous system involvement (p = 0.015), WBC < 2400 cells in μl (OR = 54.0, p = 0.0001), Prothrombin < 43% (OR = 290, p = 0.002) and ESR >56 mm/h (OR = 30.0, p = 0.0007).

**Conclusion:** We detected several clinical and laboratorial markers which reflect the severity of MAS. Presence of these signs at onset of MAS can early differentiate the prognostic unfavorable group which required more intensive care.

**Disclosure of interest:** None declared.

**P167**

**PReS-FINAL-2155: Genetic variability of methotrexate transporters in patients with juvenile idiopathic arthritis**

**Introduction:** Factors that would predict treatment outcome for methotrexate (MTX) would be of great value to clinicians. Recent pharmacogenetic studies have reported associations between single nucleotide polymorphisms (SNP) in MTX transporters and treatment outcome in childhood acute lymphoblastic leukemia and in rheumatoid arthritis.

**Objectives:** To investigate the influence of SNP in the genes for MTX transporters and treatment outcome for JIA. Methods: The data of 77 consecutive patients with JIA treated with MTX at the University Children's Hospital Ljubljana from June 2011 to February 2013 have been retrospectively reviewed. The disease activity was measured by JADAS 71 score 3 and 6 months after the beginning of treatment with MTX and at the last follow up visit. All adverse events were noted separately for different organ systems. Genotyping of single nucleotide polymorphisms (SNP) in the genes of MTX transporters was performed using real time PCR methods. The analysed SNPs were: ABCB1 3435C>T (rs1045642), ABCB2 24C>T (rs717620), ABCB2 1019A>G (rs2804402), ABCB2 1249G>A (rs2273697), ABCG2 34G>A (rs2231137), ABCG2 421C>A (rs 2231142), SLCO1B1 174Ala>Val (rs4149056), SLCO1B1 388 A>G (rs206283), SLCO1B1 int13 T>C (rs11045879) and SLCA9A1 (RFC1) 80G>A (rs1051266). Chi-square test and logistic regression were used for the statistical analysis.

**Results:** The study group included 54 girls (70%) and 23 boys (30%) with JIA at mean disease duration 63 months. Nine (12%) patients had systemic arthritis, 23 (30%) patients had polyarthritis (4 out of these were RF positive), 15 (19%) patients had persistent oligoarthritis, 14 (18%) extended oligoarthritis, 10 (13%) patients had juvenile psoriatic arthritis and one (1%) patient suffered from enthesitis related arthritis. Five (6%) patients were treated with MTX because of chronic idiopathic uveitis. Mean follow up time was 80 months. Thirteen out of 77 (17%) patients were in remission without therapy at the last follow up visit. In total 37 out of 77 patients (48%) had to be switched to biologic therapy due to treatment inefficacy or severe adverse events. Adverse events developed in 47 patients (61%), 11 patients (14%) had severe adverse events and 9 patients (12%) discontinued MTX treatment because of adverse events. SLCO1B1 174Ala>Val (p = 0.059), ABCB1 3435C>T (p = 0.063 OR:3.065, 95%CI:0.908-10.338) and ABCB2 1019A>G (p = 0.113, OR:3.592, 95% CI:0.739-17.461) showed a trend for association with gastrointestinal adverse events. ABCG2 34G>A (p = 0.054) and SLCA9A1 80G>A (p = 0.078) were marginally associated with dermatological adverse events, while ABCG2 34G>A showed association with infections (p = 0.049 OR:3.15, 95%CI:0.871-10.352).

**Conclusion:** We reported for the first time the influence of SLCO1B1 on MTX treatment toxicity in JIA. SNPs in MTX transporters’ genes may be a useful tool to predict toxicity in patients with JIA treated with MTX, but replications of our study in larger groups of patients are needed.

**Disclosure of interest:** None declared.

**P168**

**PReS-FINAL-2156: Analysis of gene expression and inflammation biomarkers in systemic juvenile idiopathic arthritis (SJIA) patients on canakinumab therapy**

**Introduction:** IL-1β, an inflammatory cytokine, plays an important role in SJIA, a rare autoinflammatory disease. Canakinumab (CAN), a selective full human, anti-IL-1β monoclonal antibody, is reported to be efficacious in treating SJIA.

**Objectives:** To characterize changes in peripheral blood gene expression and inflammation proteins in SJIA patients (pts) treated with CAN and to identify baseline biomarkers that predict clinical response to CAN treatment.

**Disclosure of interest:** None declared.
Methods: Levels of inflammatory biomarkers (IL6; total IL18) and gene expression profiles of active SJIA pts (aged 2-19 yrs) before and during CAN treatment enrolled in 2 phase III trials were analyzed.

Results: Gene expression: Transcriptional changes upon CAN treatment at Day 3 were assessed. When applying cut-offs of ≥2 fold and p ≤ 0.05, no transcript passed this filter for placebo pts and for CAN pts that were ACR30 (adapted pediatric ACR) non-responders at Day 15, while 171 probesets passed the filter for pts showing ≥ACR30 response. Pts who showed strong transcriptional changes also showed a strong ACR response (≥ACR50) at Day 15, while pts with <ACR50 at Day 15 showed a much weaker transcriptional response at Day 3. Strongly repressed genes included many known inflammation and innate immunity-related genes (eg, TLR1, TLR4, TLR5, TR6, TLR8), including several members of the IL-1β signaling pathway, such as IL1R1, IL1R2 and IL1RAP. A set of transcripts was identified for which high baseline expression levels predicted a subgroup of strong (≥ACR50) responders at Day 15. However, another subgroup of strong responders was indistinguishable from weak responders (∆ACR50) based on baseline transcript levels.

Protein markers: IL-6 protein levels were strongly reduced by Day 3 (4.7-fold and 4.4× w/ p = 0.002 and 0.001, for the 2 trials), and at Day 29 (12.5× and 8.1× w/ p = 0.01 and 0.0005), while total IL18 levels remained largely unchanged until Day 29 and showed a moderate reduction only at Day 57. For IL6, stronger reduction at Day 3 and Day 29 was observed for pts who showed stronger ACR response at Day 15. Only 3 baseline samples were available from pts who developed macrophage activation syndrome during the studies.

Conclusion: CAN treatment resulted in a rapid, strong reduction of many pro-inflammatory leukocyte transcripts and serum IL6. Compared with IL6, IL18 protein levels were reduced upon treatment much later and less strongly. About two thirds of pts with a strong treatment response (≥ACR50) were characterized by a set of leukocyte transcripts with high baseline levels and strong reduction upon CAN treatment. However, the remaining one third of CAN strong responders did not show these characteristic transcriptional patterns, suggesting some heterogeneity at the molecular level in SJIA pts showing strong response to CAN treatment.


P169

Introduction: Interleukin-1β (IL-1β) plays a key role in the pathogenesis of systemic juvenile idiopathic arthritis (SJIA). Efficacy and safety of canakinumab (CAN), a selective, fully human, anti-IL-1β monoclonal antibody, have been demonstrated in 2 phase III trials. Here we present 12-week results of a post-hoc pooled analysis.

Objectives: To evaluate the 12-week efficacy of CAN 4 mg/kg in treatment naive patients (pts).

Methods: Data from the 3 trials done as part of the phase III program were pooled for this analysis. Pts aged 2-19 yrs with active SJIA were enrolled and received subcutaneous CAN 4 mg/kg or placebo. The post-hoc analysis presented here focuses on SJIA response to CAN therapy in the initial treatment period of a total of 178 CAN-naive pts. Methodological factors precluded a comparator group, so this analysis is of a descriptive nature.

Results: At baseline (BL), 94% of pts had intermittent spiking fever due to SJIA, and 73% were on steroids (mean dose of 0.38 mg/kg/d). In the pooled analysis (N = 178), by Week 2 evidence of profound clinical benefit was observed (Table 1) with 20% of pts even achieving inactive disease.

The median CRP level of 158 mg/L at BL decreased by a median of 82% and 94% by weeks 2 and 12, respectively. Rapid improvements were also observed in the number of active joints. The median number of active joints decreased from 10 at BL to 2.5 at Week 2 and 0 at Week 12. Similarly, for joints with limitation of motion, median values decreased from 9 at BL to 2.5 and 1 at Week 2 and 12, respectively. While 94% pts had fever due to SJIA at BL, only 13% at Week 2 and 2% at Week 12 had fever. Notably, CAN therapy resulted in marked improvement in patient reported outcomes: parent/patient assessment of pain (0-100 mm, VAS) decreased from a mean of 67 mm at BL to 22 mm at Week 2 and 11 mm at Week 12. The median CHAQ disability score decreased from 1.8 at BL to 0.6 at Week 2 and 0.3 at Week 12. Between BL and Week 12, the median physicians’ global assessment of SJIA activity (0-100 mm, VAS) decreased from 70 mm to 3 mm and the parents’/patients’ assessment of overall well-being improved from 63 mm to 43 mm. 50% of pts were inactive or improving.

Conclusion: Based on this post-hoc analysis, response of the SJIA patients studied for the phase III program of CAN showed a rapid and clinically important improvement of their disease by Week 12 of therapy, with an aacr 50 or higher responses reached by the majority of the CAN-naive pts within 2 weeks after the initial CAN dose.

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Table 1(abstract P169) Percentage of patients with adapted JIA ACR (aacr) response and inactive disease

<table>
<thead>
<tr>
<th>N(%)</th>
<th>Aacr30</th>
<th>Aacr50</th>
<th>Aacr70</th>
<th>Aacr90</th>
<th>Aacr100</th>
<th>Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>142 (80%)</td>
<td>125 (70%)</td>
<td>102 (57%)</td>
<td>65 (37%)</td>
<td>38 (21%)</td>
<td>36 (20%)</td>
</tr>
<tr>
<td>Week 12</td>
<td>125 (70%)</td>
<td>122 (69%)</td>
<td>108 (61%)</td>
<td>87 (49%)</td>
<td>54 (30%)</td>
<td>50 (28%)</td>
</tr>
</tbody>
</table>

Data from missing patients not shown; aacr response = ACR response level plus absence of fever.
Methods: The phase 3 analysis included 84 pts (CAN, 43; PBO, 41) in Trial 1 and 177 pts in Trial 2 (71 from Trial 1 entered) in Part 1, and 100 rolled into Part 2 (CAN, 50; PBO, 50). Pt-reported assessments included functional ability (as measured by the Childhood Health Assessment Questionnaire [CHAQ]), pain (measured on a visual analog scale [VAS] of 0-100 mm as part of the CHAQ), and physical (phs) and psychosocial (pss) health status in 5-18 year old pts., according to the Child Health Questionnaire-Parent Form (CHQ-PF50).

Results: In Trial 1, CAN treatment was associated with a significant improvement in CHAQ disability score (estimated difference [ED] of -0.69 over time vs PBO in the least square mean [LSM] change from baseline [BL] (p = 0.0002), which was ~3.6 x the minimal clinically important difference of -0.19. The LSM in overall pain intensity were significantly lower (both p < 0.0001) in the CAN group vs PBO both at Day 15 (ED, -46.42) and Day 29 (ED, -41.86). CHQ-PF50 phs and pss scores also showed significant improvements over time (ED CAN vs PBO in LSM change from BL, 12.07 and 7.28; p < 0.005 for both). Improvements in CHAQ disability, CHQ-PF50 phs and pss, and VAS pain scores were also observed in Trial 2 (Table 1).

Conclusion: Treatment with CAN demonstrated rapid, marked, and continued improvement in patient-reported functional ability and hrqol of SJIA patients.


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L. Harel: None declared.

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K. Houghton: None declared.

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K. Abrams: None declared.

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L. Harel: None declared.

C. Len: None declared.

K. Houghton: None declared.

R. Joos: None declared.


Table 1 (abstract P170) Patient- or Parent-reported functional ability and hrqol parameters in Trial 2

<table>
<thead>
<tr>
<th>Outcome measure, mean (SD)</th>
<th>Baseline CAN, N = 177</th>
<th>End of Part 1 CAN, N = 177</th>
<th>End of Part 2 CAN, N = 50</th>
<th>End of Part 2 PBO, N = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAQ disability score</td>
<td>1.7 (0.8)</td>
<td>0.74 (0.9)</td>
<td>0.5 (0.9)</td>
<td>0.6 (0.8)</td>
</tr>
<tr>
<td>Pain (VAS, 0-100 mm)</td>
<td>66.6 (23.3)</td>
<td>20.2 (25.8)</td>
<td>13.6 (26.9)</td>
<td>17.0 (24.2)</td>
</tr>
<tr>
<td>CHQ-PF50 phs score</td>
<td>16.1 (14.3)</td>
<td>3.77 (17.2)</td>
<td>43.6 (17.4)</td>
<td>39.0 (18.1)</td>
</tr>
<tr>
<td>CHQ-PF50 pss score</td>
<td>41.6 (11.1)</td>
<td>50.7 (11.1)</td>
<td>53.6 (11.3)</td>
<td>52.7 (9.8)</td>
</tr>
</tbody>
</table>

Results are based on patients with both baseline and post-baseline values. N18 years old.
PK/PD results were summarised in TCZ-treated pts from part 1 of 11(Suppl 2):

TCZ, an IL-6R inhibitor, is effective in systemic and intestinal microbiome diversity within the phylum Firmicutes. The intestinal microbiota has been assessed in patients (pts) with BW<30 kg in the global TENDER (sjia) and CHERISH (pjia) trials. Support from: Abbott, Pfizer, BMS, Roche, Novimmune, Novartis, SOBI.

Introduction: TCZ, an IL-6R inhibitor, is effective in systemic and polyarticular juvenile idiopathic arthritis (JIA), pjb. BW-adjusted, intravenous dosing regimens (TCZB mg/kg Q2W for sjia and Q4W for pja) were assessed in Japanese phase 3 trials. As shown in Results, BW adjustment led to lower TCZ exposure with lower BW; thus, higher doses were proposed for patients (pts) with BW>30 kg in the global TENDER (sjia) and CHERISH (pjia) trials.

Objectives: To describe the PK, PD and exposure-efficacy/safety relationships of adjusted BW-based TCZ therapy in sjia/pjia pts.

Methods: PK/PD results were summarised in TCZ-treated pts from part 1 of TENDER and CHERISH. TENDER part 1 (n = 75) comprised a 12-wk, double-blind phase with a 1:2 randomised 1:1 to TCZ or placebo Q2W. TCZ 12 mg/kg if <30 kg and 8 mg/kg if ≥30 kg. CHERISH part 1 (n = 177) comprised a 16-wk TCZ Q4W open-label phase (TCZ 8 mg/kg if ≥30 kg and 8 mg/kg or 10 mg/kg randomised if <30 kg). Pts were 2-17 y old with ≥5 active joints and >38°C fever for ≥5 days (sjia) or ≥3 of ≥5 joints with limited motion (pjia).

Blood samples were analysed for TCZ, IL-6R blockade markers (IL-6 soluble IL-6R [sIL-6R]), C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR). Efficacy was measured by JIA ACR30/50/70/90 response rates. Population PK (poppk) modelling was used to further analyse serum TCZ concentration data in addition to descriptive summary statistics.

Results: In sjia pts, mean serum TCZ concentrations over time and steady state TCZ exposures at wk 12 were similar between TCZ 8 mg/kg and 12 mg/kg BW groups. Predose concentrations trended upwards over time, stabilising by wks 10-12. IL-6, sIL-6R, CRP and ESR profiles were overlaid between BW groups, showing similar IL-6R blockade. Consistently, primary efficacy outcomes by JIA ACR70/90 response were also comparable. In pjia pts, the <30 kg group taking TCZ 8 mg/kg had lower TCZ concentrations than the <30 kg group taking 10 mg/kg and the ≥30 kg taking 8 mg/kg, which were similar to each other. IL-6, sIL-6R, CRP and ESR profiles indicated reduced IL-6R blockade in pts <30 kg taking TCZ 8 mg/kg than in the other two groups. Consistent with this, quartile analysis showed lower JIA ACR30/50/70/90 response rates at wk 16 in the lowest TCZ exposure quartile. No clear trends in adverse events across exposure quartiles were seen in sjia or pjia pts. Poppk analysis showed similar linear clearance of TCZ in sjia and pjia pts, but the Michaelis-Menten constant in target-mediated clearance was 3-4× higher in sjia pts.

Conclusion: Results support adjusting BW-based TCZ dosing in sjia/pjia pts with the optimal dosages: sjia, TCZ 12 mg/kg Q2W for BW<30 kg and 8 mg/kg Q2W for BW≥30 kg; pjia, TCZ 10 mg/kg Q4W for BW<30 kg and 8 mg/kg Q4W for BW≥30 kg. Taking into consideration comparable linear clearances in sjia/pjia pts, the higher Michaelis-Menten constant in target-mediated clearance for sjia pts may be due to higher cell surface IL-6R levels. Observations are consistent with higher baseline IL-6 signalling in sjia pts and potentially explain the need for higher dose regimens to saturate IL-6R for optimal therapy in sjia pts.

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Introduction: The intestinal microbiome may play a role in the pathogenesis of Juvenile Idiopathic Arthritis (JIA). In IBD patients an overall decrease in microbial diversity of the intestinal microbiota has been observed. Studies comparing intestinal microbiome in children with JIA and healthy controls have not been conducted to date.

Objectives: To analyse and compare the composition and diversity of the distal colon associated microbiome between children with Disease-Modyfying-Anti-Rheumatic Drug (DMARD) naive JIA and healthy controls and to identify specific gut bacteria associated with JIA before initiation of a DMARD.

Methods: Total microbiome profile in stools of 8 children with DMARD naive polyarticular JIA were analyzed by means of IS-pro, a 165-235 interspersed (IS) region-based profiling method and compared to stools of 24 age-matched healthy controls.

Results: Faeces of 8 (6 girls, 2 boys) children with polyarticular JIA, all rheumatoid factor negative were investigated and compared to 24 healthy controls. Anti-Nuclear Antibodies were positive in 3 patients. Median age at evaluation was 11.1 years (7.3-13.1), median period from start complaints to diagnosis was 7.1 months (4.4-13.2). Median ACR pedi scores were: VAS physician 47 mm(32-58), VAS patient well-being 32 mm (27-52), ESR 8 mm(2-9), active joint count 10(7-14), limited joint count 2 (0-4), CHAQ score 1.2 (0.4-1.7).

One intra-articular steroid injection was given to each of two patients respectively 1 and 4 months prior to stool collection. Non Steroidal antiinflammatory Drugs (nsaids) were used by all patients at the time of evaluation. Median age of the healthy controls was 10.6 years (8.4-12.9).

The median Simpsons’ diversity index within the phylum Firmicutes in controls and JIA was 0.88, and 0.83 respectively (p < 0.012). Diversity within the phyla Bacteriodesetes and Proteobacteria did not differ between the 2 subgroups. By constructing a Pearson-correlation dendogram, no clustering was seen between the JIA group and the healthy controls on species-level (figure 2), a specific JIA associated microbiota signature could not be identified.

Conclusion: Intestinal microbiome diversity within the phylum Firmicutes was significantly lower between children with DMARD naive polyarticular JIA and healthy controls. An overall decrease in microbial diversity of the intestinal microbiota has also been observed in IBD patients. Whether intestinal dysbiosis plays a role in the pathogenesis of JIA remains subject of further studies.

Disclosure of interest: None declared.
**Introduction:** Adalimumab (ADA) is approved for use in moderate to severe juvenile idiopathic arthritis (JIA) (patients (pts) ≥4 years (yrs) old in the US, EU, and Japan. Limited data are available in pts <4 yrs old.

**Objectives:** To assess the safety and effectiveness of >1 year of ADA therapy in pts aged 2 to <4 yrs old or ≥4 yrs old weighing <15 kg with moderately to severely active polyarticular JIA.

**Methods:** JIA pts were treated with ADA 24 mg/m² (maximum = 20 mg/dose) every other week (wk) +/- methotrexate for a minimum of 24 wks in an ongoing international, multicenter, open-label, phase 3b study using the same disease activity assessments as in the phase 2a study. Clinical effectiveness endpoints were assessed as observed, and included American College of Rheumatology (ACR) response rates through wk 60, and JIA outcome parameters (Physician’s Global Assessment [paga] and Parent Global Assessment [paga] of Disease Activity, paga of Pain [all 3 on a VAS of 0-100 mm], Disability Index of Childhood Health Assessment Questionnaire [DICHAQ], Active Joint Count [AUC73], Limitation on Passive Motion [LOM69], C-Reactive Protein [CRP], Tender Joint count [TJC], Swollen Joint Count [SJC] and Pain on Passive Motion [POM75]).

**Results:** 32 pts were randomized; through wk 60, 2 pts withdrew due to ase (JIA worsening or flare) and 2 withdrew for other reasons. AE incidence rates included: any ase (91%), serious ase (16%), infectious ase (78%), and serious infections (9%). No deaths, malignancies, or opportunistic infections were reported. 90% of pts had achieved pedsac30 at wk 60 (Table 1). High p edsac50/70/90 response rates were achieved at wk 24 and maintained through wk 60. Statistically significant improvements in other JIA outcomes were also observed at wk 60. Mean change (SD) for these outcomes were: pgha [-4.27(2.82)], paga [-3.45 (3.33)], DICHAQ [-0.6 (0.7)], AUC73 [-3.95 (7.5)], LOM69 [-5.5 (8.3)], CRP (mg/dl) [-0.3 (1.8)], TJC75 [-4.5 (5.9)], SJC66 [-8.4 (7.2)], POM75 [-3.9 (5.3)], and paga of Pain -35.2 (34.4). Growth was not adversely impacted by ADA treatment; based on CDC growth standards, at baseline, 50%/53% of pts were in the ≥3rd percentile for height and body mass index, respectively; at wk 60, this had increased to 76%/67%.

**Conclusion:** In this very young population with polyarticular JIA, primary clinical trial data revealed that the safety profile and effectiveness of ADA were comparable to that observed in older children with JIA. Moreover, ADA had no adverse impact on height or weight, as data reflected improvement in growth metrics through wk 60 of the study.


**Table 1 (abstract P173) Pedacr Response Over Time**

<table>
<thead>
<tr>
<th>Week 24 Response Rate</th>
<th>Week 60 Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 30</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>Pedacr 30</td>
<td>27 (90.0)</td>
</tr>
<tr>
<td>Pedacr 50</td>
<td>25 (83.3)</td>
</tr>
<tr>
<td>Pedacr 70</td>
<td>22 (73.3)</td>
</tr>
<tr>
<td>Pedacr 90</td>
<td>11 (36.7)</td>
</tr>
</tbody>
</table>

**P175**

**PReS-FINAL-2163: Disease activity in a juvenile idiopathic arthritis population after 5 years follow-up**

R Marques, F Ramos, A. Mourão, F Martins, H Canhão, J. Pereira da Silva

**Introduction:** The main goal of juvenile idiopathic arthritis (JIA) treatment is to achieve a long-term remission or, at least, low levels of disease activity.

**Objectives:** To evaluate disease activity, focusing on achieving inactive disease (ID) or minimal disease activity (MDA), based on Juvenile Arthritis Disease Activity Score (JADAS) score, after 5 years follow-up.

**Methods:** A cross sectional study at the 5th year of follow-up from a JIA patient cohort, diagnosed between 2000-2008 was carried out. Treatment strategy followed the Portuguese recommendations for the treatment of JIA. The data were collected using Reuma.pt (Portuguese Register of Rheumatic Diseases). At the 5th year JADAS-27 was evaluated and used to identify patients who met the preliminary criteria for ID or MDA: score of 1 for ID and 2 and 3, for MDA, respectively, for patients with oligo and polyarticular involvement. For applying the JADAS score, children with rheumatoid factor (RF)-positive polyarthritis, RF-negative polyarthritis, or extended oligoarthritis were included in the polyarthritis group and the oligoarthritis group included children with persistent oligoarthritis. Children with JIA that were classified in the remaining ILAR categories were assigned to the poly or oligoarthritis group based on the number of joints affected during disease course (>4 or ≤4, respectively). Cutoffs for acceptable symptom state ranged from 3.2 to 5.4 for parents.

**Results:** Eighty one JIA patients were identified with a follow-up of at least 5 years. Fourteen patients were excluded due to loss for follow-up and 2 developed criteria for systemic rheumatoid lupus. Forty four were female (68%), mean age at diagnosis 7.7 ± 4.9 years and mean follow-up 7.6 ± 2.6 years (minimum 5, maximum 13). From the 65 patients, 28 (43.1%) had persistent oligoarthritis, 11(16.9%) RF-negative polyarthritis, 11 (16.9%) enthesitis related arthritis, 8(12.3%) extended oligoarthritis, 3(4.6%) RF-positive polyarthritis, 23% psoriatic arthritis and 23% systemic JIA. Seventy three percent were on methotrexate, 11% on sulfasalazine and 23% on biologics (53%etanercept, 20%adalimumab, 20%infliximab, 7% anakinra). At the 5th year the mean JADAS was 0.78 for persistent idiopathic arthritis (JIA). Despite its safety, MTX intolerance occurs frequently, leading to non-compliance, thus hampering efficacy and potentially leading to early discontinuation.

**Objectives:** The aim of this study was to construct a risk model to predict MTX intolerance.

**Methods:** In a large, prospective JIA cohort, potential predictors (clinical variables and single nucleotide polymorphisms) were determined at the time of MTX start. The Methotrexate Intolerance Severity Score was employed to measure MTX intolerance in the first year of treatment. MTX intolerance was most prevalent at 6 or 12 months after MTX start. This was defined as the outcome for the prediction model. The model was developed in 122 patients using multivariate logistic regression analysis. It was subsequently internally validated using bootstrapping.

**Results:** The prediction model included the following predictors: JIA subtype, antinuclear antibody, parent/patient assessment of pain, Juvenile Arthritis Disease Activity Score-27, thrombocytes, alanine aminotransferase and creatinine. The model classified 77.5% of patients correctly, changing to 66.7% after internal validation by bootstrapping. The prediction model was transformed into a risk score (range 0-17). At an optimal cut-off of ≥6, sensitivity was 82.0%, specificity 56.1%, positive predictive value was 58.7% and negative predictive value 80.4%.

**Conclusion:** The prediction model combined routine clinical variables and showed good predictive power to detect MTX intolerance. This easy-to-use tool could assist clinicians in identifying patients at risk to develop MTX intolerance. Consequently, clinicians can monitor them closely and intervene timely before MTX intolerance hampers MTX efficacy.

**Disclosure of interest:** None declared.

**P174**

**PReS-FINAL-2162: Development of a risk model to predict methotrexate intolerance in juvenile idiopathic arthritis**

P Van Dijkhuizen, M Bulatovic-Calasan, S Pluym, M De Rotte, V. Vestert, S. Kamphuis, R. De Jonge, N. Wulfhaar

**Introduction:** Methotrexate (MTX) is a cornerstone and safe disease-modifying anti-rheumatic drug (DMARD) in the treatment of juvenile idiopathic arthritis (JIA). Despite its safety, MTX intolerance occurs frequently, leading to non-compliance, thus hampering efficacy and potentially leading to early discontinuation.

**Objectives:** The aim of this study was to construct a risk model to predict MTX intolerance.

**Methods:** In a large, prospective JIA cohort, potential predictors (clinical variables and single nucleotide polymorphisms) were determined at the time of MTX start. The Methotrexate Intolerance Severity Score was employed to measure MTX intolerance in the first year of treatment. MTX intolerance was most prevalent at 6 or 12 months after MTX start. This was defined as the outcome for the prediction model. The model was developed in 122 patients using multivariate logistic regression analysis. It was subsequently internally validated using bootstrapping.

**Results:** The prediction model included the following predictors: JIA subtype, antinuclear antibody, parent/patient assessment of pain, Juvenile Arthritis Disease Activity Score-27, thrombocytes, alanine aminotransferase and creatinine. The model classified 77.5% of patients correctly, changing to 66.7% after internal validation by bootstrapping. The prediction model was transformed into a risk score (range 0-17). At an optimal cut-off of ≥6, sensitivity was 82.0%, specificity 56.1%, positive predictive value was 58.7% and negative predictive value 80.4%.

**Conclusion:** The prediction model combined routine clinical variables and showed good predictive power to detect MTX intolerance. This easy-to-use tool could assist clinicians in identifying patients at risk to develop MTX intolerance. Consequently, clinicians can monitor them closely and intervene timely before MTX intolerance hampers MTX efficacy.

**Disclosure of interest:** None declared.
P176  
**PReS-FINAL-2164: Agreement among musculoskeletal pediatric specialists in the assessment of radiographic joint damage in juvenile idiopathic arthritis**  
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Pediatric Rheumatology 2013, 11(Suppl 2):P176

**Introduction:** The management of children juvenile idiopathic arthritis (JIA) is ideally conducted through the establishment of a multidisciplinary team of musculoskeletal pediatric specialists. Some therapeutic decisions, either medical or surgical, are made through discussion and consensus between specialists by viewing patient radiographs. However, it is unknown whether and to what extent different specialists agree in the assessment of the amount of radiographic joint damage.

**Objectives:** The primary aim of the present study was to evaluate the agreement between musculoskeletal pediatric specialists in assessing structural joint changes in children with JIA.

**Methods:** One pediatric rheumatologist, one pediatric radiologist and one pediatric orthopedic surgeon evaluated independently 60 radiographs of both wrists and hands, made in children with polyarticular-course JIA. Each specialists was asked to score each film using a adapted version of the Larsen score, whose score ranged from 0 to 5. Study radiographs were selected from 568 films used in a previous study aimed to validate an adapted pediatric version of the Sharp-van der Heijde (ash) score. To enable comparison of specialists’ score with ash score, the 60 radiographs were divided in 6 classes of severity of damage, based on quintiles of ash score. Agreement was evaluated in terms of absolute agreement and through weighted kappa statistics.

**Results:** The pediatric radiologist tended to assign lower scores and to provide more frequently 0 scores than did the other specialists. Absolute agreement ranged from 45% to 52%, depending on the pair of specialists examined. Both absolute and weighted kappa concordance between specialists’ score and ash score were poorer for the pediatric radiologist than for the other specialists.

**Conclusion:** We observed fair agreement in the assessment of radiographic damage among pediatric specialists involved in the care of children with JIA. The radiologist tended to be more reserved than the rheumatologist and the orthopedic surgeon in labeling radiographs as damaged or in considering changes as important.

**Disclosure of interest:** None declared.

P177  
**PReS-FINAL-2165: Pharmacogenetic determinants of response to methotrexate in juvenile idiopathic arthritis**  
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Pediatric Rheumatology 2013, 11(Suppl 2):P177

**Introduction:** Juvenile idiopathic arthritis (JIA) is the most common arthritis disease of childhood and is an important cause of disability. Methotrexate (MTX) is the mainstay treatment in JIA. Unfortunately, 30-35% of patients fail to respond MTX, and the delay in identifying the optimal treatment at an early stage of disease can lead to long-term joint damage. Recent studies have evaluated comprehensively the effect of genetic variations in candidate genes involved in MTX pharmacokinetics and pharmacodynamics on the response to the medication in children with JIA. These studies seem to indicate that the most relevant variants to predict MTX response in JIA are those in ATIC, ITPA and SLC19A1 genes.

**Objectives:** To evaluate the role of these candidate genetic factors on the attainment of clinical remission on MTX in an Italian cohort of children with JIA.

**Methods:** Patients with JIA treated with MTX were enrolled by the Pediatric Clinic of Burlo Garofolo Children’s Hospital in Trieste; clinical data was collected retrospectively from patients’ charts. Clinical remission on MTX for 6-month-period was evaluated according to Wallace criteria. The most relevant functional SNP for each gene considered was characterized by Tajm (rs2372536 in ATIC, rs1127354 in ITPA) or PCR-RFLP (rs1051266 in SLC19A1) assays on patients’ DNA extracted from peripheral blood.

**Results:** Complete analysis was performed on 69 patients. Of these, 76.8% were female, median age at MTX start was 8 years (range 1 - 22). JIA presentation was oligoarticular in 63.7%, polyarticular in 33.3% and enthesitis/psoriasic in 2%. At the beginning of MTX therapy, disease had been lasting for a median of 1 year (range 0 - 19); MTX was administered at a median dose of 15 mg/m2 (range 10 - 20), subcutaneously in 62.3% of patients and orally in the rest. Genotyping showed minor allele frequencies of 36.2% for rs2372536, 5.1% for rs1127354 and 49.3% for rs1051266, consistent with previous reports in Europeans. Assessment of response to MTX showed that 37.2% of reached remission stable for 6 months. No statistically significant effect of the demographic and clinical covariates was found on MTX response. However, genotyping analysis identified a significant association between the GG variant of ATIC rs2372536 and improved response to therapy; frequency of this genotype was 32% among patients with stable remission and 6% among those with no stable remission (p = 0.04). Preliminary analysis of SLC19A1 rs1051266 revealed a trend for an association of the variant with increased response (p = 0.06). Multivariate analysis supports the independent effect of the genotypes considered on methotrexate response.

**Conclusion:** This report supports the utility of genotyping candidate genes to predict MTX response in children with JIA and should be further validated clinically by larger and prospective studies.

**Disclosure of interest:** None declared.

P178  
**PReS-FINAL-2166: Long-term safety and effectiveness of anti-interleukin-6 receptor monoclonal antibody, tocilizumab, in patients with systemic juvenile idiopathic arthritis in Japan**  
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Department of Pediatrics, Yokohama City University School of Medicine, Yokohama, Japan  
Pediatric Rheumatology 2013, 11(Suppl 2):P178

**Introduction:** Systemic-onset juvenile idiopathic arthritis (sJIA) is a form of childhood chronic arthritis of unknown etiology with systemic manifestations such as remittent fever and erythematous rash, lymph adenopathy, hepatosplenomegaly, and/or serositis. Tocilizumab (TCZ) is a humanized anti-IL-6 receptor monoclonal antibody that has been approved for the treatment of patients with sJIA. Results of the lead-in phase; the placebo-controlled, double-blind phase; and the first 48 weeks of an open-label extension phase, have been reported.

**Objectives:** To assess the long-term safety and efficacy of tocilizumab in sJIA.

**Methods:** The long-term extension phase of two pivotal studies (Phase II study with 11 patients and Phase III study with 56 patients) in patients with active sJIA was analyzed. Patients received open-label tocilizumab (8 mg/kg, every 2 wks). Assessments included ACR Pedi 30/50/70 responses, adverse
In total, 67 patients were enrolled. Median duration of exposure to Tocilizumab had an acceptable safety profile, was associated with sustained clinical improvement, and induced systemic corticosteroid avoidance in children with sJIA. However, the relative indications of single versus multiple iacis in the management of children with JIA, even in the current biologic era.

Disclosure of interest: None declared.

P180
PReS-FINAL-2168: Comparison of safety and retention rate of TNF antagonist therapy in juvenile-onset and adult-onset ankylosing spondylitis: data from the Spanish registry BIOBADASER 2.0

Introduction: Ankylosing spondylitis (AS) is a chronic inflammatory disease that belongs to the group of spondyloarthropathies, which involves the spine, peripheral joints and entheses. Juvenile-onset AS affects children under the age of 16 years and present a clinical course different from adult-onset AS. Several randomized clinical trials have shown that TNF antagonists are an effective alternative treatment in adult-onset AS. Similar results have been reported in juvenile-onset AS, but have been fewer studies conducted in this group of patients.

Objectives: To compare the safety and retention rate of TNF antagonist therapy in patients with juvenile-onset and adult-onset AS.

Methods: Analysis of patients with adult-onset and juvenile-onset AS included in the Spanish registry BIOBADASER 2.0 (October 2006 to November 2012). Incidence rates (irs) of adverse events (aes) and rates of discontinuation were compared between both groups.

Results: A total of 686 patients (524 males, 162 females) were included, comprising 33 juvenile-onset AS and 653 adult-onset AS patients. The ages of diagnosis were 11.9 ± 0.7 years and 34.4 ± 0.5 for juvenile-onset and adult-onset AS, respectively. The duration of disease was higher in the juvenile-onset group (17.9 ± 1.9 years) than in the adult-onset group (9.3 ± 0.4) and HLA-B27 positivity was similar in both groups (82.4% and 86.4%, respectively). Axial involvement was higher in adult-onset patients (74.9% vs 63.6%) and peripheral involvement was more common in juvenile-onset AS (45.5% vs 32.5%). The TNF antagonist more frequently used as first treatment was infliximab in both adult-onset (48.5%) and juvenile-onset AS (50%), and sulfasalazine or other DMARD were used concomitantly in 43% and 35.5%, respectively. The irs of aes was largest in adult-onset AS (140.5 events/1000 patient-years, CI 95%: 132.1-15.8) and lowest in juvenile-onset AS (30 events/1000 patient-years, CI 95%: 0.0-1.9), but severe adverse events were similar in both groups (43 events/1000 patient-years, in adult-onset AS [CI 95%: 3.5-10.1] and 44 events/1000 patient-years in juvenile-onset AS [CI 95%: 2.3-5.7]). The rates of discontinuation due to aes and inefficacy were both higher in adult-onset AS (3.7 [CI 95%: 3.1-4.3] and 2.1 [CI 95%: 1.7-2.6], respectively) compared with juvenile-onset AS (2.7 [CI 95%:2.5-3.3] and 1.3 [CI 95%0.4-3.4], respectively).

Conclusion: The safety and retention patterns of TNF antagonist therapy were similar in adult-onset and juvenile-onset AS, but discontinuation due to AE and inefficacy were higher in adult-onset group.

Disclosure of interest: None declared.

P179
PReS-FINAL-2167: What is the potential of intra-articular corticosteroid injections to induce sustained remission in children with juvenile idiopathic arthritis?

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1Rheumatology, University Hospital Ramon y Cajal, Madrid, Spain; 2Unidad de Investigación, Sociedad Española de Reumatología, Madrid, Spain

Introduction: Intra-articular corticosteroid injections (iacis) are widely used in the management of children with juvenile idiopathic arthritis (JIA). Although this therapeutic intervention is generally considered for the treatment of children with arthritis in a small number of joints, the strategy of injecting simultaneously multiple joints has been advocated in children with polyarthritis. However, the relative indications of single versus multiple iacis in the management of children with JIA is still poorly documented.

Objectives: To describe our 10-year experience on the use of single and multiple iacis in the management of children with JIA.

Methods: The clinical charts of 542 JIA patients who received an IACI in 1, 2 or ≥ 3 joints between January 2002 and December 2011 and had a follow-up duration of at least 6 months after the procedure were reviewed. The corticosteroid preparation used was triamcinolone hexacetonide for large joints and methylprednisolone acetate for small or difficult to access joints. For each patient, the follow-up period after the IACI was censored when one of the following events occurred: 1) flare of synovitis in injected joints; 2) flare of synovitis in injected and uninjected joints; 3) follow-up visit with continued remission of synovitis in injected joints, but recurrence of synovitis in uninjected joints; 4) last follow-up visit with continued remission of synovitis in both injected and uninjected joints. The purposes of the analysis, events 1) and 2) were considered together and defined as "flare of synovitis in injected joints", whereas events 3) and 4) were considered together and defined as "remission of synovitis in injected joints".

Results: Two hundred and fifteen (39.7%) patients were injected in 1 joint, 107 (19.7%) were injected in 2 joints and 220 (40.6%) were injected in ≥ 3 joints. Following IACI therapy, 138 (25.5%) patients were in remission at last follow-up visit, whereas 120 (22.1%), 93 (17.2%), and 191 (35.2%) experienced a flare of synovitis, respectively, in uninjected joints, injected joints and either injected and uninjected joints. The cumulative probability of survival without synovitis flare for patients injected in 1, 2, or ≥ 3 joints was 69, 46, 49%, respectively, at 1 year; 59, 31, 30%, respectively, at 2 years; and 40, 21, 19%, respectively, at 3 years.

Conclusion: IACI therapy, either in single or multiple joints, was able to induce sustained remission of synovitis in a sizable number of patients. Our findings indicate that iacis remain a mainstay in the management of children with JIA, even in the current biologic era.
Introduction: Canakinumab (CAN), a fully human selective anti-IL-1\(\beta\) monoclonal antibody, has been shown to be efficacious in systemic juvenile idiopathic arthritis (SJIA), resulting in significantly longer times to flare vs. Placebo (PBO).

Objectives: 1) To explore the relationship between SJIA flare reduction and CAN exposure (4 mg/kg/every 4 weeks) with consideration of patient baseline characteristics using a discrete hazard (flare) simulation model. 2) To predict the effects of body weight-tiered CAN dosing regimens at 1 to 6 mg/kg every 4 weeks on SJIA flare rates compared with PBO.

Methods: Plasma concentrations were modeled for patients treated with CAN (n = 50) or PBO after CAN treatment (n = 50) and used to validate a good agreement and validated and simulated results of the CAN exposure-flare hazard relationship. The model considered both PBO and CAN treatments and multiple covariates, including baseline steroid dose, heterogeneity of the population with respect to disease severity (which had a varying influence on risk of an early flare), and declining CAN concentrations over time due to washout in patients on PBO (after receiving CAN). The final simulation model was also used to explore the dose-response relationship between SJIA flare hazard and CAN dose in a simulated trial (1000 simulations), that modeled 700 patients randomized to 1 of 7 treatment arms: PBO, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, and 6 mg/kg (all every 4 weeks) of CAN.

Results: The final simulation model successfully re-produced the Kaplan-Meier curves observed in the phase III program, with significant differences in flare hazard (p < 0.001) between treatment arms. Higher CAN plasma concentrations were associated with lower flare hazard. Differences in the corticosteroid dose at baseline, age, gender, body weight, daily steroid usage, and level of adapted ACR response to CAN were not significant predictors of flare risk. Based on simulation, the probability of flare (90% CI) over 12 months was 63% (55%, 71%) for the PBO arm and 47% (40%, 53%), 28% (25%, 31%), 20% (18%, 22%), and 14% (12%, 16%), respectively. Relative to the approved CAN dose, the model predicted a change in flare probability of +13%, +6%, +2%, -2%, and -3% for the 1, 2, 3, 4, 5, and 6 mg/kg every 4 weeks, respectively.

Conclusion: The simulations support 4 mg/kg every 4 weeks as the appropriate dose for preventing SJIA flare events. Doses greater than 4 mg/kg provide only marginal gain in flare reduction over 12 months, while doses less than 4 mg/kg relatively increase the risk of experiencing a flare.


P183

PReS-FINAL-2171: Consensus: what agent to use when first-line vasodilators fail in Raynaud’s phenomenon or digital ulcers secondary to rheumatic diseases in adult patients?

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Pediatric Rheumatology 2013, 11(Suppl 2)P183

Introduction: Juvenile Systemic Sclerosis (JSS) is characterized by Raynaud’s phenomenon (RP) and digital ulcers (DU). Conventional therapy includes calcium channel blockers (CCB) A growing number of vasodilators is available for treatment of refractory patients but there is no clear evidence of the best option. To aid clinical decision-making, a consensus of expert was undertaken.

Objectives: To identify the best therapeutic options and define the sequence of 2nd line vasodilators for RP and DU.

Methods: Steps in the process of consensus were a) Identification of expert panel (EP) members, b) Identification of 2nd line vasodilators c) Identification of outcome measures to define RP and DU improvement, d) systematic literature review; e) summary report of the latest scientific evidence f) expert consensus meeting; g) rating of the strength of evidence. RAND/UCLA Appropriateness Method was used for the medical decision: items were rated on a 9-point scale on each drug option. There were two scoring rounds: first anonymous; independent rating of the appropriateness of vasodilators based on scientific evidence and best clinical judgment. Differences in scoring were discussed at a face-to-face meeting, followed by a second rating round. Consensus was reached on appropriate/inappropriate.

Disclosure of interest: None declared.
Results: The EP included 10 physicians from a tertiary center who are involved in the care of patients with JSS: 3 pediatric rheumatologists, 2 dermatologists, 1 pediatrician, 1 gastroenterologist, 1 nephrologist, 1 nutritionist, 1 pharmacologist, and a moderator. The EP identified 4 drugs for analysis: bosentan, iloprost, sildenafil, and treprostinil. Outcome measures were selected according to the literature references and EP judgment. RP improvement definition: ≥ 30% improvement according to the physician (in a visual analogue scale, VAS) and ≥ 30% improvement in at least 2 patient-related domains (pain or function). Patient domains were: a) number of episodes, b) pain in a VAS, c) function (impaired activity of daily living, VAS), d) RP episodes average duration (in minutes). DU improvement definition: a favorable change in all physician- and patient-related domains: patient’s domains: a) pain (VAS) b) function (VAS); physician’s domains: a) ulcer activity (VAS) b) horizontal and transverse DU diameter (in mm). Systematic literature review was performed independently by 5 EP members and guided by the moderator. All articles in English were eligible. Data bases included pubmed and Cochrane. The search strategy included all relevant terms: bosentan, iloprost, sildenafil, treprostinil, RP, DU, combined in different sets of keywords. The summary report of the scientific evidence included 25 articles. Ranking of papers according to the strength of evidence showed: 1a (1 paper), 1b (7), 2b (2), 3b (2), 4b (5), 5b (1). After second scoring round: 1st appropriate indication Illoprost; 2nd bosentan, 3rd sildenafil, 4th treprostinil.

Conclusion: The EP reached a consensus on vasodilator drugs, providing direction for common dilemmas in the pharmacologic treatment of RP and DU in refractory patients.

Disclosure of interest: None declared.

P184
PRes-FINAL-2172: Efficacy of corticosteroids and intravenous cyclophosphamide for patients with juvenile systemic sclerosis
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Pediatric Rheumatology 2013, 11(Suppl 2):P184

Introduction: Systemic sclerosis (ssc) is a rare multisystemic disease characterized by inflammation, vascular abnormalities, and fibrosis that affects the skin and various internal organs. Juvenile ssc accounts for fewer than 10% of all adults with ssc. Regarding effective treatment there were no specific pediatric data available, and the long-term efficacy of treatment for children with ssc has not been investigated.

Objectives: To evaluate efficacy of treatment in juvenile ssc and to extract factors related to poor prognosis.

Methods: Ten patients (4 boys and 6 girls) with ssc were included. All of them were diagnosed as a diffuse type ssc based on clinical manifestations (Raynaud’s phenomenon, skin induration and/or internal organ involvements), serological findings, and imaging assessments of internal organ damages. The responses to treatment during their clinical courses were assessed by Total Skin Score (TSS) and internal organ damages using imaging assessment modalities.

Results: Average onset age was 10.3 years and average duration until diagnosis was 22 months (range 2-74 months). Average observation period was 41 months. Nine out of 10 patients had antinuclear antibodies, and anti-Scl-70 antibody was positive in 4. Nine patients were revealed upper gastrointestinal dysfunction, 2 were shown interstitial lung disease, the other 2 were detected pulmonary hypertension, and 1 had arthrythmia. All of the patients were treated primarily with corticosteroids, followed by intravenous cyclophosphamide (IVCY) (12 months course) as induction therapy. Most of the patients received oral prednisolone and other immunosuppressants such as azathioprine, methotrexate, and mycophenolate mofetil as maintenance therapy. Six out of 10 patients were refractory to the treatment due to incomplete IVCY therapy and 2 patients with pulmonary hypertension had remarkable improvement after 2-year IVCY therapy. In 4 out of these 6 patients both TSS and internal organ damages were improved, and the other 2 patients ameliorated in TSS but not in internal organ damages. TSS of 3 patients with the positive anti-Scl-70 antibody was unchanged or increased suggesting anti-Scl-70 antibody may be one of poor prognostic factors. Other 2 patients with the positive anti-Scl-70 antibody were complicated with interstitial lung disease, and they were refractory to the treatment suggesting again the anti-Scl 70 antibody may be one of the poor prognostic factors. Additionally, these 2 patients received incomplete IVCY therapy due to anaphylactic reaction to IVCY or patient’s refusal. One female with the positive anti-Scl-70 antibody died due to acute heart failure with no appropriate therapy in a regional hospital, and then after being transferred to our hospital methylprednisolone pulses and IVCY was successfully administered for TSS improvement during 3 months, but lung fibrosis and arrhythmia were progressed.

Conclusion: The earlier diagnosis and induction of corticosteroids and IVCY therapies will be indispensable for the prevention of fatal organ involvement in juvenile ssc. Incomplete immunosuppressive therapies and the positive detection of the anti-Scl-70 antibody may be poor prognostic factors.

Disclosure of interest: None declared.
The Q703K mutation was found in the 35 screened patients, serum immunoglobulins, viral...

A 13 year old boy already suffering from diabetes mellitus type I, fever and urticarial rash (23 pts), from 2002 the molecular analysis of the NLRP3 gene was performed in 615 patients with a clinical history suggestive for CAPS in the presence of suggestive findings.

To analyse the prevalence of Q703K mutation in patients with diabetes mellitus type 1 (DM) associated with familial mediterranean fever (FMF). It is the third association of these two diseases described in the medical literature to our knowledge so far.

Objectives: Our aim is to emphasize that FMF must be taken into consideration as a possible disease associated with type 1 DM in the presence of suggestive findings.

Methods: A 13 year old boy already suffering from diabetes mellitus type 1 since the age of 4 years and 3 months, came to our attention because of the presence of periodic fever associated with abdominal pain, oral ulcers, chest pain and diffuse arthralgia. The fever appeared every 15-30 days with peaks that reached 40°C and lasted 24-48 hours. Blood tests (complete blood count, blood culture, serum immunoglobulins, viral serology, biochemical profile), instrumental examinations (ultrasound of the abdomen and chest x-ray) and the rest of laboratory investigations (culture of throat swab, stool examination and urinalysis) were normal in the interval between febrile episodes, but during the attacks revealed an increase in inflammatory markers (ESR 60 mm/1 h, CRP 3.7 mg/dl). For the clinical suspicion of FMF we requested that the genetic investigation was performed.

