6th European Symposium: Steps Forward in Pompe Disease

Berlin, Germany, 23-24 November 2012

Published: 29 May 2013

These abstracts are available online at http://www.biomedcentral.com/bmcmusculoskeletdisord/supplements/14/S2

ORAL PRESENTATIONS

01
Autophagy: the pathogenic agent in muscle damage
Nina Raben
Laboratory of Muscle Stem Cells and Gene Regulation, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA

BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O1

Recently autophagy has attracted considerable attention because of its role in a wide variety of diseases including neurodegenerative disorders, cancer, myopathies, and lysosomal storage diseases. Autophagy is a "self-eating" process that brings proteins and damaged organelles enclosed in double-membrane autophagosomes to lysosomes for digestion and recycling. Functional lysosomes are essential for the completion of autophagy-initiated degradation and recycling of cellular components. In the fatal lysosomal glycogen storage disorder, Pompe disease, dysfunctional autophagy and massive accumulation of autophagic debris in myofibers greatly contribute to the cellular damage and interfere with the efficacy of enzyme replacement therapy (ERT). Analysis of single muscle fibers from patients with Pompe disease confirmed that the autophagic inclusions are prominent in humans as well. Autophagic buildup persists after years of treatment and may well be the reason for disappointing clinical response. Genetic suppression of autophagy in a mouse model of Pompe disease reduced the lysosomal glycogen load and allowed for fully effective ERT in murine Pompe disease. Our group is currently exploring a new therapeutic approach to Pompe disease: this new approach involves manipulation of transcription factor EB (TFEB), which has been shown to promote lysosomal-autophagosomal fusion and biogenesis. The appeal for Pompe disease is that unlike the current therapy, modulation of TFEB holds promise to rid muscle cells of both excessive glycogen burden and accumulation of autophagic debris.

02
Advances in imaging for the diagnosis and disease monitoring of Pompe disease
Robert-Yves Carlier
Service de Radiologie, Hôpital Raymond Poincaré, Garches, France

BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O2

Imaging can play a role at different stages of Pompe disease. In most cases the clinical presentation and high CK level are very evocative and GAA activity testing is sufficient for the diagnosis. In some cases the clinical presentation is less typical and late onset or juvenile forms cannot be differentiated from limb girdle muscular dystrophies or congenital muscular dystrophies. In such cases previous descriptions of Whole body (WB) T1 weighted MRI images have shown very evocative patterns of most often affected or spared muscles. The most typically and frequently affected are tongue, scapulae fixators and especially sub-scapularis, trunk muscles like spine erectors, abdominal belt muscles and psoas. The most frequently spared are masticators, arm and forearms, and lower leg muscles. In most cases the disease is associated with complications like respiratory involvement and disabling muscle weakness. Imaging is not taken into account when considering treatment options. On the contrary, when the diagnosis is made after family screening or in patients with minor symptoms, the distribution and severity of muscles involvement established by WB MRI could influence the decision to treat. Stability over time or degradation could also impact this decision. MR description of initial distribution and progression of muscle involvement could also yield a better knowledge of the disease.

Muscle biopsies are the best indicator of treatment efficacy but patient compliance could be very low if repeated follow-up biopsies were employed. Muscle imaging and especially MRI could offer the opportunity to quantify stability or progression of muscle involvement under therapy. To achieve this goal imaging has to be quantitative and not only qualitative. Quantification techniques can be developed to assess the amount of fat into muscles (DIXON) or to detect areas of muscle remodeling activity (T2 measurement). However WB MRI is useful to determine the areas where the quantification should be performed. In totally destroyed or spared muscles quantified imaging is not very pertinent. Other imaging modalities could also be used to detect regional fat increase. DEXA scanner is not only able to detect regional bone mineral density variations but also lean mass (muscles) and fat. Muscle imaging is not always the clue for the diagnosis but it can help for recognition of atypical clinical presentations, for understanding the natural history of the disease, for the determination of patients suited for treatment as a complement of other clinical and nonclinical parameters. Medical imaging techniques of quantification could help to analyze treatment efficacy.

03
Genotype-phenotype: correlations and emerging spectrum
Arnold Reuser
Department of Clinical Genetics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands

BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O3

The Pompe disease mutation database at http://www.pompecenter.nl is a handy tool to quickly learn about the effect of sequence variations in the GAA gene. The database aims to be complete and to contain all the GAA sequence variations that have been published. The information is regularly
updated and electronically linked to relevant publications. Nevertheless, there is a shortcoming in that the database only indirectly links genotypes to phenotypes via the linked publications. This problem has, in part, been solved by inserting a column for reporting the severity of individual mutations. The 'severity score' of each sequence variant is partly based on the nature of the mutation. For instance, most frame shifts in the GAA gene are bound to cause full loss of functional enzyme. Missense mutations, however, have an unpredictable effect, but can be investigated in a transient expression system. In such case, a sophisticated scoring system provides the severity score in terms of 'very severe', 'potentially less severe', 'potentially mild' etc. A similar grading system for splice site mutations is not yet in place. Ideally, the database should also provide genetic information on patients' clinical outcomes based on genotype-phenotype correlations, if such correlations, though expected, in fact exist. The phenotype could then be predicted from the composite genotype. For instance, if both GAA mutations of the patient were listed as 'very severe', the patient would predictably develop classic infantile Pompe disease, but would predictably develop an attenuated phenotype when having one 'severe' and one 'mild' mutation. A preliminary and incomplete analysis of the data contained in the Pompe disease mutation database suggests that many mutations can be classified in terms of 'classic infantile' mutations, typically 'childhood' mutations, or typically 'adult' mutations. The most common mutation of all i.e. c.32-13T>G (IVS1) is difficult to classify. In combination with any 'classic infantile' mutation, it correlates with onset of symptoms before the first year of life till onset in late adulthood, but it is never associated with a very rapid demise. In these cases, the genotype-phenotype correlation demonstrates the impact of modifying factors. This topic will be discussed with regard to diagnosis, prognosis, and treatment.