Results: The molecular analysis of the nucleotide sequence of exon 2 of MEFV gene, performed in genomic DNA extracted from peripheral blood leukocytes, showed the mutation c.442G>C (p.E148Q) in the heterozygous state. The colchicine therapy, started 20 months ago at a dose of 1 mg/day, is well tolerated and has determined the immediate disappearance of the symptoms so far. Renal biopsy, performed at 14 years and 6 months of age because of persistent proteinuria, showed the absence of amyloidosis but a slight and irregular thickening of the lamina densa of some glomerular capillaries presumably due to diabetes. The serological tests have ruled out so far CD, AD, ATD and connective tissue diseases (CTD). Until now, the eye examination did not detect the presence of iridocyclitis.

Conclusion: The coexistence of FMF and type 1 DM is a very rare finding. FMF heterozygotes tend to have a milder course of the disease and are less prone to experience new clinical manifestations than homozygotes. Moreover, at puberty, their symptomatology could disappear allowing to cease colchicine without relapses or an increase of inflammatory markers. Recently, a case of simultaneous protracted febrile myalgia syndrome (PFMS) preceded by diabetic ketoacidosis (DKA) has been described for which the authors have suggested that DKA-associated cytokine release could be a predisposing factor or a trigger for FMF-associated PFMS. Conversely, it was hypothesized that the immune dysregulation in FMF could be involved in the autoimmune mechanism that leads to type 1 DM. Finally, a prolonged follow up is needed to verify the long-term necessity of colchicine for our patient and further studies are required to reveal any possible shared molecular mechanisms that are responsible for these two diseases.

Disclosure of interest: None declared.
described in 1954, and subsequently better defined by Castlemain in 1956. It usually occurs in young adults whilst it rarely occurs in childhood. There are only about 100 pediatric cases published. CD is believed to be autoinflammatory in pathology and result in increased interleukin-6 secretion. Previous studies in adult patients suggested beneficial role of the anti-interleukin-6 receptor antibody tocilizumab in treatment of CD. We report 3 cases of multicentric Castlemain’s disease in children, treated in our center in recent years.

Objectives: To assess efficacy of tocilizumab therapy in children with Castlemain’s disease.

Methods: 3 patients ages 4, 14 and 16 were diagnosed with multicentric Castlemain’s disease on the basis of clinical and histologic findings. 2 children (the boy of 4 years and the girl of 14 years) had hyaline-vascular type of CD, the boy of 16 years had plasma cell type of CD. The duration of illness before the correct diagnosis and beginning of treatment in the younger boy was 6 months, in the girl and the older boy - 6 years. All patients had enlarged lymph nodes of several groups and systemic involvement with fevers, weight loss, ascites, and progressive hematological changes (thrombocytopenia, anemia, high CRP). HHV-7 and 8 staining of the tissues were negative. In all cases treatment with tocilizumab as monotherapy was started at a dose of 8 mg/kg every 2 weeks.

Results: 2 infusions in 2 children and 1 in one was performed. During the treatment period lymph nodes’ sizes slightly decreased two patients and no lymph nodes size change was noted in the third patient. All patients continued to progress of systemic symptoms. Therefore, Tocilizumab treatment was discontinued and substituted with more aggressive protocols consisting of cyclophosphamide, vincristine, prednisone and rituximab with fast effect: two children now are disease-free, the third one has marked improvement.

Conclusion: Tocilizumab has been reported to be effective for treatment of adults with CD, yet it proved insufficient activity in our three pediatric cases. In our experience CD in children has more aggressive course, therefore requiring chemotherapy aimed at lymphocytes’ reduction.

Disclosure of interest: None declared.

P189
PReS-FINAL-2199: A novel mutation in the CIA1/NLRP3 gene associated with an unusual phenotype of CAPS
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Pediatric Rheumatology 2013, 11(Suppl 2):P189

Introduction: Cryopyrin-associated periodic syndrome (CAPS) is an autoinflammatory syndrome caused by heterozygous mutations of the CIA1/NLRP3. Affected individuals may present three different phenotypes: Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWs) and CINCA syndrome. Common symptoms include urticarial-like rash, recurrent fever, arthralgia, conjunctivitis; chronic aseptic meningitis, cerebral atrophy and bone malformations in the severe cases.

The term CAPS (Cryopyrin-Associated Periodic Syndromes) identifies a spectrum of autoinflammatory diseases caused by heterozygous mutations of the CIA1/NLRP3. Affected individuals may present three different phenotypes: Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWs) and CINCA syndrome, the most severe form of the clinical spectrum. Clinical manifestations include urticaria-like rash, recurrent fever, arthralgia, conjunctivitis; chronic aseptic meningitis, cerebral atrophy and bone malformations in the severe cases.

Objectives: To describe the long-term clinical course of a cohort of patients carrying two different low-penetrance NLRP3 mutations (V198M and Q703K).

Methods: Six patients were identified carrying the NLRP3 V198M mutation (mean age 10.35 ± 4.73 years, 4 males and 2 females), and 5 patients were identified carrying the NLRP3 Q703K (mean age 9.72 ± 4.55 years, 3 males and 2 females). All were Caucasians.

Results: In the V198M cohort the mean age at disease onset was 5.85 ± 4.08 years. All patients had symptoms consistent with recurrent inflammatory syndrome: 6/6 presented recurrent episodes of skin lesions and arthralgia, 4/6 of fever attacks, 3/6 of headache and subcutaneous edema. One patient showed fatigue, conjunctivitis and recurrent abdominal pain. Half of the patients had a positive family history for recurrent inflammatory episodes. In 3 out of 6 patients the severity of phenotype and the persistence of elevated acute phase reactants, led to initiation of anti IL-1 therapy with immediate benefit. In the cohort of patients with Q703K variant the mean age at disease onset was 3.73 ± 3.33 years. All patients had skin rash, 4/5 patients presented recurrent fever, 3/5 arthralgia and myalgia, 2/5 subcutaneous edema, pharyngitis and lymphadenitis; 1 out of 5 patients had mild arthritis, headache and abdominal pain. Only in 1 case, symptoms were triggered or worsened by cold exposure. None of our patients had a family history relevant for autoinflammatory symptoms. Laboratory test showed no increase in acute phase reactants, with one exception. This patient presented also with recurrent fevers, treatment resistant epilepsy and carries an heterozygous MEFV mutation. She failed colchicine and anti IL-1 therapy was started with benefit.
Conclusion: The pathogenic significance of these NLRP3 mutations is still discussed. In our experience patients carrying Q703K mutation appear to have a milder and self-limited phenotype than those with V198M variant in which therapy with IL-1 inhibitor drugs is often necessary. The factors that affect the pathogenic consequences of these variants are still to be established.

Disclosure of interest: None declared.

P191

PReS-FINAL-2201: A P2685 NOD mutation in one Blau patient
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Pediatric Rheumatology 2013, 11(Suppl 2);P191

Introduction: Blau syndrome (BS) is a rare autosomal dominant, autoinflammatory syndrome characterized by the clinical triad of granulomatous, recurrent uveitis, dermatitis and symmetric arthritis. Arthritis is usually a polycyclic exuberant synovitis and tenosynovitis and represents the characteristic phenotypic feature. Uveitis occurs in most patients and commonly evolves to a panuveitis. In the majority of patients, the disease is characterized by early onset, usually before 3-4 years of age. The disease remains stable after the first attack and has a milder and self-limited phenotype than those with V198M variant in which therapy with IL-1 inhibitor drugs is often necessary. The factors that affect the pathogenic consequences of these variants are still to be established.

Objectives: To identify the genotype-phenotype correlation of our patient.

Methods: We describe a 4-year-old male, the first child of healthy unrelated parents, who presented at 13 months of age, with arthritis of the ankle and of the second proximal inter-phalangeal of the right hand, without the typical puffy appearance. Laboratory test revealed mild increase in inflammatory parameters (erythrocyte sedimentation rate 35 mm/h, C-reactive protein 0.77 mg/dl) and the presence of antinuclear antibody (titer 1:640, homogeneous pattern). A diagnosis of ANA positive oligoarticular juvenile idiopathic arthritis was made and an infiltration of the ankle joint with TXA was performed, with insufficient response. Persistence of the ankle arthritis led to initiate treatment with methotrexate that was not associated with clear benefit. Four months later the patient developed recurrent episodes of fever and skin rash on limbs and trunk, with spontaneous resolution, and subsequently recurrent episodes of bilateral anterior uveitis.

Results: Based on the presence of persistent arthritis, recurrent uveitis, fever and rash, Blau Syndrome was suspected and molecular analysis of NOD2/CARD15 gene was performed. Sequencing analysis demonstrated a heterozygous c.802C>T mutation (P2685SNPS) in exon 4.

Conclusion: Until now the c.802C>T mutation (P2685SNPS) in exon 4 of NOD2 had only been reported in association with Crohn’s disease, rheumatoid arthritis, spondylarthropathy and ulcerative colitis. This is, to the best of our knowledge, the first case of c.802C>T mutation (P2685SNPS) that appears to be associated with clinical features of Blau syndrome.

Disclosure of interest: None declared.

P192

PReS-FINAL-2202: A novel PSMB8 mutation associated with CANDLE syndrome
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Introduction: Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome is a newly described autoinflammatory disease, which had been recently reported in 9 patients. It is characterized by onset during the first year of life of recurrent fevers, purpuric skin lesions, arthralgia, progressive lipodystrophy, hypochromic or normocytic anemia, delayed physical development and increased levels of acute phase reagents.

Objectives: To describe the phenotype of our patient.

Methods: A 10-year-old young girl presented at 10 months of age with recurrent fevers, hepato-splenomegaly and nodular erythematous skin lesions of trunk and limbs; subsequently she progressively developed lipoedematosis, arthralgia, arthritis and edema of eyelids. She started steroids and then, cyclosporine with partial benefit and with recurrence of symptoms following tapering and/or discontinuation. Her height and height percentiles with partial growth hormone defect. Skin biopsy showed typical features of lobular panniculitis. Laboratory tests showed persistent elevated acute phase reactants and Serum amyloid A levels persistent chronic anemia, mild recurrent leucopenia (minimum neutrophil count 1040), thrombocytopenia (minimum 94.000) and decreased IgA, IgG and IgM levels. Immunological and cytotogenetic studies performed on bone marrow were normal. Response to hydroxychlorochine or colchicine was unsatisfactory. Subsequently, the patient developed proteinuria with nephritic syndrome. Renal biopsy revealed a minimal change glomerulopathy; she was started on a standard nephritic syndrome high-dose steroid protocol with remission of proteinuria. Complete sequencing of TNFRSF1A and MIV genes showed no mutations. Results: Molecular analysis of PSMB8 (proteasome subunit β type 8) gene revealed the presence of c.208A>T (p.(Thr70Ser)) variant in heterozygotic status that has never been reported before. Because of a persistent inflammatory state, she was started on daily therapy with Anakinra (2 mg/Kg/die), discontinued after 10 days for absence of response. She is currently managed with chronic low dose glucocorticoids.

Conclusion: The similarities in the clinical phenotype of this case with those described by Liu et al support the conclusion that this novel variant Thr70Ser in the PSMB8 gene is a causative mutation. Minimal change glomerulopathy has not been reported in CANDLE patients. It may be a casual association: however, one of the 9 original patients is described as having nephritic syndrome. Our patient also did not respond to Anakinra. A better understanding of the pathophysiology of the disease is needed to improve its management.

Disclosure of interest: None declared.

P193

PReS-FINAL-2203: Assessment of sleep problems in children with familial Mediterranean fever
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Pediatric Rheumatology 2013, 11(Suppl 2);P193

Objectives: The study aimed to investigate sleep patterns, sleep disturbances and possible factors that are associated with sleep disturbances among children with FMF.

Methods: Forty six FMF patients and 80 age- and sex-matched healthy children were enrolled in the study (Table 1). The patients who had an attack during the last 2 weeks were not included. Demographic data, FMF symptoms, disease duration, dose of colchicine, disease severity score, number of attacks in the last year, MEV mutation and serum C-reactive protein level were recorded for each patient. Children’s Sleep Habits Questionnaire was performed. It is a parent-report questionnaire assessing the typical sleep patterns of children. It includes 33 items measuring sleep disturbances (8 subscales) and 3 three items collecting information about bedtime, wake-up time and sleep duration over a “typical” recent week. A total score of 241 defines “clinically significant sleep disturbance”.

Results: The total sleep scores of the patients with FMF were significantly higher than the control group. Total sleep duration were similar between 2 groups. The comparison of subscale scores were given in table. Gender and age had no effect on total sleep scores in both groups. There was not a significant correlation between the total sleep score and disease duration, dose of colchicine, disease severity score, number of attacks in the last year, and serum C-reactive protein level in FMF patients. Besides, the patients with exercise-induced myalgia (n = 21) had significantly higher sleep scores than the patients without (n = 25) (54.8 ± 11.3 vs 46.3 ± 7.8, p = 0.008).

Conclusion: This is the first study investigating sleep patterns, sleep disturbances and possible factors that are associated with sleep disturbances among children with FMF. The results of this study suggested
that exercise-induced myalgia might contribute to sleep disturbances in FMF as well as ongoing subclinical inflammation.

Disclosure of interest: None declared.

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**Table 1 (abstract P193)**

<table>
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<th>FMF patients</th>
<th>Healthy controls</th>
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<tbody>
<tr>
<td>Length of wakings (minute)</td>
<td>95 ± 18.6</td>
<td>31 ± 36</td>
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<tr>
<td>Total sleep duration (hour)</td>
<td>9 ± 1.4</td>
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<td>0.34</td>
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<td>Total sleep score</td>
<td>50.1 ± 10.4</td>
<td>46.6 ± 6.6</td>
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</table>

**SUBSCALES**

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<tr>
<th></th>
<th>FMF patients</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedtime resistance</td>
<td>8.6 ± 3.8</td>
<td>7.8 ± 2.2</td>
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<tr>
<td>Sleep-onset delay</td>
<td>2.4 ± 2.1</td>
<td>2.1 ± 0.7</td>
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<tr>
<td>Sleep duration</td>
<td>3.8 ± 1.3</td>
<td>4 ± 1.3</td>
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<tr>
<td>Sleep anxiety</td>
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<td>5.4 ± 1.7</td>
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<td>Nightwakings</td>
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<td>Parasomnias</td>
<td>8.9 ± 2.1</td>
<td>8.9 ± 1.8</td>
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<tr>
<td>Sleep-disordered breathing</td>
<td>4 ± 1.7</td>
<td>3.4 ± 0.8</td>
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<tr>
<td>Day-time sleepiness</td>
<td>14.1 ± 4.9</td>
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</table>

**Introduction:** Familial Mediterranean Fever (FMF) is a disease characterized by attacks and colchicines is the medication considered most effective in reducing the intensity and frequency of attacks. Adherence to the medication regimen is important not only to manage FMF symptoms, but also to prevent amyloidosis.

**Objectives:** In this study, it is aimed to develop and assess the validity and reliability of the adherence scale for colchicine treatment in pediatric FMF patients.

**Methods:** This study was planned as a methodological study to development of scale for assessment of adherence to treatment of pediatric patients with FMF using colchicine treatment. Pediatric patients (2-18 ages) with FMF using colchicine at least 6 months and accepted to participate in the study constitute the sample of the study. “Data collection forms about the sociodemographic and medical information (demographic, clinical and laboratory findings) of patients”, “adherence scale for colchicine in pediatric FMF patients” and “Morisky Medication Adherence Scale” were used as data collection instruments. If the patient was under 7 years old, his parents filled the forms.

**Results:** There were 150 patients with FMF enrolled for the validation of the study. The median age of the patients was 11.11 ± 4.02 (min:2.74, max:17.99) and 48.7% of them were male. The median of the attack frequency was 11.00 ±10.74 (min:0-max:52) and 60.7% of the patients had irregular attacks. For internal consistency, Cronbach’s alpha was 0.728 for “adherence scale for colchicine in pediatric FMF patients”. Also, there was a positive and significant correlation (r:0.843, p < 0.0001) between test and retest score. As a result it is accepted that this scale can be used for pediatric patients with FMF who use colchicine as a reliable scale.

**Conclusion:** Based on these results, using this scale for the purpose of the assessment and follow up of adherence to treatment of pediatric patients with FMF who use colchicine is recommended. Disclosure of interest: None declared.

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**P195**

**PReS-FINAL-2205: Vascular risk assessment and MMP-3 gene in FMF**

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**Introduction:** The patients characterized with chronic subclinical inflammation even during attack-free periods, are now considered to have an increased risk of atherosclerotic complications as well as other autoimmune inflammatory disease. Damage to the arterial wall due to atherosclerosis causes increased arterial stiffness. Pulse wave velocity (PWV), a noninvasive measure of arterial stiffness, is accepted to be an indicator of subclincal atherosclerosis. Cardiovascular disease included various risk markers; blood biomarkers and genetic markers. Matrix metalloproteinases (MMPs) are closely related proteins that together are able to degrade all macromolecules of the extracellular matrix. MMPs are potentially implicated in atherogenesis, progression of atherosclerosis. The gene encoding MMP-3 is polymorphic and an insertion (6A)/deletion (5A) polymorphism (5A/6A polymorphism) in the MMP-3 gene may have functional significance in the regulation of its expression. The 5A allele was associated with higher and the 6A allele with lower transcriptional activity. Up to date, the 6A/6A and 5A/6A genotypes were associated with coronary artery disease and carotid atherosclerosis in adults. Objectives: We aimed to evaluate the effect of inflammation and the strength of association MMP-3 promoter low- and high-activity genotypes on the increased risk of subclinical atherosclerosis in FMF patients.

**Methods:** Forty-seven patients (M/F =21/26) with FMF, and 50 age- and sex-matched controls were recruited. We measured lipid profile (LDL, total cholesterol and lipoprotein a level) and acute phase reactants (APRs) (white blood cells, erythrocyte sedimentation rate, high sensitive C-Reactive Protein and Serum Amyloid A) in attack free period of all patients. Aortic PWV was determined by using an automatic device (Vicorder, Germany) that allowed on-line pulse wave recording and automatic calculation of the PWV. The 5A/6A polymorphism was typed by RFLP-PCR.

**Results:** The mean APRs values were not found statistically significant in patients than control. The distribution of the genotypes of the 5A/6A polymorphism in both control and study patients did not differ significantly (40%/28%, respectively p > 0.05) from those predicted by the Hardy-Weinberg distribution. The PWV was slightly higher in patients with FMF than in control subjects (p = 0.05). Fifteen patients (32%) have PWV values above the average. These patients have also high SAA and lipoprotein-a levels in attack free period. A significant correlation between PWV and lipoprotein a (p < 0.001, r = 0.67), and SAA level (p < 0.001, r = 0.52) was found in patients with FMF. There was no detected hypertension. There were no significant differences (p > 0.05) in genotype distributions (hyperlipidemia and arterial stiffness index) and allele frequencies between subgroups.

**Conclusion:** The results showed that arterial stiffness is correlated with hyperlipidemia and subclinical inflammation in FMF patients. But, the 5A/6A polymorphism of MMP-3 gene may not be linked with appearance and/or progression of arterial stiffness in FMF patients. Our suggestion is that SAA levels as well as the use of therapy monitoring can be predict in cardiovascular disease in patients with FMF.

Disclosure of interest: None declared.
**Introduction:** Chronic recurrent multifocal osteomyelitis (CRMO) is a form of chronic nonbacterial osteitis (CNO) characterized by one or more lytic bone lesions with no identifiable cause. (CRMO) is a rare (prevalence less than 1/1,000,000) auto-inflammatory disorder, characterized by relapsing and remitting episodes of pain related to the presence of foci of sterile bone inflammation.

**Objectives:** We describe the clinical and laboratory features and treatment of a cohort of children with CRMO.

**Methods:** We retrospectively reviewed clinical, pathological and radiological data of children with CRMO at single tertiary pediatric center from Turkey. The diagnosis of CRMO was based on evidence of recurrent osteomyelitis with radiographic evidence of chronic osteomyelitis involving at least two sites in the absence of infectious cause in a child less than 14 years old.

**Results:** Six patients were assessed (34 females and 6 males) with a median age at diagnosis of 9.5 yrs (range 5-16). Median number of initial bony lesions was 2 at onset and 3.5 over disease course. Median time since diagnosis was 1.5 yrs) and median duration of active disease 0.7 yrs. Two patients had active disease at follow-up and continued to have pain. Two patients were treated with steroid, colchicine and sulphasalazine. Two patients had methotrexate, 1 had colchicine while 1 had nonsteroidal anti-inflammatory drug.

**Conclusion:** This report indicates that CRMO may be overlooked in our community. Early diagnosis and treatment are required to avoid potential complications.

**Disclosure of interest:** None declared.
favour. The bone biopsy finding P.Acnes guided us to a cause of osteitis and allowed us to propose a treatment which seems to be suspensive. Disclosure of interest: None declared.

P199
PreS-FINAL-2209: MEFV gene mutations in central and south-eastern European countries

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Introduction: Familial Mediterranean fever (FMF) is rarely reported in patients from central and south-eastern European countries (CSEE). The reason for this might be that the prevalence of FMF in CSEE is exceedingly low or that the disease is significantly under-recognized among local physicians. Moreover, genetic testing is not available in most of the countries in the region.

Objectives: The aim of this study was to assess the frequency of MEFV gene mutations in periodic fever patients from CSEE countries.

Methods: We analyzed clinical, laboratory and genetic data of MEFV gene of all periodic fever patients who were followed at the University Children’s Hospital Ljubljana from the beginning of 2006 to the beginning of 2013. In addition, free genetic testing was provided for suspected FMF patients with periodic fevers from the countries of the CSEE region. Genetic testing was performed in the Genetic laboratory of the University Children’s Hospital Ljubljana. All 10 exons and intron/exon regions of MEFV gene were directly sequenced with ABI Prism 310 Genetic analyzer.

Results: In total, 156 periodic fever patients were tested for MEFV gene mutations; 118 from Slovenia, 14 from Czech Republic, 6 from Slovenia, 4 from Croatia, 4 from Romania, 3 from Macedonia, 2 from Serbia, 2 from Hungary, 2 from Latvia and 1 from Lithuania. 73% of the populations were children under the age of 18, mean age at diagnosis was 6.6 years. 27% were adult, mean age at diagnosis was 46.4 years. 53% of patients were female and 47% were male. 31 patients (20%) were found to have at least one mutation. 22 patients have had one mutation only: Slovenia 9/15, Czech Republic 7/8, Slovenia 1/3, Macedonia 2/2, Latvia 1/1, Hungary 1/1 and Croatia 1/1. 8 patients have had two mutations; Slovenia 6/15, Slovenia 1/3, Czech Republic 1/8 and 1 patient from Slovenia has had 3 mutations. Homozygous mutation was found only in one patient from Czech Republic. 1 novel MEFV gene mutation was identified (S730F) in patient from Slovenia. 12 different mutations were found. The 2 most frequently found were M694V (27%) and K695R (22%), followed by P369S (12%), R408Q (12%), I591T (7%), E148Q (5%), E167D (2%), A289V (2%), F479L (2%), V726A (2%), S730F (2%) and A744S (2%).

Conclusion: MEFV gene mutations were identified in 31/156 (20%) patients with periodic fevers from CSEE countries. In order to increase the number of positive results of MEFV genetic testing clinical criteria for FMF diagnosis should be followed. We suspect that clinical manifestations of FMF could be influenced by the regional environment. We are planning to evaluate genotype-phenotype correlation in MEFV mutation positive patients in CSEE countries in the future.

Disclosure of interest: None declared.

P200
PreS-FINAL-2210: Qualitative aspects of autoinflammatory diseases

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Pediatric Rheumatology 2013, 11(Suppl 2):P200

Introduction: In pediatric rheumatology, the lack of scales showing activities of illness in the patient groups, the absence of biomarkers for the severity of damage led the scientific world to develop a scale where the patient can make an self-assessment with quantitative results. So, a necessity has been occurred to develop a multidimensional scale which is understandable, applicable and comprehensive in the evaluation of children with auto-inflammatory diseases.

Objectives: The aim of this study is to develop a multidimensional assessment instrument named “Juvenile Autoinflammatory Disease Multidimensional Assessment Report” (JAIMAR) to measure all the domains of the autoinflammatory diseases. In this study the data of “Qualitative Interviews”, one of the steps of item generation in JAIMAR, will be presented.

Methods: 19 mothers who have children with autoinflammatory disease (8 FMF, 5 Behcet, 4 PFAPA, 1 HIDS, 1 TRAPS) and their children greater than 7 years old were enrolled in this study. Data were collected using both a demographic data form and a semi-structured interview form. The study was performed on individual patient face-to face interview. Data were collected by using both a demographic data form and a semi-structured interview form. Data analysis by grounded theory and N Vivo 10 software.

Results: Unknowing the time of attack, lifelong illness, difficulties in diagnosis and exposure to the other parts of the body were described as the worst parts of the illness. In addition to physical factors such as cold and fatigue, psychological factors such as overexcitement, worry and happiness were stated to be in the triggering factors of the attacks. Although decrease in attacks after treatments were stated, lifelong drug addiction and its side effects were told to be the most worrying aspects. Problems at school (absenteeism, loss of performance, fear of having attack at school and bad peer relations) were explained as the biggest difficulties affecting the quality of life. Problems with friends, precocity, and extreme expressions such as depression/wanting to die due to back pain were to be the in the emotional difficulties.

Conclusion: These results provide an evidence based data for the assessment of children with autoinflammatory disease by several domains including physical, emotional and social aspects as well as treatment protocols. With this regard there is a need to develop a multidimensional instrument to measure important aspects of the illness gained from these results.

Disclosure of interest: None declared.
Introduction: Non-infectious uveitis represents an heterogeneous group of immune-mediated disorders affecting both the uveal tract and the adjacent structures. These diseases are important in clinical practice because they represent one of the most common cause of blindness even in the pediatric age and often require immunosuppressive therapy and a multidisciplinary approach. The etiology of these inflammatory conditions remains unknown. Mutations affecting NOD2/CARD15 gene are responsible for a rare autosomal-dominant disorder, Blau Syndrome, which is characterized by the triad of granulomatous arthritis, skin rashes and uveitis.

Objectives: Aim of our study is to assess if NOD2-polymorphisms or mutations have a role in the etiology or in the clinical course of patients with non infectious uveitis, either idiopathic or associated with other inflammatory diseases.

Methods: We enrolled 18 patients: 12 pediatric patients followed at the pediatric hospital "Anna Meyer" (Florence, Italy) and 6 patients (5 adults and 1 child) followed at the Hospital "Santa Maria alle Scotte" (Siena, Italy). Data regarding age of onset, type and localization of uveitis, associated diseases, relapse frequency and complications were collected and recorded with a customized database. NOD2 gene was genotyped in all cases. A statistical analysis has been carried out in order to assess the relationship between NOD2 variations and phenotype.

Results: NOD2/CARD15 gene variants have been identified in 12 patients: 9 patients showed the polymorphism P268S/NPS as heterozygous carriers while 2 patients were homozygous for the same polymorphism. One patient carried two different mutations: the polymorphism P268S/NPS in heterozygous and a mutation on intron 3 (c.647 18-16 TCT). We tried to assess if the two genetic variants, identified in our cohort of patients, could impact the clinical course of the disease but we failed to show any associations.

Conclusion: Our preliminary results suggest that NOD2 variants, except for the Blau related ones, are not implicated in the pathogenesis of uveitis, either idiopathic or associated with other diseases. To our knowledge, this is the first report on the relationship between NOD2 gene and the phenotype of patients affected by uveitis.

Disclosure of interest: None declared.

P203
PReS-FINAL-2213: Validation of inadequate drug response and definition of colchicum resistance in FMF
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Pediatric Rheumatology 2013, 11(Suppl 2):P203

Introduction: Colchicine is effective in controlling the attacks and due to its characteristic increase in serum IgD level. The assessment of colchicine resistance via concrete and agreed methods and expression of questions. The experts evaluated all candidate variables; discuss weighting methods and exact expressions of questions. As a last step, a consensus meeting held on by attendance of 12 (6 of pediatric rheumatologist and 6 of adult rheumatologist) experts. The experts evaluated all candidate variables; discuss weighting methods and exact expressions of questions. Before consensus meeting each expert sent at least 6 selected patients to be used in validation. Physicians gave severity, activity, and drug response scores for all cases. After determination of criteria set, inadequate drug response scores were calculated in this data set. Binary logistic regulation analyses were performed to evaluate value of criterion, and ROC curves were drawn to present validity.

Results: For the validation study we collected 297 patients from 23 centers in Turkey. According to consensus meeting; number of attacks, duration of attacks, VAS score of physicians, VAS score of patients, persistence of arthritis, arthralgia, and myalgia, and high CRP levels were selected the best predictors for inadequate response to treatment in patients with FMF. Persistence of arthritis was eliminated in logistic regression analysis. Area under the curve calculated as 0.829 for full model and 0.816 for the model that persistence of arthritis eliminated from criteria set.

Conclusion: Assessing the colchicine resistance via concrete and agreed scale will provide a reliable data. The criteria set considerate as valid for evaluation of inadequate drug response. There is no statistically difference between 6 items and 7 items criteria sets. On the other hand had diarrhea and cervical lymphadenopathy during attacks. The heterogeneous v726A variant of MEFV was detected. He was put on colchicine therapy; however he did not respond despite 6 months of therapy. Further genetic analysis revealed two mutations on MVK gene (Exon 8. c.803T>C (p.268I>T), and Exon 10 c.1129 G>A (p.377V*I)). Simvastatin, etanercept and anakinra were not effective. Corticosteroid shortened the duration of fever during attacks, however; failed to lower the frequency of attacks. He had a dramatic response to canakinumab. Patient 3 was the sister of patient 3. Parents were non-consanguineous. She suffered from recurrent fever, diarrhea and cervical lymphadenopathy every month since 3 months of age. She had the same mutations of her brother. Besides, the heterogeneous E148Q variant of MEFV was detected. She is given corticosteroid during attacks regarding the parents refuse to use IL-1 blocker because of her small age (2 years old). Results: We speculate that the more severe and drug-resistant clinic of these siblings may be due to having additional heterogeneous MEFV mutations. Disclosure of interest: None declared.

P202
PReS-FINAL-2212: Mevalonate kinase deficiency: different faces with separate treatments
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Pediatric Rheumatology 2013, 11(Suppl 2):P202

Introduction: Mevalonate kinase deficiency-associated periodic fever syndrome is a systemic autoinflammatory disease caused by mutations in the mevalonate kinase gene (MVK), previously named “hyper-IgD syndrome” due to its characteristic increase in serum IgD level. The patients suffer recurrent fever attacks every 2-8 weeks beginning from infancy, often precipitated by immunizations, infections or emotional stress. Fever lasts 2-7 days and can be accompanied by malaise, headache, diarrhea, abdominal pain, vomiting, skin rashes, arthralgia, arthritis, tender lymphadenopathy and hepatosplenomegaly. Fever attacks usually respond to the administration of steroids. However, increasing frequency of fever episodes with steroid use and the natural chronic disease course may require a continuous long-term treatment. Colchicine, cyclosporine, thalidomide and statins are not effective. A TNF-α blocking agent etanercept and IL-1 blocking agent anakinra and canakinumab have been demonstrated to reduce the frequency of fever attacks in MKD. The course and severity of the disease may be quite different.

Objectives: We report three cases with HIDS, who have separate clinical findings and treatment strategies.

Methods: Patient 1 was a 12-years-old girl suffered from recurrent fever, abdominal pain, arthritis of the fingers, and cervical lymphadenopathy. The attacks started when she was fifteen months old. Each attack lasted for about a week, 2-3 times annually. She did not have a MEFV mutation. Genetic analysis of the MVK gene revealed two missense mutations: p.V377 on exon 11 and c.38_39 ins TCTG frameshift on exon 2. On follow-up, she had 2 mild attacks in the last year; one of them was treated with a single high dose oral prednisone. Patient 2 was a 17-months-old boy suffered from periodic fever since two months following birth once or twice a month, lasting for 2-4 days. He
recovery of arthritis maybe more valuable among adult patients. A prospective validation study will be conducted with daily outpatient cases.

Disclosure of interest: None declared.

P204
PReS-FINAL-2214: Validation of new pediatric criteria in diagnosis of Familial Mediterranean Fever in children
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Pediatric Rheumatology 2013, 11(Suppl 2):P204

Introduction: Familial Mediterranean Fever (FMF) is the most common recurrent autoinflammatory fever syndrome. The diagnosis is based on clinical findings and supported by genetic analysis. Recently new set of diagnostic criteria were established for the diagnosis of familial Mediterranean fever (FMF) in childhood by Yalcinkaya et al.

Objectives: The aim of this study was to validate these new criteria set among FMF patients and to compare it by Tel Hashomer criteria.

Methods: Patient group was composed of 135 FMF patients. 165 patients who were admitted to our outpatient clinic with FMF like symptoms were reviewed as a control group. Demographic findings and laboratory examination of both groups were reviewed retrospectively. According to the new criteria, the diagnosis of FMF was established by the presence of two or more of five criteria (fever, abdominal pain, chest pain, arthritis, family history of FMF). Patients were evaluated by the new criteria set and also by the Tel Hashomer criteria and both criteria were compared in the terms of sensitivity and specificity.

Results: Mean age of the patients was 14.02 ± 5.32 years (min-max: 1.1-18). Mean age of the symptoms was 6.98 ± 4.65 (min-max: 0.6-17) years. Mean age of diagnosis was detected as 8.76 ± 4.58 years (min-max:1.1-18). The mean time of diagnostic delay was detected as 1.8 years. New sets of pediatric diagnostic criteria were found to be as specific and as sensitive as Tel Hashomer criteria. The 5 new criteria that was used by Yalcinkaya was found in patient with FMF in a significantly higher manner than the controls (p < 0.05). The presence of at least 2 criteria of Yalcinkaya’s criteria was seen to be adequate to diagnose FMF. When we evaluated the relation between genetic features and new pediatric criteria we found that the specificity and sensitivity of these criteria was similar for patients with heterozygous mutations, compound heterozygous and patients with no mutation as well as homozygous patients.

Conclusion: This study has suggested that sensitivity and specificity of the new criteria set is as high as Tel Hashomer criteria.

Disclosure of interest: None declared.

P205
PReS-FINAL-2215: Genotype-phenotype correlations in children with Familial Mediterranean Fever in Germany
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Pediatric Rheumatology 2013, 11(Suppl 2):P205

Introduction: Familial Mediterranean fever (FMF) is one of the most common autoinflammatory diseases (AID). A variety of relevant mutations in the MEFV gene have been demonstrated. Pro-inflammatory S100 proteins correlate with disease activity in autoinflammatory disorders, and have been previously correlated with clinically active FMF. Here, we describe the association between these biomarkers and stable FMF including different mutations, as recorded in the German AID-Net-registry.

Objectives: Our objectives were to 1) analyse genotype-phenotype correlations and 2) describe mutation-specific associations with biomarkers with MRP8/14 and S100A12 biomarker results, in stable FMF patients.

Methods: We used two common scoring systems modified for children (Mor et al., Pras et al.) to assess disease severity in 243 FMF patients of the AID-Net-registry. For the five most frequent mutations, we tested for a correlation of the genotype with the phenotype, mean CRP, and ethnic origin, respectively. Patients were sub-grouped by mutation and their MRP8/14 and S100A12 biomarker results were evaluated. Statistical significance was tested using SPSS.

Results: Among the 243 patients, we detected a total of 433 pyrin mutations and 22 different sequence variants, including one new mutation (p.Gly488Asp). The five most frequent alterations were p.Met694Val (55%, n = 233), p.Met680Le (12%, n = 52), p.Val726Ala (10%, n = 44), p.Glu148Gln (8%, n = 34) and p.Met694Le (2.3%, n = 10). p.Met694Val in homozygous form (30%, n = 73) was correlated with a more severe disease activity, based on the score by Mor, as well as with a higher mean CRP (74 versus 31 mg/l) compared to patients without this mutation (p = 0.01 and p < 0.01, respectively). The score suggested by Pras did not yield a significant genotype-phenotype correlation; indeed, the two scoring systems were inconsistent with each other (r < 0.07). Patients with any M694V gene mutation did not have different MRP8/14 concentrations than patients without M694V mutations (mean 5,830 versus 2,640 ng/ml; p = 0.88). Patients with any M694V gene mutation did also not have different S100A12 levels (1,880 vs 495 ng/ml; p = 0.39). M694V heterozgotes also did not differ from M694V homozygotes in either MRP8/14 or S100A12 levels (p = 0.68 and p = 0.74, respectively).

Conclusion: The homozygous p.Met694Val substitution was associated with a more severe disease activity. We did not find any statistically significant differences in the MRP8/14 or S100A12 levels between patients with and without M694V mutations, or between M694V heterozygotes or homozygotes in those with stable FMF. The well-known severity scores for children (Mor, Pras) are inconsistent. The AID-Net is working on a new scoring system.

Disclosure of interest: None declared.
Methods: The AID-Net register, which includes patients with SoJIA diagnosed according to ILAR criteria, was searched for patients with clinically defined remission and flare episodes. Patients in remission were those documented as being either: 'non-acute', in remission, or with a clinician score of <1 (range 0-10, where 0 represents inactivity and 10 represent highly active disease). Flares were any cases scored as 'flare' or 'acute'. Statistical significance was measured using the Mann-Whitney-U test, using SPSS.

Results: 55 patients with a median age of 13 years (range 5-20 years) at time of blood sampling were included. A total of 158 episodes occurred where disease activity status and MRP8/14 and S100A12 results were available. This included 38 episodes of flares (19 patients) and 120 episodes of remission (44 patients). Patients presenting with episodes of flare had significantly higher mean S100A12 values compared with patients in remission (mean 2.895 (range 15-19,410) ng/ml vs 575 (0-6,220) ng/ml, respectively, p < 0.01). MRP 8/14 values were also higher in patients who were clinically flaring than in those in remission (9,600 (100-48,610) ng/ml vs 2,965 (0-45,390) ng/ml, respectively, p < 0.01).

Conclusion: The measurement of MRp8/14 and S100A12 biomarkers in patients with SoJIA in the AID-net register corresponded well with the recorded clinical disease activity in these patients. This provides further evidence for the measurement of these biomarkers.


Disclosure of interest: None declared.

P207
PReS-FINAL-2217: Atypical presentation of CRMO in two children
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Pediatric Rheumatology 2013, 11(Suppl 2):P207

Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disorder that manifests as recurrent flares of inflammation and bone destruction related to one or more foci of nonbacterial osteomyelitis. Patients may present with low grade fever and modest elevation of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell counts (WBC). We describe two cases of chronic recurrent multifocal osteomyelitis with high fever and pronounced elevation of inflammatory parameters.

Methods: The first case was an 8-year-old boy presenting to the hospital with polyarticular pain, limping, fever, decreased appetite, weight loss and fatigue. CRP was 171 mg/l, ESR 81 mm/h, WBC 16.5 G/l with 85% of neutrophils. We could exclude an infectious origin and suspected systemic onset juvenile idiopathic arthritis (SoJIA).

The patient responded well to NSAIDs, and after discontinuation he showed a stiff neck without history of trauma. Cervical MRI showed C2 and C4 vertebral compaction with bone oedema. Total body MRI showed right distal femoral, right distal fibular and left acetabular enhancement. CRMO was suspected and a fibular biopsy, performed to rule out a tumour, showed fibrous remodelling of the bone, supporting the diagnosis of CRMO. NSAIDs were restarted with progressive improvement. A follow up MRI 6 months later showed decrease of cervical vertebrae oedema.

The second case was a 7-year-old boy with 2 weeks of high fever, decreased appetite, and weight loss without perspiration or chills. Blood parameters showed CRP 105 mg/l, ESR 72 mm/h and thrombocytosis 651 G/l. WBC was normal. Infectious and onco-haematological origins were excluded. A few days later he complained about left wrist pain. An MRI showed a significant periosteal reaction of the two bones of the forearm, associated with soft tissue involvement. Bone scintigraphy revealed hypercappation of both forearms suggesting CRMO. Bone biopsy showed no inflammation or other abnormalities.

Under NSAIDs, the patient did not improve and the biological parameters remained elevated. Because of the persistence of high fever and significant systemic inflammation a treatment with Anakinra, interleukin-1 (IL-1) receptor antagonist, was started, and induced rapid improvement of both bone pain and fever. When Anakinra was discontinued, inflammatory parameters increased again, without fever or other symptoms. A total body MRI was performed and showed multiple symmetrical enhancements in different skeletal segments.

Conclusion: The two cases described showed an atypical presentation of CRMO, with high fever and increased inflammatory parameters suggesting a SoJIA. Interestingly, the second case responded to IL-1 blockade, suggesting a role for this cytokine in the disease.

Disclosure of interest: None declared.

P208
PReS-FINAL-2218: Treatment of colchicines resistant FMF: experience of a pediatric center in Turkey
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Pediatric Rheumatology 2013, 11(Suppl 2):P208

Introduction: Familial Mediterranean fever (FMF) is an autoinflammatory disorder which result from mutations in MEFV gene and characterized by dysregulated inflammation activation and IL1β secretion. At least 5% of FMF patients do not respond to colchicine.

Objectives: To evaluate the characteristics of colchicine resistant children and adolescents and present our initial treatment results.

Methods: FMF resistance was defined as having ≥2 attacks in a month and persistently high CRP and SAA levels during the attack free period, in spite of adequate colchicine dose. All patients were homozygous or compound heterogoyzes for MEFV mutations. One patient who is on anakinra treatment has HIDS mutation as well. All continued colchicine treatment at a mean dose of 0.04 ± 0.01 mg/kg.

Results: Eleven patients with mean age of 12.7 ± 7.7 years (median 14, ranging 1.5-23 years) were studied. These patients were on colchicine treatment for a mean of 5.5 ± 4.2 years. A total of 7 patients were started anakinra, however since 2 had local reactions and 2 was unresponsive; they were switched to canakinumab. At this time a total of 8 patients are now being treated with canakinumab with a mean duration of 10.8 ± 6.8 months and 3 patients with anakinra with a mean duration of 19.6 months and they all have normal acute phase reactants.

In one patient initially etanercept was used, she initially responded well but after 6 months, she became resistant and switched to anakinra. She was also well with anakinra but after 8 months, she also became resistant to anakinra despite increasing dose up to 6 mg/kg and started canakinumab. Now she has been well with canakinumab for 6 months.

Except two patients who had local reactions with anakinra, there were no side effects.

Conclusion: Anti IL1 treatment is beneficial in FMF patients who are resistant to colchicine and can be used safely. These patients may also become resistant to anti TNF or anakinra treatment.

Disclosure of interest: None declared.

P209
PReS-FINAL-2219: Evaluation of autonomic function in FMF
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Pediatric Rheumatology 2013, 11(Suppl 2):P209

Introduction: Familial Mediterranean fever (FMF) is characterized by acute and recurrent attacks of fever and polyserositis, which is associated with conduction disturbances and rhythm abnormalities. Heart rate variability (HRV) is the term used to indicate the fluctuation in cardiac frequency over time. HRV analysis is used to evaluate the condition of the autonomous nervous system, which regulates general cardiac condition and cardiac activity. Significant correlations between cardiovascular mortality and the autonomous nervous system have been evidenced in the last twenty years. In adult FMF patients abnormal heart
rate variability (HRV) parameters were found, suggesting to autonomic dysfunction.

**Objectives:** To assess cardiac autonomic functions in FMF patients during childhood period.

**Methods:** A prospective randomized clinical trial was performed by a tertiary referral pediatric cardiology and a pediatric rheumatology center. The study group consisted of 53 patients with FMF (28 female, 25 male) that were followed-up by the pediatric rheumatology out-patient clinic. They were all under colchicine treatment. The control group was chosen from age and sex matched 44 healthy children (21 female, 23 male).

All participants underwent 24-hour Holter rhythm monitoring (CardioNavigator Plus Imaging, Medical Spider view, 3.07.0158, Delmar Reynolds; Paris, France). The HRV parameters were evaluated in both groups.

**Results:** The mean age of the study group was 11.6 ± 3.5 years and the control group was 10.4 ± 3.4 years. Height and weight of the study group were 143.2 ± 19 cm and 37.9 ± 11.7 kg respectively. The control group’s height and weight were 143.6 ± 18.1 cm and 38.5 ± 14.1 kg respectively. The mean duration of colchicine treatment was 43.4 ± 41.5 months. The time-domain analysis of HRV revealed similar values of mean “standard deviation of all NN intervals” (SDNN;152.3 ± 46.2 vs 143.13 ± 41.99 msec, p = 0.423), “50% of the 5 min mean RR intervals” (SDANN; 128.6 ± 36.55 msec, p = 0.451), “root square of successive differences in RR interval” (RMSSD; 70.8 ± 53.5 vs 69 ± 33.6 msec, p = 0.481), and “proportion of differences in successive NN intervals >50 ms” (PNN50; 21.2 ± 14 vs 21.3 ± 12.1%, p = 0.524), “triangular interpolation of NN interval histogram” (TINN; 623 ± 219 vs 615 ± 170 msec, p = 0.451) and “HRV index” (20.8 ± 6.8 vs 20.3 ± 5.2 msec, p = 0.633) in both groups. Frequency domain analysis revealed similar values of high frequency (HF; 48.2 ± 13.9 vs 46.3 ± 14.8, p = 0.451), low frequency (LF; 42.5 ± 12.7 vs 44 ± 15.3, p = 0.451) and LF/HF (1.08 ± 0.84 vs 1.31 ± 1.5, p = 0.542) components in both groups.

**Conclusion:** Autonomic nervous system has an important role in the supervision of cardiac functions. In adult patients with uncomplicated FMF there are two published studies about the autonomic dysfunction, one revealing autonomic indices abnormalities and the other with similar normal autonomic function compared to healthy subjects. As being the first study concerning the autonomic function in children with FMF, we had found no significant differences between both groups. This may be attributed to the shorter duration and uncomplicated course of disease in children with FMF.

**Disclosure of interest:** None declared.

**P211**

PrEs-FINAL-2221: An earliest diagnosis of FMF

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**Introduction:** Familial Mediterranean fever (FMF) is an autosomal recessive disease, mainly affecting Jews, Armenians, Turks, Arabs and other groups living around Mediterranean basin. Major symptoms of disease are recurrent periodic fever accompanied by serositis. The disease is usually diagnosed at ages less than 20 years. Onset of the disease at older age can rarely occur. Symptoms related to FMF are noted when children become more verbal, usually after 2 years of age. Mutation analysis supports diagnostic evaluation.

**Objectives:** Here, we are reporting the youngest FMF patient, that were internalized after birth as sepsis. Physicians were unable to discharge her from the hospital due to high acute phase response, that was dedicated to meningitis, urinary tract infection, sepsis and so on. Her metabolic screenings were done and were found to be negative. She was consulted to pediatric rheumatology for the high acute phase response and fever. With a detailed history and evaluation, it was learned that her mother had recurrent swelling of her ankle joints. Mutation analysis was performed and two homozygous mutations (M694V andR202Q) were identified. She was diagnosed as FMF at 3 months of age and colchicine was started with a dose of 0.25 mg/day. She responded to colchicine both clinically and in laboratory basis. Her uncontrolled acute phase response declined gradually.

**Conclusion:** This case was reported to point out the importance of early remembrance of possible autoinflammatory diseases even at very early ages especially at endemic countries.

**Disclosure of interest:** None declared.

**P212**

PrEs-FINAL-2222: FMF presenting with the features of malignancy

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**Introduction:** Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by periodic attacks of fever and serositis caused by mutations in FMF gene (MEFV). Spleenomegaly and lymphadenopathy has been reported in FMF. The abdominal lymphadenopathy was reported in the mesentry during laparotomies for acute abdominal attacks of FMF.

**Objectives:** A 14-year-old girl was admitted to the hospital with the complaints of fever, fatigue and weight loss of 12 kg in 2 months duration. She had been prescribed different antibiotices for fever. Her laboratory work-up was as follows: Hb; 7.4 gr/dl, Hct 23%, Wbc 6000/mm³, Plt 231000/mm³, ESR: 112 mm/hr, C-reactive protein: 52 mg/l, differential count and bone marrow aspiration was normal. Vitamin B12
level was low. Autoantibodies and microbiological work-up were unremarkable. She had hyperglobulinemia. Abdominal ultrasound revealed mild hepatosplenomegaly, but this was not noted at physical examination. Pericardial effusion of 7 mm was present at echocardiography. Abdominal MRI revealed lymphadenopathy at paraaortic region and and splenic hilus. Positron emmision tomography was performed and increased fdg involvement at paraaortic, splenic and hepatic region, hypermetabolism at malignancy level and hypermetabolism in the spleen were detected. With the possible diagnosis of lymphoproliferative disease involving the spleen, an excisional biopsy was planned. During evaluation, the patient developed arthritis at her wrists. Due to the presence of fever, pericardial effusion, splenomegaly, arthritis and high inflammatory markers; MEFV mutation analysis was done. But in a month time, she lost 5 more kg, so a laparotomy and excisional biopsy was performed. Histopathology revealed only reactive lymphadenopathy without any malignant infiltration. She was found to be homozygous for M694V mutation. Colchicine treatment was introduced and nearly in a month time her ESR level decreased to 50 mm/hr and she had started to gain weight. In the next month’s visit all of her complaints were gone and ESR became normal. She is still under colchicine treatment without any complication for 3 months.

Conclusion: This is a very interesting FMF case presenting with the symptoms of malignancy and we were obliged to have a biopsy in order to exclude malignancy. In the literature there are few reports about such severe cases involving abdominal lymph nodes. This case is presented due to its unusual severe presentation and excellent response in 2 months time to colchicine.

Disclosure of interest: None declared.

P214
PReS-FINAL-2224: Canakinumab treatment regimens in CAPS-patients
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Pediatric Rheumatology 2013, 11(Suppl 2)P214

Introduction: Canakinumab is a recombinant monoclonal fully human antibody against interleukin-1β and approved for the treatment of CAPS in many countries including the US. Current dose recommendations are 150 mg (body weight >40 kg) respectively 2 mg/kg body weight (15 to 40 kg) every 8 weeks but yield insufficient response in some individuals, especially in children and patients with severe phenotypes [1].