O4
Diagnostic algorithm and case conundrums: patients presenting with proximal muscle weakness
Tiziana Mongini
Center for Neuromuscular Diseases, Department of Neuroscience, University of Turin, Turin, Italy
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):C4

In the last years it has been observed that enzyme replacement therapy is mostly effective when the treatment is started at an early stage of the disease, before advanced damage has occurred in muscle fibers; consequently, the timing of diagnosis has acquired an increasingly important role, both in children and in adults. We are now aware that some LOPD cases may show for years only a persistent mild hyperCKemia with no signs or symptoms. Often the finding of high serum CK levels in this group of asymptomatic patients is incidental (visit in the emergency room for chest pain, preoperative investigations, detection of increased serum transaminases) and their diagnosis may be very difficult. Different is the case of patients who are seen when they start to manifest weakness, usually with onset in the pelvic girdle muscles. They usually report fatigue, exertional dyspnea (eg, in climbing stairs), difficulties to get up from the ground or sitting; however, these are very common symptoms, shared by a large number of primary or secondary neuromuscular disorders. In the absence of a family history of Pompe disease or a biopsy with typical vacuolar changes, the diagnosis is easily missed, and this explains the broad diagnostic delay still now registered, with consequences on ERT efficacy. Neuromuscular diseases that may present with isolated proximal weakness include lower motor neuron diseases (eg, spinal muscular atrophy), disimmune motor neuropathies, neuromuscular junction disorders (pre-and post-synaptic), and a large number of genetically defined (eg, progressive muscular dystrophies due to altered sarcolemma proteins, congenital myopathies, channelopathies) or acquired myopathies (inflammatory myopathies, toxic myopathies). Differential diagnosis is often difficult and expensive, and can be completed only in specialized tertiary centers. A diagnostic algorithm aimed to facilitate the evaluation of patients with limb-girdle muscular weakness is presented, to target the use of specific tests that can be implemented even in non-specialized structures (eg, units of general neurology or rheumatology) and allow an early detection of Pompe disease. A series of clinical cases is presented, to stimulate a discussion and to prove the validity of the algorithm.

O5
Limitations of muscle biopsy in Pompe disease
John Vissing
Neuromuscular Research Unit, Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O5

The diagnosis of Pompe disease in children and adults can be challenging because of the heterogeneous clinical presentation and considerable overlap of signs and symptoms found in other neuromuscular diseases. This review evaluates the use of muscle biopsy and other methods for the diagnosis and differential diagnosis of late-onset Pompe disease. Muscle biopsy is commonly used as an early diagnostic tool in the evaluation of muscle disease. However, experience has shown that relying solely on visualizing a Periodic acid-Schiff-positive vacuolar myopathy to identify late-onset Pompe disease often leads to false-negative results, and subsequently delays diagnosis and treatment of the disorder. Serum creatine kinase can be normal or only mildly elevated in late-onset Pompe, so is also not very helpful alone to suggest the diagnosis, but may, in combination with proximal and axial weakness, raise the suspicion for Pompe disease. The optimal initial test for confirming or excluding Pompe disease is a simple, blood-based assay to measure the level of α-glucosidase activity. In particular, measurement of GAA activity in dried blood specimens is minimally invasive, quick, cost-effective, and reliable. Blood-based assays allow for the timely and accurate diagnosis of late-onset Pompe disease, and are likely to improve patient outcomes, as care standards, including enzyme replacement therapy, can be applied and complications may be anticipated and avoided. Increased awareness of the clinical phenotype of Pompe disease is essential in order to expedite diagnostic screening using blood-based, enzymatic assays.

O6
Molecular diagnosis and next generation gene sequencing in neuromuscular clinical practice
Silvère van der Maarel
Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O6

Next generation sequencing (NGS) is revolutionizing the way we do research on genetic disorders. While earlier DNA sequencing was often the last step in disease gene discovery, nowadays it is becoming the starting point. Also, in the diagnostic setting, NGS is gaining momentum and is rapidly being implemented in laboratories around the world. With new developments trending toward more cost effective (label-free) technologies and higher throughput and fidelity, NGS instrumentation will undoubtedly become the gold standard. However, NGS in diagnostic and research settings will also impose new technical and computational challenges upon us, and raise ethical issues that will need to be addressed. Here I will discuss various NGS technologies and their specific characteristics and applications, with emphasis on translational research, bringing gene discovery into the diagnostic setting, and implications for the diagnosis of Pompe disease.

O7
Future therapeutic options
Arnold Reuser
Department of Clinical Genetics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O7

In the year 500 before Christ, the Greek philosopher Herachitus said, “if one does not expect the unexpected, one will not find it out, since the mind is not open to it, and one will not search for it.” This is, in short, the problem I have with predicting what the future therapeutic options for Pompe disease might be. Leaving out the unthinkable, there are still plenty of options left, but how realistic are they? Rather shortly after his discovery of the lysosomes, in 1953, Prof Christian De Duve hypothesized that lysosomal storage diseases could possibly be treated by enzyme therapy, the way we currently practise. Nevertheless, the first successful attempt at
Enzyme replacement therapy (ERT) in Gaucher disease, by Dr Roscoe Brady and colleagues, was not published until 1990. The trick they used to deliver human glucocerebrosidase to Kupffer cells in the liver and to macrophages in bone marrow and spleen was to modify the carbohydrates so the enzyme would be captured by the mannose-recognizer on these cells. At present, enzyme replacement therapy is applied in Pompe disease, in Fabry disease, and in the mucopolysaccharidoses MPS I, II and VI. In all these latter diseases, the enzymes are targeted to the mannose-6-phosphate receptor. In my opinion ERT works best in Pompe disease, and its effect could be further improved by starting treatment with Myozyme or Lumizyme earlier and by using more than the prescribed dose (20 mg/kg), if deemed clinically necessary. Immunologic responses are contra-effective and need to be minimized. Increasing the mannose-6-phosphate content of rhGAA chemically, or by using an alternative production platform, is expected to improve the efficacy of ERT. Improving the binding of rhGAA to the mannose-6-phosphate / IGF-II like receptor by production of a fusion protein (GILT-technology) might equally lead to greater efficacy. The co-application of chaperones is seen as a further option. Meanwhile, gene therapy is considered the solution to all problems. The principle was demonstrated in 1971, but it was only three days ago that the first gene therapy was approved by regulatory authorities in the Western world. For the treatment of Pompe disease, gene therapy also holds great promise, but there might be a long way still to go. Interference with autophagy or exocytosis has been looming at the horizon for 50 years as a potential treatment for lysosomal storage disorders. This subject was rejuvenated, and present day insight offers an exciting window of yet unknown opportunities.

O8
Long term outcome and clinical experience on immune tolerance induction therapies in infantile Pompe disease
Stephanie Austin , Priya Kishnani
Department of Pediatrics, Duke University Medical Center, Durham, North Carolina, USA
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O8

Pompe disease (glycogen storage disease type II) is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme acid alpha-glucosidase. Enzyme replacement therapy (ERT) with alglucosidase alfa has resulted in a clinical benefit in a subset of patients. Cross-reactive Immunological Material (CRIM)-negative status is associated with poor prognosis. Patients with CRIM-negative infantile Pompe disease mount a strong immune response against alglucosidase alfa ERT, resulting in a clinical decline and death despite therapy. Most develop high sustained antibody titers. Based on our clinical and laboratory experience, about 40 percent of patients with infantile Pompe disease develop HSAT. Early identification of patients at risk is needed to allow for treatment intervention with immune tolerance induction (ITI) protocols. These protocols have included the use of agents such as rituximab, methotrexate, IVIG, and agents that target the plasma cells. Different treatment approaches are needed for patients with Pompe disease treated with ITI in the naive setting as compared to patients with high sustained antibody titers. Without ITI, the CRIM-negative patients do poorly on ERT alone. We will present a successful global experience in 15 cases and discuss the safety, efficacy and feasibility of a clinical algorithm developed at our institution to identify CRIM-negative status and allow timely initiation of ERT and ITI in this vulnerable population. Our data show that the clinical algorithm of rapidly diagnosing and initiating ITI coincident with the start of ERT in CRIM-negative patients is feasible and can be achieved in a timely manner.