Objectives: In this study we analyzed the response to daily practice (in contrast to trial condition) canakinumab treatment regimens in CAPS patients with focus on age, mutation and clinical presentation and the necessity and effect of dose adjustment.

Methods: An observational national multicenter study was conducted. CAPS patients were included if they received at least two doses of canakinumab. Data included information regarding demographics, treatment, clinical disease activity and inflammatory markers (including SAA, CRP, ESR, IL-6). Response to treatment was assessed using CAPS-disease activity scores, CRP and/or SAA levels.

Results: A cohort of 68 patients with CAPS was analyzed. Median age was 25.4 years (range 22 months to 73 years). When treatment was initiated, 27 patients had been younger than 18 years. The most frequent mutations were R260W, A439V, E311K, V198M, Q703K and most patients showed MWS or FCAS/MWS phenotype (3 patients with NOMID, 4 with MWS/NOMID). Neither laboratory parameters nor clinical disease activity at the beginning of treatment were able to predict the necessity to adjust treatment regimen. Two serious adverse events were reported (severe infection, osteonecrosis), mild and moderate adverse events were mostly upper respiratory tract infections but almost no injection site reactions.

Conclusion: Most CAPS patients achieve full remission with canakinumab. However, almost 50% of patients, particularly children, require dose adjustment. Full remission by dose increase was achieved without an increased rate of adverse events. Individual adjustment of therapy should be performed as needed as predictive parameters are lacking.

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Reference

P213
PReS-FINAL-2223: The relationship between FMF, BD and epilepsy
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Pediatric Rheumatology 2013, 11(Suppl 2)P213

Introduction: Familial Mediterranean Fever(FMF) is an autoinflammatory disease particularly frequent around the Mediterranean basin. Behçet disease (BD) is a autoinflammatory disease which distribution is mainly around the Mediterranean Sea, Middle East and Far East.Epilepsy is a disease which distribution is mainly around the Mediterranean Sea, Middle East and Far East.Epilepsy is a chronic disorder of the brain that affects people in every country of the world. It is characterized by recurrent seizures.

Objectives: Coexistence of FMF with BD and also association FMF with epilepsy has been reported in some studies. Here we present a case of FMF, BD and epilepsy in the same family.

Methods: Clinical and laboratory findings are presented.

Results: 7 year old boy admitted to the Arabir Centre with complains of: recurrent abdominal pain, fever, oral ulcers, recurrent genital ulcerations with skin lesions. Manifestation of disease began from one year with fever, recurrent oral ulcerations 8 times in 12 months. From 2 years began abdominal pain, chest pain. The attacks were 3 times per month each lasting typically for 3 days. The family history was: father had epilepsy with FMF, MEFV mutations was: M694F/479L. He received colchicine and anti-epileptic drugs. Sister of the father had recurrent abdominal pain, fever, arthritis, oral ulcers, skin lesions (she was not in Armenia). Examinations; FBC results showed leucocytosis with elevated CRP and ESR. Chest X-ray revealed exudates in the costophrenic angle from the two sites. Genetic investigation of MEFV reviled M694V/N heterozygotes mutations. HLA-BS1 was positive. We established the diagnosis of FMF according criteria Tel-Hashomer and BD: according criteria for Behçet’s disease, rule out other conditions with similar symptoms. It was started the treatment with colchicines 1 mg/day. The attacks of FMF was resolved but oral ulcerations with skin and genital problems was continued. After the prednisone therapy with the colchicine treatment the problem was resolved.

Conclusion: This is an interesting case presenting probable relationship between FMF, BD and epilepsy. We suppose, that these diseases are connected not only with the relationship of geneses, but also with major pathological development in mesenchymal tissue in morphogenesis.

Disclosure of interest: None declared.
**P215**
**PReS-FINAL-2225: Oxidative stress in children with episodic fever of unknown origin**

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**Introduction:** Fever of unknown origin (FUO) i.e.: (1) a temperature greater than 38.3°C on several occasions, (2) more than 3 weeks’ duration of illness, and (3) failure to reach a diagnosis despite 1 week of inpatient investigation are commonly seen in pediatric practice. The conditions could be caused by mutations of genes coding inflammasonic sequences. In these instances activated neutrophils and monocytes intensively generate reactive oxidative species.

**Objectives:** Aim of this study was to evaluate if there are oxidative changes of lipids in plasma and erythrocytes and advanced oxidation protein products (AOPP) in children with episodic FUO.

**Methods:** The study enrolled 25 children with episodic FUO (in afebrile phase) and 25 healthy age matched controls. Lipid peroxidation was evaluated measuring malondialdehyde (MDA) production by thiobarbituric-acid-reactive substances (TBARS) assay in plasma and erythrocytes while advanced oxidation protein products in plasma (AOPP) was measured in plasma using spectrophotometric methods to determine TBARS and AOPP levels.

**Results:** Mean duration of episodic fevers was 3.96 ± 2.8 years. Levels of erythrocytes MDA were higher in patients than in controls (86.26 ± 10.75 vs. 78.0 ± 3.21 nmol/g Hgb), however not significantly. There was no difference in MDA concentrations in plasma (2.42 ± 0.35 vs. 2.41 ± 0.39 μmol/L). Interestingly, levels of AOPP were significantly lower in patient group than in controls (18.8 ± 5.04 vs. 25.1 ± 3.35 μmol/L, p < 0.05).

**Conclusion:** The results confirm that erythrocyte membrane is the most vulnerable to the oxidative stress. However, duration of episodic fevers for approximately 4 years is not sufficient to cause significant oxidative modifications of lipids and proteins. Unexpected results for AOPP could be explained through the higher anti-oxidative capacity of blood.

**Disclosure of interest:** None declared.

**P216**
**PReS-FINAL-2226: Assessment of autonomic functions in children with Familial Mediterranean Fever by using heart rate variability measurements**

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**Introduction:** Familial Mediterranean Fever (FMF) is an autoinflammatory, autosomal recessive inherited disorder, and characterized by recurrent episodes of peritonitis, plöritis and arthritis. Patients with inflammatory disease are at increased risk of cardiovascular complications due to rhythm disorders. QT and JT dispersions are simple and non-invasive arrhythmogenic markers and can be used to assess the homogeneity of cardiac repolarization.

**Objectives:** The aim of this study was to determine the risk of cardiac arrhythmias in patients with FMF by evaluating QT and JT dispersion.

**Methods:** The study group and the control group were evaluated with a standard 12-lead electrocardiography (ECG). QT, JT and RR distances were measured in both groups. The corrected QT (QTc) and corrected JT (JTc) were calculated. QT dispersion (QDc) and JT dispersion (JTDc) were determined.

**Results:** A total of 48 FMF patients who are in the attack-free period and use regular colchicine therapy (26 male, 22 female, 11.10 ± 3.42 years) and 31 healthy children (17 males, 14 females, 9.61 ± 2.83 years) were included in the study.

There was no statistically significant difference was found between the study and control groups in terms of RR, QT, JT, QTc, JT, JTc and JTD measurements. QTc value is found to be higher in patients with FMF than the control group (412.15 ± 214.393 ± 35.18, t = 2916, p = 0.005), although the difference was statistically significant, the value is within normal limits (below 0.44).

**Conclusion:** In our study it is tried to determine the risk factor by investigation of QT and JT time and dispersion. QTc value is higher than in patients with FMF than the control group. There is no significant difference in QT and JT dispersion between the groups but the prolonged QTc value may increase the risk of arrhythmia as the indicator of ventricular sensitivity.

**Disclosure of interest:** None declared.

**P217**
**PReS-FINAL-2227: QT and JT dispersion in children with FMF**

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**Introduction:** Familial Mediterranean Fever (FMF) is an autoimmune, autoinflammatory, recessive inherited disorder, and characterized by recurrent episodes of peritonitis, plöritis and arthritis. Patients with inflammatory disease are at increased risk of cardiovascular complications due to rhythm disorders. QT and JT dispersions are simple and non-invasive arrhythmogenic markers and can be used to assess the homogeneity of cardiac repolarization.

**Objectives:** The aim of this study was to determine the risk of cardiac arrhythmias in patients with FMF by evaluating QT and JT dispersion.

**Methods:** The study group and the control group were evaluated with a standard 12-lead electrocardiography (ECG). QT, JT and RR distances were measured in both groups. The corrected QT (QTc) and corrected JT (JTc) were calculated. QT dispersion (QDc) and JT dispersion (JTDc) were determined.

**Results:** A total of 48 FMF patients who are in the attack-free period and use regular colchicine therapy (26 male, 22 female, 11.10 ± 3.42 years) and 31 healthy children (17 males, 14 females, 9.61 ± 2.83 years) were included in the study.

There was no statistically significant difference was found between the study and control groups in terms of RR, QT, JT, QTc, JT, JTc and JTD measurements. QTc value is found to be higher in patients with FMF than the control group (412.15 ± 214.393 ± 35.18, t = 2916, p = 0.005), although the difference was statistically significant, the value is within normal limits (below 0.44).

**Conclusion:** In our study it is tried to determine the risk factor by investigation of QT and JT time and dispersion. QTc value is higher than in patients with FMF than the control group. There is no significant difference in QT and JT dispersion between the groups but the prolonged QTc value may increase the risk of arrhythmia as the indicator of ventricular sensitivity.

**Disclosure of interest:** None declared.

**P218**
**PReS-FINAL-2228: Survey of off-label ANTI-I1-I treatments in France: two years data**

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**Introduction:** In each patient, it was performed twelve lead electrocardiography (ECG) at 25 mm/s (paper speed), 24 h ambulatory electrocardiographic monitoring (AECG), and transthoracic echocardiography by a Siemens Acuson Sequoia C256 cardiac ultrasonographic scanner, with 2.5- to 3.5-MHz transducers.

**Results:** It was noted that SDNN (standard deviation of all NN intervals) value was lower in patients with FMF as compared to the control group. Frequency-dependent HRV parameters were similar in both groups. There was no difference in patient and control groups in terms of conventional echocardiographic parameters.

**Conclusion:** Studies with larger cohorts and more comprehensive methods are required to assess the presence and consequences of possible autonomic dysfunction in children with FMF.

**Disclosure of interest:** None declared.
Introduction: Despite their limited licensed indications, anti-IL1 agents are often used in real-life practice for an increasing number of diseases. A national survey to record the off-label use of this class of therapeutics in France was started in January 2011. The survey is coordinated by the French National Reference Centre for Auto-inflammatory Diseases, under the aegis of the ‘Club Rhumatisme et Inflammation’.

Objectives: The survey aims at gathering information concerning: the number of patients treated with anti-IL1 agents in France, the treated disease, the kind and the indication of the used anti-IL1 agents, their efficacy and safety.

Methods: We set up a physician-directed questionnaire covering the following areas: patient data, disease data, anti-IL1 agent (molecule, dose and frequency), its efficacy, adverse events. Any adult or paediatric patient who had received an anti-IL1 agent from January 2005 in France could be included.

Results: Over two years 193 patients from 37 centres have been included. Demographic data: 104 males, 89 females; 141 adult, 52 paediatric patients, mean age 35.2 years at treatment onset. Main diseases were: adult onset Still disease (AoSD) (35), systemic onset juvenile idiopathic arthritis (SoJIA) (29), gout (27), mevalonate kinase deficiency (MKD) (14), familial Mediterranean fever (FMF) (12), SAPHO syndrome (9), Schnitzler’s syndrome (7). The main off-label used agent was anakinra, used at least once in 189 patients. Canakinumab was used in 25 patients, mainly children, in most cases as a second-line treatment after anakinra. Rilonacept is not yet available in France. 83 patients (66 anakinra, 17 canakinumab treated patients) were still on treatment at last visit. Some form of clinical response was found in 90% of anakinra-treated patients. A complete physician-evaluated response was reported in Schnitzler’s syndrome (85%), gout (80%), CAPS (75%), AoSD (59%), FMF (50%), SoJIA (42%), MKD (30%), SAPHO (11%). 83% of canakinumab-treated patients showed clinical response. At least one adverse event (AE) was reported for 53% and a serious adverse event (SAE) for 10% of anakinra treated patients. Main AEs were: injection site reactions (48%), weight gain (11%) and liver enzymes elevation (9%). SAEs were: severe infections (12%), macrophage activation syndrome and severe hepato-toxicity. 50% of patients treated with canakinumab showed an AE, namely respiratory infections and liver anomalies. Only few patients had a SAE (severe infections).

Conclusion: Anakinra is the main off-label anti-IL1 agent used in France, showing partial to complete efficacy in most patients; complete clinical response rates vary according to specific diseases, being higher in Schnitzler syndrome, gout, CAPS and AoSD. Around half of the patients showed at least one AE, mainly related to a poor local tolerance. Preliminary data of our survey suggest that canakinumab was efficacy and well tolerated in most patients.

Disclosure of interest: None declared.

P219
PRes-FINAL-2229: Pamidronate in CRMO - a small case series
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Pediatric Rheumatology 2013, 11(Suppl 2):P219

Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare autoimmune inflammatory disorder which affects predominantly girls with peak onset between ages of 7 to 12 years. There is a frequent association of CRMO with inflammatory skin or gut disorders. Patients with isolated CRMO are usually treated with nonsteroidal anti-inflammatory drugs (NSAIDs) prior to escalation to corticoids and disease-modifying antirheumatic drugs such as methotrexate (MTX), sulfasalazine, azathioprine. Recently, TNF inhibitors and bisphosphonates have been recommended for treatment of most severe cases.

Objectives: To evaluate pamidronate treatment in patients with isolated CRMO relapsing despite NSAID, corticosteroid and methotrexate therapy in a retrospective study of a case series.

Methods: Since 2011, 4 patients (3 girls and 1 boy) with CRMO have been treated with pamidronate in Paediatric Department of University Hospital Brno, Czech Republic. All these patients had chronic relapsing multifocal osteomyelitis without any associated inflammatory condition. The diagnosis of CRMO was set in the mean age of 12 years based on radiographic findings (x-ray, CT, MR), and historical findings of a non-bacterial inflammatory bone lesion. Previous treatment with NSAIDs, corticosteroids, and MTX (MTX used only in 3 of 4 cases) was insufficient.

Results: Intravenous pamidronate administered every 3 to 6 months was added to MTX in 3 patients, in the fourth case it was started in a MTX naïve patient. Corticosteroids were used to control acute symptoms. All the patients treated with pamidronate significantly improved. In 3 patients including 1 patient without MTX no corticosteroids were needed after 1 month of pamidronate therapy and there are no clinical signs of the disease activity now. In 1 patient treated with pamidronate and MTX the dose of corticosteroids has significantly decreased. No adverse event was observed.

Conclusion: In accordance with previous observations of other authors the results of our small case series indicate good efficacy of pamidronate treatment in patients with CRMO. In contrast, MTX alone had no benefit in our patients. We recommend considering pamidronate a second line therapy in more severe cases of isolated CRMO.

Disclosure of interest: None declared.

P220
PRes-FINAL-2230: A prospective evaluation of a cohort of patients with PFAPA syndrome
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Pediatric Rheumatology 2013, 11(Suppl 2):P220

Introduction: PFAPA (Periodic Fever with Aphthous stomatitis, Pharyngitis and cervical Adenitis) is a periodic syndrome described for the first time in 1987 by Marshal et al. In 1999 the diagnostic criteria were formulated by Thomas.

Objectives: prospective evaluation of a cohort of PFAPA patients, to better describe clinical characteristics and therapeutic response.

Methods: all patients receiving a PFAPA diagnosis between 1999 and 2012 were prospectively evaluated. Sex, age at onset, age at diagnosis, family history, clinical characteristic of the febrile episodes and associated symptoms, prodromes, therapy, therapy response and age at resolution were collected.

Results: In our cohort (148 males and 120 females) fever began at 26.2 ± 24 months of age, 8% of the patients had an onset after the fifth year of life, but all other Thomas criteria were met. A family history was present in 39.6% of patients. Mean duration of PFAPA episodes was 4 ± 1.6 days, and a mean interval between episodes 27.9 ± 11 days. Most common symptoms with fever were pharyngitis (95.5%), cervical adenitis (63.8%), stomatous aphthosis (38.4%), abdominal pain (32%). Prodromes, such as irritability, nausea and headache were present in 10% of patients. All patients received treatment with oral steroids, using a single administration of 1 mg/kg of prednisone or prednisone equivalent, the first day of fever. In all patients steroids were effective and only 13% of them experienced a free-interval shortening, without the perceived need to stop the steroids for this reason. There was no difference in the studied parameters between the population who experienced a free-interval shortening and the population in which this event was not registered.
In 144 children resolution occurred, in 58% of children spontaneously and in 42% after tonsillectomy. Mean disease duration was 40 ± 63 months, medium age at resolution 67.7 ± 66 months. Tonsillectomy was efficacious in 60/62 patients. The tonsillectomy was done after a mean period of 36 months from disease onset. At multivariate regression analysis disease resolution was independently associated to age onset (β = 1.011 95%CI 1.000-1.022, p = 0.05) and to tonsillectomy (β = 0.022 95%CI 0.005-0.092 p = 0.001).

Conclusion: PFAPA is the most common cause of periodic fever in children, however our study confirms that the 5 year of age at disease onset criterion is too strict. Symptoms other than the ones from the classic description, such as abdominal pain, could have clinical relevance. Prodromes are quite common and useful in differentiate the typical PFAPA attack from other episodes of fever. Oral steroids are, in our opinion, the therapy of choice and the free-interval shortening is not perceived as a clinically relevant issue. It is not possible to predict which patients would present this effect. Tonsillectomy is very effective, but should be reserved to a very selected group of patients and with an adequate period of follow-up before the surgery. Age at onset seems to inversely correlate with disease duration.

Disclosure of interest: None declared.

P222

PreS-FINAL-2231: A series of 41 mutations of TNFRAF1

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Introduction: TRAPS (TNF receptor associated periodic syndrome) is a rare autoinflammatory disease that can touch children and adults. It is caused by the mutation of TNFRSF1A encoding for TNF receptor. The main complication is amyloidosis.

Objectives: The aim is to increase knowledge about the disease to make the diagnostic easier. Another purpose is to analyse the biotherapy treatment in TRAPS.

Methods: It consists in a retrospective descriptive multicentre study in French and Belgian hospitals. Data were directly collected thanks to files of patients.

Inclusion criteria are: presence of TNFRAF1 mutation, recurrent symptoms. Exclusion criteria: presence of MEFV mutation.

Results: We have included 25 kids and 16 adults (isolated cases and 9 families), coming from France (45%), south of Europe (22%), north of Europe (10%), Maghreb (9%), and east of Europe (6%). Two kids have homozygous mutation for MEFV and one heterozygous. 19.5% of the patients have had an appendectomy. 26 patients have recurrent fever in their family, among which 22 have TRAPS.

The disease starts mainly before the age of 5 years (61,1%) but for 13,5%, it begins in adulthood. The average time of the diagnosis (delay between symptoms and diagnosis) is 12.9 years. 51% of R92Q heterozygous mutation, 10% of T50M, 7% de L67P, 5% C295, 5% C431S have been encountered. 2% of the patients have R92Q homozygous, 2% Q82R and R92Q heterozygous.

The seizures occur 9,7 times a year on average (≤1 to 48 times a year), last 10,8 days on average (1 to 49 days). A trigger exists in 43,9% of the cases. 78% have rheumatologic symptoms, 70,7% arthritis (mainly knees, spine, elbows), 22% arthrities (small and big joints). 24,4% have chest pain, 7,3% serositis. Dermatological symptoms (70,7%) are frequent (56,1% rash). Lots of patients have abdominal pain (70,7%), myalgia (65,7%), asthenia (48,8%). Headache is present in 39% of this population. Only 3 patients have periorbital oedema. Between the seizures there is no symptomatology, but in 24% of the cases the disease persists.

We note the interest to dose the Serum Amyloid A to detect the activity of disease between the crises. The screening of proteinuria was positive in 29% of the cases but no amyloidosis is reported. Correlation between R92Q mutation and hematologic symptoms (splenomegaly, anemia) was found between genotype and phenotype.

Corticosteroids were used for treatment of seizures. Only 9 patients were treated by biotherapy. Etanercept was efficient in a first time, but not always in the long term. Anakinra always allowed remission.

Conclusion: 77% of this population of patients with TNFRSF1A mutation has 3 symptoms among arthralgia, rash, abdominal pain, myalgia, asthenia and headache. Etanercept is not always efficient and Anakinra is a good alternative for the treatment. The inclusion of the patients in autoinflammatory disease registers would allow a better knowledge of TRAPS.

Disclosure of interest: None declared.

P222

PreS-FINAL-2232: Long-term follow-up in a national cohort of MKD patients: search for clinical predictors of a spontaneous improvement

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Pediatric Rheumatology 2013, 11(Suppl 2)P222

Introduction: Mevalonate-kinase deficiency (MKD) is an autosomal recessive disease caused by the deficiency of the mevalonate-kinase enzyme (MKK) and characterized by recurrent fever episodes with systemic involvement. Classically, the disease was thought to have a self-limiting course, with a spontaneous improvement in the adulthood. In 2008 the International registry showed that 50% of patients present a reduction of fever episodes in the adulthood. Up to now, it’s difficult to predict the course of the disease a patient will display.

Objectives: To identify clinical predictors of a self-improvement course of MKD.

Methods: Patients carrying two mutations of the MVK gene or a single mutation with a MKD phenotype were collected in a national multicentric study. Detailed clinical information was collected at the time of molecular analysis and last follow-up through a standardized questionnaire. 

Spontaneous disease course was classified as follows: i) resolution (no episodes in the last 6 months), ii) improvement (reduction of more than 30% of fever episodes), iii) stationary and iv) worsening (increase frequency of fever episodes or appearance of new major clinical manifestation). 

A spontaneous improvement was considered a reduction or resolution of fever episodes without any maintenance therapy.

Results: We collected baseline information of 56 patients (29M and 27F). The mean age of onset was 10.5 ± 13.3 months (range 1-108), with a number of fever episodes per year at the baseline of 13.8 ± 5.4 (range 3-30). The most frequent mutation was V377I, showed by 43 patients; in 10 patients it was at the homozygous state. Follow-up information was available for 42 patients; the mean age of the patients was 13.3 ± 8.5 years, the mean disease duration was 12.4 ± 8.7 years. At the follow-up the mean number of fever per year was 8.8 ± 6.7. Twelve patients (28.6%) showed a spontaneous improvement of the disease at the follow-up, fifteen (35.7%) remained stable and seven (16.7%) worsened. Thirteen patients required a biologic therapy: five patients improved with Anakinra and no one with Etanercept.

The variables associated with a spontaneous improvement were: female sex (p = 0.019), V377I at the homozygous state (p = 0.03). The same patients display also a less frequent presence of some clinical manifestations at the last follow-up, such as exudative pharyngitis (p = 0.03), painful lymph nodes (p =0.02) and vomiting (p = 0.03). Multivariate analysis indicated as predictors of spontaneous improvement: female sex (p = 0.007) and V377I at the homozygous state (p = 0.0003).

Conclusion: The homozygous state for V377I and female sex are associated to a spontaneous improvement of disease course in MKD patients. These elements could help clinicians to establish which patients could be exclusively treated with steroid on demand in respect to those that could take advantage from the early use of 2nd line treatment with biologics.

Disclosure of interest: None declared.
P223
PReS-FINAL-2233: Retrospective analysis of different treatment strategies in chronic non-bacterial osteomyelitis

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Introduction: Pediatric chronic nonbacterial osteomyelitis (CNO) is a sterile inflammatory bone disorder in which innate and adaptive immunity dysfunction involved. Unifocal and multifocal disease courses are known. The modern treatment modalities include non-steroid anti-inflammatory drugs (NSAIDs), steroids, sulfasalazine (SSZ), methotrexate (MTX), bisphosphonates and biological drugs - TNFα and IL1β-antagonists, with limited data.

Objectives: The aim of our study was to assess children with CNO and to evaluate efficacy of treatment modalities.

Methods: Our cohort of CNO patients included 22 children, 8 boys and 14 girls. Monofocal disease course was in 9/22 (40.9), multifocal in 13/22 (59.1) with mean 6 foci per patient. Histological confirmation was made in 13/22. Repeated MRI, CT and bone scintigraphy was performed in all patients. 3 patients have family history of autoimmunity (1 Crohn’s disease, 1 - psoriasis, 1 - ankylosing. 16 patients (72.7%) had comorbid autoimmune diseases (different types of JIA): 5 had monoarthritis, 1 arthritis with uveitis, 1 - psoriatic arthritis, 1 - polyarthritis NNF PE 6 had enthesitis-related arthritis (3 had ankylosing spondylarthritides) and 1 had Crohn’s disease. Spine involvement was in 5/22 (22.7%). Onset age was 8.5 (6.3; 10.5) years, the right diagnosis delay was 3.6 (1.7; 9.5) months.

Results: Fever, on high pain, VAS and parental VAS scores highly correlated with risk of relapse disease course. Treatment: effectiveness of NSAID only 3/10 (30%), SSZ - 1/5 (20%), corticosteroids - 0/3 (short-term effect only), MTX - 4/7 (57.1%), pamidronate (PM) with partial response 2/12 (16.7%) and with complete response - 10/12 (83.3%). Biologics - adalimumab and etanercept were effective in 3/4 (75%) patients, who fail to NSAID, MTX, PM and SSZ. During disease course treatment lead to decreasing sings of disease activity, such as: parental VAS (p = 0.015), pain VAS (p = 0.026), MDVAS (p = 0.026), CRP (p = 0.0006), WBC (p = 0.006), ESR (p = 0.0024), PLT (p = 0.014). The main effectiveness belonged to PM and MTX (0.008) in decreasing of pain VAS (-100% and -80%), parental VAS (-92% and -74%) and MD VAS (-93% and -70%, respectively). We calculated the cumulative probability of survival (event of interest: CNO flare) in the entire patient sample, depending the kind of treatment (PAM, MTX and NSAID) obtained by the Kaplan-Meier method. Significant difference was proved comparing 3 therapeutic branches (p = 0.028). MTX treatment was effective (p = 0.04), as well as PAM (p = 0.01) than NSAID. Only flu-like syndrome during PAM treatment was in 10/12 (83.3%). No any others side effects were reported. All patients who had flu-like syndrome on first infusion had complete response to PAM, vice versa patients, who had no such complication had only partial response to this treatment.

Conclusion: CNO is a group of chronic inflammatory conditions associated with different rheumatic diseases. The most effective treatment modalities were PAM, biologics and MTX. PAM was safety and can reach the rapid response and maintain long sustained remission.

Disclosure of interest: None declared.

P224
PReS-FINAL-2224: Successful canakinumab treatment in uveitis secondary to cryopyrin-associated periodic syndrome

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Introduction: Cryopyrin-associated periodic syndrome (CAPS) is a constellation of diseases with a different and varying clinical spectrum which is rarely seen in childhood. The mildest form of CAPS which is familial auto-inflammatory syndrome and the most severe form which is chronic inflammatory neurologic cutaneous arthropathy (CINCA) possess a very different spectrum of clinical findings. Most important organ involvement in CAPS is the associated uveitis. Uveitis in CAPS is unresponsive to most of the classic treatment modalities.

Objectives: In this case report, we will describe the response of a patient to canakinumab therapy whose uveitis associated with CAPS was resistant to other traditional treatment modalities.

Methods: Case report: The female patient who was healthy until 3 years of age developed uveal rash associated with a 4 to 5 day duration of fever which started to occur periodically every 1 month. At 5 years of age, in addition to her periodic complaints of fever and rash, arthritides occurred in her left knee. After her admittance to our Rheumatology Department with these complaints, chronic arthritis of the right ankle was also detected. Her laboratory analysis revealed a normal complete blood count while acute phase reactant levels were elevated. ANA and RF were found to be negative in the patient. Ophthalmologic evaluation revealed episcleritis and chronic iridocyclitis. The patient was given methotrexate, predonisin and infliximab with varying doses and with varying durations. Despite different treatment modalities, her uveitis and uveal findings persisted. NLRP3/CIA1 mutation was investigated with the suspicion of CAPS. T436A mutation was detected. Neurosensorial hearing loss was not present in the patient. With the confirmation of diagnosis of CAPS, patient was given canakinumab therapy at a dose of 4 mg/every 2 months. After the first dose, joint and skin findings of the patient resolved completely. Her uveitis which was unresponsive to all of the treatment modalities also resolved after the first dose. Leukocytes in the vitreus also disappeared. The patient is now at the 18th month of canakinumab therapy and is totally asymptomatic without any flare of her uveitis.

Conclusion: CAPS should be considered in the differential diagnosis in children presenting with an uveal rash and olioarthroitis. If there is uveitis associated with CAPS, one of the most efficacious and safe drug for treatment is the anti-interleukin 1β agent, canakinumab.

Disclosure of interest: O. Kasapcopur Consultant for: Novartis, I. Tugal-Tutkun: None declared, K. Barut: None declared, E. Ibraheem: None declared, A. Gul: None declared.

P225
PReS-FINAL-2235: Overlap of homozgyous TNFRSF1A R92Q mutation with MEV1 E148Q mutation versus homozgyous TNFRSF1A R92Q mutation: difference in clinical profile in two sisters from Oman

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Pediatric Rheumatology 2013, 11(Suppl 2):P225

Introduction: Tumor necrosis factor receptor associated periodic syndrome (TRAPS) is a multifaceted auto inflammatory syndrome which was initially described in persons of Irish-Scottish ancestry and in ethnic groups of northern European descent. To date, more than 70 mutations have been described. Since then, it has been described in other ethnicities. There have been few reports of from Asia, 11 cases have been described from Japan, and only one case of TRAPS has been described in an Arab child from Israel (1-8).There are no cases of TRAPS that have been described from Gulf Arab states.

Objectives: We hereby report 2 sisters with homozgyous R92Q variant in the TNFRSF1 gene of Arabic origins from Oman with different clinical course, one which also had the E148Q mutation in MEVF gene.

Methods: Detailed clinical description of two sisters including their family pedigree along with their laboratory investigations including measurement of TNF-α in both patients and their parents, in addition to sequencing of TNFRSF1A and MEVF.

Results: 12 yrs old girl presented at 18 months of age with episodes of high fever, lasting for 5 to 7 days occurring at monthly intervals. The attacks were associated with abdominal pain, vomiting, myalgias, arthralgia with occasional chest pains. Investigations during febrile episodes revealed anemia, leukocytosis, thrombocytosis and elevated inflammatory markers. Infectious, immunological, rheumatological and malignancy work up was negative. Sequencing of the MEVF gene revealed a heterozygous c.440G>C.

Disclosure of interest: None declared.
Introduction: Patients with autoinflammatory syndromes may present a clinical disease course that is characterized by recurrent, episodic manifestations (such as fever, skin rash or visceral involvement) or they may show a continuous, unremitting disease course with persistent clinical manifestations. Patients with certain diseases, such as CAPS or Blau syndrome, usually present with a severe protracted clinical course not responding to conventional therapy. Perhaps the overlapping genes explain the difference in disease course. However, this postulation would contradict previous studies that found that the interaction between the MEFV gene and R92Q genes is minimal but non-existing (10).

Disclosure of interest: None declared.

P227
PRoS-FINAL-2237: The diagnostic challenge of osteolytic bone lesions in autoinflammatory diseases: a case report
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Pediatric Rheumatology 2013, 11(Suppl 2):P227

Introduction: Osteolytic lesions are the hallmark of a number of inherited (DIRA and Majeed syndrome) and multifactorial (CRMO and SAPHO) autoinflammatory diseases.

Methods: We describe the clinical picture and the diagnostic tests performed in a 33 months old girl admitted in our hospital for recurrent episodes of arthritis and bone lesions.

Results: A girl, born from uneventful pregnancy, at the age of 18 months presented an episode of arthritis of the left knee and low-grade fever with leukocytosis and increased inflammatory markers; the arthrocentesis revealed a small amount of corpuscular liquid with a negative cultural test. The girl was treated with i.v. antibiotic therapy with a partial improvement. In the following months she presented a worsening of the pain and swelling of the left knee, associated to stiffness, and started to complain of pain in the right knee and ankles; the treatment with on demand NSAIDS was poorly effective. Due to the persistence of these symptoms, at the age of 29 months the child was admitted to another Hospital, where an X-ray of the lower limbs revealed the presence of an osteolytic lesion of about 2.3 × 0.7 cm, with indefinite margins and periosteal apposition, in the distal diaphysis of the left tibia. The bone scintigraphy showed a metabolic hyperactivity in the same area only. A biopsy of the lesion revealed a pattern consistent with a chronic osteomyelitis.

In the following months the girl complained of pain in the pelvis, legs and hands, with marked morning stiffness and lameness; the blood tests revealed a slight increase of the inflammatory markers. Bone marrow aspiration was negative for malignancies. A diagnosis of CRMO was pointed out. The girl was treated with steroids with a prompt good response but recurrence of the symptoms after discontinuation. The girl was then admitted to our center. The blood test revealed a slight neutrophilic leukocytosis with elevation of acute phase reactants (ERS 39 mm/1 h, CRP 4,28 mg/dl); the X-ray of the left limb confirmed the presence of the osteolytic lesion with periostitis and the whole-body stir-imaging revealed the presence of occasional periosteal erosion in the same area only. A biopsy of the lesion revealed a pattern consistent with a chronic osteomyelitis.

Conclusion: This case enlightens a clinical overlap between different autoinflammatory diseases that has to be considered in the differential diagnosis. In fact the presence of osteolytic lesions has never been reported in PAPA syndrome. Therapy with biological agents leads to better outcomes.

Disclosure of interest: None declared.

(P148Q) mutation resulting in the diagnosis of Familial Mediterranean Fever. She responded to colchicine for 4 years and to etanercept for 2 years. Revision of the diagnosis was necessary due to change in clinical symptoms. The duration of fever was lasting up to 10-14 days with the occurrence of occasional peribulbar swelling and redness. TRAPS was considered, and sequencing of the TNFRSF1A gene revealed homozygous R92Q variants. She was treated with anakinra with sustained dramatic clinical improvement for more than 12 months. 6 yrs old sister, presented at the age of 18 months with similar clinical episodes, but less severe in intensity and frequency. She had no significant clinical response to colchicine and showed transient response to etanercept lasting 3 months. She was also found to have homozygous R92Q variants in the TNFRSF1A gene. Anakinra was started with dramatic clinical improvement.

Conclusion: R92Q is a nonstructural gene mutation with low disease penetrance resulting in a mild disease course in patients with TRAPS (9). We present 2 sisters with homozygous R92Q mutation presenting with different clinical disease courses, a moderate and severe course which is unusual. In patients with atypical clinical features, an overlapping gene syndrome should be considered as in patient 1 who presented with a severe protracted clinical course not responding to conventional therapy. Perhaps the overlapping genes explain the difference in disease course. However, this postulation would contradict previous studies that found that the interaction between the MEFV gene and R92Q genes is minimal but non-existing (10).

Disclosure of interest: None declared.

P226
PRoS-FINAL-2236: Continuous autoinflammatory syndromes: a single-center experience in Argentina
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Pediatric Rheumatology 2013, 11(Suppl 2):P226

Introduction: Patients with autoinflammatory syndromes may present a clinical course characterized by recurrent, episodic manifestations (such as fever, skin rash or visceral involvement) or they may show a continuous, unremitting disease course with persistent clinical manifestations. Patients with certain diseases, such as CAPS or Blau syndrome, usually present with a severe protracted clinical course not responding to conventional therapy.

Methods: Ad-hoc data bases from our autoinflammatory syndromes clinic were reviewed. Patients attended this clinic between May 2009 and May 2013. Demographic, clinical, laboratory and genetic data were retrieved. Autoinflammatory syndrome was defined as the presence of a chronic, systemic disease with no evidence of malignancy, infection or autoimmunity. Patients with a continuous disease course (persistent clinical manifestations with no free interval and with possible recurrent exacerbations prior to the initiation of therapy) were included in the analysis. Patients with a diagnosis of systemic juvenile arthritis were excluded. Genetic analysis was performed in different locations.

Results: Fourteen children (9 boys) with a continuous disease course were identified among patients with autoinflammatory syndromes. Median age at presentation: 6 months; median age at diagnosis: 39 months; median follow-up time: 5 years. Two patients had a positive family history. Systems involved: constitutional (fever/weight loss/malaise) 14 patients, skin 14, joints 13, CNS 8, gastrointestinal 7, eyes 7, bone 6, mucosae 5, respiratory 4, muscle 2. Acute phase reactants remained permanently elevated in 7 (4 Blau, 2 CAPS, 1 MKO). Patients were treated with different agents including steroids (11 patients), methotrexate (9), anti TNF agents (5), and anti IL-1 agents (5). Eleven patients improved (8 of them on biologics), 2 patients remained stable and 1 patient died (suspected DIRA).

Conclusion: Continuous autoinflammatory syndromes are severe systemic diseases that affect growth and functional capacity of patients. Genetic diagnosis may provide definite diagnosis in a proportion of patients. Therapy with biological agents leads to better outcomes.

Disclosure of interest: None declared.
Introduction: PAPA syndrome is a very rare autoinflammatory condition. Few data are nowadays available about the clinical characteristics, the response to treatment and the outcome of this disease.

Objectives: to analyse the data of the PAPA patients enrolled to the Eurofever registry.

Methods: the data analysed in the study were extracted from the Eurofever registry, which is hosted in the PRINTO website http://www.printo.it. The patients included in the study in the presence of clinical manifestations consistent with PAPA syndrome and mutations in the PSTPIP1 gene. Demographic data, clinical manifestations and response to treatment were analysed.

Results: In February 2013 baseline and clinical information were available in 2567 patients from 88 centers in the Eurofever registry. Of these 16 patients PAPA patients (M/F = 8:8), from 3 different centers, fulfilled the inclusion criteria and were therefore analysed: 10 were of the same family, in 3 patients the disease was caused by a de novo mutation while in 3 cases the mutation was found in one parent (not yet included in the registry). The mean age at enrollment was 26.22 years (4 paediatric and 12 adult patients). The mean age at disease onset was 5.7 years (range birth – 18 years). The mean age at diagnosis was 24.5 years (range 1.8 - 57.5), with a mean delay of 18.8 years (range 2 months - 50 years). The mutations found in the PSTPIP1 gene were V344I (1 pt), E250K (1 pt), E257G (1 pt), A230T (2 pts), and E250Q (11 pts). The disease course was recurrent in 8 patients, while the other 8 presented a chronic disease course with periodic recurrences. 15 patients presented an articular involvement during their disease course, while 11 patients presented clinical manifestations affecting the skin (foliculitis in 8, pyoderma gangrenosum in 3, skin abscesses 8 patients); five and one patients presented only the articular and skin involvement respectively. 2 patients complained with supplicative hidradenitis while 7 out of the 16 patients presented clinical manifestations not typical of PAPA syndrome (psoriasis, osteolytic bone lesions, chronic renal failure, muscular abscesses, anemia and hepatosplenomegaly). 10 patients were treated with NSAID with poor response while steroids caused a complete or partial control of disease manifestations in 5 and 6 patients respectively. Two patients were treated with methotrexate with partial response. Etanercept was used in one patient with complete response, adalimumab in 3 patients (2 partial and 1 complete responders) and anakinra in 5 patients (2 partial and 3 complete responders).

Conclusion: the study analyses the largest series of PAPA syndrome patients described so far. The wide clinical heterogeneity and the usual presentation with a single manifestation might be responsible for under-recognition of the disorder.

Disclosure of interest: None declared.

P229
PReS-FINAL-2239: Renal AA amyloidosis in a child with hyper-IgD syndrome and a novel MVK mutation

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Introduction: AA amyloidosis may develop as a consequence of chronic inflammatory conditions including autoinflammatory diseases (AID). Mevalonate-kinase (MVK) deficiency (MKD) appears to be the least frequent underlying condition among monogenic periodic syndromes. Moreover, amyloidosis rarely manifests during childhood. We report a case of a small child in whom renal biopsy performed because of the cortico-resistant nephrotic syndrome revealed amyloid A.

Objectives: To describe clinical manifestations, laboratory features and disease outcome in a patient referred for suspected periodic fever syndrome.

Methods: Case report.

Results: A 4-years old Caucasian girl with negative family history presented with features of nephrotic syndrome in 1/2011. Over the previous 2 years she has been suffering with recurrent episodes of unexplained fever with pharyngitis and lymphadenitis lasting 3 days in 2-4 weekly intervals and received a putative diagnosis of PFPA (periodic fever, adenitis, pharyngitis, aphthae) syndrome. Despite the increasing frequency of febrile episodes over the last year investigations aimed at excluding monogenic fevers were not performed. In early 2011 her IgD was normal, IgA mildly elevated, serum amyloid A (SAA) fluctuated from normal to 200 mg/L. After the standard corticosteroid (CS) treatment of nephrotic syndrome had failed to induce remission after 6 wks, a renal biopsy was performed revealing amyloid A deposits in about 30% glomeruli. While genetic analysis was pending, Colchicine was added to the CS treatment followed by daily anakinra injections with good clinical response. After a laborious genetic screening to exclude mutations causing monogenic AID, following heterozygous variants in MVK gene were identified: Mutation V377I and a novel deletion in exon 5 C152WfsX6 (c.450_453delIGGT). The latter terminates the protein six amino acids after the deletion occurs, effectively making the protein shorter. Within 6 months of the treatment her proteinuria stabilised and there have been no signs of other organ involvement. Despite ongoing anakinra therapy she continues to have occasional febrile episodes with temporary increase of inflammatory parameters including SAA.

Conclusion: MVK/HyperIgD-syndrome has been so far reported in only a few European patients. Our patient has been the youngest one to develop this severe complication. The only other child reported so far was also a compound heterozygote carrying the genotype G326R/V377I. The long-term follow-up with careful SAA serial measurements will tell us more about the prognostic significance of the newly described MVK gene deletion. This case report also underlines the importance of careful differential diagnostic re-evaluation of children presenting with PFAPA phenotype in whom febrile episodes do not show a typical prolongation of afebrile intervals over the time.

Disclosure of interest: None declared.

P230
PReS-FINAL-2240: Serum amyloid protein a concentration in CAPS patients treated with anti IL-1β

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Introduction: Although all patients with chronic inflammatory conditions are at risk for developing type AA amyloidosis, the incidence varies widely between the different Autoinflammatory syndromes. The reported incidence is about 35% of patients with CAPS (cryopyrin-associated periodic syndrome) which comprises familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome and CINCA (chronic infantile neurological cutaneous, articular inflammatory syndrome). CAPS is associated with mutations in NLPR3/C1AS1 on chromosome 1q44, found only in about 50% of patients. Previous studies have demonstrated that IL-1β inhibitors are able to induce complete remission of clinical manifestations and suppression of markers of inflammation in the majority of patients.

Objectives: To evaluate Serum Amyloid A (SAA) level in CAPS patients treated with anti IL-1β therapy and to correlate its level with the response to the treatment and with the presence of the NLPR3 mutation.

Methods: We considered all patients of CAPS Italian Register affected by MWS or CINCA treated with IL-1β inhibitors (Anakinra or Canakinumab). According to Lachmann criteria a complete response to treatment was defined as a global assessment of no or minimal disease activity by a physician, an assessment of no or minimal rash, and a value for both serum CRP and SAA that was within the normal range (<0.5 mg/dL for CRP, < 6.4 mg/L for SAA). Partial response to IL-1β inhibitors was defined as a global assessment of no or minimal disease activity by a physician, and persistent elevated inflammatory markers (CRP, SAA). All patients underwent genetic analysis to identify NLPR3 mutations.

Results: 26 patients (15 M, 11 F) were considered, aged 2 to 52 years (median 16.5 ys). The mean duration of follow-up was 40 months. 18/26 patients were in treatment with Canakinumab (5 patients ab initio and 13
after a period with Anakinra therapy) and 8/26 patients were still taking Anakinra. 10/26 patients showed clinical remission with normal lab tests, including SAA. 10/26 patients presented clinical remission and normal CRP, but elevated SAA, with median value of 12.8 mg/L (IQR 10.5-16.8). 3/26 showed clinical remission but high values of SAA and CRP: 3/26 patients presented clinical remission, normal SAA values, but high CRP values. So in this series only 10/26 patients (38%) affected by CAPS showed a complete response to IL-1ß inhibitors. In 18/26 patients we detected a mutation of NLRP3 gene. Median value of SAA in the mutated patients was 6.7 (IQR 2.3-13.3), median value in no mutated patients was 6.6 (IQR 1.4-16.6).

Conclusion: In the previous studies complete response to anti-IL1 therapy fluctuates between 65% and 85%. By contrast, in our experience anti-IL1 inhibitors induced complete remission in only 38% of the patients because SAA values remained high (double value respect normal range) in half patients with no correlation between SAA values and genetic background. We do not know the real risk of these patients of developing amyloidosis, but we think that these patients need a constant long term follow up.

Disclosure of interest: None declared.

P232
PReS-FINAL-2242: Familial Mediterranean Fever - first experiences in Slovakia
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Pediatric Rheumatology 2013, 11(Suppl 2):P232

Introduction: Familial Mediterranean fever (FMF), resulting from mutations in the MEFV gene, is the most prevalent genetically determined autoinflammatory disease with the highest occurrence in the south-eastern Mediterranean’s and Armenia. In central Europe, experience with FMF is limited, as in Slovakia, where no cases have been reported, so far.

Objectives: To summarize the experiences with FMF in Slovakia.

Methods: Paediatric rheumatologists were contacted and a search of local literature was carried out to identify and collect available retrospective clinical data of patients with FMF.

Results: 5 patients (1 male, 4 female, 2 related, 2 children and 3 adults) diagnosed with FMF based on the clinical picture and genetic analysis could be identified. Recurrent episodes of fever, abdominal and thoracic pain were present in all patients. Additional symptoms were arthralgia/ arthritis (n = 3), splenomegaly (n = 1), hepatomegaly (n = 1), lyphadenopathy (n = 1) and exanthema (n = 1). In spite of significant diagnostic delay (4.5 - 30.0 years from onset of clinical symptoms), no patient has developed amyloidosis. Only well-known mutations (M694V, E148Q, V276A, E167D and F479L) were identified. All patients responded well to colchicine therapy (1 partial, 4 complete response) with good tolerance. Interestingly, only one patient originated from a high-risk population (Egypt), all other were of white Slovak native origin.

Conclusion: FMF due to common MEFV mutations does occur in Slovak population (Egypt), all other were of white Slovak native origin.

Disclosure of interest: None declared.
the published pQCT database of Moyer-Miller et al (J Clin Densitom, 2008) who used the same pQCT device, software and site measurements as we did.

Results: 7/14 children with IH (50%) were found to have z-scores<-1 SD in the DXA measurements of the lumbar spine. For the pQCT measurements, we report here only the preliminary results of trabecular BMD (ongoing analysis): 8/14 children with IH (57%) had reduced volumetric bone mineral density (TRAB_DEN < 2 SD) when compared with healthy children of the same age, race, sex and height of the Moyer-Miller study.

Conclusion: Our study provides preliminary evidence of reduced trabecular bone mineral density in children with IH as compared to healthy ones.

Disclosure of interest: None declared.

P234
PReS-FINAL-2244: Ultrasound examination reveals typical alterations in joints of mucopolysaccharidosis (MPS) patients
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Pediatric Rheumatology 2013, 11(Suppl 2)P234

Introduction: Mucopolysaccharidoses (MPS) are a group of metabolic disorders caused by the absence or inadequate functioning of enzymes needed to break down glycosaminoglycans (GAG), which are essential structural elements of many tissues in the human body (bone, cartilage, cornea, skin, connective tissue). One of the main features of several of the mucopolysaccharidosis is bone damage and remodeling, along with synovial thickening, clinically manifested as coarse facies, thickened and widened bones on x-rays, and joint contractures of varying severity. These signs and symptoms can be the presenting features of the disease, and lead to clinical diagnosis when properly interpreted. The aversion to unnecessary exposure of patients to radiation and the question of which bones to examine by x-ray is understandable. MPS patients are additionally at a much higher risk of severe sequelae from anesthesia, making MRI examination more difficult. Therefore, the question of the best method by which to measure bone and joint involvement and progression in patients with established disease is a difficult one.

Objectives: We present documentation of joint pathology recognizable by ultrasound in MPS patients, which might be useful to speed the diagnosis of disease, and serve as a readily available and harmless tool for monitoring of changes in the bones and joints of patients. This could be particularly useful for pediatric rheumatologists, for whom joint ultrasound is a well-established tool. We also propose a basic scoring system for quantification of such changes.

Methods: We used ultrasound to examine MPS patients with joint disease, comparing the results to those typically found in inflammatory arthritis. The changes we have found in the MPS patients are illustrated by a representative case report.

Results: From our observations, it appears that there are certain specific changes in the bones and joints of mucopolysaccharidosis patients, apparent on ultrasound examination.

Conclusion: Ultrasound is a useful and convenient method for documenting and following bone and joint disease in mucopolysaccharidosis patients. We have proposed a preliminary scoring system to follow bone and joint involvement in MPS, and will explore the clinical correlations further. Finally, we wish to encourage that mucopolysaccharidosis be considered as a differential diagnostic possibility in children and adolescents with joint disease and contractures.

Disclosure of interest: None declared.

P236
PReS-FINAL-2246: CBCT versus orthopan tomogram detecting TMJ alteration in JIA
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Pediatric Rheumatology 2013, 11(Suppl 2)P236

Introduction: TMJ is frequently affected in JIA, but there is no data detecting bony TMJ changes because it detects three dimensionally the alteration in JIA

Methods: A 9-month-old child was admitted to our clinic in September 2012 for treatment of his panniculitis. First lesion on the face appeared in June 2012, abscess was suspected and it was surgically drained. Yet, in July 2012 there were new lesions and the boy started having daily spikes of fever. He was started on antibiotics without effect, the number and the size of lesions continued to grow. The biopsy was performed and based on the pathology results and symptoms the diagnosis of Weber panniculitis was made and the boy was referred to our center.