O9
Alglucosidase alfa: 5 years of experience in late-onset Pompe disease
Benedikt Schoser
Friedrich-Baur Institute, Department of Neurology, University of Munich, Munich, Germany
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O9

Glycogen storage disease type 2, Pompe disease, is a progressive muscle disorder with a wide range of phenotypic presentations, caused by an inherited deficiency of the enzyme acid alpha-glucosidase. Although only a few patients have been treated with recombinant human alpha-glucosidase from rabbit milk since 2004, enzyme replacement therapy (ERT) with alglucosidase alfa has been licensed for the treatment of Pompe disease since 2006. Here, a systematic review [1] evaluates the clinical efficacy and safety of alglucosidase alfa treatment in juvenile and adult patients with late-onset Pompe disease (LOPD). Studies of alglucosidase alfa treatment in patients with LOPD, published up to October 2012, were identified using an electronic search of the EMBASE and MEDLINE databases, and manual searches of the reference lists. Data on ERT outcomes were extracted from the selected papers and analyzed descriptively. No statistical analyses were performed owing to data heterogeneity. Twenty-two studies containing clinical data from 437 LOPD patients were analyzed. Overall, at least two-thirds of patients were stabilized or exhibited improvements in creatine kinase levels, and muscular and/or respiratory function following treatment with alglucosidase alfa. Enzyme replacement therapy was well tolerated; the majority of adverse events were mild or moderate infusion-related reactions. Alglucosidase alfa treatment offers an effective and well tolerated treatment that attenuates the progression of LOPD in the majority of patients. Although first insights are upcoming, further research is required to investigate reliable prognostic factors such as age at treatment start, phenotypic presentation, and genotypic characteristics, of which may enable better clinical and therapeutic management of LOPD patients.

Reference

O10
Rationale for adjuvant measures in musculoskeletal diseases
Ulf Gast
Centre for Muscle and Bone Research, Charité Universitätsmedizin Berlin, Berlin, Germany
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O10

Bone and muscle are dynamic tissues. Muscle adapts to stimuli above thresholds (energetic emptying > exhaustion). Wolff’s law states that structural bone adaptation is driven by the experienced bone strains. Osteocytes within our bones regulate bone formation and degradation in response to mechanical stimuli. The largest strains emerge from muscle contractions. A lot of diseases are associated with secondary muscle weakness (sarcopenia) and reduced bone density (osteoporosis). Both deficits cause an increase in fall incidence. About every 4th fall results in fracture. Patients after fractures become more and more immobile. Necessary stimuli decrease further. It comes to progressive deconditioning, whereby the vicious circle is complete, because it results in decreasing muscle cross-sectional area as well as bone strength. Accordingly, therapy concepts have to focus on maintenance and increasing muscle force and power. An established method is intensive resistance exercise training aimed to hypertrophy. Also the training program must ensure that forces reach the minimal effective strain and leads to bone remodelling. High-load resistance exercises effectively increase muscle and bone at the same time.

O11
Pregnancy in Pompe disease
Ursula Ploßinger
Interdisciplinary Centre of Metabolism: Endocrinology, Diabetes and Metabolism, Charité Universitätsmedizin Berlin, Berlin, Germany
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O11

Pregnancy in Pompe disease is still a rare event. Only few reports have been published. Physiological changes of pregnancy may be aggravated by Pompe disease or vice versa. Both may pose a risk for the mother and the unborn child. This talk outlines physiological changes of the cardiovascular, respiratory and hormonal system during pregnancy and delineates the impact on a 36-year-old Pompe patient with a twin pregnancy. Furthermore, recommendations for a prospective medical strategy are presented and a workflow for routine follow-up during pregnancy is suggested. Recommendations include the planning of the pregnancy, genetic counselling, and pre-pregnancy investigations.
An interdisciplinary team consisting of an obstetrician, pulmonologist, internist, endocrinologist and anesthesiologist is suggested for care of the pregnant patient with Pompe disease.

**O12 Standards of care in neuromuscular fields**

Volker Straub  
Institute of Genetic Medicine, Newcastle University, International Centre for Life, Newcastle upon Tyne, UK  
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):O12

There is general consensus that consensus guidelines for care standards are an important tool to provide both healthcare professionals and the patient community with up to date information about all aspects of best practices in a specific disease area. The specific development of care guidelines for neuromuscular diseases poses a number of challenges. All neuromuscular diseases are rare and many show a broad spectrum of clinical and genetic heterogeneity. A paucity of randomized controlled trials for most conditions means that best-practice care guidelines are often non-existent or poorly developed. Where they exist, healthcare professionals may be unaware of them. In many cases the lack of care guidelines contributes to a lack of clinical trial activity, as the implementation of care guidelines is also a prerequisite for a reliable comparison of outcome measures in clinical trials, especially in the neuromuscular disease field, where trials are normally multi-centric and international. Over the past years there have been various collaborative efforts to achieve trial readiness for a number of neuromuscular diseases by establishing care guidelines, patient registries and networks of care and trial sites. For some of the most common neuromuscular diseases like spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) there are now international care guidelines for healthcare professionals and patients and families. Key factors that have helped to establish these care guidelines were the involvement of patient organizations, translational research networks, and health agencies and combining existing evidence with consensus among a large number of experts in different care areas. Once care guidelines have been established, it is important to disseminate them to the stakeholder community through clinics, meetings, journal and website publications, media interviews, patient registries and professional training courses. It is also crucial to keep care guidelines updated and to take new therapeutic developments and health research outcomes into account. Once care guidelines have been agreed and disseminated, it then becomes important to monitor their implementation and to assess whether they do indeed have a positive impact on health. This is particularly important for guidelines that are based on expert opinions that lack higher levels of evidence. Finally, we need to better understand why, despite agreed upon care guidelines for various neuromuscular diseases, many patients do not receive the treatment they describe.

**POSTER PRESENTATIONS**

**P1** Feasibility of DBS screening to identify adult patients with Pompe disease in a neuromuscular clinic population  
Angela Genge  
Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada  
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):P1

Introduction: In January 2012, a program was set up to rapidly screen patients with undiagnosed muscle disorders who were referred to a neuromuscular specialist in an adult hospital. A nurse was trained to do the DBS procedure as part of a series of required laboratory tests. All individuals referred to a neuromuscular specialist, either within the context of a neuromuscular clinic or an EMG laboratory, were considered. Patients with an elevated CPK, symptoms and signs indicative of a metabolic myopathy or limb girdle myopathy or muscular dystrophy, and without an obvious diagnosis (myotonic dystrophy, dermatomyositis, oculopharyngeal muscular dystrophy, FSH dystrophy) were tested on the initial visit. Those with positive DBS testing had samples sent to Duke University for genetic testing. Results: 117 patients have been tested to date (number will increase by November 2012). Of these, 5 patients were found to have significant abnormalities on DBS testing. Genetic results are pending.