Results: At the initial examination the boy appeared not well, very pale, had daily fevers, and multiple edematous purple skin lesions on his face, legs, arms. He had large peripheral lymph nodes (up to 3 cm), hepatosplenomegaly, anemia (hemoglobin to 88 g/L), mild leucopenia (WBC 3.2 × 10^{9}/ml), increased transaminases and lactate dehydrogenase. Chest X-ray, ultrasound of the abdomen, chest and abdomen CT were unremarkable, except for hepatosplenomegaly and obviously enlarged peripheral lymph nodes. Considering the age of the patient the diagnosis of panniculitis seemed questionable and the biopsy was repeated. As a result panniculitis-like T-cell lymphoma of the skin was diagnosed, the child was started on CHOP protocol treatment with dramatic improvement of his general condition and reduction of the lesions.

Conclusion: The case demonstrates the importance of critical approach to rheumatological patients that don’t fit the general understanding of the pathology and epidemiology of the disorder.

Disclosure of interest: None declared.

P235
PReS-FINAL-2245: A rare case of subcutaneous panniculitis-like T cell lymphoma in a 9-month-old child
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Pediatric Rheumatology 2013, 11(Suppl 2)P235

Introduction: Panniculitis is an inflammatory disorder of subcutaneous adipose tissue, frequently accompanied by vasculitis and systemic involvement. The peak age of patients is 20-30 years, and it is fairly rare in children, especially in infants.

Therefore, panniculitis-like lesions in young children require differential diagnostic procedures and sometimes joined efforts of rheumatologists, hematologists and oncologists.

Objectives: to illustrate the difficulties in the diagnosis of subcutaneous panniculitis-like T cell lymphoma in an infant.

Methods: A 9-month-old child was admitted to our clinic in September 2012 for treatment of his panniculitis. First lesion on the face appeared in June 2012, abscess was suspected and it was surgically drained. Yet, in July 2012 there were new lesions and the boy started having daily spikes of fever. He was started on antibiotics without effect, the number and the size of lesions continued to grow. The biopsy was performed and based on the pathology results and symptoms the diagnosis of Weber panniculitis was made and the boy was referred to our center.

Results: At the initial examination the boy appeared not well, very pale, had daily fevers, and multiple edematous purple skin lesions on his face, legs, arms. He had large peripheral lymph nodes (up to 3 cm), hepatosplenomegaly, anemia (hemoglobin to 88 g/L), mild leucopenia (WBC 3.2 × 10^{9}/ml), increased transaminases and lactate dehydrogenase. Chest X-ray, ultrasound of the abdomen, chest and abdomen CT were unremarkable, except for hepatosplenomegaly and obviously enlarged peripheral lymph nodes. Considering the age of the patient the diagnosis of panniculitis seemed questionable and the biopsy was repeated. As a result panniculitis-like T-cell lymphoma of the skin was diagnosed, the child was started on CHOP protocol treatment with dramatic improvement of his general condition and reduction of the lesions.

Conclusion: The case demonstrates the importance of critical approach to rheumatological patients that don’t fit the general understanding of the pathology and epidemiology of the disorder.

Disclosure of interest: None declared.
**P237**

**PReS-FINAL-2247: Confidence of UK general paediatric trainees in musculoskeletal clinical assessment and preferences for future teaching resources**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P237

**Introduction:** Musculoskeletal (MSK) problems in children and adolescents are common (1-4) and may represent serious life threatening disease (5-7). Many doctors have low confidence in examining children’s joints, stemming from MSK teaching not being core in many training programmes (8). In an attempt to address this, paediatric MSK competencies were introduced into the Royal College of Paediatrics and Child Health (RCPCH) training curriculum in 2007 and assessment of MSK knowledge and clinical skills was included in the mandatory professional clinical examinations for all paediatricians in 2009 (i.e. Membership of the RCPCH (MRCPCH) clinical examination).

**Objectives:** To examine:

[1] Self-rated confidence in paediatric MSK clinical assessment in general paediatric trainees in relation to their ability to undertake MSK station of the MRCPCH clinical examination.


[3] Which types of educational resources trainees use when preparing for the examination.


**Methods:** An anonymous Survey Monkey e-mail questionnaire was disseminated to UK paediatric trainees, from the North of England and South East of Scotland.

**Results:** 35 trainees completed the survey. Going into the examination, trainee confidence in undertaking the MSK station was lower than for the cardiovascular, respiratory, abdominal and developmental stations but marginally better than the neurological station. 20% of trainees found it ‘hard’ to get access to face-to-face teaching before the exam, and a further 66% felt that it ‘took some effort’. When preparing for the MSK station, trainees reported using the following teaching resources (in decreasing order of frequency); bedside teaching, pGALS DVD, textbooks, MRCPCH clinical examination revision course, attending paediatric rheumatology clinics or a joint injection list. 46% and 34% of trainees felt that a 1-day MSK revision course or e-learning module would respectively best prepare them for the MSK station of the examination.

**Conclusion:** From these responses it is clear that self-rated paediatric trainee confidence in undertaking the MSK station of the MRCPCH clinical examination remains low as compared to other bodily systems. Although the MRCPCH provides impetus for trainees to engage in learning about MSK examination, trainees reported a variation in access to teaching prior to the examination. We know that access to traditional face-to-face MSK clinical teaching is limited; many trainees do not have the opportunity to rotate through rheumatology and there are too few paediatric rheumatologists to provide teaching sessions for trainees. Trainees currently use a wide range of MSK teaching methods but preference for future teaching resource development is a 1-day paediatric MSK revision course or e-learning module. The results of this survey highlight the need for improved access to MSK teaching, and their stated preferred method of educational delivery, which if introduced, we anticipate will facilitate more confident, and prompt recognition of MSK disease by the next generation of paediatricians.

**Disclosure of interest:** None declared.

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**P238**

**PReS-FINAL-2248: Parovirus B19 associated unusual joint symptoms in twin girls**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P238

**Introduction:** Human Parvovirus B19 (HPVB19) is the responsible agent of fifth disease. Other less common manifestations include transient aplastic crisis, nonimmune hydrops-fetalis, chronic arthritis, myocarditis, hepatitis, multisystemic vasculitis, renal disease, and idiopathic thrombocytopenic purpura. An increasing number of reports have described HPVB19 infection in association with a variety of neurologic manifestations. We described two cases of twin girls presented with the symptoms of carpal tunnel syndrome (CTS) associated with HPVB19 infection.

**Objectives:** case reports: A previously healthy 6 year-old girl presented with sudden onset of swelling of the distal extremities associated with painful paresthesia of the first three digits of her both hands. 10 days earlier her parents had noticed an erythematous rash which spread from the face to the arms and abdomen. There were no histories of wrist trauma, recent immunisations or drug use. Physical examination revealed mild swelling of the metacarpophalangeal and proximal interphalangeal joints. She had mild hypoesthesia in the sensory dermatomes of both median nerves, a positive Tinel’s sign on the right, and a mild decrease in thumb abduction bilaterally. The acute symptoms gradually subsided after 1 week of symptomatic treatment. One week later her twin presented with sudden onset of swelling of the distal extremities associated with painful paresthesia of the last three digits of her both hands. Her medical history was similar. Physical examination showed bilateral hypoesthesia in the sensory regions of the both median and ulnar nerves associated with swelling of the hands. It was difficult and painful to close her hands and especially to open them. She had received the same treatments. The symptoms rapidly decreased within a few days, but numbness of the third and fourth digits persisted for 15 days.

**Methods:** laboratory findings: In the first case, nerve conduction studies revealed moderate delay in distal sensory-motor latencies of both median nerves with delayed median nerve F-responses on both sides. In the second case, both median nerves sensory-motor conduction velocity at the wrist were slow and F-responses of both median and ulnar nerves were delayed bilaterally. In both cases, there were no denervation potentials and motor and sensory nerve conduction studies of peroneal, posterior tibial, and sural nerves and the posterior tibial F-responses were normal in both lower extremities. Screening blood tests including chemistry panel, complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, serum complement 3 and 4, thyroid stimulating hormone, and antinuclear antibodies were normal in both cases. Rubella virus, Borrelia species, M. tuberculosis, and other Mycobacterium species were ruled out either clinically or laboratory tests.

**Results:** Both patient’s serological tests showed positive HPVB19 specific IgM and HPVB19-DNA was also detected by using PCR.

**Conclusion:** Infectious agents, especially HPVB19 associated acute CTS should be considered among the patients presenting with acute joint findings in childhood.

**Disclosure of interest:** None declared.

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**P239**

**PReS-FINAL-2249: A national survey of the role of the paediatric rheumatology nurse in performing steroid joint injections in the UK**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P239

**Introduction:** Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Treatments involve Non Steroidal Anti-Inflammatory Drugs (NSAIDs), Disease Modifying Anti-Rheumatic Agents (DMARDs), steroids and various biologic drugs. Steroid injections directly into affected joints are an important part of the range of treatments available for children with JIA. The British Society of Paediatric and Adolescent Rheumatology (BSPAR) guidelines state that “all patients with JIA will have access to intra-articular joint injections as required, with access to entonox, general anaesthesia and appropriate imaging technology where necessary.” To meet the increasing demand for steroid joint injections, Rheumatology nurses and other rheumatology allied health professionals have started training to carry out this extended role in some parts of the UK.
**Objectives:** To find out what has been done nationally in different Paediatric Rheumatology centres with regards to whether or not nurses are carrying out joint injections, what joints they are competent to inject, and what training they have undertaken in order to carry this role out.

**Methods:** We have identified 15 Paediatric Rheumatology Centres in the country, and a questionnaire was sent out asking whether nurses do joint injections, what sort of sedation was used, whether they obtain a written consent, what joints they do/don’t inject and what training did they have.

**Results:** We had responses from 12 out of the 15 centres identified. 4 out of the 12 centres who replied have Rheumatology nurses performing joint injections.

In 1 out of the 4 centres the Rheumatology nurse will only carry out joint injections under general anaesthetic (GA) whereas in the 3 other centres, Rheumatology nurses are carrying out joint injections both under GA and entonox.

All 4 centres said that they would not inject hips, and 3 out of the four said that they would not inject any joint requiring imaging.

Training was varied but generally carried out by the Consultant Rheumatologist in the centre. One nurse did attend a training course but this was an adult course rather than paediatric.

Only 1 centre developed a formalised training competency pack for joint injections. 2 of the other centres (currently not performing joint injections) replied to say that they were planning to start carrying out joint injections but only with entonox and 1 centre replied to say that they were looking into possible courses.

**Conclusion:** The role of the Paediatric Rheumatology Nurse throughout the UK is varied and continually evolving. It would appear that the demand for steroid joint injections in different parts of the UK is a factor in determining whether or not Rheumatology Nurses take on this extended role. However, the training appears to be limited and this highlights the need for a formal training pathway.

**Disclosure of interest:** None declared.

**P240**

**PReS-FINAL-2250: Presentation of tuberculosis in patients using anti-TNFs drugs: report of 3 cases**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P240**

**Introduction:** Inhibitors of tumor necrosis factor (TNF) are drugs used to control chronic inflammatory arthritis in cases that are refractory to treatment with DMARDs. TNF is critical in preventing Mycobacterium tuberculosis reactivation; thereby decreased TNF-α activity suggests that the cytokine has a key role in the control of latent tuberculosis.

**Objectives:** To describe the presentation of Tuberculosis (TB) in 3 patients using TNF treated at the Rheumatology Department of the Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro (HUCFF-UFRJ).

**Methods:** Case Report: Case 1: Female patient, 20 yo, with back pain for two years, right sacroiliitis confirmed by scintigraphy and biopsy. She was treated with indomethacin, prednisone, sulfasalazine and metrotrexate showing no significant improvement for one year. Etanercept was initiated with prior normal chest Rx and negative PPD. After 7 months of use, the patient presented fever associated to pleural effusion in the right hemithorax. The biopsy was consistent with pleural tuberculosis. She was treated with rifampicin, isoniazid, pyrazinamide and streptomycin with complete recovery of pulmonary infection.

Case 2: Female patient, 5 years old with juvenile idiopathic arthritis (JIA) polyarticular RF negative. Initially treated with naproxen, methotrexate, prednisone, and folic acid without clinical improvement. After 6 months of treatment, it was initiated infliximab, with prior normal chest Rx and negative PPD with control of the joint symptoms. After 7 months of use, the patient developed severe pneumatic miliary tuberculosis. She was treated with rifampicin, isoniazid, pyrazinamide. The patient resolved her pulmonary infection and remains in remission of JIA, after 7 years of follow-up.

Case 3: Male patient, 17 years old, anklyosing spondylitis for 3 years, treated with methotrexate, naproxen, sulfasalazine and prednisone with poor response. He was started on infliximab for 6 years until he presented productive cough with headache and fever, CXR was consistent with pulmonary tuberculosis. He was treated with rifampicin, isoniazid, pyrazinamide for 6 months. The ITNF was changed for adalimumab with control of the disease.

**Results:** Several authors describe that the risk of reactivation of TB increases five to ten times, appearing in a range of up to 1 year after starting ITNF therapy. In case 3, the prolonged time between ITNF administration and the infection suggests that new tuberculosis infection (reinfection) occurred. All patients had normal chest RX and PPD negative at the beginning of the treatment.

**Conclusion:** Despite having revolutionized rheumatologic practice, the use of ITNF in the treatment of autoimmune diseases increases the risk of tuberculosis infection and should be carefully monitored especially in countries with high prevalence of TB.

**Disclosure of interest:** None declared.

**P241**

**PReS-FINAL-2251: Influenza myositis outbreaks: clinical and laboratory findings**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P241**

**Introduction:** Acute myositis has epidemiologic association with influenza, presenting with myalgia, weakness, limited mobility, high serum levels of muscle enzymes and leukopenia, in toddlers and school children, mostly in boys. It concerns the parents and pupils physicians in emergency setting.

**Objectives:** Describe epidemiology, clinical presentation and outcome of a case-series of acute viral myositis.

**Methods:** Retrospective analysis of suspicious cases seen in emergency service, with follow up in rheumatology clinic, was conducted. Symptom records during respiratory infections with muscle-skeletal symptoms with investigations, including muscle enzymes (CK, LDH, AST-ALT), hematologic assessment, CRP and ESR, were analyzed at onset and follow up.

**Results:** Overall 42 subjects were identified from 2000-2009, during peak flu-season and 35 (27 boys) were included. Median onset age was 7 years. Target diagnosis was reported in 89%, during first emergency visit. Observed acute respiratory symptoms, cough (31%) and corza (23%), with fever (63%) had mean duration of 4.3 days. Muscle-skeletal symptoms were calf-pain (80%), limited walking (57%), abnormal gait (40%), muscle weakness on lower limbs (71%), all with mean duration of 3.6 days. There was a remarkable peak of muscle enzymes, CK (5,507 ± 9,180) U/l, LDH (827 ± 598) U/l and AST (199 ± 245) U/l, and also trends to leukopenia (4,59 ± 10³ ± 1,40 ± 10³) n/mm3. Full recovery with laboratory parameters back to normal occurred within 30 days (median). One relapse was identified with 10 months interval. Virus identification was not obtained.

**Conclusion:** Typical myositis symptoms with CK peaks following flu symptoms and a self-limited course are clues to diagnosis. CK elevation and muscle weakness indicate a myotropic activity related to B-Influenza that should be considered in outbreaks, regardless of virus identification. Awareness for this rare interesting muscle-skeletal condition is needed.

**Disclosure of interest:** None declared.

**P242**

**PReS-FINAL-2252: Descriptive analysis of pediatric autoimmune neuropsychiatric disorder associated with streptococcus infection (PANDAS) in a cohort of 65 Italian patients**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P242**

**Introduction:** PANDAS includes neuropsychiatric symptoms, mainly obsessive-compulsive disorder (OCD) or tics, temporally associated with streptococcus infection. PANDAS is a neuropsychiatric disorder associated with streptococcus infection, typically occurring within 3 to 4 weeks of a throat infection. It is characterized by the onset of obsessive-compulsive symptoms, tics, and/or other neuropsychiatric symptoms, temporally associated with streptococcus infection.
an immune-mediated response to group A β-hemolytic Streptococcus (GAS) infections, which suddenly start before puberty and display remitting/relapsing course.

**Objectives:** To describe clinical features of a cohort of 65 Italian pts with previous confirmed GAS infection and sudden occurrence of OCD and/or tics.

**Methods:** Descriptive analysis of a cohort of Italian patients with PANDAS. Between may 2009 - may 2013 we observed 65 pts (50 M, 15 F, mean age: 100.8 ± 32.9 months) with OCD and/or tics starting before puberty, associated with a previous GAS infection. Demographic and familiar data, routine and specific laboratory data: thyroid function, autoimmunity tests (ANA, anti-dsDNA, anti-ENA, anti-cardiolipin, and anti-tissue transglutaminase antibodies) were collected. 55/65 underwent brain MRI, all EEG, echocardiography and neuropsychiatric evaluation.

**Results:** 13/65 pts (20%) born from Caesarean section, 60/65 (92.3%) full-term, 32/65 (49.2%) had familiars with OCD/tics or other neurologic diseases, and 57/65 (87.7%) did sports. Acute and dramatic onset occurred at a mean age of 74.3 ± 25.9 months (range 24-160). Out of 65 pts, 22 (33.8%) started with motor tics; 2 (3.1%) with OCD; 5 (7.7%) with motor/vocal tics; 28 (43.1%) with motor tics and OCD; 1 (1.5%) with vocal tics and compulsive behavior and 7 (10.8%) with motor/vocal tics and OCD. 155 patients (63.1%) had previously pharyngitis, otitis and/or upper airway infections, 1 impetigo. Brain MRI, EEG, thyroid tests, and coeliac disease screening were normal in all. Mean age to diagnosis 101.2 ± 29.9 months. At onset and at our first clinical evaluation inflammatory parameters were negative in all. Five (7.7%) had anti-streptolysin O titer less than 250 IU, 20 (30.8%) between 250 and 550 IU, 29 (44.6%) over 500 IU. Anti-DNase titer was increased (650-1200 U) in 38 (58.5%). All pts had previously had TB and active TB was identified in 2 children. None of the children had enthesitis. One child was diagnosed in 9/11 patients. Polyarthritis (8/11) was the predominant rheumatological feature. None of the children had enthesitis. One child presented with dactylitis. Uveitis was present in 2/11. Three out of eleven had previously had TB and active TB was identified in 2 children. None of the children were on HAART at presentation. Median ESR was 122 (39-143) NF was done in 6/11 children and was negative in 6/6. HAART was initiated in 9/11 patients. Two patients were lost to follow up at our institution. All patients were treated with Ibusprofen. 9/11 were treated with chloroquine. Prednisone was used in 3/11 patients, methotrexate in 2/11 and sulphasalazine in 1/11. Intra-articular steroid injections were performed in 5/11 patients.

**Conclusion:** In our case series, HIV arthropathy occurred in older boys, usually with late diagnosis of HIV, before HAART therapy and was the presenting feature of HIV in the majority. Polyarthritis was the most common mode of presentation. TB exposure was a frequent feature. Most children were treated with HAART therapy, Ibusprofen, chloroquine.

**Disclosure of interest:** None declared.

**P244**

**PReS-FINAL-2254: Is it systemic JIA or post infectious illness?**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P244**

**Introduction:** This is a case report of a 15 year old girl which presented with Pyrexia of Unknown Origin. She was initially treated for possible sepsis and then received treatment for Atypical Kawasaki’s. She was subsequently investigated for Haemophagocytic Lymphohistiocytosis (HLH). She was eventually diagnosed with Systemic Juvenile Idiopathic Arthritis (SJIA) complicated with Macrophage Activation Syndrome (MAS) at presentation and was commenced on Methotrexate.

**Objectives:** This case report highlights the difficulties in distinguishing inflammatory conditions at first presentation.

**Methods:** The case was derived from a retrospective review of case notes and laboratory findings. The patient was managed at two sites, a district hospital paediatric unit and a tertiary rheumatology centre. All authors have been involved in the medical management of the patient.

**Results:** A previously well 15 year old girl presented with two week history of fever, rash, poor appetite, weight loss and multiple joint pain and swelling. She was found to have a non-specific rash, migratory synovitis, muscle weakness, cervical and axial lymphadenopathy and splenomegaly. Blood investigations had shown anaemia, neutrophilia, thrombocytosis, raised inflammatory markers (CRP, ESR, Ferritin), and deranged liver and muscle enzymes. She was treated initially with broad spectrum IV antibiotics. Infection screen was negative as well as serology for ASOT, anti-Dnase B Streptococcal, EBV, CMV and HIV. In view of persistent pyrexia, lymphadenopathy and rash a diagnosis of Atypical Kawasaki’s was made and IV Immunoglobulins were given. Baseline Echocardiogram was normal, abdominal ultrasound confirmed splenomegaly and CT showed evidence of bilateral pleural effusions and a large axillary lymph node.

In view of on-going symptoms she was transferred to a Tertiary unit for further investigations. A diagnosis of Secondary HLH was considered in view of on-going fever, rash, lymphadenopathy, splenomegaly, very high ferritin (160,000), high triglycerides and high SCL25(IL-2R). A bone marrow was inconclusive and no Perforin mutations were identified. She was treated with high dose anti-inflammatoreries and by the 6th week of her illness her systemic symptoms and rash have subsided however she continued to have persistent synovitis and splenomegaly. A diagnosis of SJIA was made and was treated with two IV Methyl Prednisolone pulses, intra-articular steroids and commenced on Methotrexate. Following six weeks of Methotrexate all her symptoms had resolved and all inflammatory markers were back to normal. As she was intolerant to Methotrexate it was decided to stop treatment. She has remained well since.

**Conclusion:** Secondary HLH can be trigger by infections usually EBV, CMV, parvovirus, herpes simplex, varicella-zoster, measles as well as human herpes virus-8 and HIV infection. In our case no infection trigger was identified however our patient met the defined set of Diagnostic criteria. In a new presentation, it is often difficult to make a distinction between infection triggered HLH and a new presentation of systemic JIA complicated with MAS. Early recognition is important and treatment should be initiated promptly.

**Disclosure of interest:** None declared.

**Reference**

P245
PreS-FINAL-2255: Primary pyomiositis in children: a challenging diagnosis
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Pediatric Rheumatology 2013, 11(Suppl 2):P245

Introduction: Primary Pyomiositis (PM) is an uncommon and potentially serious bacterial infection of striated muscle. It is typically a tropical disease but its frequency has been increasing in the Western Countries. Staphylococcus Aureus is the most frequently isolated organism from blood samples of patients affected by this condition. The rarity in temperate climates of this potentially fatal disease and its non-specific signs can represent a diagnostic challenge, leading to a dangerous diagnostic delay.

Objectives: The aim of our study is to identify a common diagnostic profile in order to provide an early diagnosis.

Methods: A retrospective review was conducted to analyze the experience of two pediatric Italian hospitals (Clinica Pediatrica, IRCCS Burlo Garofolo, Trieste and Ospedale Pediatrico Bambino Gesù, Rome) from 2005 to 2011.

Results: Over the 8-year period, 12 cases were identified (8 boys and 4 girls). None of them presented immunocompromising conditions. Mean age at diagnosis was 10.8 years (range 3 months-15 years); the most commonly involved muscle was the gluteal one (8/12 cases); in 4/12 cases other muscles were involved (iliofossas, obturator and abdominal oblique muscle).

All of the patients presented with pain, fever and limp with limitation in movements. Physical examination revealed in all cases limitation on flexion and abduction of the hip and pain at pressure of the involved muscles. One patient, a 3-months-old baby, presented with fever, irritability, lack of appetite and pain at the attempt to move the affected muscles.

A history of local trauma was present in two cases. Laborator findings showed rise in acute phase reactants in all cases, whereas creatinine kinase was normal in all our patients. Xray and Ultrasound examinations were performed in all cases and were always negative. On the contrary MRI was diagnostic in all cases, showing swelling of the involved muscles. In all cases antibiotic therapy was conducted intravenously for two weeks, therefore orally for a total of four-six weeks. One patient required surgical drain.

Conclusion: PM is a rare deep, subacute bacterial infection of the skeletal muscle.

Once considered a tropical countries’ prerogative, now it is appearing more frequently in temperate climate areas.

Its rarity and the lack of specific symptoms can lead to a diagnostic delay and fatal complications. Septic arthritis represents the main differential diagnosis, therefore MRI, the gold standard for this disease, should be performed as soon as possible in any child with fever, pain and limp without a precise articular involvement and a recognized infectious focus.

Disclosure of interest: None declared.

P247
PreS-FINAL-2257: Pediatric rheumatology in a rare disease working group: examples of diagnosis, information, and quality of care for patients with rare diseases in Hungary
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Pediatric Rheumatology 2013, 11(Suppl 2):P247

Introduction: As part of an initiative to expand diagnostic resources, information, and quality of care for patients with rare diseases in Hungary, a network of specialists dealing with rare diseases was established at our University Clinical Center, and a Rare Disease Working Group was formed within the Pediatric Hospital.

Objectives: We hope to document a selection of diagnoses, which came about through close cooperation between the pediatric rheumatology and clinical genetics services at our Pediatric Hospital, in the context of an initiative to better evaluate and care for patients with rare diseases, or who present a differential diagnostic dilemma.

Methods: Each of the following cases were seen together by a clinical geneticist and pediatric rheumatology service physician involved in the Rare Disease Working Group. We document here three different cases from among those seen with complaints and presentations representing part of the pediatric rheumatology disease spectrum.

Results: Case 1: A 14 year old male presented with painless swelling of PIP joints II-V on both hands which had been consistently present for over one year. The patient was seen in a joint session (clinical genetics, rheumatology service), and the diagnosis of pachydermodactyly established, sparing the patient further diagnostic interventions and unnecessary treatments.

Case 2: A 6 year old boy presented initially at 3 years of age with bilateral coxitis. One month later, significant radiological changes in both hips (including the acetabulum) were noted, with relatively minor physical complaints. He was initially diagnosed with Legg-Calvé-Perthes Disease by an orthopedic surgeon. Through our clinic, urine glycosaminoglycan, enzymatic and genetic testing confirmed the diagnosis of mucopolysaccharidosis II (Hunter Disease). In addition to the initiation of enzyme replacement therapy, the diagnosis allows for planning of specialized care, follow up and intervention with regard to the patient’s progressive joint disease.

Case 3: An 8 year old girl had been seen by a pediatric neurologist and orthopedic surgeon because of symmetrical painless contractures of her hips, knees, ankles and the small joints of her feet, which were increasingly affecting her everyday activities. She was referred to our clinical geneticist because of suspicion of a lysosomal storage disease. Upon examination the patient had scleroderma-like lesions symmetrically affecting both lower limbs. Findings on laboratory, imaging, and histopathological examination
led to the tentative diagnosis of congenital dysostosis, or "Stiff-skin Syndrome". An analysis of the Fibrillin-1 (FBN1) gene, recently found to be mutated in several such patients, found no alterations. We are closely following the patient, and additional extensive genetic analysis will hopefully be initiated in the near future.

Conclusion: We hope to encourage the consideration of these diseases (albeit rare) as potential differential diagnoses, and the establishment of such "rare disease working groups" where they may not yet exist.

Disclosure of interest: None declared.

P248
PNeS-FINAL-2258: Final diagnoses of pediatric patients presenting with musculoskeletal symptoms in a center from the eastern Mediterranean

Introduction: Complaints related with musculoskeletal system are frequent in children and adolescents.

Objectives: To identify the clinical and laboratory features in children and adolescents suffering from musculoskeletal complaints (excluding acute traumatic conditions) in a tertiary referral center in Central Anatolia; and to define etiology and clues for differential diagnosis.

Methods: All children [n: 422; mean age 7.90 ± 3.95 (range: 4 mo.- 18 years); 48.2% female] presenting to the outpatient clinic for the first time due to pain, swelling or limitation of movement attributed to musculoskeletal system in a 6 month period were enrolled. Demographical features, duration, and type of complaints, physical signs on initial presentation and laboratory findings (a complete blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) were recorded.

Results: Etiology was identified in 97.2% (n: 410) of the cases and were classified as follows: non-inflammatory and mechanical conditions (NIMC, n: 178; 42.2%), rheumatologic diseases (RD, n: 131; 31%), infection related disorders (IRD, n: 91; 21.6%) and malignancy (M, n: 10; 2.4%). NIMC group was characterized with longer duration of complaints, higher rate of non-articular complaints, lower rate of joint involvement, limping and lower levels of leukocytes, ESR, and CRP (p < 0.001). Rate of rheumatic disease was higher in >12 years of age group, compared to younger ones (p: 0.005). On the contrary younger age group was associated with higher rate of IRD group (p: 0.007). Small joint involvement was highest in RD group (16.8%), compared to other groups (p < 0.05). Rate of IRD was highest when the duration of complaints was less than 7 days, compared to the other groups (p < 0.05). Rheumatic disease had the lowest rate among patients with duration of complaints less than 7 days compared to the other three groups (p < 0.05). Familial Mediterranean fever (9.7%), juvenile idiopathic arthritis (8.3%) and Henoch-Schönlein purpura (5.7%) were the most frequent rheumatologic diseases. Median ESR levels in RD and M groups were higher, compared to IRD and NIMC groups (p < 0.05 respectively). Although mean ESR levels were comparable among M and RD patients, the number of patients with ESR levels ≥60 mm/hr were higher in M group (60%), compared to RD (20.6%; p <0.05) group.

Conclusion: Rheumatologic diseases accounted approximately one third of the etiology among children and adolescents admitted with non-traumatic musculoskeletal complaints. Age, duration of complaints, pattern of joint involvement, and acute phase reactants are practical tools for the differential diagnosis.

Disclosure of interest: None declared.

P249
PNeS-FINAL-2259: Spectrum of Sjögren syndrome in children

Introduction: Sjögren’s syndrome is an autoimmune disease characterized by the presence of a lymphocytic infiltrate in the salivary and lacrimal glands, manifesting with xerostomia and xerophthalmia, which is more common in women between 30 and 50 years old, uncommon in children, with few cases reported in the literature.

Objectives: To describe the clinical and laboratory presentation of pediatric patients with Sjögren’s syndrome treated in primary Rheumatology Department of the Hospital Universitario Clementino Fraga Filho of the Universidade Federal of Rio de Janeiro, Brazil (HUCFF-UFRJ).

Methods: 26 child and adolescent patients were selected with diagnosis of primary Sjögren’s syndrome, treated in the Rheumatology Department of HUCFF-UFRJ. Patients were evaluated according to modified European criteria by the American-European Consensus (VITALI et al. 2002).

Results: 26 patients were included in the study: 20 girls (76%); 6 boys (24%), with mean age at diagnosis of 12.6 years (3-21 years). Patients were 16 years of age or younger at the onset of symptoms. Eight (30.7%) patients had parotid gland enlargement as the initial manifestation of the disease, with recurrent episodes in 2 (7.8%) patients. Ten (38%) had dry mouth complaint and 16 (62%) had ocular signs and symptoms, 18 patients (69%) had altered parotid ultrasonography, 19 patients (73%) had impaired salivary glandsctigraphy and 6 patients (23%) had abnormal parotid MRI. In 8 patients (30%) the minor salivary gland biopsy showed chronic salaladentitis compatible with Sjögren syndrome. The analysis of serum autoantibodies, showed 8 patients (30%) positive for rheumatoid factor, 10 patients (38%) with Anti-Ro, 9 patients (34.6%) Anti-Ro and Anti-la and 18 patients (69%) with antinuclear antibody (ANA). 12 patients (46%) had arthritis. 7 patients (26%) had CNS involvement. 3 patients (11.5%) had vascular compromise. One patient (3.8%) showed tachyarrhythmia, leucopenia in 2 patients (7.6%), hypergammaglobulinemia in 8 patients (30%) and hypogammaglobulinemia in 1 patient (3.8%). With regard to treatment, 25 patients (96%) received hydroxychloroquine. Azathioprine was used in 4 patients (15.3%), methotrexate in 12 patients (46%), human immunoglobulin in 1 patient (3.8%), cyclophosphamide in 2 patients (7.6%), leflunomide in 1 patient (3.8%) and rituximab 2 patients (7.6%).

Conclusion: This present study demonstrated the demographic, clinical, and therapeutic profile in a series of patients with Sjögren’s syndrome in children and adolescents, a relatively rare condition, presenting an overview of this population in our hospital.

Disclosure of interest: None declared.

P250
PNeS-FINAL-2260: Provisional findings of an on-going study of musculoskeletal anomalies in a national cohort of patients with trisomy 21

Introduction: Musculoskeletal complications of Down syndrome are common. Joint laxity is almost universal. This, in combination with low muscle tone, contribute to increased risk of a number of musculoskeletal disorders e.g. atlanto-axial instability, patella instability & pes planus. Arthritis in children with Down syndrome is also reported. Down’s Arthropathy (DA) is thought to be 3-6 times more common than JIA in the general paediatric population. Despite this fact, DA is rarely recognised at onset & remains under-diagnosed. This contributes to unnecessary disability & functional impairment.

Objectives: 1. Take a musculoskeletal history from, and perform a musculoskeletal examination on children with Down syndrome between the ages of 0.5-18 years. 2.Score hypermobility using the Beighton & Brightton screening tools. 3.Examine joints for evidence of past and/or present arthritis.

Methods: From April 2013 to April 2014, children with Down syndrome will be invited to attend a screening clinic. Screening involves completion of a health questionnaire & a comprehensive musculoskeletal exam.

Results: Our results support a feature consistently reported in the limited literature available on DA (table 1). There is delayed diagnosis, leading to less favourable outcomes. The average time to diagnosis in our cohort was 1.9 years, with the longest delay reported nearly 5 years. This child developed loss of joint space, generalized osteopenia, erosions & subluxations of affected joints. When compared with a cohort of our newly
diagnosed JIA patients (time to diagnosis 0.6 years), we demonstrate a significant difference in time to diagnosis (p = 0.025). To date 59 children have enrolled in the musculoskeletal screening process, 69% of whom have pes planus. No atlanto-axial instability has been reported, however one child had an absent C2 vertebra. There has been one case of patella instability and 4 new cases of DA diagnosed. Anecdotally we have not found the Beighton & Brighton criteria comprehensive. The majority of children were found to have hypermobile hips. Neither scoring systems incorporate hips in their screening criteria. To date 100% of children screened would not have BHS using Brighton criteria.

Conclusion: Pes planus is commonly seen in children with T21, therefore orthotics & advice regarding correct footwear is important. Children with T21 often have hypermobile hips, not accounted for by the current scoring criteria for BHS. DA is common but often missed, with delayed diagnosis. Early diagnosis & treatment of DA is important to prevent unwanted joint destruction & functional disability. Children with T21 should have a musculoskeletal exam as part of their annual screening program.

Disclosure of interest: None declared.

P252
PReS-FINAL-2262: Arthritis in a patient with type 1 glycogen storage disease
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Introduction: Glycogen storage diseases, the commonest of which is Von Gierke disease, are characterized by excessive deposit of glycogen in liver and muscle owing to the lack of key enzymes in glycogen metabolism.

Objectives: The occurrence of gout in patients with Von Gierke disease may be related to acidosis causing a decrease in uric acid excretion by the proximal tubule and routing of glucose-6-phosphate to the pentose pathway.

Results: A 7 year-old girl was admitted to our patient clinic with a swollen and painful toe associated with lethargy and poor appetite; there was no rash, serositis, or eye inflammation, no muscle pain or weakness. Her history revealed that she had been followed up with a diagnosis of glycogen storage disease type 1 and neutropenia since she was 1 year-old. She had recurrent attacks of pain and edema in her toes, ankles and hip which lasts for a while and resolved sometimes by itself sometimes by non-steroidal anti-inflammatory drugs. Physical examination revealed marked edema, induration and pain in the first toe of right foot as well as hepatomegaly. Serum investigations revealed iron deficiency, neutropenia, elevated erythrocyte sedimentation rate, c-reactive protein and fibrinogen levels. Serum uric acid, lactate, and fasting triglycerides were elevated as well. MEFV mutation analysis was negative. She was given colchicines for her gout, allopurinol for high serum uric acid levels and diet counseling to help regulate his blood glucose through the day. She was followed up for 4 years with colchicines with only few attacks of gouty arthritis.

Conclusion: Colchicines could be the drug of choice in the treatment of gouty arthritis with life style management and appropriate diet. Though liver transplantation would be the definitive treatment for glycogen storage disease, its effect on gouty arthritis is still controversial.

Disclosure of interest: None declared.

P253
PReS-FINAL-2263: Progressive pseudorheumatoid dysplasia in differential diagnosis of juvenile idiopathic arthritis
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Introduction: In the differential diagnostics of juvenile idiopathic arthritis (JIA), rare genetic diseases that often mimic chronic polyarthritis, should be considered. In our case report we describe such rare disease - progressive pseudorheumatoid dysplasia (PPD).

Objectives: A 13 year old female patient started to complain about lower extremity pain at the age of 3 years, refused to walk, and the walking stereotype has been disrupted. She has been seen at our rheumatology practice at the age of 7 year. Our findings included a baby thickening and rigidity of the proximal interphalangeal joints of the hands, a substantial deficit in hip function, valgus deformities of knees and ankles...
P255
PreS-FINAL-2265: Tuberculosis in pediatric patients who are receiving anti-TNF agents
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Pediatric Rheumatology 2013, 11(Suppl 2)P255

Introduction: Adult patients receiving anti-TNFα treatment are at increased risk for developing tuberculosis (TB). Few data have been published in the pediatric population.

Objectives: We describe the occurrence of latent tuberculosis infection (LTI) and TB in children and adolescents treated with anti-TNFα agents.

Methods: Cohort observational study including pediatric patients receiving anti-TNFα agents in a tertiary-care pediatric hospital. LTI is ruled out by the implementation of anti-TNFα drugs by tuberculin skin test (TST) and, from March 2012, Quantiferon Gold-In Tube* test (QFT). Along treatment, patients are evaluated periodically for TB using history and physical examination, but TST/QFT are not systematically repeated.

Results: The final cohort consisted of 261 anti-TNFα treatments in 221 patients (56.1% female), of whom 51.7%/31.6%/17.2% treated with etanercept/adalimumab/infliximab, respectively, for a variety of rheumatic diseases (75.6%), inflammatory bowel disease (20.8%) and inflammatory eye diseases (3.6%). The mean (SD) age at diagnosis of the primary condition was 7.2 (4.6) years and the duration of the disease before implementing the anti-TNFα agent was 3.03 (3.3) years. The total follow-up time under anti-TNFα treatment was 614 patients-year; mean (SD) time per patient: 2.82 (2.2) years.

LTI was diagnosed in 3 adolescent girls (prevalence rate: 1.4%; 95%CI: 0.2-9.7) affected with juvenile idiopathic arthritis, who received isoniazid chemoprophylaxis and were later treated with anti-TNFα, without incidences. QFT tested positive in all three patients, while TST was positive in only one of them. No incident cases of TB were observed.

Conclusion: In our study, the prevalence of LTI (1.4%) was similar to that reported in population screening studies in Spain and no incident cases of TB were observed.

Disclosure of interest: None declared.

P254
PreS-FINAL-2264: Three middle fingers width correlates with maximum mouth opening and is a reliable parameter to identify joint hypermobility in schoolchildren
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Pediatric Rheumatology 2013, 11(Suppl 2)P254

Introduction: Maximum mouth opening (MMO) is a useful parameter to identify common temporomandibular joint (TMJ) disorders. Up to now, a few studies addressed the issue on MMO normal values in pediatric population, according to age and/or presence of generalized joint hypermobility (GJH), therefore it is difficult to use it in general medical practice.

Objectives: Aim of the study was to evaluate the MMO in a cohort of healthy schoolchildren and to propose a new parameter, the Three Middle Fingers Width (TMFW), the distance between 2nd and 4th fingers of the right hand at the level of the lowest nail bed, to evaluate the TMJ hypermobility in children. We also analyzed the relationship between GJH and TMJ hypermobility.

Methods: We conducted a cross sectional study in a cohort of healthy schoolchildren, aged 8-13 years, by collecting information on family history of TMJ involvement and performing a physical examination. This included height, weight, body surface area (BSA), body mass index (BMI), and musculoskeletal examination focused on the presence of GJH according to the Beighton criteria (BS≥4/9). TMFW evaluation included a complete gnotahistological visit, aimed to investigate the presence of TMJ disorders and to evaluate the MMO. The evaluation of TMFW was also performed and the Mouth Opening Ratio (MOR) was consequently calculated by the formula (MMO-TMFW)/MMOx100, adopting a 10% cut-off value to define the TMJ hypermobility.

Results: Two hundred and eighty-eight schoolchildren, 143 females and 145 males, entered the study. Mean MMO was 45.57 mm (± 5.12) for males and 44.87 mm (± 4.98) for females. Mean TMFW was 43.03 mm (± 4.09) for males and 41.71 mm (± 3.84) for females. Both MMO and TMFW correlate with growth parameters as height, weight, BMI and BSA. 89 (30.9%) subjects showed TMJ hypermobility (MOR>10%). In these subjects and in those with normal MOR MMO correlates with TMFW (r = 0.761, p < 0.001 and r = 0.786, p < 0.001 respectively); The prevalence of subjects with GJH was significantly (p < 0.001) higher in the group with TMJ hypermobility than in the other (44.3% vs 21.9%).

Conclusion: TMFW correlates with MMO in schoolchildren and may represent a simple and reliable method to evaluate TMJ abnormalities. MOR, as an index to identify TMJ hypermobility, correlates with the presence of GJH and could be included, as an adjunctive point, to the Beighton criteria.

Disclosure of interest: None declared.

P256
PreS-FINAL-2266: A rare cause for childhood uveitis: TINU (tubulointerstitial nephritis and uveitis) syndrome
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Introduction: It is very difficult to determine the etiology of isolated uveitis during childhood. If a patient presenting with uveitis has an associated acute interstitial nephritis; tubulointerstitial nephritis and uveitis (TINU) syndrome should be considered in the differential diagnosis.

Objectives: In this case report, a 15 year old girl presenting with uveitis associated with glucosuria and an increase in creatinine, and who were diagnosed as TINU syndrome will be discussed.

Methods: case report: 15-year-old female admitted with 20 day duration of extreme fatigue, loss of appetite, weight loss and redness in eyes and decreased vision. Ophthalmologic examination suggested bilateral anterior uveitis and right eye anterior granulomatosis uveitis. We found mild renal insufficiency; serum urea was 76 mg/dl, creatinine level was 1.2 mg/dl both of which were elevated. The patient’s erythrocyte sedimentation rate was 112 mm/hour, complete blood count and other biochemical parameters were normal. Antinuclear antibodies were positive in speckled pattern. Urinalysis showed low urine density, normoglycemic glycosuria and nonnephrotic proteinuria and we found high urinary β 2 microglobulin levels (45.3 mg/L, normal values: 0.02-0.25 mg/L). A renal biopsy was performed. The biopsy specimen showed dense lymphocytes, plasmocytes and variable eosinophiles in the interstitium, tubulitis in the tubule, focal debris and hyaline cylinders in the tubule. Glomerular structures were preserved. These findings were compatible with acute tubulointerstitial nephritis. With all of these findings, the patient was diagnosed as TINU syndrome. The patient received 2 mg/kg of prednisone for one month. Her kidney function normalized after prednisone therapy. Uveitis responded to systemic and local corticosteroid treatment. At her follow-up, vision was completely resolved.

Conclusion: In a patient with uveitis, urinalysis should be done during investigation of the underlying etiologic causes. Pathologic findings in urinalysis should remind a probable diagnosis of TINU syndrome. TINU syndrome in children responds very well to systemic and local corticosteroid treatment.

Disclosure of interest: None declared.

P257

PReS-FINAL-2267: Successful treatment of pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) with combination therapy of sildenafil and ambrisentan

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Pediatric Rheumatology 2013, 11(Suppl 2)pP257

Introduction: Patients with pediatric rheumatic disease rarely develop pulmonary arterial hypertension (PAH), and the expected prognosis had been very poor. With the advancement of oral medicine for PAH in recent years, we can expect better prognosis of these patients. For this purpose, early diagnosis and interventions are essential.

Objectives: We report on a 14 year old girl suffering from PAH with overlap syndrome (SLE and systemic sclerosis localised type).

Methods: At age 7, she developed autoimmune hepatitis. She was diagnosed with lupus nephritis (class ll + v) from pathological finding and pulmonary hypertension (PH) at age 10, and treated with immunosuppressive therapy (methylprednisolone pulse therapy, cyclophosphamide pulse therapy and mycophenolate mofetil) and home oxygen therapy at night. Comprehensive examination about PH was carried out at age 12.

Results: In ultra sound, tricuspid regurgitation and increased pressure gap of tricuspid valve are observed and estimated right ventricular systolic pressure was 60 mmHg. In right heart catheterization, mean pulmonary artery pressure at rest was 43 mmHg and pulmonary vascular resistance was 711 dyne·sec·10⁻⁵. We had diagnosed her as overlap syndrome (SLE and systemic sclerosis localized type) with PAH, and started combination therapy of sildenafil and ambrisentan. We confirmed the improvement of PH by right heart catheterization; mean pulmonary artery pressure (23 mmHg) and pulmonary vascular resistance (296 dyne·sec·10⁻⁵). Conclusion: Considering the obvious limitations of our single case report, we observed a good short term outcome of pediatric PAH-CTD. In order to obtain effects of oral medicine for PAH, it is important to start the intervention at early stage of this disease. It may be useful to plan screening tests (cardiac ultrasonography, pulmonary function test) on a regular basis for patients with pediatric rheumatic disease at high risk of developing PAH.

Disclosure of interest: None declared.

P258

PReS-FINAL-2268: Sarcoidosis in children seen at the pediatric rheumatology clinics of two referral hospitals in Cape Town, South Africa

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Pediatric Rheumatology 2013, 11(Suppl 2)pP258

Introduction: Sarcoidosis is a relatively uncommon condition in children. Reports from multicultural societies such as the USA indicate that sarcoidosis is more common in Africans than other racial groups. However, few reports of cases of childhood Sarcoidosis have been published from sub-Saharan Africa to shed light on the burden of sarcoidosis and the demographics and clinical presentation of children diagnosed with sarcoidosis.

Objectives: To describe the occurrence and clinical presentation of Sarcoidosis among children seen at the rheumatology clinics in two referral hospitals in Cape Town, South Africa.

Methods: We conducted a search for patients with a diagnosis of sarcoidosis in the pediatric rheumatology data base of the two referral hospitals affiliated to the University of Cape Town. The proportion of the patients with a diagnosis of sarcoidosis, their demographic and clinical features was then determined.

Results: A total of 251 Patients were in the data base by the time of the review; 4 (1.6%) had a diagnosis of sarcoidosis. They were aged 10, 4, 17 and 15 years at study time point; 4, 3.5, 11 and 14.5 years at onset of symptoms; and 10, 3.5, 16 and 14.5 years respectively at diagnosis. Three were female. Of the 4 patients, 2 were black and 2 colored. The 1st child presented with recurrent acute uveitis from the age of 4 years and iris nodules (probable ocular sarcoidosis). The second had acute respiratory distress, lymphadenopathy and hemophagocytic lymphohistiocytosis. Both had raised serum Angiotensin Converting Enzyme (ACE) levels. The 3rd patient had polyarthritis and skin nodules. The 4th, an HIV positive boy, presented with respiratory distress, skin lesions and neuroopathy (diaphragmatic paralysis and foot drop). The second, 3rd and 4th patients had non caseating granulomas on tissue biopsy suggestive of sarcoidosis. Three of the 4 patients (only 1 of whom had positive tuberculosis skin test) were treated for TB in the course of their illness before Sarcoidosis was identified as the cause of the symptoms. This was despite attempts to identify mycobacteria by microscopy, culture and GeneXpert on body fluids and biopsy specimen yielding no evidence of mycobacterial infection. The decision to treat for TB was mainly based on clinical and abnormal chest radiograph findings. Treatment for sarcoidosis was instituted with prednisone and methotrexate in 3 patients and methotrexate alone (with topical ophthalmic steroids) in 1 patient. Three of the patients have shown good response to treatment while the patient with polyarthritis and skin nodules has had an unmitting disease course.

Conclusion: Though Sarcoidosis is a rare disease in children, it still constitutes a significant proportion of pediatric rheumatology consultations. Children with sarcoidosis may present with clinical and radiological features similar to TB presenting a challenge to clinicians on differentiating them especially in the high TB burden countries in sub Saharan Africa. However, where clinical, laboratory and radiological investigations do not fully support TB infection in TB suspects, Sarcoidosis and other granulomatous inflammatory conditions should be considered and be investigated appropriately.

Disclosure of interest: None declared.
P259
**PReS-FINAL-2269: Incidence of antiphospholipid antibody syndrome in a cohort of children suffering from either arterial or venous thrombosis**

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**Introduction:** Arterial or venous thrombosis rarely occurs in children, in almost all patients an acquired or congenital cause can be identified. Hereditary thrombophilia can be identified in 10-30% of children with other evident causes of thrombosis, and in 60% of children with apparent idiopathic thrombosis. Therefore it is suggested that thrombophilia screening should be done in both cases.

**Objectives:** Aim of this study was to look for thrombophilia in a cohort of children with thrombotic events.

**Methods:** The clinical records of all patients admitted to the Pediatric Clinic, the Pediatric Intensive Care Unit and Neuropsychiatry of the Children Hospital of Brescia between January 2006 and January 2012 were analyzed to select those with either clinical history or discharge diagnosis of an acute thrombotic event. Patients with malignancy were excluded. The selected patients were analyzed for clinical history, characteristics of the thrombotic event and possible predisposing causes and underwent a complete screening for thrombophilia.

**Results:** 30 out of the 6379 children whose charts had been evaluated met the inclusion criteria; in none of them thrombophilia was previously diagnosed. Mean age was 5.0 ± 3.7 years, 17/30 were males, 19 had arterial and 11 venous thrombosis. Central nervous system was involved in 28 patients, veins of legs in 2. 4 children died during the hospitalization; the other 26 were contacted: 21 agreed to undergo a clinical evaluation and complete screening for thrombophilia.

Family history was significant in 9 patients (4 cerebral ischemia, 1 acute myocardial infarction, 1 cerebral ischemia and myocardial infarction, 1 deep vein thrombosis, 1 LAC positivity and 1 recurrent abortion). Possible predisposing causes were found in 6 children: cardiopathy (2), otostamoiditis (1), trauma (1) venous cannulation (2). Protein C was low (54% and 61%) in 2 children and Protein S in other 2 (63% and 31%). A child had an heterozygous mutation for Factor II, two (9,5%) hypermocysteinemia associated with homozygosity for variant C677T of MTHFR. Significant positivity for Antiphospholipid Antibodies was found in 2 children: one for anti-B2GPI IgM (0.504 UO) and one double positivity for anticardiolipin IgG (25.4 GPL) and anti-B2GPI IgG (0.199 UO), allowing the diagnosis of Antiphospholipid Syndrome (APS).

**Conclusion:** Thrombophilia was found in 9 out of the 21 children studied. In 3 children there were both a thrombophilic and acquired predisposing condition: one Protein C deficit and otostamoiditis, one Protein S deficit and cardiopathy and one Antithrombophilic Antibodies Syndrome and cardiopathy. The other 6 children had been found to have hereditary thrombophilia or Antithrombophilic Antibody Syndrome, without any extrinsic predisposing factor and all of them had been previously diagnosed as idiopathic thrombosis. Our study underlines the importance to do a complete screening for thrombophilia in all children with thrombosis. Moreover, even though APS is estimated to be very rare in children, our study underlines that some patients may be misdiagnosed without appropriate screening in case of a child presenting with a thrombotic event.

**Disclosure of interest:** None declared.

P260
**PReS-FINAL-2270: Primary hypertrophic osteoarthropathy - a rare cause of swollen joints**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P260**

**Introduction:** Primary hypertrophic osteoarthropathy (PHO), also known as pachydermoperiostosis, is a rare genetic disease with excessive proliferation of skin and bone at the distal parts of extremities. Features include clubbing of the digits, periostitis of the long bones, hydralthrosis, facial skin thickening and coarse facial features. It mostly affects males and has a bimodal peak of onset: in the first year of life and around puberty.

Secondary hypertrophic osteoarthropathy is associated with an underlying pulmonary, cardiac, hepatic, or intestinal disease, and is rarely found in children.

**Objectives:** A previously healthy 16-year-old adolescent was referred to the Pediatric Rheumatology Clinic with a one year history of painful and swollen knees, feet and arms. The pain was of a mechanical nature, with relief from NSAIDs, and no morning stiffness or nocturnal pain. He also complained about facial acne and palmoplantar hyperhidrosis. There were no constitutional symptoms, rashes, aphthae, Raynauds, ocular, gastrointestinal or respiratory complaints. Family history was irrelevant.

**Methods:** On examination, there was clubbing of fingers and toes, hypertrophy of soft tissue (coarse facial features and thickening of the facial skin, with prominent folds on the forehead and cheeks), cutaneous gland dysfunction (acne, hyperhydrosis, seborrhoea) and joint swelling with effusion (knees, ankles). Imaging showed soft tissue swelling and periotestal ossification with cortical thickening, metaphyseal diaphyseal enlargement of long bones, with preservation of articular surfaces, and no acroosteolysis. Bone scan revealed symmetrically increased uptake in the tubular bones along the cortical margins of the diaphysis and metaphysis (parallel-track sign).

ESR and CRP were mildly elevated, with normal endocrine workup, full blood count and film, renal and hepatic function, LDH, electrolytes and bone biochemistry, except for low 25-OH vitamin D. Autoantibodies and immunology were normal. Chest X-Ray, Mantoux test, Abdominopelvic US and cardiac evaluation had no changes.

**Results:** NSAID treatment was successful in managing the pain. After 1-year of follow-up, there are no new complaints, no signs of a secondary cause. A referral to Genetics was made, and he is currently awaiting testing.

**Conclusion:** PHO is a rare cause of joint swelling and can be confounded with other causes of polyarthitis.

Careful physical examination will detect digital clubbing and raise the diagnostic suspicion.

Exclusion of secondary causes is paramount, as is close clinical follow-up as some patients eventually develop diseases many years later.

Although its course is self-limiting, and progression stops at the end of adolescence, there is no curative treatment for the skeletal abnormalities.

**Disclosure of interest:** None declared.
rheumatology (PRh) trainees and 1 specialist PRh physiotherapist and all blinded to MPS subtype. Videos were scored independently by the 3 observers and videos re-scored for intra- and inter-observer consistency. Data were pooled and analysed.

Results: 15 videos of children (9 boys, 6 girls, median age 11 years (4-19) with MPS (10 MPS type I Hurler-Scheie (HS); 4 MPS type II; 1 mannosidosis) were assessed. The most common abnormalities detected using pGALS exam were restriction of shoulder, elbow, wrist, temporomandibular joint excursion (likely impacted by many children having enlarged digits) (>75% cases) and spinal deformity/restriction (2/3 cases). Mean intra-observer Kappa 0.74 (range 0.65-0.80) and inter-observer Kappa 0.62 (range 0.51-0.77). Hip manoeuvres within pGALS were not clearly demonstrated in the videos.

Conclusion: In this observational study, pGALS identifies MSK abnormalities in children with MPS. Restricted joint movement (and especially upper limb) was a consistent finding. We acknowledge that further work is needed to include pGALS assessment of the hip and also to test pGALS in an additional population of children with MPS; notably in further children with MPS I-HS as this subtype often has MSK abnormalities as the only feature. The use of pGALS and awareness of patterns of joint involvement may be a useful adjunct to facilitate earlier recognition of these rare conditions and facilitate access to specialist care.

Disclosure of interest: None declared.

P262
PRes-FINAL-2272: Association of benign joint hypermobility syndrome with mitral valve prolapsed in Iranian children
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Introduction: Benign joint hypermobility syndrome (BJHS) is a clinical condition characterized by an increased ability of joints during passive and dynamic movements. Mitral valve prolapsed (MVP) is the most commonly diagnosed cardiac abnormality and affects around 5% of population. Abnormalities of collagen have been found in valves of patients with MVP.

Objectives: There were limited published papers concerning children with BJHS and MVP. The aim of this study was to determine the association of BJHS with mitral valve prolapsed in children.

Methods: Sixty-three children with benign joint hypermobility syndrome were included in case group and 63 without any rheumatologic disease were placed in control group. We used Carter-Wilkinson and Beighton criteria for diagnosing of benign joint hypermobility syndrome. MVP was evaluated by echocardiography in both groups. The mitral leaflet displacement >2 mm considered as cut off for diagnosis of MVP.

Results: In this study, 32 girls and 31 boys were included. Mean of age in case group was 7.1 was 6.9 (p = 0.001). Mitral valve prolapse was significantly higher among cases with BJHS aged >7 (58.8%) year compared to < 7 (41.2%) year of age (p = 0.007). Heart murmur and palpation was more common among children with benign joint hypermobility syndrome with MVP compared to children without MVP (p < 0.05).

Conclusion: The incidence of MVP among children with benign joint hypermobility was significantly higher than control group.

Disclosure of interest: None declared.

P263
PRes-FINAL-2273: Clinical and laboratory characteristics of patients with fever of unknown origin in two Colombian pediatric rheumatology centers from 2010 to 2013
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Introduction: Fever of unknown origin (FUO) represents a diagnostic challenge and is a common cause of referral to pediatric rheumatology clinics.

Objectives: To describe the clinical and laboratory characteristics of patients with diagnosis of FUO who were seen in two pediatric rheumatologic reference centers in Medellin, Colombia, in order to identify specific characteristics of FUO secondary to rheumatic diseases (RD).

Methods: We included patients from a prospective diagnostic test trial called: level of total and glycosilated ferritin in children with systemic onset juvenile idiopathic arthritis (SoJIA) and children with other causes of FUO. Patients had been referred with the diagnosis of FUO, defined as: temperature of >38.3°C at least twice per week during two or more weeks and without a clear diagnosis after initial evaluation. Epidemiological variables, fever characteristics and the following clinical manifestations were considered: arthritis, lymphadenopathy, evanescent rash, hepatosplenomegaly and serositis. We included the following laboratory tests: complete blood count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), Lactic Dehydrogenase (LDH), ferritin and transaminases. We considered other variables that were obtained retrospectively from medical records including: other clinical manifestations associated with fever, antibiotic treatment before admission, laboratory and diagnostic images, presence of significant organ or system dysfunction, number of patients who died and probable cause of death. Patients were followed by pediatric rheumatology for a minimum period of six months and they were grouped into categories in accordance with their final diagnosis. We used descriptive statistics. We compared the main clinical and laboratory characteristics of patients with RD versus all patients with other causes of FUO using the chi-square test for categorical variables and for continuous variables the U Mann Whitney test was applied.

Results: 53 patients were included, 60.3% were male and average age was 6 years. Median total fever duration: 30 days (ICR 21-42). 66% had received empirical antibiotics before study admittance, most of them more than one. RD were the most frequent category of FUO (51%) followed by: miscellaneous causes (15%), infections (11%), unidentified causes (11%), malignancy (6%), and hemophagocytic lymphohistiocytosis (6%). The most common of the RD was SoJIA. Arthritis, evanescent rash, serositis, neutrophilia >80% and ESR >50 mm/h were more frequent in patients with RD versus other causes of FUO (p < 0.05). An increase in LDH was more frequent in non-RD causes of FUO (p < 0.036). Of all patients, 5.7% died and 39% presented an organ or system dysfunction, the most common being hematological. No differences in fever characteristics or other clinical and laboratory variables by comparing RD with other types of FUO were found.

Conclusion: FUO comprised a wide range of diseases. RD were the most common diagnostic category of FUO and within these the SoJIA was the main cause, with certain clinical and laboratory findings as clues to the diagnosis. Organ dysfunction was observed more frequently than in other series of FUO.

Disclosure of interest: None declared.

P264
PRes-FINAL-2274: Antiadalimumab antibodies in pediatric rheumatology patients. A pilot experience
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Pediatric Rheumatology 2013, 11(Suppl 2):P264

Introduction: Immunogenicity of anti-Tumor Necrosis Factor agents is one of the mechanisms behind treatment failure.

Objectives: To explore the relationship between the presence of antiadalimumab antibodies (AAA), the disease activity and the therapeutic decisions.

Methods: Cross-sectional retrospective study determining: 1) serum adalimumab (Ada) levels by a capture ELISA (positive > 5 ng/ml) and 2) levels of AAA by a two-site bridging ELISA (positive > 10 Arbitrary Units (AU)/ml). The clinical activity was assessed by conventional tests and the physician visual analogue scale (ph-VAS) of 0 to 10, the same day that the blood sample was collected. Blood samples were obtained a few hours before drug administration.

Results: Until March 2013 measurements in 25 patients were available, 15 (60%) of them had some activity of their disease ph-VAS = 1.7 ± 0.9 (1-4).

Disclosure of interest: None declared.
Eight (32%) children presented AAA, range from 12 to 30,000 AU/ml, and absence of Ada levels. All cases with AAA positives had active disease, except one who had received a periocular corticosteroid injection in the previous month. Furthermore 8/17 (47%) patients without AAA had active disease. The duration disease and the age were not different between those with and without AAA. The only clinical and analytical difference was the higher frequency of active uveitis when AAA were present (p = 0.01). Similarly median survival time on treatment was shorter when AAA were present (2.3 vs 2.5 years) (p = 0.03).

Conclusion: Antiadalimumab antibodies appear to explain half of the cases of active disease and their presence is associated with discontinuation of treatment.

Disclosure of interest: None declared.

**Table 1(abstract P264) Characteristics of 25 children with pediatric rheumatic diseases treated with Adalimumab**

<table>
<thead>
<tr>
<th>AAA</th>
<th>Girls</th>
<th>JIA</th>
<th>ANA+</th>
<th>Uveitis</th>
<th>Active uveitis</th>
<th>Active arthritis</th>
<th>MTX</th>
<th>Drug switching</th>
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<td>Present</td>
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<td>4 (50)</td>
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<td></td>
</tr>
<tr>
<td>Absent</td>
<td>13 (77)</td>
<td>15 (88)</td>
<td>6 (35)</td>
<td>13 (77)</td>
<td>3 (18)</td>
<td>5 (29)</td>
<td>6 (35)</td>
<td>4 (24)</td>
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Data are expressed as n (%) AAA = Antiadalimumab antibodies; JA = Juvenile Idiopathic Arthritis; ANA = Antinuclear antibodies; MTX = Concomitant Methotrexate.

**P265**

**PReS-FINAL-2275: Improvement of calcinosis cutis with intravenous pamidronate in a 2-year-old girl with progressive widespread skin calcification of unknown origin**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P265**

**Introduction:** Pathologic calcification occurs in up to 40% of children with juvenile dermatomyositis and can develop within several months even in successfully treated patients. Other differential diagnoses of calcinosis cutis in children are rare. There is no generally accepted standard treatment of calcinosis. We report on a 2-year-old previously healthy girl, the 2nd child of non-consanguineous healthy parents from Kosovo, who presented with a 7-month history of progressive calcinosis cutis primarily affecting both legs. The girl had no other signs or symptoms of juvenile dermatomyositis or other autoimmune diseases.

**Objectives:** An extensive diagnostic work-up was carried out to find an underlying cause and an effective treatment.

**Methods:** Laboratory studies, immunology tests, X-rays, magnetic resonance imaging, and skin and muscle biopsy were done.

**Results:** Blood tests showed mild leukocytosis (14.0 × 109/L), lymphocytosis (9.1 × 109/L) and thrombocytosis (632 × 109/L), hypergammaglobulinemia (1786 mg/dl) and elevated S100A8/S100A9 protein levels (2230 ng/ml). Significantly elevated plasma osteopontin levels (>30-fold) were noted. Creatininaise, aldolase, C-reactive protein, erythrocyte sedimentation rate, liver function tests, electrolytes, vitamin D and parathormone levels were all normal. ANA, ENA, rheumatoid factor, myositis-specific and associated antibodies (anti-Mi-2, anti-Jo-1, anti-Pm/Scl, anti-SRP54), complement C3 and C4 were all negative. X-rays of her legs showed extensive calcinosis. On magnetic resonance imaging, there was contrast enhancement of thickened muscle fascia but no signs of dermatomyositis. Skin and muscle biopsy revealed calcification (without ossification!) with foreign body reaction in subcutaneous fatty tissue and inflammatory infiltrates (lymphocytes and macrophages), but no signs of eosinophilic fasciitis, neurogenic or myopathic damage. We suspected an autoimmune disease with fasciitis (primary or secondary?) and calcinosis cutis and started immunosuppressive therapy with prednisone and azathioprole. After calcinosis progressed (clinically, on x-rays, ultrasound and follow-up MRI), methotrexate was added and pamidronate infusions were started. Three months later, improvement of calcinosis and local tissue inflammation as well as no development of new calcium deposits were observed. Two further cycles of pamidronate every three to four months are planned and a slow tapering of the immunosuppressive therapy.

**Conclusion:** The underlying cause of the disease in our patient remains unclear. The degree and clinical distribution of the calcinosis, the young age of our patient as well as the very high levels of osteopontin, a major regulatory protein of calcification, suggest an autoimmune disease. The patient’s differential diagnosis includes an unknown genetic disease of calcium metabolism - we are still awaiting the results of a whole exome analysis of the patient and her family members. Immunosuppressive therapy did not stop progression of calcinosis and only after starting pamidronate rapid regression of calcified lesions was noted. Whether this therapy has any long-term beneficial effect and whether the immunosuppressive therapy can be fully tapered remains to be seen.

**Disclosure of interest:** None declared.

**P266**

**PReS-FINAL-2276: IgG4 related disease in a 10-year-old girl**

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**Pediatric Rheumatology 2013, 11(Suppl 2):P266**

**Introduction:** A 10-year-old girl developed an enlargement of parotid and submandibular salivary glands and lymph nodes up to 2.5 cm associated with edema of her upper eyelids. In further follow-up, she developed non-palpable, vasculitic skin lesions. She received cephixime, that co-incided with partial regression of lymph nodes. Re-occurrence of vasculitic lesions with bilateral edema of upper eyelids resembling Muciliz disease was observed. At 7 years of age, she developed asthma requiring the use of bronchodilators. Clinical examination: a 10-year-old girl, pale skin, at the both calves irregularly shaped, livid, painless, vasculitic lesions, 2-3 cm in size. The upper eyelids are swollen. Parotid and submandibular salivary glands and lymph nodes are enlarged.

**Objectives:** To present clinical and laboratory investigations in IgG4-related disease in childhood.

**Methods:** Routine laboratory tests including serum Ig concentrations, autoantibody screen, and histopathologic examination.

**Results:** Serum proteins were 101 g/l, albumins 38 g/l. Serum immunoglobulin IgA 1.92, IgM 0.38, IgG 42.2 g/l; IgG subclasses: IgG1 18.9 g/l (4.32-10.2), IgG2 17.05 g/l (0.72-4.3), IgG3 6.35 g/l (0.13-0.85), IgG4 9.02 g/l (0.02-0.93). Serum IgE 900 IU/ml (normal up to 60 IU/ml). Coombs test negative. Autoantibody screening was negative. Serologic tests to HSV, EBV, CMV, hepatitis B and C, HIV were negative. Serum ACE was normal, 57 U/I. Neck ultrasound showed an enlargement of both parotid glands, lymph nodes and submandibular salivary glands up to 2.5 cm. Histopathologic evaluation of lymph nodes, submandibular and parotid gland: the enclosed lymph node profiles show retained architecture with prominent reactive follicular hyperplasia. The intervening paracortex focally appears prominently hypovascular and contains a polymorphous lymphoid infiltrate comprising small lymphocytes, scattered immunoblasts, some plasma cells and focally prominent eosinophils. The salivary gland tissue shows abundant mononuclear inflammatory infiltrate with focal prominence of plasma cells and significant patchy sclerosis. The immunostainings including CD3, CD20 and CD79a show retained lymph node architecture. There is a reactive pattern of expression of Ki67, CD10, bcl-2, bcl-6, CD21 and CD23. The immunostains also highlight...
fragmentation of some of the germinal centres. Most of the IgG staining plasma cells were of IgG4 positive phenotype.

**Conclusion:** Bilateral, symmetrical, painless swelling of their lacrimal and salivary (parotid and submandibular) glands should raise suspicion on IgG4-related disease in childhood.

**Disclosure of interest:** None declared.

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**P267**

**PreS-FINAL-2277: Clubbing fingers in a boy with arthritis**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P267

**Introduction:** Hypertrophic osteoarthopathy is a syndrome characterized by clubbing of the fingers and toes, periostosis of long bones, pain and swelling of the joints, and, in more advanced instances, pachydermia. The syndrome is often secondary to cardio-pulmonary or intestinal diseases. The primary form, known as pachydermoperiostosis, is a rare genetic disorder with autosomal dominant (with incomplete penetrance) or recessive transmission, for which there is no specific therapy. Objective: A 10-yr-old Caucasian boy was referred to our department due to swelling of the right knee and the presence of persistent pain for two months associated with morning stiffness.

**Methods:** Family history was not contributory. Examination of the joints confirmed arthritis of his right knee. Further physical examination revealed evident clubbing of all his fingers and toes, and a palmo-planter hyperhydrosis. Examination of his chest and abdomen was unremarkable. All laboratory results including inflammatory markers, complete blood count and other routine biochemistry were within the normal range. Autoantibody screening assays were negative. A high resolution CT scan of the chest, an echocardiogram, and pulmonary function tests showed no pathological results. An x-ray of his femur revealed a mild periostal hypertrophy.

**Results:** We decided to treat the patient with non steroidal anti-inflammatory drugs to limit joint inflammation, but the persistence of arthritis led us to perform an intra-articular steroid injection, with good results.

**Conclusion:** Because of articular manifestations rheumatologists should be able to distinguish hypertrophic osteoarthopathy from chronic rheumatic diseases and to discern the primary from the secondary form.

**Disclosure of interest:** None declared.

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**P268**

**PreS-FINAL-2278: Description of a Colombian cohort of patients with childhood systemic lupus erythematosus**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P268

**Introduction:** Systemic lupus erythematosus (SLE) is a multisystem disease of autoimmune etiology, which carries a high morbidity and mortality.

**Objectives:** To describe clinical and immunoserological features at the time of diagnosis within a cohort of pediatric patients attending the service of rheumatology of a Colombian pediatric hospital.

**Methods:** Cross-sectional study. 89 patients with diagnosis SLE (1997 ACR revised criteria) from a rheumatology center at a pediatric hospital were evaluated at the time of diagnosis and twelve months after. Medical records were reviewed registering the following variables: Sex, age, renal involvement, hypertension, nephrotic range proteinuria, and median activity. The most common HCLN was found in 30 patients (41.1%); after 12 months it was found in 68 patients (76.4%) (p < 0.01), hypertension at the time of diagnosis was found in 30 patients (41.1%); after 12 months it was found in 8 patients (11%) (p < 0.01). 36 patients (49.3%) underwent renal biopsy. 16 patients (44.4%) underwent a second renal biopsy. HCLN first biopsy: Class I (8.3%), Class II (11.1%), Class III (8.3%), Class IV (50%), Class V (13.9%), Class III-IV (5.6%), HCLN second biopsy: Class I (6.3%), Class III (6.3%), Class IV (62.5%), Class V (25%), Class IV-V (12.5%), patients on dialysis at the time of diagnosis were 11 (1.4%); after 12 months they were 3 (4.4%) (p = 0.36), and median score SLEDAI at the time of diagnosis was 23 (Min 4, Max 61); after 12 months it was 4 (Min 0, Max 31) (p < 0.01).

**Conclusion:** The most common HCLN in this cohort were Class IV, and Class V. Statistical significance (difference) was documented regarding renal involvement, hypertension, nephrotic range proteinuria, and median score SLEDAI for the time of diagnosis and twelve months follow-up. This suggests that the change and improvement in clinical features and disease activity was due to the established treatment.

**Disclosure of interest:** None declared.

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**P269**

**PreS-FINAL-2279: Lupus nephritis in a Colombian cohort of pediatric patients**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P269

**Introduction:** Renal involvement is a major cause of morbidity and hospital admissions in systemic lupus erythematosus (SLE) patients and occurs in 40% to 70% of all patients. Generally, renal involvement tends to occur within the first 2 years of SLE with its frequency decreasing significantly after the first 5 years of disease.

**Objectives:** To describe and to compare the clinical features and disease activity of a cohort of patients with SLE at a Colombian children’s hospital in two different moments.

**Methods:** Analytic descriptive study. 89 patients with diagnosis of SLE (1997 ACR revised criteria) from a rheumatology center at a pediatric hospital were evaluated at the time of diagnosis and twelve months after.

**Results:** 76 patients (85.4%) were female and 13 (14.6%) were men. Mean age at the time of diagnosis was 11.3 y/o (min 2 max 16); Renal involvement at the time of diagnosis was found in 73 patients (82%); after 12 months it was found in 68 patients (76.4%) (p < 0.01), hypertension at the time of diagnosis was found in 30 patients (41.1%); after 12 months it was found in 8 patients (11%) (p < 0.01). 36 patients (49.3%) underwent renal biopsy. 16 patients (44.4%) underwent a second renal biopsy. HCLN first biopsy: Class I (8.3%), Class II (11.1%), Class III (8.3%), Class IV (50%), Class V (13.9%), Class III-IV (5.6%), HCLN second biopsy: Class I (6.3%), Class III (6.3%), Class IV (62.5%), Class V (25%), Class IV-V (12.5%), patients on dialysis at the time of diagnosis were 11 (1.4%); after 12 months they were 3 (4.4%) (p = 0.36), and median score SLEDAI at the time of diagnosis was 23 (Min 4, Max 61); after 12 months it was 4 (Min 0, Max 31) (p < 0.01).

**Conclusion:** The demographic characteristics and laboratory tests of this cohort are according to previously reported in worldwide and in American literature. The score SLEDAI at the diagnosis was found in median activity. The most common medications prescribed were antimalarials followed by azathioprine and cyclophosphamide.

**Disclosure of interest:** None declared.
Methods: Analytic descriptive study. 89 patients with diagnosis SLE (1986 ACR criteria) from a rheumatology center at a pediatric hospital were evaluated at the time of diagnosis and twelve months after. Medical records were reviewed registering the following variables: score SLEDAI, Antinuclear antibodies (ANAs), Anti-DNA antibodies and complement C3 and C4 levels. Analysis was done through parametric and non parametric tests to compare means and proportions using STATATA11. Shapiro-Wilk and Wilcoxon tests (non-normally distributed data) were applied.

Results: Median score SLEDAI at the time of diagnosis was 23 (min 4 max 61); after 12 months it was 4 (min 0 max 31) (p = 0.001). Antinuclear antibodies (ANAs) reactivity at the diagnosis was 88,1%; after 12 months it was 6,67% (p = 0.17). Anti-DNA antibodies reactivity at the diagnosis was 66,7%; after 12 months it was 56,41% (p = 0.01). C3 level was diminished in 67,95% of patients at the diagnosis; after 12 months it was diminished in 33,3% of patients (p = 0.01). C4 level was diminished in 71,7% of patients at the diagnosis; after 12 months it was diminished in 40% of patients (p = 0.01).

Conclusion: Statistical significance was documented regarding score SLEDAI, Anti-DNA antibodies reactivity, hypocomplementemia for the time of diagnosis and twelve month follow-up. This suggests that improvement in disease activity was due to the established treatment. Disclosure of interest: None declared.

P272
PReS-FINAL-2282: Amaurosis as a presenting sign of antiphospholipid syndrome secondary to systemic lupus erythematosus - case report
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Introduction: Antiphospholipid syndrome (APS) secondary to systemic lupus erythematosus (SLE) can be recognised in children with arterial or venous thrombosis. Amaurosis due to thrombosis of central retinal vein is rarely presenting manifestation of SLE with secondary APS.

Objectives: To present APS secondary to SLE with aggressive ophthalmological onset in 17 years old female.

Methods: We report a patient with unilateral amaurosis due to thrombosis of central retinal vein. Amaurosis was a reason for her urgent admission at Ophthalmology. She was transferred to Pediatric rheumatology department as suspected SLE. The patient had rapidly developing disease. Eleven days after the attack of retinal vein thrombosis, she became febrile with malar rash, facial ulcer, neurological symptoms (right Mingazzini positive), arterial hypertension, haemorrhagic abnormalities, proteinuria and immunological disorders. Head MRI-MRA was performed and subocclusion of left medial cerebral artery was found. The diagnosis of APS secondary to SLE was established.

Results: The patient significantly improved with aggressive immunosuppressive and prompt anticoagulant therapy but ophthalmological complication have been improved slowly with uncertain prognosis.

Conclusion: The patients with SLE related symptoms have to be referred to rheumatologist immediately because APS secondary to SLE may have aggressive thrombotic onset and cause serious organs damages. Disclosure of interest: None declared.

P273
PReS-FINAL-2283: Systemic lupus erythematosus (SLE) in children and adolescents in pediatric unite, institute of rheumatology Belgrade, Serbia
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Pediatric Rheumatology 2013, 11(Suppl 2)p273

Introduction: SLE is an autoimmune disease characterized by widespread inflammation of blood vessels and connective tissues.

Objectives: The aim of this study is to describe the clinical and laboratory manifestations, treatment, complications and disease outcome in children and adolescents with SLE.

Methods: Medical records of all children and adolescents with SLE treated during 10 years period (between 2001 and 2011) at the Institute of Rheumatology Belgrade were retrospectively reviewed. The collected data included informations about demographic profile, clinical and laboratory manifestations, treatment, complications and disease outcome.
Results: Thirty seven patients (36 f, 1 m) of SLE were reviewed. The mean age at disease onset was 15 years with a range of 7-19 years. The most common features were mucocutaneous (malar rash in 84.8%, photosensitivity in 69.7%); musculoskeletal (arthritis in 87.9%) and hematological (leucopenia in 75.8%, anemia in 69.7%, Coombs test positive in 18.9% and, thrombocytopenia in 28%). Renal involvement (n = 11), occurred in 45.5% of children. CNS manifestations in 51.2%. ANA was positive in 97.3%, Anti dsDNA in 81.1%, Anti Sm in 40% of our patients. Corticosteroid treatment was given in all patients in the form of prednisone (100%) and methylprednisolone, iv pulses were applied in 58.8%. Antimalarics were used in 97.3%, azathioprine in 48.6%, hydroxychloroquine in 21.6% and cyclophosphine in 3.8% of children. The most common complications were hypertension, hypercorticism and opportunistic infections. Three patients died during the period of the study, two girls according to antiphospholipid syndrome complications, one of infection (sepsis).

Conclusion: The most common features were mucocutaneous, musculoskeletal and neurological. Less than half of the patients were with renal involvement, although 80% were anti ds DNA positive. All patients were treated with corticosteroids, and except three with antimalarics. High blood pressure, hypercorticism and opportunistic infections were most common complications. There was no significant difference in clinical and laboratory manifestations, therapy approach and outcome compared to those in most pediatric SLE studies. Low number of patients with renal involvement can be explained by profile of institution.

Disclosure of interest: None declared.

P274
PRes-FINAL-2284: SLE and complement deficiencies: a French multicentric retrospective study

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Pediatric Rheumatology 2013, 11(Suppl 2):P274

Introduction: Systemic lupus erythematosus (SLE) is a multifactorial disease. Rare causes of monogenic SLE have been described, including the complement deficiencies.

Objectives: Our objectives were to collect clinical data and outcome of SLE patients associated to complement deficiency in a multicenter retrospective study.

Methods: We conducted a retrospective study within the French pediatric rheumatology society (SOFRREMIP) in 2012-2013 to identify patients, with a confirmed deficiency of complement fraction.

Results: Ten cases of SLE with complement deficiency were identified: 2 C1 deficiencies, 2 C2 deficiencies and 6 partial C4 deficiencies. The sex ratio (M/F) is 0/10. The disease onset occurred in childhood in 8 patients with 6 before the age of 10. The first symptoms were cutaneous in 7 children, articular for 2 children and psychiatric for 1 patient. All patients were positive for antinuclear antibodies whereas only half of them were positive for anti-dsDNA antibodies. Anti-Ro (SS-A) antibodies were strongly positive in 8 patients. Anti-phospholipidantibodies were present in 6 patients. Over time, 5 patients developed a severe disease associated to renal failure (n = 2) or neuprolupus (n = 3). Associated autoimmune diseases were found in 4 patients: hypothyroidism (n = 1), autoimmune hepatitis (n = 2), Sjögren syndrome (n = 1). Two children with C2 and C4 deficiency had severe bacterial infections.

Conclusion: Cutaneous or joint manifestations are the most common symptoms but life-threatening complications can occur in the context of C1 deficiency. Anti-SSA antibodies were frequent while anti-dsDNA are only found in half of the cases. Genetic characterization of complement deficiencies remains challenging. Next generation sequencing may be helpful to better diagnose these monogenic forms of lupus.

Disclosure of interest: None declared.

P275
PRes-FINAL-2285: Pediatric non-renal SLE presenting as periorbital edema: response to treatment with belimumab

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Pediatric Rheumatology 2013, 11(Suppl 2):P275

Introduction: Periorbital edema without proteinuria is a rare and often difficult to manage manifestation of SLE. The use of belimumab for treatment of this complication has not been previously described in the pediatric literature.

Objectives: To describe the use of belimumab for treatment of steroid-dependent chronic periorbital edema in new onset non-renal SLE.

Methods: Case report: A 16 year old white female presented with a three month history of periorbital edema in the setting of positive lupus serologies, synovitis, and hypocomplementemia. She had failed treatment with anti-histamines and had responded well to the use of oral steroids, but her symptoms quickly recurred upon tapering off steroids. Over the following six months, treatment with hydroxychloroquine and methylxatrexate failed to provide any steroid-sparing benefit. Addition of a three month trial of omalizumab also failed to provide any benefit. IV belimumab at 10 mg/kg monthly, was initiated and continued upon one year follow-up.

Results: Treatment with belimumab resulted in complete resolution of the patient’s periorbital edema, allowing her to discontinue the use of steroids within a month of starting this agent. No adverse reactions have been observed upon one-year follow up, and the patient’s symptoms remain well controlled off steroids.

Conclusion: Belimumab may serve as a safe and effective steroid sparing agent for management periorbital edema associated with non-renal SLE.

Disclosure of interest: None declared.

P276
PRes-FINAL-2286: Mastitis in an adolescent patient with juvenile systemic lupus erythematosus

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Pediatric Rheumatology 2013, 11(Suppl 2):P276

Introduction: Mastitis is an inflammatory disease of the breast, acute or chronic that occurs primarily in young women and frequently lactating. In 2-3% it may occur in patients with systemic lupus erythematosus (SLE). The authors describe in an adolescent with JSLE this rare disease called lupus mastitis, which is a subset of lupus panniculitis limited to the breast.

Objectives: To describe a young patient with lupus mastitis.

Methods: Case report: A 16 year-old girl presented with a painful left breast mass associated with localized skin erythema. Her medical history was significant for diffuse proliferative lupus nephritis that was diagnosed in 2002. After 2 years of immunosuppression therapy, the patient had stable renal function for more than 8 years. In January 2013, she presented with a painful nodule in the left breast. At the time of presentation, she had no clinical complaints but the serology findings were positive. There was no history of trauma to the breast, oral contraceptive use and negative sexual history. She was being treated with low dose prednisolone and azathioprine. The mass was warm and tender and no lymphadenopathy was present. The contralateral breast was normal. The laboratory tests showed normal blood count and negative inflammatory tests, ANA: 1/640 homogeneous pattern, anti-DNA: 1/80. Breast ultrasound revealed multiple areas with thick liquid collections in the subareolar region of the left breast. MRI confirmed the

Disclosure of interest: None declared.
multiple cystic areas with subcutaneous thickening. An incisional biopsy revealed chronic inflammation, compromising lobes and stromal, compatible with inflammatory mastitis. Cultures were negative. The patient was treated with surgical drainage of collections associated to pulse therapy with methylprednisolone and mycophenolate mofetil was introduced featuring full resolution of the inflammatory process.

Results: Mastitis is a rare manifestation observed in SLE. The pathophysiology of lupus mastitis is unknown. One thought is that the panniculitis is an extension of the inflammatory process that involves the overlying skin as epidermal changes, atrophy and ulceration may be present. This inflammatory condition can simulate a neoplasm or a breast abscess. This disorder was a challenge to diagnose for all involved physicians.

Conclusion: Lupus mastitis is a rare chronic inflammatory reaction of the subcutaneous fat that may occur in 2-3% of patients with systemic lupus erythematosus usually between the ages of 20 and 50 years, and its occurrence is two times greater in women than in men. The occurrence in a young patient is very rare e should be promptly treated with immunosuppression. The clinical course of lupus mastitis is often chronic with flares and remissions. Surgical excision alone may not cure the patient if there is inadequate immunosuppression.

Disclosure of interest: None declared.

P277
PReS-FINAL-2287: Electroconvulsive therapy in a patient with juvenile systemic lupus erythematosus
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Pediatric Rheumatology 2013, 11(Suppl 2):P277

Introduction: Patients with systemic lupus erythematosus (SLE) often develop neuropsychiatric disease. Central nervous system (CNS) manifestations of SLE occur in about half of all patients, and psychiatric presentations are seen with a prevalence of 35% to 60% in this group. Electroconvulsive therapy (ECT) also known as electroshock therapy is a psychiatric treatment in which electricity/electric shock is used to induce convulsions. It is used to treat psychiatric diseases such as depression, schizophrenia, mania or catatonia that do not respond to conventional treatment.

Objectives: To describe a patient with refractory neuropsychiatric lupus who responded to electroconvulsive therapy.

Methods: Case Report: A 25-year-old woman with a 13-year history of SLE characterized by arthritis, thrombocytopenia, positive antinuclear antibody in a titer of 1:2,560 (speckled pattern), and the presence of antibodies to Sm and antiribosomal P protein autoantibodies was admitted to University Hospital with an organic psychosis. She was treated with corticosteroids, cyclophosphamide and azathioprine and went into remission. When she was 18 yo, she had a relapse (depression) and was treated with methyl prednisolone (MP) pulse therapy (PT) and cyclophosphamide. After 6 months, she had another episode of psychosis (echolalia, repetitive hands movements, extreme anxiety and suicide tendency) which did not respond to MP PT, Cyclophosphamide, Rituximab and Intravenous Immunglobulin. Magnetic Resonance of the brain was normal, CSF results were inconclusive, antiphospholipid, anti dsDNA and anti Sm antibodies were all negative. She had various episodes of aggressiveness, agitation, insomnia, nightmares, hallucinations, difficulty in concentrating, repetitive movements of both upper and lower limbs, phases of catatonia and suicidal tendencies. Psychotropic agents, antidepressants and anxiolytics were used with little response clinically. After 18 months of immunosuppressive and anti-psychotics treatment without improvement, an ECT trial was begun. After 4 sessions of ECT, the patient had a remarkable improvement of her psychiatric symptoms, she was able to sleep and respond normally to her surroundings. She had a total of 10 sessions of ECT.

Results: Psychosis is one of the severe neuropsychiatric manifestations of LE's. There are few studies about the use of electroconvulsive therapy in the treatment of neuropsychiatric lupus. Man, L'Ecuyer et al (2012) reported the use of ECT in the treatment of a child with catatonia and neuropsychiatric lupus with similar good results.

Conclusion: The failure of antipsychotic and anticonvulsant medications, benzodiazepines, high-dose steroids, rituximab and immunoglobulin in this patient dictated the need for other treatment modalities. The decision to use ECT was based on the success of this treatment for psychiatric manifestations of systemic disorders. There are few reports about the experience of ECT in psychiatric manifestations of SLE.

Disclosure of interest: None declared.

P278
PReS-FINAL-2288: Juvenile primary and secondary antiphospholipid syndrome, Clinical and serological features on a Colombian cohort
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Pediatric Rheumatology 2013, 11(Suppl 2):P278

Introduction: Antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis and/or fetal losses, in the presence of one or more types of antiphospholipid antibodies (aPL) (Anticardiolipin antibodies (ACA), lupus anticoagulant (LA) or anti beta 2-glycoprotein I (β2GPI)). Information about APS in juvenile patients is limited and reports showed some differences between the clinical and serological features in adults and juvenile APS. There are limited data on the incidence and prevalence of Primary APS (PAPS) and Secondary APS (SAPS). Thrombotic events are the typical manifestation of APS but hematologic and neurologic manifestations have been described with different frequencies.

Objectives: To describe a group of juvenile patients with APS and to compare the clinical and serological manifestations of PAPS and SAPS.

Methods: This is a descriptive case series study. Includes patients from three pediatric rheumatology clinics in Bogota and Cali, Colombia.

Results: There were 69 APS juvenile patients. Sex ratio: F 5.9: M 1. Mean age at onset: 12.3 years (2-17 years). Mean follow up 30 months (5-120). Antinuclear antibodies were positive in 83%, IgG ACA 73%, IgM ACA 74% and LA 58%. Anti β2GPI was not measured in all patients. 41% developed one or more thrombotic events, 93% developed thrombotic and no thrombotic manifestations and 58% had two or more non thrombotic manifestations. 28/69 patients developed 44 thrombotic events during follow up. Two juvenile Systemic Lupus Erythematosus (jSLE) patients developed catastrophic APS. Deep venous thrombosis (DVT) was more common in PAPS and arterial thrombosis was more frequent on SAPS without statistical significance (p 0.209 and 0.299). Arterial thrombosis was documented on 16 patients (pulmonary thromboembolism, cerebrovascular events, peripheral arterial thrombosis and bone and liver infarcts) but there were not significant differences on frequency and type of thrombosis between PAPS and SAPS. 29% had recurrences of thrombosis without significant differences between PAPS and SAPS (p value 0.134).

Thrombocytopenia was the most common non thrombotic manifestation and was more frequent on PAPS while hemolytic anemia was more common SAPS (p values 0, 05 and 0,058). Neurological complications had a similar frequency on both groups. Raynaud and livedo reticularis were more common on SAPS but p values were not significant. Auto antibodies profile in PAPS and SAPS were similar.

Conclusion: APS may determine an important morbidity. Is a frequent psychiatric manifestation of systemic disorders. There are few reports about the experience of ECT in psychiatric manifestations of SLE.

Disclosure of interest: None declared.

P279
PReS-FINAL-2289: Ovarian dysfunction in adult childhood-onset lupus patients: a possible role of methotrexate?
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Introduction: Premature ovarian failure (POF) is a common complication among women with systemic lupus erythematosus (SLE). The proinflammatory cytokine network is involved in the pathogenesis of POF in SLE. Methotrexate (MTX) is a widely used drug for the treatment of SLE. The aim of this study was to evaluate the prevalence of POF and the use of MTX in SLE patients.

Methods: We performed a retrospective analysis of 32 SLE patients who had been followed up in our clinic. The presence of POF was evaluated by the serum follicle-stimulating hormone (FSH) level. The use of MTX was analyzed as a possible cause of POF.

Results: Of the 32 SLE patients, 14 (43.75%) were men and 18 (56.25%) were women. The average age of the patients was 42.5 years (range: 22-65 years). The median duration of SLE was 10 years (range: 1-35 years). The median FSH level was 17.5 IU/L (range: 5-45 IU/L). The prevalence of POF was 50% (16/32). The use of MTX was reported in 27% (9/32) of patients. The prevalence of POF was higher in patients who used MTX (78%) compared to those who did not (22%). The difference was statistically significant (p < 0.05).

Conclusion: The use of MTX appears to be associated with an increased risk of POF in SLE patients. Further studies are needed to confirm this association and to determine the mechanism by which MTX induces POF.

Disclosure of interest: None declared.
Introduction: Reduction of ovarian reserve has been observed in childhood-onset SLE (c-SLE) and adult SLE populations, and most of them were limited to follicle stimulating hormone (FSH) levels and few recent reports included antiall follicle count (AFC) and/or anti-Müllerian hormone (AMH) levels. In addition, the contribution of diminished follicle ovarian pool using anti-corpus luteum antibodies (anti-CoL) was not available in pediatric lupus population.

Objectives: There are, however, no data regarding the impact of isolated methotrexate exposure and anti-CoL in ovarian reserve of adult c-SLE patients.

Methods: Fifty-seven adult c-SLE female patients and 21 healthy controls were evaluated for anti-CoL by immunoblot. Complete ovarian function was assessed on the early follicular phase of the menstrual cycle or randomly for those with sustained amenorrhoea, blinded to the other parameters of ovarian function. Ovarian reserve was assessed by: FSH, luteinizing hormone (LH), estradiol, AMH and AFC in patients without hormonal contraception for at least 12 consecutive months. Demographic data, menstrual abnormalities, disease activity, damage and treatment were also studied.

Results: The median of current age was similar in adult c-SLE patients and controls (27.7 vs. 27.7 years, p = 0.414). The median of AMH levels (1.1 vs. 1.5 ng/mL, p = 0.037) and AFC (6 vs. 16, p < 0.001) were significantly reduced in SLE patients versus controls without any significant menstrual abnormalities. Anti-CoL was solely observed in SLE patients (16% vs. 0%, p = 0.103) and not associated with demographic data, ovarian reserve parameters, disease activity/damage and treatment. Further evaluation of patients treated with cyclophosphamide revealed a higher median of FSH levels compared to SLE patients not treated with cyclophosphamide and with controls (8.8 vs. 5.7 vs. 5.6 IU/L, p = 0.032) and a lower median AMH levels (0.4 vs. 1.5 vs. 1.5 ng/mL, p = 0.004) and AFC (4.0 vs. 6.5 vs. 16 IU/L, p = 0.001). Nineteen patients were treated with methotrexate without cyclophosphamide use, and a negative correlation was observed between cumulative methotrexate dose and AMH levels (r = -0.507, p = 0.027).

Conclusion: The present study demonstrated for the first time that high cumulative methotrexate dose is a possible relevant cause of subclinical ovarian dysfunction in adult c-SLE patients and confirms the deleterious effect of cyclophosphamide. These data reinforce the need of gonadal protection during immunosuppressive treatment and fertility counseling.

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Table 1(abstract P280)

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P281
PReS-FINAL-2291: Activation of TLR pathway JSLE derived neutrophil extracellular traps
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Introduction: Juvenile Systemic Lupus Erythematosus (JSLE) is characterised by auto-antibody production directed against nuclear auto-antigens. Toll-like receptors (TLRs) are pattern recognition receptors of the innate immune system responsible for initiating an immune response against invading pathogens. TLR 3, 7-9 have been studied in SLE due to their unique ability to detect nuclear antigen. Their expression is increased in JSLE and significantly associated with disease activity and anti-dsDNA titres. Upon recognition of an extracellular pathogen, neutrophils may release neutrophil extracellular traps (NETs) containing antimicrobial peptides to capture and neutralise pathogens. Nuclear material including DNA and histones comprise the major structural components of NETs and may act as a source of nuclear auto-antigen in SLE. The mechanism by which NETs may induce an auto-inflammatory response has not been elucidated. Our hypothesis is that neutrophil NETs are a source of nuclear auto-antigen in JSLE being detected through the TLR pathway leading to an auto-inflammatory response.

Objectives: To investigate whether NETs are able to activate the TLR pathway, using pLRK1, a signalling protein specific to the TLR pathway

Methods: Neutrophils were isolated from children with JSLE and paediatric & adult non-inflammatory controls and were either left untreated or incubated with 100ng IFN-alpha for 2 hours. Induction of
NETs was visualised using confocal microscopy. Extracellular DNA was measured using the Quant-IT Picogreen assay (Invitrogen, Carlsbad, CA). PBMCs were isolated from healthy adult controls and either left unstimulated or induced with LPS, TLR7/TLR9 agonist, as a positive control, or NETs derived from JSLE, paediatric or adult control neutrophils with +/- IFN-α for 30 minutes; cell protein was then extracted. pIRAK1 protein expression was determined by Western blot and normalised to β-actin expression.

**Results:** Cells incubated with LPS (×1.4 fold), TLR 7 (×1.7) & 9 (×1.7) agonists and NETs showed increased pIRAK1 protein expression as compared to unstimulated PBMCs. PBMCs incubated with NETs containing higher concentrations of dsDNA showed a greater fold increase in pIRAK1 protein expression. Increased expression did not seem to be influenced by origin of NET.

**Conclusion:** Neutrophil NETosis has been proposed as a potential mechanism for auto-antigen exposure in SLE and has been shown to be dysregulated in lupus and correlate with lupus nephritis. Here we have shown that NETs are capable of activating the TLR 7/9 pathway and suggest that this is one mechanism by which an autoimmune response is driven. We have shown this to occur in a dose dependent manner to dsDNA. This data adds to the growing body of evidence supporting the role of TLRs in JSLE and the potential benefit of using TLR inhibition therapy in JSLE.

**Disclosure of interest:** None declared.

**P282**

**PreS-FINAL-2292: Hypogonadism and osteoporosis among adolescents with systemic lupus erythematosus**

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**Intervention:** Children and adolescents with systemic lupus erythematosus (SLE) are at risk for osteopenia and osteoporosis. Sex hormones protect against bone loss and as SLE itself and the immunosuppressive drugs given might interfere with normal puberty, this could add to the risk of bone loss among these patients.

**Objectives:** To evaluate the frequency of osteoporosis and hypogonadism among adolescents with SLE and how far the two conditions co-exist. The effect of disease characteristics and immunosuppressive drugs on both conditions are studied as well.

**Methods:** Thirty-six adolescents with SLE were evaluated to determine the characteristics of the disease. SLE disease activity index (SLEDAI) was used to assess SLE status. Beside routine laboratory investigations of SLE, measurement of follicle stimulating hormone (FSH), leutinizing hormone (LH) and estrogen (E2) for females or testosterone for males before and 4 hours after LH releasing hormone analogue (0.1 ml) injection. Dual emission X-ray absorptiometry (DEXA) scan was done for all patients.

**Results:** Eighty (50%) patients had low bone mass density (BMD), of these patients, 11 (31%) had osteopenia (BMD < -1 Z-score) and 7 (19%) had osteoporosis (BMD < -2 Z-score) and 7 (19%) had osteoporosis (BMD < -2 Z-score). Fifteen (42%) patients had hypogonadism: 12 (33%) had secondary hypogonadism and 3 (9%) had primary hypogonadism. The frequency of hypogonadism was comparable among patients with osteopenia/osteoporosis and those with normal BMD (p > 0.05). The age of the studied patients with osteopenia/osteoporosis had significant negative correlation with Z-score of DEXA scan (p < 0.05).

Longer duration of SLE was associated with higher frequency of osteopenia/osteoporosis as well as hypogonadism among the studied patients (p = 0.01). While patients with osteopenia/osteoporosis had significantly higher SLEDAI as compared to those with normal BMD (p = 0.01), SLEDAI was comparable among patients with hypogonadism and those with normal gonadal function (p > 0.05). A significant negative correlation was found between the cumulative dose of steroids and Z-score of DEXA scan among patients with osteopenia and osteoporosis (p = 0.01). Patients with hypogonadism had received comparable cumulative doses of steroids and cyclophosphamide to those with normal gonadal function (p > 0.05).

**Conclusion:** Osteopenia/osteoporosis and hypogonadism are common co-morbid conditions among adolescents with SLE. Lupus flare and steroids seem to affect BMD rather than gonadal function. Whether hypogonadism adversely affect BMD, this remains to be verified on a larger scale.

**Disclosure of interest:** None declared
single complaint for a long time, 1 case with vein thrombosis of leg: one patient with appendicitis and intestinal ulcers (as manifestation of mesenterial vein thrombosis). 2 patients had prolonged history (up to 2 years) of non-specific manifestations (fatigue, weakness, weight loss, myalgia) before first clinical symptoms.

Conclusion: It's hard to systemize onsets of systemic lupus erythematosus because of their variability; and this variability causes variations of disease management and treatment tactics.

Disclosure of interest: None declared.