Discussion: This approach was designed to further define the clinical phenotypes of patients with Pompe disease. A second objective was to create a system in an adult setting whereby DBS is used routinely, thereby increasing the ability to identify Pompe patients with previously undiagnosed myopathies. The setup is user friendly, eliminates the need for muscle biopsy in a percentage of patients, and can easily be expanded to include patients referred to other neuromuscular specialists in the hospital system, as well as pulmonologists following patients with undiagnosed neuromuscular respiratory failure. Future plans include expanding to include these other patient populations.

**P2** Three years experience with dried blood spot α-glucosidase screening for Pompe disease in British Columbia, Canada  
Gabriella Horvath*, Sandra Sirrs, Sylvia Stockler, Ramona Šalvarinova-Zivkovic, Hilary Vallance, Paula Waters  
British Columbia Children’s Hospital, Vancouver, British Columbia, Canada  
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):P2

Introduction: Pompe disease is autosomal recessive lysosomal storage disease caused by mutations in the glucosidase alpha (GAA) gene. The acid glucosidase enzyme is required for the degradation of cellular glycogen, and its reduced activity results in accumulation of glycogen in muscle and cardiac tissues with variable clinical presentation. Demonstration of deficient acid alpha-glucosidase (GAA) enzyme activity is diagnostic, and molecular testing is available for confirmation or clarification. As Pompe disease is in the differential diagnosis of a wide variety of myopathies, simple first-line tests are needed. Use of dried blood spots (DBS) has logistical advantages over the traditional approach of enzyme assay in isolated lymphocytes, and enzyme stability permits DBS shipment to a central laboratory.

Methods/results: Patients were referred for enzyme testing who presented with muscle weakness, muscle pain, respiratory insufficiency, and/or cardiomyopathy in infancy. Dried blood spot (DBS) acid α-glucosidase testing, with neutral α-glucosidase as a control enzyme, was measured using a previously described fluorimetric method [1,2]. Out of 149 samples tested, three cases of Pompe disease were detected by DBS assay during a three year period. Two patients with low values for acid α-glucosidase in DBS were confirmed to carry hypomorphic alleles not associated with clinical disease. Two patients with low values, overlapping those of the two patients with hypomorphic alleles, had no mutations detected. Two further patients had normal results on a second DBS card, suggesting that the initial blood spots might have been compromised.

Conclusion: Since the introduction of the DBS alpha-glucosidase method, several new Pompe cases have been diagnosed at our centre. A repeat DBS should be requested to confirm initial low results before proceeding to further testing. In a significant proportion of false positive cases, benign hypomorphic alleles provide an explanation for reduced activity of acid α-glucosidase.

References

**P3** Spectrum of Pompe disease in childhood – The Toronto experience  
J Rainard1, S Bendick1, S Hevinson1, M Mecija1, I Narangi2, M Saunders1  
1Division of Clinical & Metabolic Genetics, Hospital for Sick Children, Toronto, Ontario, Canada; 2Division of Respiratory Medicine, Hospital for Sick Children, Toronto, Ontario, Canada  
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):P3

Introduction: Pompe disease, caused by the deficiency of acid alpha glucosidase (GAA), ranges from the severe infantile to attenuated adult
forms. We present clinical features and treatment outcomes from 4 paediatric cases from our centre in the last 4 years.

Results: 1) A 4-month-old female presented with hypotonia and cardiomegaly. She was CRIM negative and homozygous for p.R854X. She successfully received immunotolerance induction therapy (ITI) prior to ERT at 4.5 months. She remained antibody negative until 12 months, when titers rose to 1:800. Hex4 increased from 48.4 at baseline to 108.8. LVMI decreased from 220 at baseline to 119 g/m2. She started nocturnal BiPAP at 11 months, then developed pneumonia and became ventilator dependent, leading to cessation of ERT and death at 14 months.

2) A male infant born at 30-weeks was investigated for hypertrophic cardiomyopathy and skeletal myopathy. He was diagnosed at 4 months, was CRIM negative, and homozygous for c.546+2 T->C. He received ITI started ERT at 4.1 months, and remains antibody negative. Nocturnal BiPAP was started at 5 months. Hex4 dropped from 59.7 at baseline to 54.9 at the last follow up. LVMI decreased from 445 at baseline to 101.7 at 24 months. He remains on ERT at 24 months and has achieved minor motor gains.

3) A 6-month-old male infant presented with cardiomyopathy and skeletal myopathy and was BiPAP dependent. He was CRIM negative and had a 0.2%44% decrease in complex deletion. The family elected not to pursue ERT and he died at 7 months.

4) A 25-month-old male presented with recurrent respiratory infections, proximal limb weakness, ventricular hypertrophy and speech delay. He was CRIM positive and heterozygous for p.P361L/p.R854X. He started ERT at 23 months. Hex4 dropped from 195.5 at baseline to 70. Positive antibody titer of 1:200 at 2 months rose to 1:800 after 15 months. He remains on ERT after 18 months with motor stability and has made developmental support (particularly respiratory). Pre ERT ITI was well tolerated.

P4

Pompe practice survey of Canadian (Ontario) rheumatologists
Carter Therrien1, Mark Tarnopolsky2
McMaster University, Hamilton, Ontario, Canada
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):P4

Introduction: Pompe disease (glycogenosis II, acid maltase deficiency, OMIM 232300) is a treatable autosomal recessive disorder of glycogen metabolism caused by deficiency of the lysosomal enzyme acid alpha-glucosidase. A hallmark of Pompe disease is the presence of glycogen-loaded lysosomes. Pompe disease has frequently been misdiagnosed as other myopathies, such as polymyositis, and mistreated and treated with steroids. A rheumatology based practice survey is being designed to establish the incidence of Pompe disease and other myopathies in patients with atypical steroid-unresponsive presumed myopathies (ASUPM).

Methods: Five to ten self-identified rheumatologists with an interest in myopathies and ‘community’ practices located in Ontario, Canada, will review medical records to identify patients with ASUPM. A standardized chart review tool to help expedite the review will be developed and approved by the participants. Charts of any patient seen in the past five years with a diagnostic code of 710, 729, 739 or 781 will be identified and data extracted using the standardized CRF; data extraction will be performed by the physician or a trained delegate. Central IRB approval will be obtained, and participants will be eligible for CPD credits. Physicians will also provide demographic information (i.e., years in practice, practice profile, total charts reviewed, etc.), and patient data will include, but is not limited to the following: CK values, serology findings, biopsy results, steroid responsiveness, and diagnoses (e.g., polymyositis, dermatomyositis). Identified patients will be referred to a single neuromuscular practitioner (Mark Tarnopolsky) who will perform dried blood spot, enzymatic, and genetic tests to determine the exact nature of the myopathy and the incidence and prevalence of these steroid non-responsive myopathies in the ASUPM population.

Discussion: Presentation at the 6th Annual European Symposium will provide an opportunity for us to further develop this project based on expert feedback. Our overarching goals are to: 1) develop strategies/tools to facilitate efficient, systematic chart review; 2) ascertain cases of atypical myopathy/myositis or other unclear diagnoses that may be Pompe disease; 3) improve physician awareness of uncommon and rare diagnoses; and 4) share the results with a wider rheumatology community.

P5

Stapedius reflex testing shows altered small muscle function in untreated Pompe patients and improvement after enzyme replacement therapy
M Hilz1,2, U Hoppe1, S Moeller1, J Kohn1
1Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany; 2Departments of Neurology, Medicine, Psychiatry, New York University, New York, NY, USA
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):P5

Introduction: Pompe disease primarily affects skeletal and cardiac muscles. It is difficult to assess therapeutic efficacy of enzyme replacement therapy (ERT) using primary end points based on changes in weakness of large limb-girdle muscles, gait-endurance, and respiratory function, which all depend on variable day-to-day patient performance. In contrast, muscle improvement might be shown by assessing function of very small muscles, such as the stapedius and tensor tympanic muscles. We therefore tested whether ERT benefits in Pompe patients can be shown by stapedius reflex testing before and after ERT.

Results: In four Pompe patients, we assessed ipsilateral stapedius reflex thresholds in the right and left ear one and two years after patients received first dosage of biweekly ERT with alglucosidase alfa (Myozyme™, 20 mg/kg i.v.). In two patients, stapedius reflex thresholds were also assessed before ERT-onset. Muscle tension of the stapedius and tensor tympanic muscles were determined by measuring acoustic impedance at the tympanic membrane in response to single bursts of 0.5, 1, 2 and 4 KHz tones. Reflex thresholds between 70 and 90dB HL are within the normal range; higher responses indicate impaired thresholds. Patient 1 (female, 46 years) had no stapedius reflex responses before ERT-onset, reflex thresholds of 98.8/87.5dB (right/left; R/L) after one year of ERT, and reflex thresholds of 91.3/85.5dB (R/L) after two years of ERT. Patient 2 (male, 65 years) had reflex thresholds of 98.8/93.8dB (R/L) before ERT-onset, reflex thresholds of 86.3/91.3dB (R/L) after one year of ERT, and reflex thresholds of 90.0/91.3dB (R/L) after two years of ERT. Patient 3 (female, 53 years) had reflex thresholds of 93.8dB (R) and no stapedius reflex responses (L) after one year of ERT, and reflex thresholds of 96.3/87.8dB (R/L) after two years of ERT. Patient 4 (female, 69 years) had reflex thresholds of 85.0/85.0dB (R/L) after one year of ERT, and reflex thresholds of 80.0/81.3dB (R/L) after two years of ERT.

Conclusion: In untreated Pompe patients, stapedius reflex testing demonstrates impaired small muscle function. After one and two years of ERT, stapedius reflex thresholds improved. Consequently, stapedius reflex testing can objectively demonstrate significant improvement of muscle function with ERT.

P6

Cytokines in treated and untreated Pompe patients
N Karabul1, S Göcke, M Kirchner, W Mannhardt, E Mengel
Center for Pediatric and Adolescent Medicine, University Medical Center, Mainz, Germany
BMC Musculoskeletal Disorders 2013, 14(Suppl 2):P6

Introduction: Glycogen storage disease type II (Pompe disease or acid maltase deficiency) is an autosomal recessive metabolic disorder caused by a deficiency of the lysosomal enzyme acid-alpha-glucosidase. Accumulation of glycogen in the lysosomes damages muscle cells throughout the body. In response to that damage, we hypothesized that cytokines (a family of proteins that mediate innate and adaptive immunity) would be elevated. We investigated 30 (15 female, 15 male) Pompe patients before ERT start and 1 year after ERT and used high-resolution ELISA.

Results: Before ERT start in 20 patients (12f, 8m) we saw elevated TNFγ and Interleukin-2. After treatment more than 50% TNFγ was normalized. But after treatment some cytokines were elevated. We don’t see any correlation between antibody levels against ERT in these patients.

Conclusion: Our results showed that some patients had elevated cytokines and monocytes. Our hypothesis is that also immunological factors play also a role in disease, causing the development of pain in Pompe disease. Now we are looking for correlations between pain and cytokines levels, and results will follow.
**P7** Pompe disease: the role of MRI

C Pérez Fernández, I Bosanska, U Pöllinger
C. Pérez Fernández, L. Bosanska, U. Pöllinger
Klinik für Radiologie und Klinik m.s. Hepatologie und Gastroenterologie, Charité Universitätsmedizin Berlin, Berlin, Germany

BMC Musculoskeletal Disorders 2013, 14(Suppl 2):P7

Introduction: Glycogen storage disease type II (Pompe disease) is a rare, progressive muscle disorder with a wide range of phenotypic presentations. It is caused by an inherited deficiency of acid α-glucosidase (GAA), which leads to lysosomal glycogen accumulation in various tissues, most notably cardiac, skeletal, and smooth muscle. The gradual pathologic storage of GAA in muscle cells causes irreversible muscle damage, with different signs and symptoms, including respiratory insufficiency and muscle weakness. In Pompe disease, defining severity grades is essential for prognosis and for monitoring responses to enzyme replacement therapy (available since 2006). The purpose of this analysis was to describe the MRI-imaging findings of patients with Pompe disease being treated in our institution between 2010 and 2012 (n=10).

Results/discussion: MRI-imaging techniques from skeletal musclecuture with special fat saturated sequences, together with noninvasive measurement of the urinary glucose tetrasaccharide biomarker, provide an excellent alternative to invasive, often risky, and insufficiently sensitive muscle biopsies. In particular, the T1-weighted turbo spin echo sequences were suitable for depicting muscle atrophy and fibro-fatty muscle degeneration.

Conclusion: MRI techniques may be appropriately and effectively used to describe muscular changes in patients with Pompe disease.

---

**P8** Successful twin pregnancy in a 38-year-old woman with Pompe disease despite interruption of enzyme replacement therapy (ERT)

C Cipullo, S Sampaolesi, O Farina, M Simonetti, M Cirillo, G Di Iorio

Dipartimento di Scienze Mediche, Chirurgiche, Neurologiche, Metaboliche e dell’Invecchiamento - Seconda Università di Napoli, Naples, Italy

BMC Musculoskeletal Disorders 2013, 14(Suppl 2):P8

Introduction: Clinical features of Pompe disease are limb-girdle muscle weakness and respiratory insufficiency. Data on pregnancy with or without ERT are rare. Herein, we report on a twin pregnancy in a 38-year-old primiparous who declined ERT during pregnancy.