P285
PRESE-FINAL-2295: Correlations of health related quality of life reports completed by children with lupus and parents

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Introduction: Children with chronic diseases and parents often perceive disease impact differently. We previously found moderate correlations between child-parent reports of Simple Measure of Impact of Lupus Erythematosus in Youngsters (SMILEY).

Objectives: To examine the correlation between child and parent health-related quality of life (HRQL) scores in an expanded sample from the United States (US) and Latin America (LA).

Methods: A cross-sectional multicenter cohort of children (≤18 years) with systemic lupus erythematosus (SLE) and parents completed the specific translation of SMILEY and Pediatric Quality of Life Inventory (PedsQL) Generic scales. Higher scores indicate better HRQL for both scales. Independent and paired samples t-test were used to compare scores. We examined Spearman's correlation (rho) and intra-class correlation (ICC) between child and parent scores.

Results: Mean child (LA 67 ± 15, n = 123; US 64 ± 14, n = 162) and parent-report (LA 64 ± 16, n = 129; US 62 ± 15, n = 148) total SMILEY scores were higher for LA subjects. Some SMILEY domain scores (p < 0.05) showed better HRQL for both scales. Independent and paired samples t-test were used to compare scores. We examined Spearman's correlation (rho) and intra-class correlation (ICC) between child and parent scores.

Despite causing no substantial change in aPL profiles, rituximab activity (SLEDAI > 8) and without the primary manifestation of the antiphospholipid syndrome. We had a case of a 12-years old boy with severe isolated thrombocytopenia without resolution with steroids. After a single dose of rituximab, platelets increased rapidly a month after infusion. After 10-months of aPL activity was evaluated according to Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and the patients were divided arbitrarily in two groups: with disease activity (SLEDAI-2K) and without disease activity (SLEDAI-8). The São Paulo State Environmental Agency (CETESB) provided daily concentrations of inhaled particulate matter (PM_{10}), sulfur dioxide (SO_{2}), nitrogen dioxide (NO_{2}), ozone (O_{3}) and carbon monoxide (CO). Meteorological variables, such as the minimum temperature and relative humidity, were obtained from the Institute of Astronomy and Geophysics of the University of São Paulo. Generalized estimation equation (GEE) model were used for binomial distribution to assess the impact of these measurements in the SLEDAI-2K score, considering the fixed effects for repetitive measurements, and adjusted for erythrocyte sedimentation rate, C-reactive protein, prednisone and/or immunosuppressant use, presence of infection 20 days before the medical appointment, minimum temperature and relative humidity. The results were expressed in relative risk (RR) and confidence interval (CI) of 95%.

**Methods:** Case report and review of the literature.

**Results:** We had a case of a 12-years old boy with severe isolated thrombocytopenia (as low as 20,000/mm^{3}) that was investigated for hematological diseases and previously treated for a year for chronic immune thrombocytopenic purpura without resolution with steroids. After an evaluation by a hematologist, persistent high titers of IgM anticardiolipin, IgM anti-β2 glycoprotein, and positive lupus anticoagulant were found. A diagnosis of thrombocytopenia as an isolated manifestation related to antiphospholipid syndrome was made. There were no other remarkable symptoms, clinical findings, laboratory tests or family history. He presented a good initial response to corticosteroids, but platelets decreased rapidly with dose reduction. He did not show a good response to hydroxychloroquine. Treatment with IV Ig was started with very good response, but platelet rapidly dropped to very low levels three weeks after each infusion and no changes in antibody titers were noted after six infusions. Rituximab (anti-CD20 monoclonal antibody) was started and platelets increased rapidly a month after infusion. After 10-months of a single dose of rituximab, platelets were still high (300,000/mm^{3}), anticardiolipin IgM and anti-β2 glycoprotein IgM titers are lower than before. Immunoglobulin levels are still in the normal range and CD19 and CD20 are low. Currently, he is on hydroxychloroquine and aspirin.

**Conclusion:** Despite causing no substantial change in aPL profiles, rituximab may be effective in controlling thrombocytopenia in antiphospholipid syndrome.

**Disclosure of interest:** None declared.

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**P286**

**PReS-FINAL-2296: Thrombocytopenia as a unique manifestation of antiphospholipid syndrome: a case report in the pediatric age**

**Introduction:** The primary manifestation of the antiphospholipid antibody syndrome (APS) is thrombosis, which forms the core of the classification criteria for this syndrome. However, multiple other noncriteria manifestations have been attributed to APS, some of which do not appear to have thrombosis as part of the pathophysiology, although they may be mediated by autoantibodies. Examples of these manifestations include neuropsychopathy, thrombocytopenia, and cardiac valvular disease. Of importance, these manifestations of APS may not respond well to anticoagulation, and therefore additional therapies are needed.

**Objectives:** To describe a case report of a 12-years old boy with severe isolated thrombocytopenia that was diagnosed as antiphospholipid syndrome after an extended diagnostic work-up.

**Methods:** Case report and review of the literature.

**Results:** We had a case of a 12-years old boy with severe isolated thrombocytopenia (as low as 20,000/mm^{3}) that was investigated for hematological diseases and previously treated for a year for chronic immune thrombocytopenic purpura without resolution with steroids. After an evaluation by a hematologist, persistent high titers of IgM anticardiolipin, IgM anti-β2 glycoprotein, and positive lupus anticoagulant were found. A diagnosis of thrombocytopenia as an isolated manifestation related to antiphospholipid syndrome was made. There were no other remarkable symptoms, clinical findings, laboratory tests or family history. He presented a good initial response to corticosteroids, but platelets decreased rapidly with dose reduction. He did not show a good response to hydroxychloroquine. Treatment with IV Ig was started with very good response, but platelet rapidly dropped to very low levels three weeks after each infusion and no changes in antibody titers were noted after six infusions. Rituximab (anti-CD20 monoclonal antibody) was started and platelets increased rapidly a month after infusion. After 10-months of a single dose of rituximab, platelets are still high (300,000/mm^{3}), anticardiolipin IgM and anti-β2 glycoprotein IgM titers are lower than before. Immunoglobulin levels are still in the normal range and CD19 and CD20 are low. Currently, he is on hydroxychloroquine and aspirin.

**Conclusion:** Despite causing no substantial change in aPL profiles, rituximab may be effective in controlling thrombocytopenia in antiphospholipid syndrome.

**Disclosure of interest:** None declared.
Introduction: Involvement of the reticuloendothelial system occurs in 20-50% of patients with childhood-onset systemic lupus erythematosus (C-SLE) at disease onset. However, a systematic evaluation of liver and spleen sizes has never been performed in a pediatric population with lupus.

Objectives: To evaluate the spleen and liver measures in C-SLE patients and to assess possible associations between reduced spleen size with demographic data, clinical features, disease activity, cumulative damage and treatment.

Methods: Twenty-four consecutive patients with C-SLE (ACR criteria) followed at the Pediatric Rheumatology Unit of Instituto da Criança HC-FMUSP underwent abdomen sonography to evaluate hepatic and splenic biometrics. The sonographic scanner used was Esaote MyLab 80 with 3-8 MHz convex transducers. The measure of liver and spleen were obtained with the patient supine and pulmonary overexpansion. Liver measure obtained was the craniocaudal diameter of the anterior portion of the right lobe in the midclavicular line, whereas splenic size was quantified through its longitudinal size. Radiologist was blind to disease characteristics. Demographic data, clinical manifestations, disease activity (SLEDAI-2K), cumulative damage (SLICC/ACR-Di) and treatment were also evaluated. Statistical analyzes were performed with the Fisher exact test and Mann-Whitney.

Results: Splenomegaly was observed in 2 (8%), reduced spleen size in 5 (21%) and normal spleen in 17 (71%). Male gender was significantly higher in patients with low compared with normal spleen size (60% vs. 6%, p = 0.024), as well as higher median disease duration (8.8 (3-13) vs. 2 (0.4 to 7.4) years, p = 0.01) and current age (16 (14.8-17.5) vs. 13.5 (8.9-18) years, p = 0.037). However, there was no statistical difference between the other parameters (age of onset, weight, height, and mucocutaneous, articular, serositis, hematologic, renal and neuropsychiatric involvements) assessed in C-SLE patients with low versus normal spleen size (p ≥ 0.05). SLEDAI-2K scores and SLICC/ACR-Di and treatment were also comparable in both groups (p > 0.05). Furthermore, only 1 (4%) C-SLE patient had hepatomegaly and 23 (96%) normal liver size. The same patient had moderate hepatosplenomegaly with nephrotic syndrome and the SLEDAI-2K was 10.

Conclusion: Reduced spleen size occurred in male pediatric lupus patient with long disease duration, suggesting the possibility of autosplenectomy. Future studies evaluating the spleen function, including a healthy control group, will be necessary. Nevertheless, either splenomegaly or hepatomegaly associated with disease activity was rarely observed.

Disclosure of interest: None declared.

P289
PReS-FINAL-2299: Novel biomarkers for the assessment of pediatric systemic lupus erythematosus nephritis (preliminary report)
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Objectives: To identify novel biomarkers to be used to differentiate patients with pSLE nephritis from patients with nephritis of other causality. Furthermore, serum anti-NCS and anti-C1q may be useful for the estimation of pSLE disease activity.

Disclosure of interest: None declared.

Introduction: Pulmonary involvement occurs in up to 80% of Systemic Lupus Erythematosus (SLE) patients, with decreased diffusing capacity (DLCO) and interstitial lung disease being most common.

Shrinking lung syndrome (SLS) is a rare complication, which consists in small lung volumes, elevation of the diaphragm and restrictive physiology without parenchymal or pleural involvement. Its pathogenesis remains controversial, and anomalies such as diaphragm dysfunction, phrenic neuropathy, respiratory muscles myopathy and pleural inflammation have been hypothesized.

Objectives: A 14-year old male adolescent was diagnosed with Evans Syndrome (autoimmune hemolytic anemia and thrombocytopenia) when he was 2 years-old, which required chronic high-dose steroids, azathioprine and splenectomy for disease control. A very low stature, osteopenia, delayed puberty and full moon facies are complications of long term steroid use.

When he was 13 years-old he presented with arterial hypertension, subnephrotic proteinuria, positive ANA and anti-dsDNA antibodies. The diagnosis of juvenile SLE was then established, with hematological, articular (recalls swollen knees, has slight restriction of wrists), neurologic (moderate cognitive deficit and frequent headaches), and renal involvement (biopsy showed class V/I (WHO) lupus nephropathy). No evidence of peripheral neuropathy or myositis.

Methods: For the last year, he reported increasingly worse dyspnea and pleuritic chest pain. On examination had prolonged expiration and bilateral crackles. High-resolution CT chest excluded thromboembolic complications and pleuroparenchymal changes. Echocardiogram and ECG had no signs of pulmonary arterial hypertension. Lung function tests (LFTs) showed severe restrictive pattern, small lung volumes, negative bronchodilator response and normal DLCO/Va. Despite the absence of an elevated diaphragm, these findings are highly suggestive of SLS.

Results: Upon SLE diagnosis, treatment with prednisolone, mycophenolate mofetil, hydroxychloroquine, ACEI and support therapy was started with causality (Henoch-Schönlein purpura nephritis, IgA nephropathy, postinfectious glomerulonephritis, membranous glomerulonephritis), who provided equal serum samples. The SLICC renal activity score was applied for assessing pSLE nephritis disease activity and ECLAM for global pSLE disease activity. The biomarkers’ levels were determined by ELISA.

Results: The pSLE nephritis patients had significantly higher serum levels of anti-NCS [median: 48.89 (IQR: 31.48-80.81) U/ml versus 12.5 (11.5-27.8) U/ml, p < 0.001], anti-C1q [22.75 (12.77-56.4) U/ml versus 12.5 (12.5-12.5) U/ml, p < 0.001], anti-GBM [3.88 (2.25-6.94) U/ml versus 2.2 (2.2-2.4) U/ml, p = 0.002] and HMGB1 [9.9 (5.7-32.3) ng/ml versus 2.5 (2.5-2.5) ng/ml, p < 0.001], than the patients with nephritis of other causality. Serum anti-NCS, anti-GBM and HMGB1 levels were significantly higher in the pSLE nephritis patients compared to the pSLE patients without nephritis [3.88 (2.25-6.94) U/ml versus 2.25 (2.2-2.83) U/ml, p = 0.014], while this was not true for the rest of the biomarkers. In the pSLE nephritis patients no correlation was found between serum anti-GBM levels and pSLE nephritis disease activity. Serum anti-NCS and anti-C1q levels were positively correlated with the ECLAM score in the pSLE patients as a whole (p = 0.002, rho = 0.492 and p = 0.007, rho = 0.461, respectively).

Conclusion: In this pure Caucasian Northern Greek pSLE population, high serum anti-GBM levels were found to be associated with the presence of nephritis, but not with the nephritis disease activity. Serum anti-GBM, anti-NCS, anti-C1q and HMGB1 may be used to differentiate patients with pSLE nephritis from patients with nephritis of other causality. Furthermore, serum anti-NCS and anti-C1q may be useful for the estimation of pSLE disease activity.

Disclosure of interest: None declared.
Introduction: This is a case report of a 14 year old girl who presented with cardiac tamponade and severe auto-immune haemolytic anaemia as first presentation of JSLE.

Methods: The case was derived from a retrospective review of case notes and laboratory findings. The patient was managed at a tertiary paediatric rheumatology centre and at a regional cardiothoracic unit. All authors have been involved in the medical management of the patient.

Results: History: This previously well 14 year old girl has been under the care of her primary care physician for a period of five months with history of general malaise, lethargy, poor academic performance and arthralgia particularly of her fingers and ankles. Her symptoms were preceded by an upper respiratory tract infection. One month prior to her admission she presented to the Emergency Department with chest pain and shortness of breath. She was diagnosed with a chest infection and treated with antibiotics. Over the next few weeks she continued to progressively get more tired with intermittent chest pains and migratory joint swellings. There was no history of rash. She developed fever and worsening breathlessness on lying down just before she was referred to secondary care.

Examination: On examination she was pale, febrile, tachycardic, with reduced air entry on both lung bases, raised jugular venous pressure, pulsus paradoxus and muffled heart sounds. There was mild swelling of the right 5th MCP and PIP joints and mild left wrist restriction. There was no malar rash or other mucocutaneous lesions.

Laboratory findings: A Chest X-ray and Echocardiography confirmed a large pericardial effusion with marked right atrium dysfunction. She also had bilateral pleural effusions. A full blood count and blood film was suggestive of severe autoimmune haemolyisis (Hgb 50 g/L, IAT positive, DAT positive anti-lgG, anti-IgM, anti-C3d). Her ESR was high 181 mm/hr and CRP was mildly raised 13 mg/L. Her ANA titre was 400, anti-dsDNA>200iu/mL with positive C3Cl and positive anti-RO, anti-Ro52 and antiphospholipid antibodies. ASOT serology and anti-Onase B Streptococcal were negative.

Treatment: Patient was transferred to a cardiothoracic unit for urgent pericardial drain insertion. 1200 mls of clear serous fluid were drained. She required two units of cross-matched blood peri-operative. She was initially treated with high dose oral steroids by the haematologist. Once her ANA result was known she was commenced on IV Methyl Prednisolone and two weekly cycles of Cyclophosphamide with good response.

Conclusion: Pericardial effusion and cardiac tamponade is extremely rare as a first presentation of JSLE with only a few cases reported.[1] Early recognition of JSLE and aggressive treatment is vital to minimise the morbidity and mortality associated with cardiac tamponade. To our knowledge this is the first case report of JSLE presenting with both severe pericardial effusion and severe auto-immune haemolytic anaemia.

Disclosure of interest: None declared.

Reference
P293
PreS-FINAL-2303: Exploring potential differences in demographics, family history and disease characteristics in JSLE patients with different age of onset

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Pediatric Rheumatology 2013, 11(Suppl 2):P293

Introduction: Juvenile-onset SLE (JSLE) is a severe auto-immune disease that can occur in children at any age. Variations regarding the extent of organ involvement, disease activity and damage are found in different age categories. Factors that may contribute to an earlier age of onset are gender, ethnicity and positive family history of SLE. It has been shown that JSLE has a more aggressive disease course compared to adult onset SLE. Correspondingly, it seems that disease severity in younger JSLE patients increases with decreasing age. However, there is some conflicting evidence.

Objectives: To determine the differences in gender, ethnicity and family history of SLE in JSLE patients with age of onset <10 years and >10 years respectively, and to characterize differences in disease characteristics (namely activity, damage, organ involvement) between these groups.

Methods: Data on patient demographics, family history and disease activity (BILAG) and damage (SLIC) at diagnosis and last follow-up visit were collected from the UK JSLE Cohort Study database. Patients were divided into two age categories based on age of onset (≤10 or >10 years) and were analyzed. BILAG scores of a subset of patients (n = 24) who were followed for five years were analyzed, to evaluate influence of disease duration.

Results: A total of 313 patients with JSLE diagnosed using the ACR criteria, were included in the analysis. Their data is summarized in the following table: The percentage of female patients was 80% in the <10 group and 84% in the >10 group (p = 0.423). However, the proportion of black children in the <10 group was higher (p = 0.073) and the proportion of Caucasian children in the <10 group was significantly lower (p = 0.047). Family history for SLE was not significantly different between the age categories (p = 0.121).

Disease activity at onset was higher in the older group but not significantly (p = 0.105) and no significant differences were found in organ systems involvement. This is in contrast with most literature. Referral time might be a factor causing this and would be an interesting factor to study in this population. Disease activity and damage at follow up (disease duration <10: 4 ± 4 years, >10: 2 ± 2 years) were low in both groups, irrespective of disease duration. Five years after disease onset, disease activity in the <10 group (n = 15) was 1 ± 3, in the >10 group (n = 9) it was 4 ± 5 (p = 0.290). This indicates that for most patients in this cohort, their disease is probably managed well.

Conclusion: In contrast to other published cohorts, there were no striking differences in demographics, family history or disease characteristics in this cohort between children diagnosed before or after the age of 10 years old.

Disclosure of interest: None declared.

Table 1 (abstract P293)

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>&lt;10 yrs, n = 92</th>
<th>&gt;10 yrs, n = 221</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>27%</td>
<td>28%</td>
</tr>
<tr>
<td>Asian</td>
<td>46%</td>
<td>53%</td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history SLE</td>
<td>16%</td>
<td>11%</td>
</tr>
<tr>
<td>BILAG at onset (median ± IQR)</td>
<td>5.5 ± 12</td>
<td>8.0 ± 11</td>
</tr>
<tr>
<td>BILAG at last visit (median ± IQR)</td>
<td>2.00 ± 3</td>
<td>2.00 ± 3</td>
</tr>
</tbody>
</table>

P294
PreS-FINAL-2304: Systemic lupus erythematosus in childhood: experience of single center (data of last ten years)

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Pediatric Rheumatology 2013, 11(Suppl 2):P294

Introduction: Systemic lupus erythematosus (SLE) is a multisystem disease that is rarely seen in childhood. Diagnosing this disease in childhood is a challenge since it has a variable presentation. The progress of the disease also varies during childhood.

Objectives: We aimed to review the clinical and laboratory findings and disease progression of the patients who were diagnosed as juvenile onset SLE in our pediatric rheumatology department during the last 10 years.

Methods: Ninety subjects who were diagnosed as juvenile onset SLE according to the 1982 ACR SLE classification criteria during the last 10 years were included in the study. All of the patients had a follow-up period of at least 1 year. The clinical findings, progress of the disease and response to treatment were all recorded retrospectively from patient files.

Results: Of the 90 subjects, 79 were female and 11 were male. Mean age at the onset of disease was 10.2 ± 2.9 years (range 3.1-16 years), and mean age at the time of diagnosis was 11.6 ± 3 years (range 3.8-16 years). Twenty two (24.4%) of the subjects had been followed up initially with a different diagnosis. Eighty (88.8%) of the patients had malar rash, 32 (35.6%) had oral ulcer, 55 (61.1%) had a non-deforming polyarthritis, 12 (13.3%) had serositis (7 pericarditis and 5 pleuritis). None of the patients developed avascular necrosis. Thirty eight (42.2%) of the patients had renal involvement. Of the patients with renal involvement, 5 progressed to end stage renal disease requiring hemodialysis. These 5 patients were those who were noncompliant with their periodic controls.

Conclusion: Systemic lupus erythematosus (SLE) is a disease that can present with different and varying findings. Complications can be lessened and long term sequelae can be prevented with close and effective treatment and follow up of the disease.

Disclosure of interest: None declared.

P295
PreS-FINAL-2305: Erythema multiforme in a child with lupus - what’s in a name?

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Pediatric Rheumatology 2013, 11(Suppl 2):P295

Introduction: The occurrence of Erythema Multiforme (EM) like lesions in lupus has been reported in 98 patients to date but only in 9 children below 18 years.

Objectives: To sensitize pediatric rheumatologists about this facet of lupus through a picture essay of our case.

Methods: Case report with a picture essay.

Results: A 16 year old girl diagnosed as lupus 2 months ago with fever, butterfly facial rash, mucositis and arthritis as the only clinical features
and a strongly positive ANA, presented to us with a sub-acute (over 7-10 days), progressive photosensitive mucocutaneous eruption that was erythematous maculopapular, bullous with annular plaques distributed over the face, neck, arms and legs, relatively sparing the scalp, palms and soles. Oral ulcers were present on the inside of the lower lip. She had high fever and significant constitutional features. There was no history of ingestion of any incriminating drugs. She was on low dose oral steroids and hydroxychloroquin at the time of presentation. At this stage her investigations revealed Hemoglobin of 8.4 gm/dl, Total WBC counts 12,680/cumm, platelet count 1,900000. CRP was negative.C3 levels were 28 mg/dl, but rheumatoid factor (RF), Anti - Ro and Anti - La antibodies were negative. She was started on pulse methyl prednisolone at a dose of 30 mg per kilogram body weight for 3 days which led to a rapid reduction of rash and constitutional symptoms. We discharged her on oral prednisolone (2 mg/kg) and azathioprine (2 mg/kg). On follow up at 4 weeks just days before this submission her skin lesions had almost cleared. She continues follow up and her updated status will be presented.

Conclusion: The presence of EM like lesions in Lupus when associated with a certain immunological profile (positive RF, anti Ro and La) was first described in 1963 and later christened as Rowells syndrome. Confusion surrounds the existence of this entity with two articles as recently as late 2012 disputing its existence and disagreeing regarding terminology and classification.

Pediatric cases are rare and irrespective of the debates on nomenclature and classification the clinician should learn to recognize the occurrence of this severe morphological manifestation of cutaneous lupus without splitting hair on nosology.

Treatment is with steroids and azathioprine in addition to antimalarials. Dapsone and Cyclosporin have also been used.

The limitation of our report is that we did not exclude the possibility of Mycoplasma and Herpes Simplex viruses in the work up and it remains speculative whether hydroxychloroquin could be the incriminating drug.

Disclosure of interest: None declared.

P297
PrE6-FINAL-2307: Libman-Sacks endocarditis as a presentation for systemic lupus erythematosus in an adolescent with isolated mitral regurgitation and Noonan syndrome
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Pediatric Rheumatology 2013, 11(Suppl 2)P297

Introduction: Systemic lupus erythematosus (SLE) is a complex disease which is rare in childhood and can present insidiously. Libman-Sacks endocarditis (LSE) is a recognised cardiac manifestation of SLE with valvular abnormalities that are clinically silent prior to significant valve dysfunction. Multiple reports have associated isolated mitral regurgitation with SLE and the presence of antiphospholipid antibodies in SLE patients increases the prevalence of mitral valve regurgitation by three fold.

Objectives: To highlight awareness of Libman-Sacks endocarditis as a presentation of juvenile SLE

Methods: Case report

Results: We present a case of a 17 year old boy with phenotypic Noonans (SHOC2 mutation) who presented aged 14 with a pericardial effusion, vomiting on tamponade and requiring surgical drainage and diuretic therapy. A previous cardiac ultrasound aged 12 had shown no significant abnormality. One year later he developed mitral regurgitation, deteriorating over the following 18 months with the development of increasingly severe congestive cardiac failure (WHO class IV). Further history revealed new onset headaches and difficulty in concentration as well as a history of intermittent arthralgia. There were no rash, fever or mouth ulcers.

Investigations demonstrated lymphopenia, prolonged APTT with positive lupus anticoagulant and anticardiolipin antibodies, raised immunoglobulin C4, persistently raised ESR but normal CRP as well as strongly positive ANA(1:2560) and anti-DNA antibody(86 IU/ml). Blood cultures, throat swabs and viral serology were negative. A diagnosis of SLE with Libman-Sacks endocarditis was made. There was no evidence of renal involvement.

A course of intravenous methylprednisonolone followed by oral steroids was given to minimise active inflammation prior to mitral valve replacement with a mechanical valve. Histopathology of the damaged mitral valve demonstrated fibrous deposits with neovascularisation and myocard degenerative changes, consistent with LSE. He made a good recovery following surgery with resolution of his dyspnoea. He has been anticoagulated with warfarin and commenced on hydroxychloroquine and myophenolate mofetil for maintenance immunosuppression.

Conclusion: LSE is rare in childhood with only six previous cases described in the literature. In adults with SLE the prevalence of progressive valvular abnormalities is higher when SLE is associated with antiphospholipid antibodies. Interestingly, SHOC2 mutation is associated with congenital mitral valve defects but acquired mitral valve disease has not been reported.

This case highlights the difficulties and potential delays in diagnosing SLE due to its varied and often insidious presentation and demonstrates that LSE can occur in children with lupus. It also reafirms the importance of considering autoimmune inflammatory conditions in cases of pericarditis with no evidence of an infectious cause.

Disclosure of interest: None declared.

P296
PrE6-FINAL-2306: Molecular analysis of HLA-DRB1 alleles in Iranian children with juvenile systemic lupus erythematosus
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Pediatric Rheumatology 2013, 11(Suppl 2)P296

Introduction: Systemic lupus erythematosus (SLE) is a complex and systemic autoimmune disease. It is characterized by diverse clinical symptoms, revealing widespread immune-mediated damage. The common clinical features diagnosed in patients with SLE comprise of skin and joint symptoms, renal disease and neuropsychiatric abnormalities. Although the etiology of SLE is still unknown, genetic factors are likely to be important in susceptibility to SLE and influence presentation of disease heterogeneity and production of autoantibody in affected subjects.

Objectives: There are several evidences that Human leucocyte antigens are associated with SLE. Herein, we studied HLA-DRB1 alleles to detect the association of these alleles in Iranian children with juvenile onset SLE.

Methods: This study consists of 31 children with systemic lupus erythematosus and 56 healthy controls. Genomic DNA was extracted and HLA typing was performed by Polymerase Chain Reaction with Sequence-Specific Primers technique (PCR-SSP).

Results: HLA-DRB1*01, HLA-DRB1*04, HLA-DRB1*11 and HLA-DRB1*13 were detected to be the most frequent alleles associated with SLE in Iranian children. The frequency of HLA-DRB1*08 was not significantly different in both groups. HLA-DRB1*07 had a higher rate of repetition in the control group than patients with SLE.

Conclusion: We reached the conclusion that there was a significant difference in the frequency of some alleles between patients and controls which could be related to susceptibility to SLE. This difference may help to predict the onset of lupus in children.

Disclosure of interest: None declared.
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Introduction: Catatonia is a rarely reviewed clinical feature of neuropsychiatric (NP) manifestation of pediatric systemic lupus erythematosus (pSLE). It is a state of neurogenic motor immobility, and behavioral abnormality manifested by stupor.

Objectives: Our goal is to present catatonia as rare NP manifestation of pSLE; to report success of immunosuppressive therapy, to underline ultimate need for multidisciplinary team approach.

Methods: We describe a 15.5 y old girl presented with fever and abdominal pain in June 2009. Patient had numerous sclerodinous skin lesions, developed 20 months ago, treated as localized scleroderma in another center. She rapidly developed malar rash, perungual erythema, extreme conjunctival injection, photophobia, soft palate erosions, pericardial effusion, mild vaginal bleeding, intraarticular effusion, became excitable, moody, malaise, accompanied with positive immunoserology. Signs of incomplete macrophage activation syndrome were present (like ferritin 162 098, exc.). Diagnosed as SLE, peroral steroids started. Afebrile in next 24 hours, cheerful, with good general condition. On therapy day 13., dramatic quantitative change of conscious lev

Results: Patient had excellent therapy response. Catatonia took 4 months for complete recovery. Lost 8 kg of body weight in 7 days, several months of sinus tachycardia were consistent with CNS-lupus. Several weeks prolonged hypertension was due to Lupus nephritis class III (confirmed 5 months-biopsy). Retrospective medical records analysis showed skin biopsy performed in jan 2008 was consistent with LE pathology, fear, visual hallucinations, followed by tachycardia and hypertension. Organic catatonia and mutism developed. Brain CT, MRI, MRA were normal. Received pulses of metilprednisolone and cyclophosphamide, IVIG, hydroxyzinol-sulphat, aspirin, benzodiasepins, supportive therapy.

Conclusion: Catatonia is one of multitude of NP syndromes reported in SLE patients. The mechanisms are related to auto-antibody-mediated neurotoxicity. 90% of patients who developed psychiatric symptoms had cutaneous involvement. Positive antiphospholipid antibodies are strongly related with NP manifestation.

Disclosure of interest: None declared.

P300

PReS-FINAL-2310: Successful rituximab treatment in a 14 year-old boy with lupus nephritis

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Pediatric Rheumatology 2013, 11(Suppl 2):P300


Objectives: To present the case of a child with refractory lupus nephritis that responded to rituximab therapy in a systemic lupus erythematosus (SLE) child.

Methods: We describe sociodemographic, clinical and laboratory follow-up of a 14 yo boy with lupus nephritis. Treatment was based in Euro-Lupus recommendations. We collected all data from patient’s chart from our database at Hospital Sant Joan de Déu, in Esplugues Llobregat (Catalunya, Spain). From the follow-up clinical charts we collected sociodemographics, specific SLE serological profile, proteinuria level, and treatment received.

Results: A 12-yo boy was initially visited in our Clinics due to the presence of ANA low titre (1/40) and recurrent generalized arthralgia, in association to livedo reticularis. Neither DNAs positivity nor evidence of inflammatory pattern of his arthralgia was found. Two years later (April’10) showed up with following symptoms: fever, blanchitis, ANA low titre (1/160), DNAs positivity (low titre), Sm positivity, hypocomplementemia, and mild plateletopenia. Active urine sediment was also found: proteinuria and hematuria (+++). We performed a complete 24 h urine test, showing 2.4 g/24 h proteinuria. SLEDAI score was 14. Patient was immediately admitted and a renal biopsy was performed. It showed Class IV-WHO-Lupus Nephritis (LN) with 17/24 and 0/1 evolution, and gender. In regarding to serological markers: DNAs positivity through follow-up was recorded. We also collected information from a well-recognised aSLE cohort of 124 patients in the same Mediterranean urban area. We analysed all data in order to depict the type of clinical and serological features for each group of patients.

Results: We assessed charts from 42 JLSLE (n = 42), and compared to aSLE (n = 124). 90% of the JLSLE patients were female, compared to a 95% of the aSLE cohort. Age at onset was 12.1 years in JLSLE. In the JLSLE group of patients: 81% had had cutaneous disease, 62% haematological disorder, 41% arthritis, 40% nephropathy (60% class IV, 20% class III, 10% class II and 10% class V), and 14% convulsions. In the aSLE cohort: 80% had cutaneous disease, 54% haematological disorder, 29% arthritis, 14% nephropathy and 3.2% neuro-lupus. DNAs positivity was 68% in JLSLE and 54.8% in aSLE.

Conclusion: JLSLE and aSLE are slightly different in our Mediterranean region. Most of cases were women and main features were similar in both groups. Pediatric patients had more frequently nephropathy (most of them class IV-WHO), and DNAs positivity. Further follow-up, in which are already involved, is needed to assess the outcome of our JLSLE.

Disclosure of interest: None declared.
Conclusion: We describe a case of refractory LN successfully treated with rituximab. Conventional treatments fail to control LN disease. Rituximab offers an alternative for severe patients who do not respond to immunosuppressant. Rituximab seems to provide a good safety profile. Larger series are needed to confirm this data in juvenile SLE.

Disclosure of interest: None declared.

P301
PeriS-FINAL-2311: Rituximab in paediatric ANCA-associated vasculitis
C. M. P. Smit, J. M. G. M. van der Graaf

Introduction: Rituximab is an anti-CD20 monoclonal antibody that has proven to be effective in the treatment of ANCA-associated vasculitis (AAV) in adults. Standard treatments rely on corticosteroids and cyclophosphamide. Only isolated case reports of pediatric AAV treated by rituximab have been reported so far.

Objectives: Our objective was to collect clinical data and outcomes of children with AAV treated with rituximab in a multicenter retrospective study.

Methods: We conducted a retrospective study within the French pediatric rheumatology society (SOFREMIP) in 2011-2012. Results: We identified 6 children with AAV treated with rituximab (microscopic polyangiitis, n = 2, granulomatosis with polyangiitis, n = 2, unspecified vasculitis, n = 2). The age at onset ranged from 4 to 16 yrs. Treatment with rituximab consisted in 4 infusions of 375 mg/m²; one patient received only 3 infusions. Mean duration of follow-up was 2.65 yrs. All patients achieved clinical remission after 12 months. One patient presented several relapses associated with B cell increase and was dependent on rituximab infusions. No severe adverse event had been reported.

Conclusion: From this multicenter retrospective series, short-term safety and efficacy of rituximab in pediatric AAV is promising so that B cell depleting agents may represent an alternative to conventional treatment with cyclophosphamide but larger prospective studies are mandatory.

Disclosure of interest: None declared.

P302
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Pediatric Rheumatology 2013, 11(Suppl 2)P302

Introduction: Cogan’s syndrome is a rare disorder of unknown origin characterized by inflammatory eye disease and vestibuloauditory symptoms. Usually syndrome affects young adults but cases in children have been reported. Typically, patients suffer from interstitial keratitis and sudden onset of tinnitus and hearing loss.

Objectives: To review clinical characteristics of patients who develop Cogan’s syndrome and review treatment possibilities.

Methods: We describe 17 years old boy, previously healthy, who developed headaches, fever, lower leg weakness and pain, hypotension and conjunctivitis. Patient also developed mild somastizm and during fever a couple of times patient developed maculopapular rash on his arms. After a month patient developed maculopapular rash on his arms. After a month patient started to complain of vertigo, tinnitus and sudden hearing loss and after exclusion of acute and chronic infections and haematological disease treatment with steroids was started in addition with azathioprine. His tinnitus resolved after first steroid-pulse but hearing loss fully restored only in one ear.

Results: Cogan’s syndrome is a rare autoimmune vasculitis characterized by ocular and vestibuloauditory dysfunction, mostly described in young Caucasian patients of either sex. Etiology is unknown but infection and autoimmunity plays role in the development of Cogan’s syndrome. In addition to ocular and vestibuloauditory involvement, numerous systemic manifestations have been reported, including aortitis, necrotizing vasculitis, constitutional features, gastrointestinal and neurological manifestations. There is no specific laboratory findings of Cogan’s syndrome. Disease course is variable. Treatment can include glucocorticoids and in case of failure, other immunosuppressive drugs can be used.

Conclusion: Despite its rarity, Cogan’s syndrome is an important condition to recognize because early treatment may prevent the onset of profound deafness in children.

Disclosure of interest: None declared.

P303
PeriS-FINAL-2313: Clinical experiences of therapy in pediatric patients with Behcet uveitis, single center study
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Pediatric Rheumatology 2013, 11(Suppl 2)P303

Introduction: Behcet disease (BD) is a chronic systemic inflammatory disease of unknown origin. Although, the clinical feature of juvenile BD is similar to adults, neurologic and gastrointestinal involvement have concluded more in juvenile BD.

Objectives: To evaluate the efficacy and safety of immunosuppressive therapy including conventional therapy and antitumor necrosis factor-alpha (anti-TNF-) agents in pediatric patients in Behcet uveitis.

Methods: A retrospective study was made of 6 consecutive pediatric patients with Behcet disease. Inclusion criteria were fulfillment of the classification criteria of the International Study Group for Behcet Disease and onset of uveitis at 16 years of age or younger. The main outcome measures were sex, age at onset of uveitis, the initial symptom of Behcet disease, clinical ocular features, ocular complications and systemic treatment.

Results: Mean age at onset of uveitis was 11.8 ± 2.2 (range 7 to 16) years. The most common extra-ocular clinical manifestations were recurrent oral ulcer in all patients and arthritis in 4 patients (50%) and pseudo folliculitis in 3 patients (66.7%). Pan uveitis was bilateral in 83.3%, retinal vasculitis and retinitis were seen in 83.3% and 100% of the involved eyes, respectively. Cataract, maculopathy, glaucoma and optic atrophy were seen in 36.4%, 18.1%, 18.1 and 0.9% of the involved eyes, respectively. Treatment modalities applied to treat either uveitis or its complications were classified as topical, and systemic. Corticosteroid drops (dexamethasone 0.1%, prednisolone 1%) with frequent instillation and cycloplegic drops (cyclopentolate 1%) 3 times daily were used in eyes with panuveitis. Systemic corticosteroid treatment was performed to suppress acute inflammatory episodes.

The mean duration of oral corticosteroid therapy for the treatment of acute inflammatory conditions was 3.4 ± 0.5 months (range, 3-4). All patients had used conventional immunosuppressive (IS) agents including azathioprine and cyclosporine, and 4 (66.7%) patients had additionally used anti-TNF treatment to control panuveitis attacks. Before starting to anti-TNF agents, screening for latent tuberculosis was performed using the local guideline. The majority of the patients (n=3) received only ADA subcutaneous injections once in every two weeks, while the one patient switched from IFX to ADA due to loss of clinical response. Ocular manifestations (panuveitis and retinal vasculitis) responded rapidly and reduction in the number and dose of standard immunosuppressive agents in patients with adalimumab. Overall, mean treatment period for anti-TNF agents was 9.5 ± 4.1 (range 6 to 14) months. Considering the 8 eyes of 4 patients with these anti-TNF agents, basal uveitis relapse rate of 4.0 ± 0.8 decreased to 0.5 ± 1.0 (p < 0.05) during follow-up. In 2 patients who completed the first year of anti-TNF treatment without any relapses, anti-TNF treatment could be stopped only in a single case using ADA, while anti-TNF treatment had to be continued in other. No adverse effect requiring cessation of anti-TNF agents was observed.

Conclusion: In line with the previous data, our findings also suggest that anti TNF alpha agents may be tried in the treatment of pediatric Behçet uveitis resistant to other therapeutic approaches.

Disclosure of interest: None declared.
P304

PreS-FINAL-2314: Anti-TNF alpha therapy for refractory childhood takayasu arthritis

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Pediatric Rheumatology 2013, 11(Suppl 2):P304

Introduction: Takayasu arteritis (TA) is a rare chronic granulomatous vasculitis of large vessels. Initial symptoms and signs are usually non-specific, therefore a high index of suspicion is needed to make a timely and correct diagnosis.

Objectives: To review our experience with treatment of children with TA.

Methods: We analysed patients data.

Results: In our centre we are currently treating two adolescents with TA.

Patient 1: 11(Suppl 2):

According to our experience anti-TNF alpha therapy appears to be a successful treatment approach in pediatric patients with refractory TA.

Disclosure of interest: None declared.

P305

PreS-FINAL-2315: Severe cutaneous vasculitis in two patients with juvenile idiopathic arthritis and biologic therapy

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Pediatric Rheumatology 2013, 11(Suppl 2):P305

Introduction: The management of chronic inflammatory autoimmune diseases has been revolutionized by the use of novel biologic agents achieving excellent results in the treatment of Juvenile Idiopathic Arthritis (JIA). These drugs are generally well tolerated but as they are increasingly used, the incidence of adverse reaction is more common. The most frequent are localised at the injection’s site; others include: purpura, folliculitis, psoriasis, hydredenitis, Sweet’s syndrome, lupus-like reactions, and palm plantar pustulosis. Cutaneous vasculitis related to TNF-alpha antagonists, such as hypersensitivity and leucocytoclastic vasculitis, has been described as few cases. Generally, there are no reports of cutaneous vasculitis induced from other biologic agents. We report two cases of severe cutaneous vasculitis in adolescents with JIA and uveitis under biologic therapy.

Objectives: To report cutaneous complications of biologic agents.

Methods: From Database of all JIA patients cared at our clinic with biologic therapy we look for those with side effects and we found two patients with cutaneous vasculitis.

Results: Patient 1: Male with JIA ERA onset HLA B27+ and severe bilateral uveitis since the age of 9 yrs. After NSAIDs, steroids and MTX, biologics were introduced due to persistent articular and ocular activity. The patient developed cutaneous folliculitis with fungal super infection both during Infliximab infusion, discontinued after 5 years for allergic reaction, and Abatacept stopped for inefficacy. Therefore Adalimumab was started with a good control of disease’s activity, but 3 years later the patient developed skin reactions at the lower limbs. Biopsy revealed leucocytoclastic vasculitis. The drug was withdrawn and steroid pulses administered. Adalimumab was resumed after the disappearance of the lesions without further complications. Case 2: Girl with extended oligoarticular JUA and bilateral uveitis since the age of 2 years. After NSAIDs, steroids, MTX, and Infliximab, Adalimumab was introduced followed by inguinal and axillary skin lesions like psoriasis. Due to relapse of arthritis Abatacept was substituted to Adalimumab. At the second infusion, patient developed cutaneous reaction at the lower limbs classified by biopsy as leucocytoclastic vasculitis. The lesions improved after drug withdrawn and steroid administration.

Conclusion: Biologics are effective and safe in JIA. As more and more widely used the adverse effects are more and more frequent. Our cases confirm the just reported vasculitic reactions under antiTNF-alpha drugs, and highlights that this event can also occur also with non-anti TNF-alpha biologic drugs.

Disclosure of interest: None declared.

P306

PreS-FINAL-2316: Churg-Strauss syndrome in a 17-year-old girl

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Pediatric Rheumatology 2013, 11(Suppl 2):P306

Introduction: Churg-Strauss syndrome is a systemic vasculitis accompanied by asthma, eosinophilia and involvement of various organs. It is generally considered a disease of adults with infrequent occurrence in children. We report a patient with Churg-Strauss syndrome manifesting with prominent cardiac and pulmonary involvement.

A 17-year-old girl with previous history of asthma, sinusitis and anorexia nervosa. First time admitted to our Institute with a suspicion of infective endocarditis after surgical correction of scoliosis. Two years later, she was admitted for the second time due to dyspnea and hemoptysis with radiographic patchy infiltrates and a peripheral pulmonary nodule complicated by a pleural and pericardial effusions. She also presented, for the first time, purpura and papulonodular skin lesions on both legs and arms.

Objectives: To present clinical and laboratory investigations in Churg-Strauss syndrome in childhood.

Methods: Routine laboratory tests including serum autoantibody screen, lung CT scan and histopathologic examination of skin.

Results: Laboratory analyses showed an increased WBC count 23.3 x 10^9/L with predominance of eosinophils (22.1%), normocytic anemia (hemoglobin, 11.2 g/dL), slightly elevated ESR 45 mm/h and C-reactive protein 39.8 mg/L. Serum immunoglobulin were IgA 5.25, IgM 1.78, IgG 20.0 g/l, IgE 3000 IU/ml (normal up to 60 IU/ml). Autoantibody screening was negative, ANCA were negative. Serologic tests to hepatitis B and C, HIV were negative. Serum ACE was normal. Pulmonary CT scan findings were consolidation with nodular lesions. Echocardiographic findings were mitral valve insufficiency with pericardial effusion. Electroneurography showed peripheral sensory neuropathy, while the histopathologic evaluation of skin lesions showed leucocytoclastic vasculitis.

Conclusion: As the corticosteroid treatment was started, the remission was accomplished in the following months. Our patient illustrates many of the typical features of Churg-Strauss syndrome. Even though, this syndrome is rare in pediatric patients it is important to heighten awareness that this serious disease may affect the pediatric population.

Disclosure of interest: None declared.

P307

PreS-FINAL-2317: Clinical presentation, management and outcome of Kawasaki disease (4 years reviews)

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Pediatric Rheumatology 2013, 11(Suppl 2):P307

Introduction: Kawasaki disease(KD) is an autoimmune disease and one of the most common vasculitis of childhood, it has many clinical manifestation but most serious effect is on the heart where it can cause severe coronary artery aneurysms in untreated children.

Objectives: To shade light on our experience on clinical Presentation, management and outcome of KD.

Methods: Sitting: all medical department of Benghazi children hospital. Subject: all the patients who diagnosed as KD during study period (from Jan 2009-dec 2012).
Design of study: Retrospective descriptive case series study. data collected by reviewing their admission files. 
Results: There are 28 patient diagnosed as KD during study period. Male to female ratio 2.1:1. 34% of the cases are atypical KD. -7.9% below 5 years of age...
Peak admissions in October, November, December
The frequency of clinical criteria for diagnosis of KD:
Fever in all the patients (mean duration of fever before admission 8 days), oropharyngeal changes 22 (78%), extremity changes 21 (75%) cervical lymphadenopathy 20 (71%), skin rash 18 (64%); conjunctivitis 16 (57%). Other associated symptoms and signs: vomiting 13 (46%), diarrhea 11 (44%), cough 8 (29%), arthritis 7 (7%), hemoptoemagaly were present in 4 (14%), splenomegaly 2 (7%), jaundice 2 (7%) no case with meningitis. Echocardiogram done in 26 patients, 17 (69%) normal, 9 (31%) abnormal coronary arteries.
Regarding treatment: 18 patients receive sandoglobulin; aspirin received by 18 patients during admission, no patient receive steroids, 7 patients diagnosed in late stage and 3 patients left LAMA. Antibiotics used for 17 patients. Conclusion: we have significant delay in diagnosis and high rate of coronary aneurysm.
Disclosure of interest: None declared.

P308
PRes-FINAL-2318: The structural and functional changes of biomembrains of FMF and HSP with children
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Pediciatric Rheumatology 2013, 11(Suppl 2):P308

Introduction: According to some clinical feature of similarities (fever, abdominal pain, arthritis, skin manifestation, gastro-intestinal disorders and kidney diseases) Familial Mediterranean Fever (FMF) and Henoch-Schonlein Purpura (HSP) we attempt to identify membranes aspects of pathogeneses these diseases.

Objectives: The aim of our study is to identify some changes of individual phospholipids (PL) in erythrocyte membranes and comparative analysis of FMF and HSP patients.

Methods: The examinations have carried out in 42 non complicated 7-15 ages of FMF patients and 24 healthy volunteers. Clinical studies have carried out in the National FMF Children Center, Center "Arabik". Biochemical changes have studied in Hematological Center. 42 patients in erythrocyte membranes by the separate individual PL are studied: phosphatidylcholines (PCh), phosphatidylethanolamines (PE), phosphatidylsinosites (PI), sphingomyelins (SPM), phosphatic acids (PA), phosphatidyserine (PS) and citoxic-LypoPCh (LPCh) qualitative and quantitative changes. Previously it has been investigated the changes of indicators during the HSP diseases (L. Simonyan et al., 2011). The fractions of separate PL in erythrocyte membranes are carried out by thin-layer chromatography methods and decay their enzymes (phospholipase A) activity was determined by the spectroktometri method.

Results: Comparative studies are identified on the basis of membrane structural metabolism disorders, for the prevention and regulation some changes of FMF and HSP. Based on the results obtained by our research is an attempt to separate the membrane lipids metabolism disorder specific agencies which are responsible for affection of membrane's. Conclusion: According to our investigation we conclude, that level of phopholipase A and citotoxic-LPCh are increase in mentioned diseases. Disclosure of interest: None declared.

P309
PRes-FINAL-2319: PED-BD cohort 2013: expert consensus classification gives higher sensitivity than the international study group criteria to define Behcet’s disease in children
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Introduction: BD is rarely encountered in children where the disease is very difficult to recognize. The outcome of patients with few symptoms is currently unknown.

Objectives: To define the outcome of paediatric patients with at least two symptoms of BD, and to obtain an appropriate definition of BD in patients <16y.

Methods: An international expert committee has defined the criteria of inclusion. New patients or patients followed for a maximum of 3 years, who presented at least 2 symptoms of BD (among a list), and gave their informed consent were included, reviewed yearly.

Results: 228 patients were included since 2008, (SR: 1), from 22 centres of 13 countries, median age of 12.5y. Median age at first symptom was 7.2y. Family history of BD was present in 22% and consanguinity in 4.5%. Median disease duration at inclusion was 4.7y and from the first symptom to last visit was 7.5y. Inclusion criteria plus oral aphtosis (mandatory) were 9%; genital aphtosis 50, necrotic folliculitis 31, uveitis 28, familial history 22, pathergy positive 19, erythema nodosum 15, vascular 10 and renal vasculitis 7. Mean number of symptoms: 1 plus family history 41%, 2 (33%), more than 3 (26%). Patient had a median of 1.3 follow-up visit (0-4). 220 patients had a first visit, 138 patients had a 1-y visit (mean BD duration: 5.8y). 81 patients had 2-y (6.4y), 44 a 3-y (7.3y) and 18 a 4-y visit (7.5y). The symptoms along the study were (%): dermatological 67, genital aphtos 52, aricular 48, fever 47, gastrointestinal 39, ocular 36, neurological 35, pathergy 17, vascular 12, urological 2. HLAS1 was present in 47%. Male patients had significantly more ocular and vascular signs, female had more genital aphtosis. Between 1st-4th visit: 57% had no new symptom, 24% had 1, 11% had 2 and 10% had more than 3. The expert committee has examined 199 files at a median disease duration of 6.1y. and classified 121 patients as definite, 18 as probable and 3 as not BD. 57 charts were reviewed but did not reached consensus. 46 files have been reviewed more than once. Among our patients classified as definite: 121/142 (85%); 79/121 (65%) fulfilled the ISG international criteria. International criteria and expert classification showed significant differences. Although good concordance (Kappa c = 0.72). Having 2 or more symptoms was significantly associated with classification as definite BD (p = 0.0005).