Results: After successful insemination of 2 foetuses, ERT was stopped at the patient’s request. Investigations were performed before and during pregnancy until week 30. The Walton/Gardner Medwin Scale was stable during the preceding 2y on ERT and during pregnancy. Echocardiography demonstrated normal left-ventricular function. No changes were observed in creatine kinase (CK) levels, GAA activity, or quality of life (SF-36). In contrast, pulmonary and functional scores clearly deteriorated: FEV1 (58% vs 56%), forced expiratory volume in 3 seconds (FEV3) (47% vs 45%), and supine VC (61 ± 55%) vs 68 ± 56%), 6-min walk test 324 ± 240m (73%) vs 277 ± 204m (60%), climbing 4 steps 4 ± 1.5sec (128%) vs 4 ± 1.3sec (135%), standing from supine 4.5sec (128%) vs 4.2sec (132%), and supine VC (61 ± 55%) vs 68 ± 56%)

Discussion: The patient’s request to halt ERT at week 24 was accompanied by a deterioration of cardiovascular and pulmonary function. This may have been due to drug-related side effects, such as a decrease in the effectiveness of the ERT or to the progressive natural course of the disease. The patient was able to carry out her daily activities and to breastfeed her twins with normal GAA levels, which were not significantly different from those of the mother. The twins were delivered by cesarean section at 35.5 weeks of gestation, weighing 1900 and 1850g respectively, with normal GAA levels. No changes were observed in the urinary glucose tetrasaccharide levels of the mother and twins. The twins’ development was normal, and they were able to feed and to be discharged home.

Conclusion: Despite the interruption of ERT, the twins were delivered safely with normal GAA levels. This case highlights the importance of individualized ERT management during pregnancy.

---

**P9** Clinical, morphological and genetic features of a cohort of late onset GSD II patients: typical and atypical presentations

L Barca, O Musumeci, C Rodolico, A Ciranni, G Vita, A Toscano

Department of Neurosciences, University of Messina, Messina, Italy

BMC Musculoskeletal Disorders 2013, 14(Suppl 2):P9

Introduction: GSDII (Pompe disease) is a rare, autosomal recessive disease due to alpha-glucosidase (GAA) deficiency that presents with infantile and late-onset forms. Herein, we describe a cohort of 29 late-onset patients (15 males and 14 females, aged 9 to 76), and discuss some unusual clinical features seen in 4 of them.

Methods: Clinical evaluations were performed in all patients using the Walton and Gardner-Medwin, MRC and GSGC scales, and the 6MWT. Respiratory function was assessed using FVC% in upright and supine positions. All patients underwent morphological and biochemical examinations, muscle MRI, neurophysiological studies, and molecular genetic analysis.

Results: Out of 29 patients, 15 received enzyme replacement therapy (ERT). 57% initially had limb-girdle involvement, 29% an isolated hyperCKemia, and 14% respiratory insufficiency. Neurophysiological studies revealed a myopathic pattern in 48% of patients, neurogenic or mixed in 28%, whereas 24% of patients did not show any electrical abnormality. In the examined patients, muscle MRI showed early involvement of ileopsoas, gluteus and posterior thigh muscles. Morphological studies revealed vacular myopathy in 68% of patients, and biochemical analysis showed residual alpha-glucosidase activity ranging from 0.01% to 25%. Molecular genetic analysis confirmed N131T-G as the most common mutation, but we also identified three novel point mutations. Atypical clinical features were observed in 4 out of 29 patients: a 66-year-old female with disease onset involving distal upper limbs muscles; a 70-year-old male with mesial temporal sclerosis without epileptic or cognitive disorders; a 46-year-old male with severe neurosensory hearing loss (with very early hearing difficulties); and a 51-year-old female with a congenital absence of a thyroid lobe.

Conclusion: Our study confirms the clinical, morphological and molecular genetic heterogeneity of late-onset GSDII. Muscle MRI is a very useful tool for muscle damage evaluation, especially at the early stages of the disease.

Based on our experience with some atypical cases, we suggest always performing a complete clinical and laboratory evaluation of patients in order to highlight unusual muscular (e.g. distal involvement) and/or CNS presentations. These cases reinforce the hypothesis that modifier genes and/or epigenetic factors may contribute to clinical presentations of Pompe disease.

---

**P10** Cerebral vascular anomalies in a large Italian family with late-onset glycogenosis II

F Cipullo, S Sampaolesi, O Farina, M Simonetti, M Cirillo, G Di Iorio

Dipartimento di Scienze Mediche, Chirurgiche, Neurologiche, Metaboliche e dell’Invecchiamento - Seconda Università di Napoli, Naples, Italy

BMC Musculoskeletal Disorders 2013, 14(Suppl 2):P10

Introduction: Basilar artery dolichoectasia, ectasia of internal carotids and intracranial aneurysm have been described in late-onset glycogenosis II (GSD II). Incidence of these anomalies and their relationship to the genotype are unknown. Also, because studying cerebral vessels is not recommended for diagnosis of late-onset GSDII, the frequency of these anomalies may be underestimated. Therefore, we investigated the occurrence of vascular anomalies in eight siblings (4M, 4F) of an Italian family affected by late-onset GSDII due to a compound mutation (c.118C>T in exon 2 and c.2647-T>G in intron 18) of the acid α-glucosidase (GAA) gene (17q21-23).

Results: The clinical picture in these siblings is typical of late-onset GSDII: Patients never complained of symptoms of cerebro-vascular disease and there was no cardiac involvement. Blood pressure and blood glucose were normal. Brain Magnetic Resonance Angiography (MRA; Angio-RM TOF 3D axial Siemens Symphony 1.5 T) was performed in 7 (4M, 3F) out of 8 patients (one female carried a paramagnetic prosthesis), and in 10 controls. Vessel total square diameter was measured at the apex and middle third of the basilar artery and at the middle portion of both right and left internal carotid artery. Blind measurements were carried out by three
investigators. Basilar artery dolichoectasia (0.06% in the general population) was found in 3M and 2F, and a slight dilatation of internal carotids compared to controls was found in all patients.

**Conclusion:** These data confirm that anomalies of main cerebral vessels are relatively frequent in late-onset GSDII patients. The role of genotype in determining these anomalies is uncertain because studies on informative families are rare. Particularly intriguing is the relation of these vascular anomalies with the risk of stroke in these patients. Even though all have ventilatory insufficiency with reduced blood oxygen saturation, nocturnal apnea, and impaired glycogen metabolism, a minority suffers TIA or stroke. Therefore, an imaging study of the cerebral circulation is recommended in all patients with late-onset GSDII. In those with anomalies, further research is needed to evaluate cerebral metabolism and to search for specific vascular risk factors.

**P11**

Quantitative muscle MRI and functional measures in a cohort of late-onset GSDII patients

O Musumeci1, M Gaeta2, E Barca3, A Mileto3, G Vita1, A Toscano1
1Department of Neuroscience, Psychiatry and Anesthesiology, University of Messina, Messina, Italy; 2Department of Radiology, University of Messina, Messina, Italy

**BMC Musculoskeletal Disorders** 2013, 14(Suppl 2):P11

**Introduction:** Adult onset GSDII presents with a wide spectrum of clinical features and variable rates of progression. Three main clinical presentations have been observed: a myopathy with limb girdle muscle involvement (LGMD), asymptomatic hyperCKemia (HCK), and respiratory muscle deficiency preceding limb-muscular weakness. Our study used a new MRI technique with quantitative analysis of muscle fat fraction (MFF) to explore different patterns of muscle involvement and to analyze possible correlations with different clinical aspects in 12 patients with late-onset GSDII.

**Methods:** 12 patients with late-onset GSDII were recruited before starting enzyme replacement therapy and were divided into three cohorts based on clinical presentation (LGMD, HCK, or respiratory insufficiency). Clinical assessments included the Walton scale, 6MWT, GSGC, FVC% and MRC scores. The muscle MRI protocol was performed using dual-echo, dual-flip-angle spoiled gradient-recalled imaging, which allowed us to accurately quantify and display the muscle fat fraction (MFF). We evaluated the MFF of all respiratory muscles in 12 ambulant patients with late-onset Pompe disease. MRIs included the lower girdle, paraspinal, abdominal, and respiratory muscles. Statistical correlations were performed using the Spearman Rho test.

**Results:** MFF of the lower girdle muscles was correlated with functional muscle measures such as the 6MWT, GSGC, and MRC. In particular we found a positive correlation with ileopsoas and gluteus muscles. Moreover, we found a statistically significant correlation between the degree of diaphragm atrophy and pulmonary dysfunction, especially in the upright position.

**Conclusion:** MFF is a reliable, relatively fast, and sensitive technique for visualizing muscle involvement, and it provides an accurate fat quantification when compared to muscle biopsy findings in different neuromuscular disorders. In the present study, we show that this technique can be used to evaluate the degree of muscle involvement and is correlated with clinical data currently used as functional outcome measures in Pompe disease. Our data suggested that muscle MRI studies may be a useful tool to evaluate muscle impairment even in the early stages of disease.

**P12**

Heterozygous individuals with mild phenotype in late-onset glycogen storage disease type 2: a new cohort of patients?

L Vercell1, E Vittottana, S Grifoni, L Chado-Piat, E Rolle, M Spada, C Danesi1, G Comi, T Mongini3
1Centre for Neuromuscular Diseases, Department of Neuroscience, University of Turin, Turin, Italy

**BMC Musculoskeletal Disorders** 2013, 14(Suppl 2):P12

**Introduction:** Late-onset glycogen storage disease type 2 (GSDII) is a genetic but heterogeneous disorder, which may present anywhere along a continuum of severity from an isolated hyperCKemia to a profound, generalized muscle weakness with pulmonary involvement. The gold standard for diagnosis is confirmation of low or absent levels of acid alpha-glucosidase (GAA) enzyme activity (usually in the range of 1-40% of normal levels), which is confirmed only in some cases by molecular analysis of the GAA gene. In the literature, heterozygous individuals are usually considered to be asymptomatic, although they can have reduced enzymatic activity. Since enzyme replacement therapy (ERT) became available in 2006, it has improved the prognosis for severe infantile-onset Pompe disease, as well as for late-onset forms by improving muscle/respiratory function and/or stabilizing clinical progression. Because the disease is now treatable, it is essential to understand which patients may benefit from ERT.

**Results:** In the database of the Centre for Neuromuscular Diseases, we found 7 patients with only one mutated GAA allele: 2 female patients showed proximal weakness, pathologic muscular biopsy and reduced GAA enzyme activity in muscle tissue. These patients started ERT four years ago, and now there is no evidence of disease progression. The other 5 subjects (two are familiar cases, one father and his son) have mild signs of myopathy (i.e., slight scoliosis, proximal weakness, hyperlordosis, fatigability, recurrent episodes of respiratory deficit) or isolated hyperCKemia. Muscle biopsies showed non-specific signs, and reduced enzymatic activity (below 40%) was confirmed in all patients using at least two methods (dried blood spot and/or leukocytes and/or muscle homogenate).

**Conclusion:** Heterozygotes with one GAA gene mutation are not always asymptomatic individuals; in our experience, they can develop a mild myopathy, have non-specific muscle biopsy results, and reduced GAA enzyme activity. We followed and monitored this cohort of patients (not receiving ERT) and found that they did develop clinical evidence of disease. In conclusion, mild symptomatic subjects and heterozygotes are an emerging group of patients. Further molecular investigations and follow-up are required to identify patients in this cohort that may benefit from ERT.

**P13**

Evaluation of muscle biopsy in late-onset GSDII patients before and after enzyme replacement therapy (ERT)

R Violano, M Ripolone, V Lucchini, L Villa, M Sciacco, G Comi, P Toton, M Filosto, S Prevalti, T Mongini, L Vercelli, E Vittottana, A Toscano1, O Musumeci1, E Barca, C Angelini, S Raviglia, C Lamperti, M Mora, L Morandi1, M Moggio1
1Neuromuscular Unit - Fondazione I.R.C.C.S. Ca’ Granda, Ospedale Maggiore Policlinico, Dino Ferrari Centre, University of Milan, Milan, Italy; on behalf of the Italian group of GSDII

**BMC Musculoskeletal Disorders** 2013, 14(Suppl 2):P13

**Introduction:** Glycogen storage disease II (GSDII), or Pompe disease (OMIM 23230), is an autosomal recessive lysosomal storage disorder that results from a deficiency in the acid alpha glucosidase (GAA) enzyme. The disease is characterized by progressive accumulation of lysosomal glycogen in various tissues, primarily in cardiac and skeletal muscles. The histopathological hallmarks in the muscle are fiber vacuolization and autophagy. GSDII is clinically classified as a severe infantile; or an attenuated, later-onset form affecting children and adults. Recombinant human GAA (rhGAA) is the only approved enzyme replacement therapy (ERT) available for the treatment of Pompe disease, and it is effective in infantile patients, whereas in adults, improvements are more variable among different patients. Our project aims to assess the effects of ERT in 19 late-onset patients using both biochemical and morphological (histological, histochemical, and immunohistochemical) evaluations of skeletal muscle biopsies before and after 6 months to 1 year on ERT.

**Methods:** Using baseline and post-ERT muscle biopsy tissue, we monitored autophagy by immunohistochemical analysis of the following proteins belonging to vesicular pathways: EE1 early endosome, LC3 autophagosomal marker, and LAMP-2 lysosomal marker. Quantitative evaluations of fiber diameter, CSA, the number of vacuolated fibers, the degree of glycogen accumulation, and the percentage of vacuolization in type I and type II fibers were also performed.