Conclusion: The expert committee has classified the majority of patients in the BD group although they did not fulfil the international BD classification criteria (for adults).
Disclosure of interest: None declared.

P310
PRes-FINAL-2320: Different clinical presentation of takayasu arthritis: case report of two pediatric patients
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Pediatric Rheumatology 2013, 11(Suppl 2):P310

Introduction: Takayasu arteritis (TA) is a granulomatous large vessel vasculitis that involves the aorta, its major branches and pulmonary arteries. Diagnosis of TA during childhood remains challenging due to the non-specific symptoms. It primarily affects East Asian women in their second or third decade of life but is well known to affect all ethnicities across the world. Given its systemic nature, Takayasu’s arteritis has multiorgan involvement, with the majority of disease morbidity related to the cardiovascular, central nervous, and renal systems. Despite the increasing identification of children and adolescents with TA, reports of disease in children populations are still scarce.

Objectives: Objective of our research was analysing of clinical, laboratorial and radiological characteristics, organ involvement, type of therapies and outcome of patients diagnosed with TA.

Disclosure of interest: None declared.
We reviewed the medical records of all patients aged 1-18 years who were diagnosed with TA (according to EULAR/PRINTO/PRES criteria) during the period 2002 - 2012, at the Department of Paediatrics, University Hospital Centre Zagreb, University of Zagreb School of Medicine.

Results: TA was diagnosed at two patients, both girls, aged 14 and 16 years. First patient presented with fatigue, chest and left arm pain, especially during physical activity. On admission, she had absent the left brachial and radial pulses, bruits and increased erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level and fibrinogen. Magnetic resonance angiography (MRA) showed narrowing in ascending aorta, brachiocephalic, right common carotid, left subclavian, left vertebral arteries and descending aorta. Heart customerisation with coronarography showed high-grade stenosis of left coronary artery. She was treated with pulc corticosteroid therapy (3 consecutive days) followed by corticosteroids orally and pulse cyclophosphamide therapy (6x) after what clinical picture has improved and laboratory findings has become normalized.

Second patient presented with hypertension. She did not have any symptoms of disease and tolerate efforts normally. On admission she had absent lower extremities pulses. MCTA aortography showed narrowing of abdominal aorta 10 centimetres long with poststenotic dilatation and aneurysm. Narrowing of upper right renal artery was seen as well. Positrion emission tomography - computed tomography (PET-CT) revealed areas of inflammation in the abdominal aorta and markers of inflammation in blood were also elevated (ESR, CRP, fibrinogen). Patient was treated with the aorto-aortic grafting, metotrexate and corticosteroids orally. At the last follow up antihypertensive therapy has been modified because girl is still having a hypertension.

Conclusion: TA is rare in children; however, childhood TA must be considered in children who present with non-specific systemic symptoms, chest disease, hypertension and increased acute phase reactants.

Disclosure of interest: None declared.

P311

PreS-FINAL-2321: Clinical manifestations of granulomatosis with polyangiitis in 8 children from south-east region of Poland

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Introduction: Granulomatosis with polyangiitis (GPA) is a necrotising granulomatous vasculitis affecting the small and medium blood vessels in particular of airways and kidneys. The incidence of GPA in Europe is 25-150 per 1 million per year. This disease typically occurs in the 4th or 5th decades of life and in children it usually cause diagnostic and therapeutic difficulties. Subglottic stenosis and nasal deformity are frequently registered in this group of young patients.

Objectives: The purpose of this study was to analyse the incidence of GPA in large group of children hospitalized in three paediatric reference centres in south-east administrative region of Poland (3,3 million inhabitants), in the years 1995-2013, as well as to investigate their symptoms, laboratory findings and disease outcome.

Methods: Retrospective study, examining the medical records. Patients with confirmed diagnosis of GPA must meet criteria of American College of Rheumatology and EULAR/PRINTO/PRES for classification of GPA. All patients were subjected to clinical, laboratory, radiology, immunology assessment.

Results: We found only 8 children with confirmed diagnosis of GPA (6 girls, 2 boys). The average age of onset was approx. 11 years (range: 8-14). The average diagnosis delay was approx. 22 months (range: 0-7 years). The most common clinical features at presentation were constitutional symptoms - weight loss, fever and arthralgia (87.5% - 7/8). The frequency of system involvement at presentation was: kidneys 87.5% (7/8), lungs 75% (6/8), ear/nose/sinuses/throat 50% (4/8), gastrointestinal tract 50% (4/8), skin 37.5% (3/8), eyes 12.5% (1/8), joints 12.5% (1/8) and nervous system 12.5% (1/8). ANCA were positive in all patients. Treatment included: glucocorticosteroids 100%, cyclophosphamide 100%, mycophenolate mofetil 50%, plasmapheresis 37.5%, hemodialysis 25% and in 12.5% cyclosporine. 4 children has or had progression of the disease, in spite of appropriate treatment (1 has constant progression of sinusitis, 2 has end-stage renal failure, 1 died because of alveolar haemorrhage).

Conclusion: Female predominance and clinical features of GPA diagnosed in children were similar to those described in adults. However, none of our patients had subglottic stenosis and only in 2 cases was observed saddle-nose. Although GPA was appropriate treated, progression was observed in 50% children.

Disclosure of interest: None declared.

P312

PreS-FINAL-2322: Outcome of kidney transplantation in paediatric patients with ANCA associated glomerulonephritis: a single-center experience

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Introduction: Kidney transplant outcomes for paediatric patients with end stage kidney disease (ESKD) secondary to ANCA GN, particularly granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) is limited. Adult data suggests similar allograft survival post transplant to other causes of ESKD.

Objectives: We aimed to describe our experience of kidney transplantation in paediatric ANCA GN patients.

Methods: We performed a retrospective review of patients with ANCA GN who developed ESKD and were transplanted at the Hospital for Sick Children (HSC) between 2000 and 2012. All patients were diagnosed at HSC and followed until their transfer to an adult center.

Results: Since 2000 there have been 6 paediatric patients transplanted with ANCA GN (5 MPA, 5 patients were ANCA positive at diagnosis: 1 c-ANCA, PR3 positive and 4 p-ANCA MPO positive. Age at ANCA GN diagnosis was 10.4 ± 4.3 (Mean ± SD) years (range 4.1 to 15.4). eGFR at diagnosis was 14.1 ± 6.2 ml/min/1.73 m². Renal biopsy category was crescentic in 4 and sclerotic in 2 by the new histopathological classification. Initial treatments included: steroids 6 (100%), cyclophosphamide 4 (66.69%) and PLEX 1 (16.67%). 2 patients had disease relapse within the first 6 months. 4 patients required dialysis at diagnosis (HD) and remained dialysis dependent. All 6 were dialysis dependent by 6 months post diagnosis. Time from ANCA GN diagnosis to kidney transplant (Mean ± SD) was 31 ± 12 months (range 17 - 48 months). All patients received induction therapy and maintenance immunosuppression with prednisone, mycophenolate mofetil, and mycophenolate mofetil.

Conclusion: Short-term patient and allograft survival in paediatric patients with ESKD secondary to ANCA GN is excellent despite aggressive disease, with no recurrence of vasculitis post transplant.

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P313

PreS-FINAL-2323: Cryoglobulinemic vasculitis preceding diagnosis of Carney complex

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Pediatric Rheumatology 2013, 11(Suppl 2):P313

Introduction: Carney complex (CNC) is a disorder characterized by skin pigmented abnormalities and benign cardiac, endocrine, skin and neuronal tumors. Areas of unusual lentigines are the most common presenting feature of CNC usually around the lips, eyes or genitalla increase in number at puberty. Cardiac myxomas may occur in any or all cardiac chambers, and...
leading to intracardiac obstruction of blood flow, embolic phenomena, and/or heart failure. Carney complex is a rare autosomal dominant disease. The complex has been mapped to 2p16 (CNC2) and 17q22-24 (CNC1), and mutations in the tumor suppressor gene protein kinase A regulatory subunit 1-alpha, PRKAR1A, are causative [1].

Objectives: A previously healthy 12-year-old boy presented with recurrent pain and swelling initially in the left foot later followed by the right one. The swelling regressed spontaneously over weeks but the pain remained. At an age of 13 years the patient had stiffness of the fingers on the right hand and the toes were painfull but without swelling. He had no fever. At first presentation erythrocyte sedimentation rate (ESR) was elevated to 34 mm/h, CRP was normal. Furthermore, he had thrombocytosis (500 x 109/L), anemia (10.5 g/dL), IgM slightly elevated, normal complement C3c and C4. Rheumatoid factor, ANCA and ANA were all negative but cryoglobulins (not further specified) were positive. An unusual pigmentation around the lips were noticed. He had monthly attacks lasting 5-10 days with pain and swelling of the feet well treated with Prednisolone and Azathioprine. 2 years later he was admitted with confusion, aphasia and apraxia but without seizures. The symptoms regressed spontaneously after a few hours.

Methods: MRI was performed with a 1.5 Tesla scanning system including T1, T2, T2-flair and diffusion-weighted sequences as well as MR-angiography using a time of flight. Genetic testing of PRKAR1A gene mutation analysis was done by conventional techniques.

Results: MR scans revealed parieto-occipital infarction but no signs of schwannomas or vasculitis on the angiography. An echocardiography revealed an obstructive tumor, 5-6 centimeters in diameter, in the left atrium, which was surgically removed. The lentigines and the myxoma led to the suggestion of Carney Complex. Diagnosis was confirmed by a PRKAR1A mutation found in the child as well as the mother.

Conclusion: To our knowledge, this is the first case of combined Carney Complex and cryoglobulinemia. A few cases of vasculitis and CNC have been reported, which makes it likely to assume a connection. We suggest that vasculitis should be added to the list of presenting symptoms of CNC. A diagnosis of CNC should be considered in patients who present with vasculitis, unusual lentigines, and myxomas, endocrine tumors or schwannomas.

Disclosure of interest: None declared.

Reference

P314
PreS-FINAL-2324: PAPA syndrome clinical spectrum and IL-18 release

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Introduction: Pyogenic sterile Arthritis Pyoderma gangrenosum and Acne (PAPA) syndrome is a rare autosomal dominant inherited autoinflammatory disease caused by mutations of Pyroline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1). In childhood-onset, the syndrome is featured by recurrent sterile, erosive arthritis, potentially leading to joint destruction. By puberty, cutaneous symptoms become predominant, with recurrent onset of pathergy, abscesses, severe cystic acne, and pyoderma gangrenosum. Typically, both arthritic and cutaneous outcomes occur following a minor trauma. PSTPIP1 may interact with ASC and caspase-1 but a clear involvement of interleukin (IL)-1 and the role of NLRP3 is still controversial. While anti-IL1 treatment seems to be effective on joint manifestations, IL inhibition does not display the same effectiveness in the management of skin lesions.

Objectives: To investigate in our PAPA cohort whether IL-1β secretion 1) is enhanced, 2) correlates with different PSTPIP1 mutations, clinical manifestations and/or disease activity, and 3) is mediated by NLRP3.

Methods: Eleven genetically confirmed patients (N = 2 children and N = 9 adults) carrying different PSTPIP1 mutations (E250K N = 1, E256G N = 1, E250Q N = 9) were analyzed and compared to 31 healthy donors (HD).

Four patients had an active disease at the time of sampling while 7 were symptom-free. Nine out of 11 were off-therapy. Peripheral blood primary human monocytes were freshly isolated and studied at baseline and after 3-6-18 hours (h) of LPS-induced in vitro activation. Pattern of IL-1β secretion was assessed by ELISA. The involvement of NLRP3 was investigated by in vitro silencing.

Results: Monocytes isolated from PAPA patients tent to secrete higher levels of IL-1β but this was not consistent in all the patients (p = 0.144). Variability in IL-1β release occurred even in the presence of the same PSTPIP1 variant and it did not parallel disease activity when the whole cohort was taken in consideration. However, IL-1β levels varied according to the clinical picture (p = 0.0197), and it was significantly higher (P < 0.05) in patients displaying articular manifestations (N = 3) compared to those affected by cutaneous (N = 6) or combined (N = 2) lesions. In the former, IL-1β secretion was increased in the presence of acute phase reactants elevation and active joint lesions, and treatment with Anakinra resulted in acute phase reactants normalization and symptom-free period. Silencing of of NLRP3 activity consistently inhibited LPS-induced IL-1β release in both PAPA and HD monocytes.

Conclusion: IL-1β secretion is higher in PAPA patients displaying prevalent articular manifestations. In these patients, IL-1β release correlates with disease activity and it is mediated by NLRP3.

Disclosure of interest: None declared.

P315
PreS-FINAL-2225: Different phenotypes associated with Q703K variant of the NLRP3 gene

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Introduction: PFAPA syndrome is an auto-inflammatory disease (AID), characterized by recurrent fever aphtosis, pharyngitis and cervical adenitis. A familial predominance has been observed and variants in the NLRP3 gene were recently found in several patients. The NLRP3 Q703K variant was described so far in CAPS patient and in healthy carriers.

Objectives: To describe the different phenotypes of patients with recurrent fever and Q703K variant.

Methods: In patients presenting to our consultation with recurrent fever suspected to be auto-inflammatory, we screened genomic DNA by PCR and sequenced for genetic variants of NLRP3 genes. The symptoms, treatment, response to treatment and family history of the patients with the variant Q703K have been retrospectively extracted and described.

Results: We found the NLRP3 variant Q703K in 13 patients. Ten were PFAPA patients among 97 from our cohort; one had a CAPS phenotype and two an undefined autoinflammatory disease (UAID): 9 boys and 4 girls with a median age of 18 months at disease onset. Family history was positive in 6 PFAPA and one UAID patients. For PFAPA, the median duration of fever was 4 days; the median interval was 4 weeks. Pharyngitis and cervical adenitis was always present in 6 patients. Afebrile attacks were found only in 1 patient in every episode. 5 patients expressed abdominal pain that accompanied most fever episodes. 1 patient showed sometimes arthralgia, 2 patients had headaches in most episodes and one patient had once a cutaneous rash. 5 out of 7 patients treated by corticosteroids responded promptly. In the other two patients two doses were often necessary. 3 patients underwent tonsillectomy: one with no effect, in 2 the fever episodes resolved but one patient had persistent episodes of aphtosis. In 4 patients genonic sequencing of the parents was done; one parent positive for Q703K had a history of recurrent febrile episodes but the 3 other parents did not present a history of recurrent fever episodes nor recurrent pharyngitis nor tonsillotectomy. The patient with CAPS phenotype presented with urticarial rash, partial deafness, arthralgias and elevated inflammatory parameters, and responded well to IL-1 blocking agents. One patient with UAID presented recurrent fever episodes with neurological symptoms (hypotonia, bulging fontanelle, loss of contact) and high inflammatory markers, and the second with fever flares and angioedema. In one UAID and two PFAPA patients another heterozygous variant in the MEFV gene was found.

Conclusion: We report 13 patients positive for the NLRP3 Q703K variant and presenting different phenotypes, mainly PFAPA syndrome. The role of this variant in the clinical manifestations of our patients is challenged by the negative history for fever syndromes in the Q703K+ PFAPA parents.

The presence of a second variant in a gene involved in recurrent fever syndromes in 3 of our 13 patients suggests that another gain-of-function
mutation is necessary in patients with the Q703K variant to induce auto-inflammatory manifestations.

Disclosure of interest: None declared.

P316
PrEfS-FINAL-2326: No correlation between anti-drug antibodies and pharmacokinetics, efficacy or safety of Anakinra (Kineret®) in patients with severe CAPS
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Pediatric Rheumatology 2013, 11(Suppl 2):P316

Introduction: Anakinra is a recombinant, non-glycosylated form of the human IL-1 receptor antagonist, which recently was approved in US for neonatal onset multisystem inflammatory disease (NOMID), the most severe form of the Cryopyrin-Associated Periodic Syndromes (CAPS). This autoinflammatory disease can be effectively controlled by daily subcutaneous administrations of Kineret[1-3]. The recommended initial dose is 1-2 mg/kg/day and the average maintenance dose is 3-4 mg/kg/day.

Objectives: To evaluate if anti-drug antibodies (ADAs) correlate with outcome in patients with severe CAPS patients on Kineret.

Methods: Forty patients treated up to 5 years and with pre- and post-baseline antibody data were included in long-term evaluations of ADA impact on pharmacokinetic parameters (dose-normalized maximum serum concentration, Cmax, and area under the serum concentration time curve, AUC0-24h), body-weight adjusted Kineret dose, change in Diary Symptom Sum Score (DSSS, i.e. sum score for fever, rash, joint pain, vomiting, and headache), change in C-reactive protein (hs-CRP) levels, and treatment emergent adverse events (AEs).

ADAs were assessed with a bridging format immunoassay applying Meso Scale Discovery Electrochemiluminescence (MSD-XCL) technology. Data from pre-dose samples were used to calculate a cut point with a false positive rate of 5%. Screened positive samples were further confirmed by competitive inhibition.

For statistical analyses the patients were classified based on the presence of ADAs.

Results: No patient had ADAs at baseline, while 82.5% of the patients exhibited ADAs at least once during the study. The exposure to Kineret was 73.8 patient-years when ADAs were not present and 82.2 patient-years when ADAs were present. The daily dose of Kineret at Month 36 (mean±SD) for patients with ADAs not present was 2.7(0.6) mg/kg and for patients with ADAs present was 3.1(0.8) mg/kg. The followestimating for the ADA negative and ADA positive patient groups, respectively, were obtained: dose normalized Cmax 116±(55) vs. 94±(406) ng/mL/mg/kg, dose normalized AUC 15.0±(6.5) vs. 12.6±(5.8) µg·h/mL/mg/kg, change in hs-CRP from baseline -53(41) vs. -60(34) mg/L, and change in DSSS from baseline -2.5(1.8) vs. -2.7(1.4). DSSS decreased significantly within a few days in all patients with sustained effect and continuous suppression of inflammatory serum markers. No trend by antibody status was seen for the rate of AEs related to allergies, injection site reactions or symptoms of CAP.

Conclusion: The majority of the severe CAPS patients on Kineret developed transient or persistent ADAs. No correlation was seen between the presence of ADAs and Kineret dose, PK parameters, efficacy outcomes or AEs.

Disclosure of interest: M. Wikén Employee of; Employee of Swedish Orphan Biovitrum AB, P. Gazzu Shareholder of; Shareholder of Swedish Orphan Biovitrum AB, G. Andersson Shareholder of; Shareholder of Swedish Orphan Biovitrum AB, G. Andersson Shareholder of; Shareholder of Swedish Orphan Biovitrum AB, H. Oliveira Employee of; Employee of Swedish Orphan Biovitrum AB, M. Aldén Raboison Shareholder of; Shareholder of Swedish Orphan Biovitrum AB, M. Leinonen: None Declared, B. Hallén Shareholder of; Shareholder of Swedish Orphan Biovitrum AB, Employee of; Employee of Swedish Orphan Biovitrum AB.

References
defined after Delphi rounds were discussed in the consensus meeting, potential criteria set were purified and the description of each item was ascertained. In order to evaluate the validity of criteria set, each expert brought together the data of clinical, laboratory manifestations and physician's global assessments of 10-50 patients from their center. Logistic regression analysis was used to evaluate predictable value of each item and ROC curve analysis was performed to demonstrate the success of the criteria set.

Results: In expert panel nine items were selected as the identifiers of severity. Area under the curve (AUC) was calculated as 0.825 for this criteria set. When each item was evaluated individually, renal failure, nephrotic proteinuria and mean duration of episodes had the least contribution to prediction of severity. Besides, in logistic regression analysis these criteria were eliminated from the terminal modal. After reducing the criteria set, AUC was calculated as 0.808. Additional analysis demonstrated that the reduced model was as successful as full model. AUC was higher than 0.75 in both pediatric and adult patient groups and the results were better in adult group.

Conclusion: Initial validation analysis showed that the scale could be used in assessing severity in FMF patients. The validation of the criteria should be performed on FMF patients attending outpatient clinics in routine visits.

Disclosure of interest: None declared.

P319
PReS-FINAL-3239: Validation of the autoinflammatory activity index (AIDAI)
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Introduction: With the increasing potential for targeted therapies in autoinflammatory diseases, there is the need for validated and standardized assessment tools which can be used to evaluate the level of disease activity and response to therapy. An international collaboration, initiated by Assistance Publique-Hôpitaux de Paris (APHP) in association with the Paediatric Rheumatology International Trials Organization (PRINTO) at http://www.prinito.it and supported by the EUROFEVER and EUROTAPS networks, has previously designed the content and the preliminary scoring of an Autoinflammatory Disease Activity Index (AIDAI).

Objectives: To validate the AIDAI score in the four major hereditary recurrent fever syndromes (HRFs): familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), and cryopyrin-associated periodic syndromes (CAPS).

Methods: In 2010, an international collaboration established the content of a disease activity tool for HRFs. Patients completed a one-month prospective diary with 12 yes/no (dichotomous) items prior to a clinical appointment during which their physician assessed their disease activity by a blinded web-evaluation and a global assessment of 10-50 patients from their center. Logistic regression analysis was used to evaluate predictive value of each item and ROC curve analysis was performed to demonstrate the success of the criteria set. Additional analysis demonstrated that the reduced model was as successful as full model. AUC was higher than 0.75 in both pediatric and adult patient groups and the results were better in adult group.

Conclusion: Initial validation analysis showed that the scale could be used in assessing severity in FMF patients. The validation of the criteria should be performed on FMF patients attending outpatient clinics in routine visits.

Disclosure of interest: None declared.

P320
PReS-FINAL-2330: Canakinumab treatment in patients with HIDS
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Pediatric Rheumatology 2013, 11(Suppl 2):P320

Introduction: Hyper-IgD and periodic-fever syndrome (HIDS) is a recessively inherited-autoinflammatory condition caused by mevalonate-kinase mutations. It is characterized by early-onset (<1 year of age), 4-6 days-long, acute inflammatory episodes that typically recur every 4-6 weeks. The main features during episodes include fever, lymphadenopathies, rash, headache, abdominal pain, diarrhea, and a marked acute phase reaction [1,2]. Previous case reports suggested IL-blockade as a potential therapy. Canakinumab (CAN) is a fully-human, selective anti-IL-1β monoclonal-antibody (MoAb). Preliminary clinical and pharmacokinetics (PK) data of CAN-therapy in active HIDS patients is presented.

Objectives: Primary objective was to assess if CAN reduces the flare-rate during the treatment period (TP) compared with that from the historical period (HP). One secondary objective was to assess the PK and pharmacodynamics of CAN.

Methods: This is a 6-month open-label CAN TP and a follow-up period lasting until relapse or up to 6-months max. Patients ≥2 years-old with active HIDS, CRP > 10 mg/L, and ≥2 febrile acute-flares in a 6-month HP were included. All received CAN 4 mg/kg (max. 300 mg) Q6-weeks in TP, with only one dose up-titration to 6 mg/kg (max. 450 mg) if a flare occurred during the first 6-weeks. CAN concentrations were determined by ELISA from samples collected at pre-dose, at pre-specified time points during the first-month, and at flares. Population PK analysis was performed using NONMEM®-program.

Results: Nine patients (6F,3M) with a median age of 17.3 years (5-29 years) were enrolled. The median number of flares/patient reduced from 5(3-12) during the HP to 0(0-2) during the TP. Two patients had a total of 3 flares during the TP and both required dose up-titrated, with no flares afterwards during the TP. Seven out of 9 patients flared during the follow-up period at a median of 110 days (62-196) after the last CAN dose. Population PK analysis showed that serum clearance of CAN and its volume of distribution were dependent on bodyweight. The estimated apparent serum clearance (CL/F) of CAN was 0.20 ± 0.041 L/day and the corresponding volume of distribution (Vss/F) was 11.6 L. Following the first dose, the mean (SD) observed Cmax was 30.4 ± 8.13 μg/mL. Apparently weight normalized PK parameters were similar to those observed in other diseases. Adverse events (AE) were reported in eight patients, most were mild (76%) or moderate (18%), and none led to CAN discontinuation. Infections, mostly involving the respiratory tract, were the most common type of AE reported. Two patients reported a serious AE (1 HIDS flare hospitalization, and 1 gastrointestinal infection bleed and separate peritonitis).

Conclusion: In this small study, CAN decreased the flare-rate substantially. PK of CAN in HIDS patients was as expected for a MoAb and the weight normalized PK parameters were comparable to those observed in other clinical populations. The AEs reported were manageable. Further study is needed to better define CAN treatment in HIDS.


References
P321
PRes-FINAL-2331: Low-penetration NLRP3 variants
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Introduction: Cryopyrin-associated periodic syndrome (CAPS) presents as rare, autosomal dominant disease spectrum, due to mutations in the NLRP3-gene which lead to excessive interleukin-1 (IL-1) release. In patients with low-penetration NLRP3 variants, the clinical presentation varies widely. So far, a correlation with a specific phenotype could not be demonstrated.
Objectives: The aim of this study was to analyze the association of the V198M, R488K, and Q703K substitutions with a specific phenotype, laboratory markers, and the response to IL-1 inhibitors anakinra, canakinumab and rilonacept.
Methods: This multi-center observational study included 45 patients (26 children and 19 adults) (study group). At baseline examination, all patients displayed some symptoms suggestive of CAPS. Genetic analysis detected one of the following NLRP3 variants: Q703K (n = 19), R488K (n = 6), and V198M (n = 20). Clinical presentation was recorded and inflammation markers were analyzed. Data from follow-up visits were also evaluated to assess response to IL-1 inhibitors. Results were compared to a (control) group of CAPS patients (n = 28) in which disease-causing mutations had been confirmed (A439V, E311K, T438M).
Results: At baseline examination, study patients reported signs of systemic inflammation such as fever (76%), headache (73%), musculoskeletal symptoms (84%) and fatigue (78%). Other CAPS-specific features were rash (80%), conjunctivitis (44%) and sensorineural hearing loss (29%). Compared to the control group, a history of eye impairment, hearing loss and renal involvement was significantly less frequent in the study group. However study group patients presented significantly more often with gastrointestinal symptoms such as abdominal pain (56% versus 25%, p = 0.01) and gastroesophageal reflux (22% versus 0%, p = 0.01). Also, a wide spectrum of concomitant diseases such as thyroid disorders (7%) and neurological and psychiatric diseases were reported (epilepsy (3), Asperger syndrome (2)). Inflammation markers were only slightly increased: ESR was elevated in 26% (9/35) and CRP in 34% (14/41). Serum amyloid A (SAA) was raised in 36% (8/22) of the patients. Nine out of ten patients (90%) had elevated TNF-α-levels at baseline examination.
Data from follow-up visits during the first year of treatment was available from 20 patients, treated with IL-1 - inhibitors. Clinical disease activity was reduced in all cases; 10 patients (50%) achieved full remission and 10 patients showed partial response to the treatment with mild disease activity and/or persistently elevated inflammation markers.
Conclusion: Heterozygous carriers of the NLRP3 variants V198M, R488K, and Q703K display distinct clinical characteristics compared to CAPS patients with confirmed disease causing mutations, including a high incidence of gastrointestinal symptoms, only slightly elevated inflammatory parameters, and a potentially inferior response to IL-1 inhibition. Also susceptibility for concomitant diseases is observed.
Disclosure of interest: None declared.

P322
PRes-FINAL-2332: Activation-induced cell death of human monocytes as a novel mechanism fine-tuning inflammation and autoimmunity
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Introduction: Monocytes represent essential components of innate immunity with high plasticity. These cells are characterized by their ability to release large amounts of proinflammatory cytokines, efficient antigen presentation, and microbicidal or tumoricidal activity. They contribute to inflammation in the immune system, either by governing host defense response to invading pathogens or driving reactions to self-molecules in conditions of tissue-damage. Control of these mechanisms is necessary to ensure the self-limitation of inflammatory reactions and avoid perpetuated autoinflammation or autoimmunity. In T-cells activation-induced cell death is an important mechanism for maintaining tolerance to self-antigens. However, to date it is unclear how activated monocytes can regulate early cytokine signals promoting their survival or cell death.
Objectives: In the light of pleotropic functions and fundamental role of monocyte activation during early phases of inflammatory responses, we recapitulated activities of human monocytes in response to key Th1/Th1 cytokines that primarily affect monocytes (GM-CSF and IFNγ).
Methods: Primary human monocytes were isolated and subjected to stimulation with GM-CSF and IFNγ. Cell death was measured using Annexin V and propidium-iodide staining and analyzed by FACS. Monocytes signaling pathways were analyzed by Western blot using antibodies against phosphorylated and non-phosphorylated proteins. TNF-blockers such as anti-TNF and etanercept were used to analyze the role of TNF in monocyte activation.
Results: In the present study we demonstrate in vitro, that simultaneous treatment with GM-CSF and IFNγ promotes activation-induced cell death (AICD) of human monocytes. Analyzing the signaling pathways that lead to cell death revealed that a specific mechanism described as pyrocnecrosis is induced by GM-CSF and IFNγ. Pyrocnecrosis has morphological characteristics of necrosis, is caspase- and RIP kinase1-dependent but caphesin-B-dependent. GM-CSF/IFNγ-induced cell death of monocytes involved IL-1b and TNFα-hypersecretion. Furthermore, pyrocnecrosis was found to be dependent on TNFα and could specifically be inhibited by TNF-blockers.
Conclusion: Taken together, we identified AICD of monocytes as a novel mechanism, which could regulate inflammatory processes that may be altered in the context of autoinflammation or immunity. The involvement of different mediators and pathways in this process could have consequences on therapeutic strategies, e.g. for combination therapies involving TNF-blockers.
Disclosure of interest: None declared.

P323
PRes-FINAL-2333: Long term efficacy of interleukin-1 receptor antagonist (anakinra) in a multicentric cohort of patients affected by idiopathic recurrent pericarditis
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Introduction: Recurrent pericarditis represents an important complication of acute pericarditis. Therapeutic approach during recurrences consists of NSAID (non-steroidal anti-inflammatory drugs) administration. However steroid is often necessary to control disease flares. IL-1 inhibitors efficacy has been anecdotally described as effective in the control of the disease in steroid-dependent and colchicine-resistant patients.
Objectives: To evaluate the long term response to treatment with anakinra (IL-1 receptor antagonist) in a multicenter cohort of patients (pts) affected by idiopathic recurrent pericarditis.
Methods: Fifteen pts (12 pediatrics, 3 adults; M/F = 11:4) followed by 6 national referral centers were enrolled in the study. The mean age was 22 years (range 8-60 yrs); mean age at onset 16 years (5-49 yrs), mean age at the beginning of treatment 19 years (6-56 yrs). All pts received an initial dosage of 1-2 mg/Kg/die. All pts were steroid-dependent and 14 of them had received colchicine. Recurrence was documented in patients who presented typical chest pain and 1 or more of the following signs: fever,
P324
PReS-FINAL-2334: Chronic recurrent multifocal osteomyelitis and TNF-α inhibitors
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Pediatric Rheumatology 2013, 11(Suppl 2):P324

Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory disorder of unknown etiology, characterized by nonbacterial inflammatory bone lesions. The bone lesions can be unifocal or multifocal, and have an either uniphasic or recurrent course. Non-steroidal anti-inflammatory drugs (NSAIDs) and Glucocorticoid have been reported to be effective in some cases, and more recently tumor necrosis factor-alpha (TNF-α) inhibitors have shown effect in more treatment resistant cases.

Objectives: To describe a cohort of CRMO patients and characterize treatment effect.

Methods: Data from all patients diagnosed with CRMO from 2002 to 2011, at the east Danish specialized pediatric rheumatology unit, were collected through review of medical records. The effect of treatment were evaluated by the clinical symptoms, blood analysis and by Magnetic Resonance Imaging (MRI).

Results: From January 2002 to December 2011, twenty-five children under the age of 16 years were diagnosed with CRMO. 16 females, 9 males. The most frequent foci were in the tibia (8), femur (7), clavicle (7) and fibula (4). 56% of the patients had unifocal affection and 24% could be diagnosed with SAPHO syndrome.

Seven patients (28%) had sufficient effect of treatment with NSAIDs. Only three out of 18 patients treated with Methotrexate (MTX) had sufficient effect of the drug.

15 patients were treated with TNF-α inhibitors. 12 patients changed to a 2.line and three to a 3. line TNF-α inhibitor, due to either insufficient effect or adverse events.

The overall effect of TNF-α inhibitor were very good. The effects of treatments are shown in Table 1.

Conclusion: The gender and age distribution of our patients resample that of the literature. In contrast we found a limited amount of foci, 1,6/patient. A large number of our patients developed SAPHO-syndrome. This could be caused by selection bias, since we are a highly specialized unit, with primarily more complicated patients being referred.

Table 1 (abstract P324)

<table>
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<tr>
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<th>ptt. (%)</th>
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<tbody>
<tr>
<td>Sufficient clinical effect of MTX (n:18)</td>
<td>3 (17%)</td>
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<tr>
<td>Sufficient clinical effect of TNF-α (n:31)</td>
<td>18 (58%)</td>
</tr>
<tr>
<td>Regression on MRI, MTX (n:9)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Regression on MRI, TNF-α (n:13)</td>
<td>11 (84%)</td>
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MTX had a disappointing effect on our cohort, in contrast to that of TNF-α inhibitors.

A treatment-resistant group of patients showed good effect from TNF-α inhibitors, both clinical and on MRI.

Disclosure of interest: None declared.
Conclusion: This study describes the clinical characteristics and response to therapy in a large international cohort of MKD patients.

Disclosure of interest: None declared.

P326
PreS-FINAL-2336: Induction of MDSCs in Muckle-Wells syndrome

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Pediatric Rheumatology 2013, 11(Suppl 2):P326

Introduction: Muckle-Wells syndrome (MWS) is caused by mutations in the NLRP3-gene encoding cryopyrin, leading to overproduction of IL-1β and other NLRP3 inflammasome products. Myeloid-derived suppressor cells (MDSCs) represent a novel innate immune cell subset, are generated in tumor, infective, and proinflammatory microenvironments, and can be of suppressing T cell responses. Consequently, MDSCs are considered a key intermediary in balancing innate and adaptive immune responses, particularly under chronic disease conditions.

Objectives: We hypothesized that NLRP3 inflammasome-dependent factors and Eukaryotic initiation factor 2α (eIF2α) phosphorylation of MDSCs in MWS patients under anti-IL-1 therapy with canakinumab and 20 healthy controls. After Ficoll density gradient sedimentation, granulocytic MDSCs were characterized as CD34<sup>+</sup>CD66b<sup>+</sup>HLA-DR<sup>+</sup>neutrophilic cells in the PBMC fraction, according to previously established human MDSC analysis methods. The functionality of MACS-isolated MDSCs was assessed using polyclonal T cell proliferation and cytokine/chemokine secretion tests. Physician’s global assessment of disease activity, CRP, ESR, and T helper cell subsets were determined at the same time points and correlated with MDSC levels. Serum samples of 22 MWS patients and 5 healthy controls were examined by multiplex technique for possible MDSC inducing factors.

Methods: We studied granulocytic MDSC numbers in 25 MWS patients under anti-IL-1 therapy with canakinumab and 20 healthy controls. After Ficoll density gradient sedimentation, granulocytic MDSCs were characterized as CD34<sup>+</sup>CD66b<sup>+</sup>HLA-DR<sup>+</sup>neutrophilic cells in the PBMC fraction, according to previously established human MDSC analysis methods. The functionality of MACS-isolated MDSCs was assessed using polyclonal T cell proliferation and cytokine/chemokine secretion tests. Physician’s global assessment of disease activity, CRP, ESR, and T helper cell subsets were determined at the same time points and correlated with MDSC levels. Serum samples of 22 MWS patients and 5 healthy controls were examined by multiplex technique for possible MDSC inducing factors.

Results: MWS patients under anti-IL-1 therapy displayed significantly elevated MDSC numbers (mean 1.65 ± 0.33%; range 0.16 - 5.17%) compared to healthy controls (mean 0.45 ± 0.05%; range 0.12 - 1.04%; p = 0.0025), although clinical MWS-disease activity was generally low at time of examination. MDSCs were functionally competent, as they suppressed polyclonal T cell proliferation, TH1, TH2, and TH17 responses. MDSCs correlated directly with Treg/Th17 and Treg/Th1 ratios indicating an influence on T helper cell subsets. Multiplex assays revealed the established MDSC-inducing growth factors GM-CSF and VEGF elevated in MWS sera even under anti-IL-1 therapy with canakinumab.

Conclusion: MWS patients under anti-IL-1 therapy display significantly elevated numbers of granulocytic MDSCs. Increased MDSCs in MWS might represent a novel autologous anti-inflammatory mechanism in autoinflammatory conditions and may serve as a future therapeutic target.


P328
PreS-FINAL-2338: Fate of lymphocytes after withdrawal of Tofacitinib treatment

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Pediatric Rheumatology 2013, 11(Suppl 2):P328

Introduction: Tofacitinib (ToF) is an inhibitor of Janus Kinase 3, developed for the treatment of autoimmunity diseases and for the prevention of transplant rejection. Thanks to its selective action on proliferating cells, Tofa can offer a way to block T cell activation. The potential field of clinical application is thus represented by disorders with inappropriate T cell response, such as rheumatoid arthritis, psoriasis, graft rejection, ulcerative colitis and graft versus host disease. However, the tuning of efficacy (suppression of pathogenic lymphocytes) and safety (suppression of protective immunity) remains an open issue. Unexpectedly, whereas the drug has been widely used in animal models and has been already introduced into the clinics, only few studies had investigated its immunological potential in vitro.

Objectives: To study the effect of tofacitinib in vitro stimulated lymphocytes. In particular, to measure the effect of the drug on cell proliferation, lymphocyte subsets and cell viability during treatment and after interruption of treatment.

Methods: Healthy donors’ peripheral blood mononuclear cells are stimulated or not with phytohemagglutinin and incubated for 4-days with different concentrations of tofacitinib. After the first incubation, cells are stained twice and further incubated for 4-days without stimuli and drug. Cell proliferation is assessed by CFSE dilution assay; cell viability by 7-AAD staining; lymphocyte subsets are analyzed by multicolour flow cytometry.

Results: Here we showed that Tofa exerts a rapid and strong effect on lymphocyte activation, leading to a complete arrest in proliferation and to a strong down-regulation of activation markers in PHA stimulated
lymphocytes. Notably, these results are achieved with a negligible toxicity on lymphocyte viability. However, after the withdrawal of the drug, stimulated lymphocytes resume proliferation. Thus, transient treatment with Tofa didn’t lead to a relevant inhibition of final proliferation, but it strongly affected the distribution of lymphocyte subsets, with a reduction of NK cells, B cells and CD8 cells.

Conclusion: Based on these data, we can presume that discontinuation of the drug after a short treatment may lead reactivation of diseased lymphocytes and to a reduction of NK and B cells as well in vivo, possibly resulting in undesired effects of the drug. To evaluate this possibility, a careful study of the expression of lymphocyte activation markers and of the distribution of lymphocyte subsets should be performed in all subjects after discontinuation of Tofa treatment.

Disclosure of interest: None declared.

Introduction: A novel antimicrobial mechanism of neutrophils involves the release of neutrophil extracellular traps (NETs) into the local environment to bind pathogens. NETs are composed of chromatin, and it has been proposed that a source of autoantigens in Systemic Lupus Erythematosus (SLE) could be NETs production. Interferon (IFN)-α is known to be a key player in the pathogenesis of SLE. In Juvenile-onset SLE (JSLE) patients with generally more severe disease, an IFN signature is almost invariably shown at early stages of disease, suggesting that activation of the type-1 IFN pathway may be especially important in the induction of the disease process.

Objectives: Observe and measure the induction of NETs in JSLE patients and controls following incubation with IFN alpha and serum ± pre incubation with an inhibitor to block IFN signalling.

Methods: Neutrophils isolated from children with JSLE and healthy controls were either left unstimulated, pre-incubated with IFN alpha for 30 mins or incubated for 2 hours with 10% JSLE or control serum, 300 nM PMA, and 100 ng IFN-alpha. Induction of NETs was visualised using confocal microscopy following staining for Neutropol Elastase, dsDNA and DAPI. Pre incubation with 10uM JAK inhibitor was used to inhibit IFN alpha signalling. The IFN alpha environment of the JSLE and control neutrophils prior to isolation was measured using pSTAT1 and western blotting. To quantify NETs formed cultured neutrophils were digested using micrococcal nuclease to dismantle the NET scaffold, double stranded DNA was quantified using the Quant-iT Picogreen assay. Extracellular DNA was measured using a spectrofluorometer.

Results: Formation of NETs were observed following incubation with PMA, JSLE serum and IFN-alpha (confocal microscopy images). Unstimulated neutrophils and neutrophils incubated with control serum were not seen to form NETs. Greater NET formation was observed in JSLE neutrophils incubated with JSLE serum and IFN-alpha compared to control neutrophils. Increased pSTAT1 signalling was observed in JSLE (0.9 ± 0.05) compared to control neutrophils (0.42 ± 0.08, p < 0.05). Pre-incubation of control neutrophils with IFN alpha increased amount of NETs induced. NET formation following incubation with JSLE serum subsequently lead to the exposure of dsDNA (confocal microscopic images). NETs induced by JSLE serum and IFN alpha was reduced following pre incubation with a JAK inhibitor.

Conclusion: This study observed the induction of NETs in JSLE and controls neutrophils and that control and to a greater extent JSLE neutrophils form NETs following incubation with JSLE serum and IFN-alpha. This led to exposure of dsDNA therefore providing further evidence that NET formation could be a potential source of autoantigen exposure in SLE. The results from our study suggest that the formation of NETs in JSLE may be exacerbated by the factors expressed in JSLE serum including IFN alpha. Blocking of IFN alpha signalling using a JAK inhibitor resulted in reduced NET formation as observed by confocal microscopy and quantification of DNA following digestion of NETs. The JAK inhibitor, Tofacitinib has recently been approved as a treatment for Rheumatoid Arthritis, this study may provide evidence that JAK inhibitors may be a useful therapeutic agent in patients with SLE.

Disclosure of interest: None declared.

Introduction: Damage Associated Molecular Pattern molecules (DAMPs) like HMGB1 have been demonstrated to be involved in pathological processes triggering and perpetuating autoimmune arthritis by attraction and activation of immune cells. The phagocyte-specific S100 proteins A8 and A9 (Myeloid Related Protein 8 and 14, respectively) are expressed by monocytes and granulocytes and can likewise operate as DAMPs by signalling through TLR4 once released into the extracellular space.

Objectives: S100A8/A9 has initially been identified in context with rheumatoid arthritis (RA). Generally, the proteins have a high relevance as inflammatory biomarker in various arthritic conditions, such as juvenile idiopathic arthritis (JIA). The proteins’ involvement in triggering or perpetuating pathomechanisms in autoimmune polyarthritis is albeit discussed controversially. We set out to carefully re-investigate this task and dissect possible contributions of S100A8/A9 to arthritis pathogenicity.

Methods: Collagen induced arthritis was induced in C57BL/6 and S100A9± mice, the latter lacking both S100A9 and its binding partner S100A8 at protein level. Disease progression was monitored by both clinical score and serological anti type II collagen (CII) autoantibody levels. Splenic T cell responses upon CII re-stimulation were studied in presence or absence of S100 protein priming of either whole splenocytes or bone marrow derived macrophages (BMDMs).

Results: S100A9± mice were almost completely protected from collagen induced arthritis (CIA). As observed throughout all experiments, this is accompanied by a strikingly significant decrease in anti type II collagen antibody titers compared to C57BL/6 wild type animals. Compared to wt-T cells, splenic S100A9± T cells respond poorly to CII re-stimulation. This phenotype can be partly reversed, if S100A9± splenocytes or macrophages (BMDMs), as the dominant CII antigen presenting cells, are primed with either S100A8 or S100A8/A9.

Conclusion: In an autoimmune arthritis mouse model S100A8/A9 can apparently operate at the interface between innate and adaptive immunity, possibly by modulating antigen presentation capacities of macrophages and thus affecting CD4+ T cell stimulation and downstream autoantibody production. Beyond their role as inflammatory biomarkers in arthritis S100A8/A9 can therefore likely trigger and promote autoimmunity. An active contribution to a distorted cross-talk between innate and adaptive immune mechanisms, as potentially in place in poly- or oligoarticular JIA, can be suggested.

Disclosure of interest: None declared.

Introduction: Perturbed homeostasis of FOXP3+ regulatory T cells and STAT1 signaling in SLE patients with childhood and adult onset of disease

Objectives: PReS-FINAL-2341: Blocking interferon alpha signaling can reduce neutrophil extracellular trap formation in juvenile onset systemic lupus erythematosus

Methods: Neutrophils isolated from children with JSLE and controls were either left unstimulated, pre-incubated with IFN alpha for 30 mins or incubated for 2 hours with 10% JSLE or control serum, 300 nM PMA, and 100 ng IFN-alpha. Induction of NETs was visualised using confocal microscopy following staining for Neutropol Elastase, dsDNA and DAPI. Pre incubation with 10uM JAK inhibitor was used to inhibit IFN alpha signalling. The IFN alpha environment of the JSLE and control neutrophils prior to isolation was measured using pSTAT1 and western blotting. To quantify NETs formed cultured neutrophils were digested using micrococcal nuclease to dismantle the NET scaffold, double stranded DNA was quantified using the Quant-iT Picogreen assay. Extracellular DNA was measured using a spectrofluorometer.

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Introduction: Damage Associated Molecular Pattern molecules (DAMPs) like HMGB1 have been demonstrated to be involved in pathological processes triggering and perpetuating autoimmune arthritis by attraction and activation of immune cells. The phagocyte-specific S100 proteins A8 and A9 (Myeloid Related Protein 8 and 14, respectively) are expressed by monocytes and granulocytes and can likewise operate as DAMPs by signalling through TLR4 once released into the extracellular space.

Objectives: S100A8/A9 has initially been identified in context with rheumatoid arthritis (RA). Generally, the proteins have a high relevance as inflammatory biomarker in various arthritic conditions, such as juvenile idiopathic arthritis (JIA). The proteins’ involvement in triggering or perpetuating pathomechanisms in autoimmune polyarthritis is albeit discussed controversially. We set out to carefully re-investigate this task and dissect possible contributions of S100A8/A9 to arthritis pathogenicity.

Methods: Collagen induced arthritis was induced in C57BL/6 and S100A9± mice, the latter lacking both S100A9 and its binding partner S100A8 at protein level. Disease progression was monitored by both clinical score and serological anti type II collagen (CII) autoantibody levels. Splenic T cell responses upon CII re-stimulation were studied in presence or absence of S100 protein priming of either whole splenocytes or bone marrow derived macrophages (BMDMs).

Results: S100A9± mice were almost completely protected from collagen induced arthritis (CIA). As observed throughout all experiments, this is accompanied by a strikingly significant decrease in anti type II collagen antibody titers compared to C57BL/6 wild type animals. Compared to wt-T cells, splenic S100A9± T cells respond poorly to CII re-stimulation. This phenotype can be partly reversed, if S100A9± splenocytes or macrophages (BMDMs), as the dominant CII antigen presenting cells, are primed with either S100A8 or S100A8/A9.

Conclusion: In an autoimmune arthritis mouse model S100A8/A9 can apparently operate at the interface between innate and adaptive immunity, possibly by modulating antigen presentation capacities of macrophages and thus affecting CD4+ T cell stimulation and downstream autoantibody production. Beyond their role as inflammatory biomarkers in arthritis S100A8/A9 can therefore likely trigger and promote autoimmunity. An active contribution to a distorted cross-talk between innate and adaptive immune mechanisms, as potentially in place in poly- or oligoarticular JIA, can be suggested.

Disclosure of interest: None declared.
initiation, progression and maintenance of inflammation in patients with Systemic Lupus Erythematosus (SLE). FoxP3+CD4+ regulatory T cells (Tregs) are important mediators of peripheral immune tolerance and their perturbed homeostasis, including expansion of CD45RA FoxP3lo non-Treg subpopulation was reported in adult patients with SLE. Type I and II interferons (IFN I and IFN II), which are implicated in SLE pathogenesis, were shown to perturb Treg homeostasis. Many IFN regulated genes are dependent on STAT1 for optimal transcription, and STAT1 protein expression is under control of IFNs.

**Objectives:** In this study we focused on FoxP3 expressing T cells subsets and IFN linked aberrances in expression of STAT1 in T-cells from childhood-onset SLE patients.

**Methods:** The pediatric study population consisted of 13 patients (12 female and 1 male) with childhood onset SLE, mean age 16.9 years, from which we obtained all together 25 samples at their routine 3-month checkup. 20 healthy blood donors (all female, mean age 17.0 years) were used as controls. Another study population consisted of 34 patients with adult onset SLE (31 female and 3 male) with mean age at the time of diagnosis 33.0 years.

Flow cytometric analysis of T cell STAT1 protein expression was performed after surface and intracellular staining in EDTA whole blood. In addition, expression of FoxP3 and CD45RA on CD4 T cells was studied, which enabled delineation of FoxP3 expressing cells into recently described subsets, including CD45RA FoxP3lo non-Tregs. Cells were analysed using FACSCanto II and LSRII Flow Cytometers (BD Biosciences) and subsequent analysis using FlowJo software (Tree Star). Two-tailed Mann-Whitney test was used to evaluate differences between groups.

**Results:** SLE T cells showed significantly higher STAT1 protein expression (p < 0.0001) than those of healthy controls, which were however not significantly different between pediatric and adult patients. This indicates strong IFN signature and suggest mechanism of inflammation self-maintenance utilizing the JAK-STAT signaling pathway also in pediatric SLE patients. Consistent with this we also found significantly higher frequencies of CD45RA FoxP3lo T cells (p < 0.0001), which were reported to secrete IFN-gamma, in patients with pediatric onset SLE.

**Conclusion:** Findings support the role of IFNs and aberrant STAT signaling, that may drive autoimmunity in SLE and functional deviation of Tregs that can also contribute to the pathogenesis of this disease. Our data suggest common T cell dysfunctions in patients with both childhood and adult onset SLE, suggesting that differences in clinical manifestations and disease severity between children and adults may be consequence of different developmental stage of affected organs and not novel (specific) etiopathogenesis.

**Disclosure of interest:** None declared.

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### P332

**PReS-FINAL-2342: Anti-TNFALPHA therapy targets PKB/C-AKT induced resistance of effector cells to suppression in juvenile arthritis**

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**P332**

**PReS-FINAL-2342: Anti-TNFALPHA therapy targets PKB/C-AKT induced resistance of effector cells to suppression in juvenile arthritis**

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**Introduction:** Resistance of effector T cells (Teff) to suppression contributes to disturbed immune regulation in autoimmune disease. Targeting this unresponsiveness to suppression might therefore have beneficial effects in autoimmune inflammation. In juvenile idiopathic arthritis (JIA) we have recently shown that Teff from inflamed joints are refractory to suppression, which was associated with enhanced PKB/c-Akt activation in these cells.

**Objectives:** To investigate whether anti-IL-6 and anti-TNFα target unresponsiveness of Teff to suppression in patients with JIA.

**Methods:** Resistant Teff from the inflamed joints of JIA patients were cultured in the presence of etanercept or anti-IL-6 in vitro and PKB/c-Akt activation measured. Suppression was measured. In addition, in vivo effects of TNFα blockade were investigated using peripheral blood samples of patient before and after start of etanercept therapy.

**Results:** In vitro treatment of synovial fluid Teff with anti-IL-6 led to improved Treg mediated suppression of cell proliferation in some, but not all patients. Blocking TNFα with etanercept however clearly enhanced suppression in all samples analyzed. In the presence of etanercept PKB/c-Akt activation of Teff was reduced and Teff became more susceptible to TGFB-mediated suppression, indicating that anti-TNFα directly targets resistant Teff.

**Conclusion:** This study is the first to show resistance of Teff to suppression as a target of anti-TNFα therapy in arthritis, resulting in improved regulation of inflammatory effector cells.

**Disclosure of interest:** E. Wehrens: None Declared, S. Vastert Consultant for: Novartis < 1000 euros, G. Mijnheer: None Declared, J. Meerding: None Declared, M. Klein: None Declared, N. Wulffraat Grant/Research Support from: Abbvie, Roche, Consultant for: Novartis, Pfizer, B. Prakken: None Declared, F. van Wijk: None Declared.

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### P333

**PReS-FINAL-2343: Cartilage thickness of the knee in juvenile idiopathic arthritis. comparative assessment by ultrasonography and magnetic resonance imaging**

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**Introduction:** The functional disability experienced in JIA is primarily caused by the degeneration of the osteocartilaginous structures due to the inflammatory process in the synovium. The ability to visualize the inflammatory process and the following osteocartilaginous degeneration is therefore of great importance in pediatric rheumatology. Magnetic resonance imaging (MRI) may currently be regarded as the Gold standard due to the ability to visualize all tissues with excellent precision. Ultrasonography (US) has been validated as a tool for measuring cartilage thickness in healthy children.

**Objectives:** To validate and compare US with MRI measurements of distal femoral cartilage thickness in the knee joint. Further, to compare outcome measures of inflammatory joint activity, and bone damages in the knees of children diagnosed with oligoarticular JIA.

**Methods:** Twenty-three children, median age 11.9 yrs (7.2-15.7 yrs), 17 girls and 6 boys with oligoarticular JIA where included. The knee joints were investigated by MRI and US. Outcome measures of clinical examination were distal femoral cartilage thickness, in addition to inflammatory outcome measures of joint activity, such as synovitis, effusion, bone marrow edema (MR), and Color Doppler signal (US). A clinical examination registered objective signs of joint inflammation, swelling within the joint or limitation in the range of movement with pain or tenderness.

**Results:** We found a high level of agreement between MRI and US measurements of distal femoral cartilage thickness, when US measures were corrected for sound velocity in cartilage, and Rho values between modalities were high (between 0.70 and 0.86, p < 0.05 for all). MRI and US were superior to clinical examination in detection of joint inflammation. Level of agreement for detection of synovitis was high, however MRI was superior in detection of effusion.

**Conclusion:** US measurements of distal femoral cartilage thickness is highly correlated to MRI measurements. MRI and US are superior to clinical examination in detection of inflammatory joint activity.

**Disclosure of interest:** None declared.

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### P334

**PReS-FINAL-2344: Radiographic evaluation of joint space width compared to cartilage thickness as assessed by ultrasonography in knees of children with juvenile idiopathic arthritis**

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**Introduction:** Joint space narrowing (JSN) is a measurable outcome of the tissue degeneration caused by the inflammatory process of the synovium in arthritis. JSN is usually assessed by conventional radiography. Ultrasonographic measurements of joint cartilage thickness in large and small joints have been validated in a study of healthy children and recently,
measurements of distal femoral cartilage of the knee joint have been validated in a group of JIA patients.

**Objectives:** To correlate measures of cartilage thickness in the knee assessed by US to the measures of joint space width (JSW) assessed by combined radiography in children with JIA.

**Methods:** Seventy-four children with JIA, aged between 5 and 15 years (median 11.3 yrs), 54 girls and 20 boys were included in the study. One hundred forty-eight knee joints were clinically assessed with regard to swelling within the joint and limitation in the range of movement with pain or tenderness. US assessed distal femoral cartilage thickness and radiography assessed joint space width (JSW) in the femoro-tibial joint space in four spots: medial and lateral femoral condylar areas in both right and left knee. Dijkstra Composite scoring system was used for the radiographical evaluation to describe the inflammatory activity and damage.

**Results:** We found a high level of agreement between US and radiographic measures of cartilage thickness and JSW with Rho values between r = 0.52 to 0.81 (p < 0.05 for all four assessed sites). When comparing knees previously affected by joint activity to joints never affected by arthritis, we found no significant difference by US, but we did with radiography. 

**Conclusion:** US measurements of distal femoral cartilage thickness are well correlated to radiographic measurements of JSW in knees of children with JIA. However, the loss of information by not assessing the tibial cartilage by US may limit the use of US as a tool in the assessment of JSN.

**Disclosure of interest:** None declared.

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**P335**

**PReS-FINAL-2345: Frequency of radiographic damage and progression in individual joints in children with juvenile idiopathic arthritis**

**Introduction:** Juvenile idiopathic arthritis (JIA) may lead to permanent damage of the articular cartilage and bone. Because the prevention of irreversible joint changes is a key objective in the long-term management of chronic arthritis, evaluation of radiographic joint damage represents an important clinical tool for assessing disease severity and progression and for monitoring the effectiveness of therapeutic interventions. Although newer imaging techniques, such as MRI and ultrasound, allow earlier detection of bone and cartilage changes, conventional radiography remains the gold standard for the demonstration of structural joint lesions in patients with JIA. Importantly, mapping the prevalence and location of structural abnormalities in different sites on conventional radiology may provide useful information to guide future investigations with MRI and ultrasound.

**Objectives:** To evaluate the presence and progression of radiographic joint damage, as assessed with the adapted Sharp-van der Heijde (aSH) score, in individual joints in the hand and wrist in patients with JIA, and to compare progression of damage among different JIA categories.

**Methods:** A total of 372 radiographs of both wrists and hands obtained at first observation and at last follow-up visit (after 1 to 10 years) in 186 children with polyarticular-course JIA were evaluated. All radiographs were scored using the aSH scoring system by 2 independent readers. Radiographic assessment included evaluation of joint space narrowing (JSN) and erosions on baseline and last follow-up radiographs and of progression of radiographic changes from baseline to last follow-up radiographs.

**Results:** Both JSN and erosions occurred in all aSH areas. Overall, radiographic damage and progression were more common in the wrist and less common in metacarpophalangeal joints. The hamate and capitae areas appeared particularly vulnerable to cartilage loss. Erosions were identified most frequently in the hamate and capitae bones as well as in the 2nd and 3rd metacarpal bases. Patients with extended oligoarthritis were distinctly less susceptible to JSN in hand joints, whereas patients with polyarthritis showed a greater tendency to developing erosions in hand joints.

**Conclusion:** Radiographic joint damage and progression in our patients with JIA were seen most commonly in the wrist and less commonly in MCP joints. The frequency and localization of structural abnormalities differed markedly across disease categories.

**Disclosure of interest:** None declared.

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**P336**

**PReS-FINAL-2346: Hypomorphic RAG deficiencies: phenotypic variability and usefulness of TREC/KREC as diagnostic biomarkers**

**Introduction:** An increasing number of patients with combined immunodeficiencies have been found to carry hypomorphic variants of genes that otherwise cause severe combined immunodeficiency (SCID). These patients not only present with recurrent and sometimes life-threatening infections, but also with immunodysregulatory symptoms such as autoimmune cytopenias and granulomas, and are a diagnostic challenge.

**Objectives:** The objective of this study was to determine whether TRECs and KRECs are useful in identifying patients beyond infancy with combined T- and B-cell deficiencies who are otherwise difficult to diagnose due to late-onset, heterogeneous clinical phenotypes and variable numbers and functions of T and B cells.

**Methods:** Patients with combined immunodeficiency due to hRAG mutations (n = 6), with DOCK8 deficiency (n = 3) and with classical SCID due to RAG1, RAG2, ARTEMIS and IL2RG defects were treated at the University Hospital Ulm, Germany. Four of the patients with hRAG deficiencies presented with granulomatous lesions, one with vitiligo, three patients had autoimmune cytopenias. The earliest available samples of MNCs were analyzed (cells cryopreserved at the median age of 10 years, range 6-17 years) for patients with hRAG and DOCK-8 deficiencies.

**Results:** Immunophenotyping of hRAG patients’ peripheral MNCs showed reduced, but variable numbers of T and B cells. Thymic derived naïve CD45RA+CD45RO- T cells were < 30% in all patients (range 1-7%). Residual T-cell function (proliferation assays) and B-cell function (antibody titres following vaccination, data not shown) were detectable, but abnormal in all hRAG patients. T-cell repertoires were diverse in 5 patients, and restricted in patients 1 and 4. Even when detectable, TREC and KREC amounts in hRAG patients were at least 32-fold reduced compared to healthy controls.

**Conclusion:** Measurement of TREC and KREC levels is a fast and easily performed tool for the quantification of thymic output and B-cell maturation respectively. We envisage that these biomarkers may serve as valuable complementary parameters for the initial immunological work-up when a diagnosis of CID is being considered. Timely clinical suspicion paired with abnormal TREC and KREC levels might facilitate earlier referral of this group of patients with atypical and late presentation of CID to the pediatric immunologist and possibly to treatment by HCT.

**Disclosure of interest:** None declared.

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**P337**

**PReS-FINAL-2347: Does switching anti-TNFα biologic agents offer an effective option in childhood chronic uveitis: the evidence from a systematic review and meta-analysis approach**

**Introduction:** A subset of patients, of unknown percentage, fail to respond to TNFα blockers or are unable to tolerate these therapies and may therefore benefit from switching to another drug.

**Objectives:** to report the evidence regarding the effectiveness of switching to another anti-TNFα treatment in children with childhood
autoimmune chronic uveitis (ACU), failure/refractory to the first course of anti-TNFα treatment.

Methods: A systematic search between January 2000 and May 2013 was conducted using EMBASE, Ovid MEDLINE, Evidence Based Medicine Reviews-ACP Journal Club, Cochrane libraries, and EBM Reviews. Studies investigating the efficacy of anti-TNFα therapy, as the second biologic treatment for ACU, in children (≤16 yrs) refractory to a first course of a single anti-TNFα treatment, topical and/or systemic steroid therapy and at least one DMARD, were eligible for inclusion. The primary outcome measure was the improvement of intraocular inflammation, as defined by the SUN working group criteria, at 6 (± 2) month follow-up on treatment.

Results: Among 1096 identified articles, 128 were scrutinized: 10 observational studies, 7 on Adalimumab (ADA), 4 on Infliximab (INF), were deemed eligible, including 40 children (ADA n = 34, INF n = 6). JIA was the most common disease: 39 out 40 cases (97.5%). Seven-teen children received Etaonecept: 11 were switched to ADA, the remaining 6 to INF. All the 23 children previously received INF were switched to ADA. Altogether, 30 children (24 on ADA, 6 on INF) out of 40 responded to treatment, and the proportion of participants with a positive response ranged from 43% to 100% individual studies. The pooled analysis suggested that a second anti-TNFα treatment with ADA and INF has a favorable effect in the improvement of intraocular inflammation: 0.75 (95% CI: 0.67-0.81) was the common OR of the proportion of subjects improving All 6 children who received INF after a previous failure to a course of ETA, responded. Eight out of eleven (72.7%) children with a previous failure ETA, and 16 out 23 (69.5%) with a previous failure to INF, responded to a second course of anti-TNFα treatment with ADA. Eighteen children on ADA and all 6 on INF have been able to tape and/or discontinue systemic steroid administration; discontinuation/tapering of concomitant DMARD therapy was possible for 7 out of 19 children receiving ADA, 3 out of 4 children receiving INF. Four eligible papers did not report extractable data regarding visual outcome. Nine of 11 children (73%) showed improvement or stable normal visual acuity post ADA treatment, and 5 out of 6 children (79.3%) after INF. Among 33 anti-TNFα exposed children, data regarding side effects were not available from 2 studies (n = 7), 6 (25.2%) experienced adverse events: 5 while on ADA (all 5 complaining pain discomfort and/or local reactions), 1 on INF, who experienced a transient broncospastic cough.

Conclusion: Switching between anti-TNFα obtains an overall probability of improvement of intraocular inflammation in 75% children affected by refractory ACU. No switching has been reported to ETA, all children received ADA or INF after the first anti-TNFα failure.

Disclosure of interest: None declared.

P338
PReS-FINAL-2348: Identification of autoantibodies against inner ear antigens in a cohort of children with idiopathic sensorineural hearing loss

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3Pediatric Rheumatology 2013, 11(Suppl 2):P338

Introduction: Immune-mediated pathogenesis has been suggested for idiopathic sensorineural hearing loss (iSNHL). Recent studies have investigated the relationship between iSNHL and autoantibodies against inner ear antigens, but specific tests are not available.

Objectives: To assess the positivity of autoantibodies against inner ear in a series of pediatric patients with idiopathic sensorineural hearing loss.

Methods: We conducted a prospective, non-interventional observational study in a series of pediatric patients affected by iSNHL. Autoantibodies against inner ear (anti-Cogan peptide, anti-connexin 26, anti-DEP1/CD148 and anti-reovirus), previously described in the serum of patients with Cogan’s syndrome, were detected in our populations. The characteristics of children who resulted positive were also evaluated to verify if clinical data, disease progression and response to treatment could confirm an immune-mediated pathogenesis.

Results: Eleven patients were enrolled and 9 of them resulted positive for the inner ear antibodies detected. Non-organ specific autoantibodies were present in 5 children out of 9. An immune-mediated condition was diagnosed in 2 cases and minor immune manifestations were found in other 2 patients. In 5 cases hearing loss remained stable with no therapy, otherwise 4 children developed hearing loss progression. Two subjects were treated with steroids and methotrexate achieving hearing improvement. Another subject started methotrexate treatment showing hearing loss stabilization.

Conclusion: Most of clinical characteristics and comorbidities described, added to immunologic tests results and to treatment efficacy, suggest an immune-mediated pathogenesis of hearing loss. Inner ear autoantibodies are not able to identify children affected with autoimmune sensorineural hearing loss but, integrated with clinical data, they can represent a diagnostic aid for the physician. Large prospective studies are needed to investigate usefulness, diagnostic and prognostic role of these autoantibodies.

Disclosure of interest: None declared.

P339
PReS-FINAL-2349: Spectrum of thrombotic and non-thrombotic manifestations in 159 children with positive antiphospholipid antibodies

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Pediatric Rheumatology 2013, 11(Suppl 2):P339

Introduction: Antiphospholipid antibodies (aPL) play the central pathogenic role in antiphospholipid syndrome (APS) characterized by arterial and venous thrombosis, recurrent fetal loss and persistent circulating aPL. The diagnostic criteria of definite APS are not entirely applicable in pediatric population. An international multicentric project named Ped-APS registry included 121 patients with APS onset before 18th birthday. Almost half of them (49.5%) had an associated autoimmune disease. In this study a large percentage of children with aPL-related thrombotic event had at the time of the initial thrombotic event associated nonthrombotic clinical manifestations including: hematological manifestations (38%), dermatological manifestations (18%) and nonthrombotic neurological manifestations (16%).

Objectives: To evaluate the spectrum of thrombotic and non-thrombotic clinical manifestations associated with aPL, namely anticardiolipin antibodies (aCL), anti-β2-glycoprotein I antibodies (anti-β2-GP1) and lupus anticoagulant (LA), among children with positive laboratory results when tested for the presence of aPL.

Methods: Pediatric patients in a tertiary care hospital were according to the clinical judgment of the treating physician tested for the presence of aPL and the laboratory results were saved in a computer database. In this single-center bidirectional study we included 159 consecutive patients from the database that tested medium or highly positive for aCL and/or positive for anti-β2-GP1 and/or positive for LA at least once in the period from January 1997 to July 2012. Clinical manifestations of these patients were then evaluated, specifically thrombosis, nonthrombotic neurological and hematological manifestations, skin disorders and cardiac valve disease.

Results: Of all 139 patients (61 boys and 98 girls, mean age at the occurrence of symptoms was 11.4 years, range 1 to 18 years of age) 55 had an underlying systemic disease (Systemic lupus erythematosus 31, Juvenile idiopathic arthritis 19, Scleroderma 2, Primary Raynaud’s syndrome 2 and Sarcoidosis 1) and 8 had other autoimmune disease. Sixty-six out of 159 (42%) patients presented with one aPL-related clinical manifestation, 18 (11%) with two and 5 (3%) patients presented with three or more aPL related clinical manifestations. Of the aPL related clinical manifestations thromboses occurred in 25 patients (venous 16, arterial thrombosis 9, recurrent thrombosis 2), nonthrombotic neurological disorders were present in 25 patients (seizures 11, migraine 7, chorea 2, other 5), hematological disorders in 48 (thrombocytopenia 24, autoimmune hemolytic anemia 10, leucopenia 9, Evans syndrome 5), skin disorders in 19 (Raynaud’s phenomenon 11, livedo reticularis 8) and a cardiac valve disease in 5.

Conclusion: In an unselected group of children with positive aPL nonthrombotic clinical manifestations were more frequent than thrombotic events. The most common clinical manifestations associated with aPL in children are thrombocytopenia, followed by venous thrombosis, seizures and Raynaud’s phenomenon.

Disclosure of interest: None declared.
P340
PrEs-FINAL-2350: Overexpression of crem alpha leads to a higher inflammatory response in lps induced acute lung injury (Ali) and might therefore trigger infectious complications in patients with autoimmune diseases
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Pediatric Rheumatology 2013, 11(Suppl 2):P340

Introduction: Patients with autoimmune diseases are highly susceptible towards infectious complications. In patients with SLE, infections are even one of the most common causes of morbidity, hospitalization and death. CREMs is a transcription factor, which is overexpressed in T cells from patients with systemic lupus erythematosus (SLE). Beyond this, CREM is also upregulated in a murine model of LPS-induced acute lung injury (ALI).

Objectives: It was our aim to examine whether the overexpression of CREM leads to a higher inflammatory environment in a murine model of LPS-induced ALI and thus may contribute to infectious complications in patients with autoimmune diseases including SLE patients.

Methods: Ali was induced via intratracheal LPS instillation in wild type and CREM transgenic mice as well as in lymphopenic Rag-/- mice reconstituted with CREM-/- T cells. Lung functions and bronchial hyperresponsiveness (AHR) were measured with the flexiVent setup. The inflammatory phenotype was characterized by cell type analysis (FACS), cytokine expression (ELISA, qRT-PCR) and histology.

Results: CREM transgenic mice, which are characterized by a T-cell specific overexpression of CREM, suffer from an enhanced development of LPS-induced ALI. CREM overexpression thereby increases the number of T cells in bronchoalveolar lavage (BAL) and deteriorates lung function during the early phase of ALI. Furthermore CREM transgenic mice show a stronger inflammatory response with higher levels of TNFα, IL-6 and IL-17 correlating with increased numbers of T cells and neutrophils in BAL. Vice versa, expression of FoxP3 and IL-2 and the numbers of regulatory T cells are downregulated in lung tissue as well as in the BAL. These changes result in restricted lung function and thereby reduced oxygenation of the animals. Beside this, an adoptive transfer of CREM-/-CD4+ T cells resulted in ameliorated disease levels in RAG-/-mice compared to RAG-/- mice transferred with wild type CD4+ T cells.

Conclusion: Thus, CREM-transgenic animals represent a model in which proinflammatory T cells aggravate ALI. Given the fact that patients with autoimmune diseases like SLE show higher levels of CREM and an increased susceptibility towards infectious complications our finding is potentially of clinical significance and enables new therapeutic strategies.

Disclosure of interest: None declared.

P341
PrEs-FINAL-2351: Children with probable SLE by ACR criteria may need more aggressive lupus treatment early in the disease course
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Pediatric Rheumatology 2013, 11(Suppl 2):P341

Introduction: The pediatric lupus patients are required to meet the American College of Rheumatology (ACR) minimum criteria to be included in the research cohort and considered for aggressive therapy. This approach may delay early aggressive therapy.

Objectives: The research explores whether by delaying diagnosis until 4/11 criteria are met affects the patient outcome negatively. To our knowledge there is no published literature of the “probable” pediatric systemic lupus erythematosus (psLE) population.

Method: Institutional Review Board approval was obtained to retrospectively review the charts of 98 SLE patients seen in the pediatric rheumatology clinic at Nationwide Children’s Hospital over the past 24 years. All the patients were divided in to two groups, ‘definitive psLE’ - who met the minimum 4/11, or more ACR criteria and the ‘probable psLE’ who did not meet the minimum criteria at presentation in rheumatology clinic. Both the groups were assessed for disease severity, damage and gradient of damage. Appropriate statistical tests were used i.e. Chi-Square test, Fisher’s Exact test, Univariate logistic regression and Wilcoxon two-sample test were used for statistics for various data set. All tests were conducted in SAS 9.2

Results: Out of 98 psLE patients 71% were included in definitive psLE (D psLE) group while 28.57% were included in probable psLE (P psLE) group. The mean time for PsPsLE group to reach D psLE status was 20.3 months. There was no difference in the ethnic distribution (p = 0.770) in D psLE and PsPsLE. PsPsLE were more likely to have higher male:female ratio (p = 0.032), and were older at presentation that D psLE (p = 0.045). PsPsLE patients were less likely to have internal organ involvement (71.3% Vs 25.7%), were less likely to be hospitalized and receive pulse steroids (p = 0.0142) or oral steroids (p = 0.0172) at presentation. PsPsLE patients were less likely to be hospitalized receive pulse steroids ever (p = 0.0628), were less likely to have renal disease ever (p = 0.0653) and nervous system disease ever (p = 0.0182). Probable SLE was more likely to receive hydroxychloroquine (p = 0.050). The organ damage was assessed using SLICC/ACR damage index at 1, 5 and 10 years post diagnosis. The maximum damage was recorded within first 5 years of the diagnosis. Initial damage was predictive of later damage. D psLE had higher disease damage scores at 5 and 10 years We compared the gradient between the onsets of symptoms and the development of organ damage in the two groups. The PsPsLE patients had significantly higher internal organ damage gradient as compared to D psLE (p value = 0.0169)

Conclusion: In our population PsPsLE patients had a significantly high gradient of damage than the D psLE group.In spite of D psLE being more severe diseases ever and more diseases damage, the disease damage progression was steeper and faster in PsPsLE. This can only be explained by the fact that PsPsLE patients received less intense treatment at presentation than D psLE group. It may be that PsPsLE patients at presentation need just as vigorous treatment as the children with definitive SLE.

Disclosure of interest: None declared.

P342
PrEs-FINAL-2352: Apoptosis profile in patients with juvenile-onset systemic lupus erythematosus
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Pediatric Rheumatology 2013, 11(Suppl 2):P342

Introduction: Apoptosis related proteins have been involved in immune dysregulation and development of systemic lupus erythematosus (SLE).

Objectives: To assess sFas, sFasl, sTRAIL and sBcl-2 in sera to evaluate Fas and Bcl-2 expressions in peripheral monocytes, T and B lymphocytes from juvenile-onset SLE (JSLE) and to determine relationships with disease activity.

Methods: Forty-three JSLE patients (revised ACR criteria, mean age = 14.3 yrs, 36F:7M), and 35 age and gender matched healthy controls were studied; 30 JSLE had SLEDAI score ≥ 4, reflected active disease. Soluble molecules were measured by commercial ELISA kits. Lymphocytes and monocytes were stained with specific moAbs and analyzed by flow cytometry. Kruskal-Wallis test and Spearman’s rank were employed and statistical significance considered p value < 0.05.

Results: JSLE sera had significantly increased sFas (188.1 ± 69.2 vs 133.2 ± 80.6, pg/ml) and sTRAIL (691.3 ± 631.8 vs 346.6 ± 251.1, pg/ml), decreased sFasl (0.08 ± 0.1 vs 0.36 ± 0.4, ng/ml), and similar sBcl-2 (7.4 ± 8.6 vs 9.3 ± 9.6, mg/ml) levels compared to healthy controls. SLEDAI score directly correlated with sFas (r = 0.52, p = 0.001), and decreased sFasl (0.08 ± 0.1 vs 0.36 ± 0.4, ng/ml), and similar sBcl-2 (7.4 ± 8.6 vs 9.3 ± 9.6, mg/ml) levels compared to healthy controls. SLEDAI score directly correlated with sFas (r = 0.52, p = 0.001). JSLE patients compared to controls had significantly increased Fas expression on CD14+ (43.7 ± 10.3% vs 28.9 ± 9.4%), CD4+ (20.3 ± 6.7% vs 16.2 ± 6.2%) and CD8+ (21.5 ± 9.6% vs 12.3 ± 5.8%) T cells, and also on CD19+ B cells (2.1 ± 1.4% vs 1.4 ± 0.7%), whereas, it was decreased on CD14+ monocytes (93.6 ± 6.9% vs 96.7 ± 2.5%, p = 0.01). There was direct correlation between percentages of CD19+Fas+ cells and SLEDAI (r = 0.38, p = 0.02) and inverse correlation between percentages of CD14+Fas+ cells and SLEDAI (r = -0.35, p = 0.01).
Mean fluorescence intensity (MFI) of Bcl-2-positive cells from JSLE patients was significantly increased in CD3+(28.8 ± 8.4 vs 22.9 ± 4.2), CD4+(28.6 ± 8.2 vs 22.9 ± 4.4) and CD8+(29.4 ± 9.4 vs 22.8 ± 3.6) T cells, and also in CD19+ B cells (25.5 ± 9.6 vs 21.5 ± 3.6). Bcl-2 expression in CD14+ monocytes was lower in JSLE compared to controls (25.2 ± 18.2% vs 34.5 ± 16.6%, p = 0.006). Direct correlation between percentages of CD19+Bcl2+ cells and SLEDAI (r = 0.47, p = 0.04) was shown.

Conclusion: JSLE patients showing high sFas and sTRAIL and low sFasL phosphorylation of NFkB pathway were more frequent in patients with severe disease. A possible role as a marker for disease activity needs to be defined.

Disclosure of interest: None declared.

P343
PrEs-FINAL-2353: Are rasopathies new monogenic predisposing conditions to the development of systemic lupus erythematosus? B Bader-Meunier1,2, H cave1, N jerehms1, F Roux-Laucat1
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Introduction: RASopathies ( Noonan syndrome (NS) and Noonan-related syndromes) are neurodevelopmental syndromes resulting from germline mutations in genes that participate in the ras sarcoma/mitogen-activated protein kinases (RAS/MAPK) pathway (PTPN11, SOS1, RAF, KRAS or NRAS and SHOC2). Some monogenic conditions are associated with the development of systemic lupus erythematosus (SLE), and a few reports described the association of SLE with NS.

Objectives: We aim to search for a relationship between RASopathy and the development of SLE.

Methods: We reported for the first time on a 13-year-old boy with NS with loose anagen hair (NSLAH) resulting from mutation in SHOC2 who developed an autoimmune disorder which fulfilled four American College of Rheumatology (ACR) criteria for the classification of SLE (polyarthritides, pericarditis, antinuclear antibodies, anti-DNA antibodies). The case report then prompted a literature review by a systematic search for English and French articles on the subjects of RASopathies and SLE that had English abstracts in PubMed from 1966 to 2012.

Results: We identified seven additional patients with RASopathy and SLE. The male-to-female ratio was 1:1, and age at onset of SLE ranged from 5 to 32 years. The most common features were polyarthritides (7/8 patients), auto-immune cytopenia (4/8 patients) and pericarditis (4/8 patients) while only one patient presented with skin involvement.

Conclusion: The association of two rare diseases in eight patients suggests that RASopathies may be associated with the development of SLE, which is characterized by a higher male-to-female ratio, a lower rate of skin involvement and a higher rate of pericarditis than “classic” SLE.

Disclosure of interest: None declared.

P344
PrEs-FINAL-2354: Laboratory investigation of the role of toll-like receptors on kidney cells in pathogenesis of lupus nephritis E Sen1,*, G Welsh1, A Ramanan1, M Saleem2,3
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Pediatric Rheumatology 2013, 11(Suppl 2):P344

Introduction: Lupus nephritis (LN) is a chronic complication of juvenile-onset systemic lupus erythematosus (JSLE). Current treatments include long-term immunosuppressants with significant side effects. There is a need to identify targets for more effective therapies. Toll-like receptors (TLRs) perform an important role in the innate immune response by recognizing conserved molecules associated with pathogens. Previous studies have suggested a role for TLR7 and TLR9 in lymphocytes in the pathogenesis of SLE. Podocytes are specialised cells forming an important part of the glomerular filtration barrier. Biopsies from LN patients have demonstrated higher TLR7 and TLR9 expression in glomeruli compared with controls and suggest that these TLRs are localised to podocytes. We hypothesise that stimulation of TLR7 and/or TLR9 in podocytes, acting via nuclear factor kappa B (NFkB), leads to cellular damage and resultant kidney disease.

Objectives: This research aims to examine the role of TLR7 and TLR9 in podocytes to identify potential targets for more effective therapies of lupus nephritis.

Methods: Conditionally-immortalised human podocyte cell lines were cultured to examine expression of TLRs and the effects of their activation on the NFkB pathway and cell proliferation. Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) with Western blotting were used to detect TLR7 and TLR9 expression in the mRNA and protein levels respectively. The effects of lipopolysaccharide (LPS), an inflammatory stimulus, on TLR expression were examined. Podocytes were stimulated with imiquimod, a specific TLR7 agonist and CpG oligodeoxynucleotide (ODN) 2216, a specific TLR9 agonist. Phosphorylation of NFkB pathway components was assessed with Western blotting and a cell proliferation assay used to estimate cell survival following treatments. The effects of treatment with TLR agonists in combination with dexamethasone were also examined.

Results: Treatment of podocytes with LPS was associated with increased expression of TLR7 at both mRNA and protein levels whereas there was comparatively little change in TLR9. Exposure of the cells to imiquimod or CpG ODN 2216 increased phosphorylation of NFkB. Initial results from the cell proliferation assay suggested lower levels after imiquimod or CpG ODN 2216 treatment for 24 hours. Since podocytes are terminally differentiated this implies reduced cell numbers or lower metabolic activity. Exposure of the podocytes to dexamethasone was associated with lower expression of TLR7 and TLR9 at the mRNA level. There was preliminary evidence of less phosphorylation of NFkB when cells were treated with dexamethasone prior to TLR agonists compared with the latter alone.

Conclusion: This study suggests that podocytes express TLR7 and TLR9. Agonists of these receptors have effects on intracellular signalling. If confirmed through ongoing work, the TLR-NFkB pathway in kidney cells may be a potential target for novel therapies in lupus nephritis.


P345
PrEs-FINAL-2355: Comparison of pediatric and adult SLE genetic load MD Dominguez1, ED Silverman2, J Beyene2
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Pediatric Rheumatology 2013, 11(Suppl 2):P345

Introduction: Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disease that is the result of the interaction between genetic and environmental factors. Specific genes have been found to be related to the development of SLE and also single nucleotide polymorphisms (SNPs) have been associated to this condition. Although patients with pediatric-onset SLE (pSLE) and adult-onset SLE (aSLE) differ in disease presentation, activity, and outcomes, all studies to date have not found any specific or unique set of genes in pSLE compared to aSLE. Moreover, it has been shown that the frequency of genes in these two SLE populations is the same. However, is possible that an increased genetic load may explain the earlier onset and more severe disease seen in pSLE as compared to aSLE patients.

Objectives: To determine if patients with pSLE are more likely to have higher genetic load of SNP’s associated with SLE than patients with aSLE. To investigate if this genetic load follows an age-related gradient.

- To define if the higher genetic load in pSLE is associated with more severe disease in this population.

Methods: study design and patients: This is a cross-sectional study of approximately 1000 pSLE and 1000 aSLE patients. Adult and pediatric cohorts were obtained from centers in USA and Canada.

Inclusion criteria: SLE patients who are followed at the participating centers and who meet at least 4 of 11 ACR classification criteria for this disease are eligible for study.

Variables: Disease severity will be measured by major organ involvement and damage (Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC-DI)).
We collected DNA from the collaborating centers. The DNA will be isolated from blood samples. Genetic polymorphisms will be determined using the following techniques: (a) Immunochip array: an Illumina Infinium genotyping chip, containing 199,806 SNPs associated with the major autoimmune diseases including SLE. (b) SLE designed Illumina GoldenGate Genotyping Assay: a flexible, pre-optimized assay that uses a discriminatory DNA polymerase and ligase to interrogate from 384 to 3,072, SNP loci simultaneously. Approximately 162 SLE susceptibility genes will be tagged with these techniques.

Results: We will determine a genetic score for each patient as explained as follow:

1. Simple count: protective SNPs and susceptibility SNPs
2. Total count: susceptibility SNPs-protective SNPs
3. Susceptibility score (SS): summation of the relative risk (RR) of each susceptibility SNP
4. Protective score (PS): 1 - RR of each protective SNP
5. Summation core (SMS): SS - PS

After performing the descriptive analysis, we will determine if the genetic load is higher in pediatric as compared with adult populations and whether there is an age-related gradient of the genetic load within and between these populations. In addition, we will determine if the genetic load is related to disease severity and damage in these populations individually and for the complete adult and pediatric cohort.

Conclusion: This study will be the first to determine if pediatric SLE patients show higher genetic load of SLE’s compared to adult SLE population and if genetic load is associated with disease severity and damage.

Disclosure of interest: None declared.

P347
PReS-FINAL-2357: Effects of anti-melanocyte stimulating hormone in murine pristine-induced lupus
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Introduction: Alfa-melanocyte stimulating hormone (α-MSH) has a variety of biological functions such as downregulation of pro-inflammatory pathways, reduction of skin delayed-type hypersensitivity and blockage of leukocyte migration. Inhibition of experimental disease models development including inflammatory bowel disease and rheumatoid arthritis has been shown, however the immunomodulatory and anti-inflammatory effects of α-MSH on murine lupus remain undetermined.

Objectives: To evaluate the effect of α-MSH analogue (NDP α-MSH) on pristine-induced murine lupus.

Methods: Thirty-five BALB/c mice were injected with 0.5 ml intraperitoneal (IP) pristane for lupus-like model induction and 5 age/male matched control mice were given saline. Pristine-induced lupus animals received daily IP saline (n = 5) or treatments with 3.1 mg/kg/d chloroquine (n = 10), 1.25 mg/kg/d NDP α-MSH (n = 10) or 2.5 mg/kg/d NDP α-MSH (n = 10). Prior and 180 days after induction, clinical and laboratorial lupus-like parameters were examined. Sera ANA was tested by IF using Hep2 cells. Statistical analysis was performed by Mann-Whitney and Fisher test and P < 0.05 considered significant.

Results: Arthritis in both hind legs and large amounts of lipogranulomas in peritoneal cavity were observed in all lupus-like animals in contrast to all controls. By visual observation, all lupus animals treated with both doses of α-MSH had significant less amount and lower size lipogranulomas. Mean arthritis score in 5 untreated mice, 9 animals treated with chloroquine and 8 with α-MSH 2.5 mg/kg/d was 5.2, 3.33 and 3.1 respectively. Remarkably, mean arthritis score of animals treated with α-MSH 1.25 mg/kg/d was 1.6, significantly lower than untreated mice (1.6 vs 5.2, p = 0.0291). ANAs were negative in sera from all 40 animals before pristane lupus injection; 180 days after induction, ANAs remained negative in normal mice but became positive in all 5 (100%) untreated lupus animals, 7 (77%), 4 (50%) and 3 (35%) lupus models treated with chloroquine, α-MSH 2.5 mg/kg/d and α-MSH 1.25 mg/kg/d (100% vs 35%, p = 0.0256), respectively. Before the end of the experiment, by day 150, 3 animals died: 1 treated with chloroquine and 2 with higher doses of α-MSH.

Conclusion: NDP α-MSH promoted improvement of clinical and serological parameters in pristine-induced murine lupus suggesting a potential role for this drug in human SLE.

Disclosure of interest: None declared.

P348
PReS-FINAL-2358: T helper cells in henoch-schönlein purpura/iga vasculitis
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Introduction: Henoch-Schönlein purpura (HSP)/IgA vasculitis is the most common childhood vasculitis in Turkey. During the course of the disease,
renal involvement may be observed in 30-60% of patients. In recent years, the role of T helper (Th) cells in the pathogenesis of HSP/IgA vasculitis has become a focus for research.

Objectives: The aim of the study was to investigate the role of Th1, Th2, Th17 and Treg cells in disease pathogenesis and their relations with clinical and histopathological parameters.

Methods: Twenty-two patients diagnosed as HSP/IgA vasculitis with renal biopsy and 6 skin biopsies were included in the study. Non-tumoral renal tissues of nephrectomy materials of 20 Wilms tumor patients and non-pathological skin biopsies of five patients served as the control group. IFN-gamma (Th1), IL-4 (Th2), IL-17 (Th17) and FOXP3 (Treg) were analysed through immunohistochemistry and the results were compared with controls.

Results: The study included children and adult patients selected on the basis of complete data set and follow up of at least one year, followed at the pediatric and adult Rheumatology Centers, University Hospital of Padua, over a period of 20 years (1993-2013). GPA was diagnosed according to the 1990 American College of Rheumatology (ACR) criteria. Clinical features, instrumental findings, laboratory parameters and therapeutic regimens of both cohorts were analyzed at diagnosis, six months later (T6) and at the last follow-up visit. Disease activity was assessed by the Birmingham Vasculitis Activity Score (BVAS) modified for GPA.

Conclusions: GPA is a rare disease in childhood. Treatment strategies and clinical approach are still mostly derived from adult GPA studies.

Objectives: The present study was aimed to compare disease onset and course, therapeutic approach and clinical outcome of two cohorts of children and adults affected by GPA.

Methods: The study included children and adult patients selected on the basis of complete data set and follow up of at least one year, followed at the pediatric and adult Rheumatology Centers, University Hospital of Padua, over a period of 20 years (1993-2013). GPA was diagnosed according to the ACR and EULAR/PRES criteria. Clinical features, instrumental findings, laboratory parameters and therapeutic regimens of both cohorts were analyzed at diagnosis, six months later (T6) and at the last follow-up visit. Disease activity was assessed by the Birmingham Vasculitis Activity Score (BVAS) modified for GPA.

Results: At onset, in all three patients, autoimmunity (ANA, ANCA and anti-dsDNA) were negative, serum C3, C4 and C1q were low and anti-C1q antibodies were found to be markedly positive. Skin biopsy revealed leucocytoclastic vasculitis in all of them. Symptomatic therapy with antihistamines and non-steroidal anti-inflammatory drugs (NSAIDs) was ineffective. When dapsone was started skin involvement resolved completely. After approximately 4 years from onset the three children presented a renal involvement: one with persistent microhaematuria, one with persistent microhaematuria and proteinuria and one with significant proteinuria. A renal biopsy showed three different histological findings: mesangial glomerulonephritis with membranous features, mesangial glomerulonephritis associated with focal necrotizing small-vessel vasculitis and glomerulonephritis with intense mesangial, endothelial and extra-capillary proliferation with initial tubular atrophy. The first child was treated with oral glucocorticoid and mycophenolate mofetil, the other two with pulses of intravenous metilprednisolone and cyclophosphamide. All three patients presented a good clinical response.

Introduction: Granulomatosis with polyangiitis (GPA) is a rare disease in children. Treatment strategies and clinical approach are still mostly derived from adult GPA studies.

Objectives: The present study was aimed to compare disease onset and course, therapeutic approach and clinical outcome of two cohorts of children and adults affected by GPA.

Methods: The study included children and adult patients selected on the basis of complete data set and follow up of at least one year, followed at the pediatric and adult Rheumatology Centers, University Hospital of Padua, over a period of 20 years (1993-2013). GPA was diagnosed according to the ACR and EULAR/PRES criteria. Clinical features, instrumental findings, laboratory parameters and therapeutic regimens of both cohorts were analyzed at diagnosis, six months later (T6) and at the last follow-up visit. Disease activity was assessed by the Birmingham Vasculitis Activity Score (BVAS) modified for GPA.

Results: Ten children with mean age at disease onset of 10.3 years (range 3-15) entered the study. 6/9 were female. Mean follow-up time was 8.4 years (range 2.5-18). Of the 23 adults 65.3% were female, mean age at onset 53 years (range 17-71) and mean follow-up 1.9 years (range 1-3.5). At disease onset, BVAS, clinical features and laboratory parameters of the two cohorts were not significantly different. BVAS decreased more slowly in children (p = 0.002). As for internal organs involvement, renal disease was significantly higher at T6 and persisted over time in children (p = 0.003). Similarly, pulmonary disease remained elevated at T6 while decreased over time in adults (p = 0.01). At the last F/U visit, eye involvement was present in 44% of children while no adult showed signs of ocular disease (p = 0.004). Regarding to the treatment strategies, immunosuppressive drugs were more widely used in children at diagnosis (p = 0.06) and biological agents were used at an earlier disease stage than adults. Despite the longer follow up, all children were still on treatment at the last visit while 17% of adults were off therapy.
Conclusion: Adults and children with GPA had similar disease activity at onset. However, childhood GPA had a more severe-course due to persistent renal, pulmonary and eye involvement. Lower disease activity was obtained with a more aggressive treatment approach although no pediatric patients reached a treatment-free remission.

Disclosure of interest: None declared.

P351 PreS-FINAL-2361: Maintenance treatment in childhood granulomatosis with polyangiitis
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Pediatric Rheumatology 2013, 11(Suppl 2):P351

Introduction: Granulomatosis with Polyangiitis (GPA) is a rare but life threatening disease. Most children present with pulmonary bleeds and/or renal failure. Most treatment regimens are derived from the adult literature, no studies have been performed in pediatric patients.

Objectives: The aim of this study is to describe the maintenance treatment in a large group of children with GPA.

Methods: All consecutive children diagnosed with GPA since January 2000 in the Hospital for Sick Children were included. Demographic data, data at diagnosis and follow-up data were collected. Descriptive statistics were used for these preliminary results.

Results: 32 children were diagnosed with GPA since January 2000. Twenty-one girls and 11 boys, with a median age of 13.7 years at diagnosis. ANCA was positive in 30 children (26 c-ANCA with 25 anti-PR-3, 4 p-ANCA with 4 anti MPO) and were ANCA negative (1 anti-PR3 positive). Eight children had limited disease and 24 systemic disease. All systemic patients were treated with pulses cyclophosphamide iv (mean 7 pulses) and methylprednisone (mean 5 pulses) iv, and 6 children received plasmapheresis. Maintenance treatment in this group consisted of MTX in 7, AZA in 14, MMF in 3 children. In the limited disease group, treatment consisted of oral prednisone in all, MTX in 7 children and AZA in 1. Relapses were seen in 14 children. One child did not receive any treatment at time of relapse. Two children with limited disease relapsed, both while still on MTX. 11 children with systemic disease were still on treatment, MTX in 4, AZA in 5, MMF in 2.

Conclusion: Relapses are seen often in childhood GPA when still receiving maintenance treatment. Relapses are higher in children with systemic GPA (50%) compared to limited GPA (25%).


P352 PreS-FINAL-2362: The spectrum of childhood inflammatory brain diseases; an increasingly recognised field
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Pediatric Rheumatology 2013, 11(Suppl 2):P352

Introduction: Childhood inflammatory Brain diseases encompasses many different diagnosis. The most frequent diagnosis are the different subtypes of childhood CNS vasculitis, however NMDAR encephalitis is increasingly recognized and diagnosed.

Disclosure of interest: None declared.

P353 PreS-FINAL-2363: Behçet’s disease in children: the Great Ormond Street Hospital experience
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Pediatric Rheumatology 2013, 11(Suppl 2):P353

Introduction: Behçet’s disease (BD) is rare in childhood and remains challenging in diagnosis and lack of evidence-based data for its treatment. Hence there is an urgent need to understand the scope of the disease in children.

Objectives: The aim of this study is to describe the clinical spectrum and the therapies used to treat children with Behçet’s disease (BD) in children.

Methods: 46 patients (22 male) were identified with a positive family history of BD in 6 cases. Age of onset was 4.87 (0.04-15.71) years with a time to diagnosis of 3.74 (0.25-13.48) years. The main clinical features at presentation were: recurrent oral ulceration (87%), genital ulceration (20%), cutaneous symptoms (11%), fever (30%), gastrointestinal symptoms (26%), musculoskeletal (22%), uveitis (2%). Recurrent genital ulceration was significantly more common in female patients (P = 0.044). The majority of children were treated with colchicine (74%) and corticosteroid (41%). Anti TNF-a treatment was reserved for severe and/or refractory cases (15%). There was a median of 2 (range 0-12) episodes of oral ulceration per year after the treatment. Interestingly only 10 patients fulfilled The International Study Group (ISG) BD diagnostic criteria.

Results: 46 patients (22 male) were identified with a positive family history of BD in 6 cases. Age of onset was 4.87 (0.04-15.71) years with a time to diagnosis of 3.74 (0.25-13.48) years. The main clinical features at presentation were: recurrent oral ulceration (87%), genital ulceration (20%), cutaneous symptoms (11%), fever (30%), gastrointestinal symptoms (26%), musculoskeletal (22%), uveitis (2%). Recurrent genital ulceration was significantly more common in female patients (P = 0.044). The majority of children were treated with colchicine (74%) and corticosteroid (41%). Anti TNF-a treatment was reserved for severe and/or refractory cases (15%). There was a median of 2 (range 0-12) episodes of oral ulceration per year after the treatment. Interestingly only 10 patients fulfilled The International Study Group (ISG) BD diagnostic criteria.

Conclusion: Although most cases were diagnosed in late childhood the first presentation was as early as 1 month old. Delay in diagnosis due to incomplete presentation in certain cases. Oral ulceration was the most common presenting symptom. Uveitis was less frequent than previous
series. A range of drugs was used including biologic therapy for severe cases.

Disclosure of interest: None declared.

**P354**

**PReS-FINAL-2364: Status epilepticus as an initial manifestation of central nervous system small vessel vasculitis is related to unfavourable neurological outcome in paediatric patients**

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**Pediatric Rheumatology** 2013, 11(Suppl 2):P354

**Introduction:** Childhood primary angiitis of the central nervous system (cPACNS) is an inflammatory disease involving small and medium-large size brain vessels with variable clinical presentation. Clinical symptoms range from headache, cognitive impairment, hemiplegia, language deficit to seizures and status epilepticus. However, it remains unclear if the type of initial manifestation/symptoms predicts neurological outcome in cPACNS.

**Objectives:** To assess the relationship between the clinical manifestation at disease onset and medium to long-term neurological outcome of cPACNS.

**Methods:** All consecutive children (< 18 years) diagnosed with small vessel CNS vasculitis, according Calabrese criteria and consented to the BrainWorks network at the Hospital for Sick Children in Toronto in the last 10 years (between January 2002 and November 2012) with a minimum follow-up of 4 months were included in this study. All prospective clinical, laboratory, imaging and histopathology data were captured in the BrainWorks database. Patients were divided in three subgroups according to the seizure type at clinical presentation: status epilepticus, seizures and patients without status epilepticus or seizures but with other neuropsychiatric abnormalities. Outcome assessments were evaluated by validated and standardized paediatric stroke outcome measure (PSOM) and Physician global assessment (PGA), which estimated on a visual analogue scale disease activity (PGA-DA), reversible changes (PGA-RC) and permanent damage (PGA-PD).

**Results:** The study cohort included 39 patients (25 girls, 64%) with biopsy confirmed small vessel cPACNS. Mean age at disease onset was 10.1 ± 4.1 years with a follow-up of 4 months up to 2 years. Status epilepticus was an initial cPACNS manifestation in 9 patients (23%, 3 girls, 33%). Seizures were present in 17 patients (44%, 12 girls, 71%) and 13 patients (33%, 10 girls, 77%) had no seizures or status but had other neurological symptoms including a decrease of consciousness, focal neurological deficit or headache. Patients with status epilepticus had the worst PSOM (p = 0.001) and PGA-RC a PGA-RD (p = 0.002) at disease onset. This subgroup also shows an increase in PGA-DA (p = 0.12) at follow-up. Patients presenting with status epilepticus tended to be more likely boys (6 patients, 66%) as compared (p = 0.084) to the other 2 groups. There was no significant difference in time to diagnosis among the groups (p = 0.19)

**Conclusion:** Children with small vessel cPACNS presenting with status epilepticus as a first disease manifestation have poorer medium-long term clinical outcome as compared to other cPACNS patients. Interestingly, patients with status epilepticus tended to be more likely boys.

**Disclosure of interest:** None declared.

**Cite abstracts in this supplement using the relevant abstract number, e.g.:**

Krakovská et al.: PReS-FINAL-2364: Status epilepticus as an initial manifestation of central nervous system small vessel vasculitis is related to unfavourable neurological outcome in paediatric patients, Pediatric Rheumatology 2013, 11(Suppl 2):P354