**Results:** All patients clinically improved after ERT. Pre-treatment muscle biopsies showed a histopathologically divergent spectrum, ranging from almost normal morphology with very few scattered vacuoles, to severe
vacular myopathy. Post-treatment muscle biopsies morphologically improved in two patients, whereas no significant histopathological modifications were seen in all the other subjects. Immunohistochemical analysis of the autophagic pathways was very complex and showed variable binding of the three antibodies in both the first and the second biopsies. Conclusion: This study highlights the effectiveness of ERT in patients with adult onset GSDII and helps shed light on the role of autophagy in the pathogenesis of the disease.

Objective: Classic infantile Pompe disease affects many tissues, including the brain. Untreated infants die within their first year. While enzyme-replacement therapy (ERT) significantly increases survival, its potential limitation is that the drug cannot cross the bloodbrain-barrier. We therefore investigated long-term cognitive development in patients treated with ERT.

Methods: We prospectively assessed cognitive functioning in 10 children with classic infantile Pompe disease who had been treated with ERT since 1999. Until 2004, infants and young children were assessed with the Bayley Scales of Infant Development (BSD-II; number of tests = 23). After 2004, we switched to the Griffiths Mental Developmental Scales (Griffiths; number of tests = 19), expecting it to differentiate better between various domains. Older children were assessed using the Wechsler Intelligence Scales for Children (WISC-III; number of tests = 5). For children with tetraplegia, we used the Raven Colored or Standard Progressive Matrices (number of tests = 3). For those with impaired hearing, we used the Snijders Oomen Nonverbal Intelligence test-Revised (SON-R 2½-7, number of tests = 1). In total, 51 tests were performed. Brain imaging was performed in six children.

Results: During the first four years of life, developmental scores in 10 children ranged from above average development to severe developmental delay; they were influenced by the type of intelligence test used, severity of motor problems, speech/language difficulties and age at start of therapy. Five of the children were also tested from five years onwards. Among them were two tetraplegic children whose earlier scores had indicated severe developmental delay. These scores now ranged between normal and mild developmental delay, and indicated that at young age poor motor functioning may interfere with proper assessment of cognition. We found delayed processing speed in two children. Brain imaging revealed periventricular white-matter abnormalities in four.

Conclusion: Cognitive development at school age ranged between normal and mildly delayed in our long-term survivors with classic infantile Pompe disease treated with ERT. The oldest was 12 years. We found that cognition is easily underestimated in children under five with poor motor functioning.

Objective: To evaluate the effect of ERT on survival in adult patients with Pompe disease. Given the fact that ERT was only registered in 2006, this may be considered as a very promising finding.

Introduction: Fatigue is a common and often disabling symptom among both mildly and severely affected adult patients with Pompe disease. Our objective was to determine whether enzyme replacement therapy (ERT) reduces fatigue in adult patients with Pompe disease.

Methods: Data was collected as part of an international observational study conducted between 2002 and 2011 in which patients were followed on an annual basis. Time dependent covariate Cox's proportional hazards models were used for univariate and multivariate analyses of the risk of death. Patients who discontinued treatment were censored at the time of discontinuation. Additionally, we used an 'intention to treat' approach.

Results: Overall, 283 adult patients with a median age of 48 years (range, 19-81 years) were included in the study. Seventy-two percent of the patients started ERT at some time during follow-up and 28% never received ERT. During follow-up (median, 6 years; range, 0.04 to 9 years), 46 patients died, 28 (61%) of whom had never received ERT. After adjustment for age, gender, country of residence, and disease severity (based on wheelchair and ventilator use), ERT was positively associated with survival (hazard ratio 0.41, CI 95% 0.19-0.87). The hazard ratio for ERT in the multivariable analyses of the intention to treat approach was 0.33 (CI 95% 0.15-0.73).

Conclusion: Our prospective study provides novel data on the positive effect that ERT has on survival in adults with Pompe disease. Given the fact that ERT was only registered in 2006, this may be considered as a very promising finding.
Introduction: Pompe disease is a metabolic myopathy caused by the deficiency of acid a-glucosidase. In addition to enzyme replacement therapy (ERT), exercise training may help improve patients’ fitness and physical functioning. Thus, we studied the safety and efficacy of exercise training in adult Pompe patients.

Methods: Inclusion criteria were:
1. ERT ≥ 1 year,
2. no walking aids,
3. no ventilators.
4. no antibodies.

The 12-week training program consisted of aerobic, resistance, and core stability exercises in 36 sessions. Plasma creatine kinase (CK) was measured biweekly. Aerobic fitness, muscle strength, muscle function, core stability and body composition were evaluated before and after the program.

Results/discussion: 23 patients successfully completed the training program with no significant side-effects. Aerobic fitness improved, shown by increases in workload (100W ± 52 to 122W ± 53, p<0.01), maximal oxygen uptake (69.4% of normal ± 17.4 to 75.9% of normal ± 18.0, p<0.01), and anaerobic threshold (16.7 ± 4.3 ml/min/kg to 18.5 ± 4.7 ml/min/kg, p<0.01). Small increases were observed in total muscle strength and in proximal lower extremities using hand-held dynamometry (both p<0.01). This increase was mainly due to an eight percent-point increase in strength of the hip flexors (p<0.01). At the end of the program, timed muscle function tests indicated that patients took significantly less time to climb four stairs (0.3 second less, p=0.04) and rise from supine to standing (1 second less, p=0.03). The time to run 10 meters did not significantly change. The number of patients able to perform the core stability exercises rose during the training program, and the total time patients were able to remain in balance improved dramatically for all four positions (58% increase for the balance board, 229% and 223% for the left and right side bridges, respectively, and 86% for the abdominal bridge; p<0.05). No changes in body composition were found.

Conclusion: This is the first study to prove that a combination of aerobic, strength and core stability training can be safely performed and leads to improvements in aerobic fitness, muscle strength, muscle function, and core stability in patients with Pompe disease receiving long-term ERT.

P19

A higher dose of enzyme therapy in patients with classic infantile Pompe disease seems to improve ventilator-free survival and motor function

C van Gelder, I Pluij, M Kroos, A Reus, A van der Ploeg

1Department of Pediatrics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands;
2Department of Clinical Genetics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands;
3MRC Centre for Neuromuscular Diseases and UCL, Institute of Neurology, John Radcliffe Hospital, Department of Clinical Neurology, Oxford, UK;
4Department of Genetic Medicine, Newcastle University, International Centre for Life, Newcastle upon Tyne, UK

Introduction: Enzyme replacement therapy (ERT) with Myozyme® has significantly improved the prospect for patients with classic infantile Pompe disease. Yet, about 50% of patients still do not survive ventilator-free beyond 2.5 years. In the present study we compared the safety and efficacy of treatment with 40 mg/kg/week to that of 20 mg/kg/week (eow) in 10 infantile patients to determine if a higher/more frequent dose would improve outcomes. All patients were treated for at least one year and received the same dose throughout the study.

Results: Our outcome parameters included survival, ventilator free survival, left ventricular mass index, motor outcome, and infusion associated reactions. A total of six patients received 20 mg/kg/eow, and four patients received 40 mg/kg/week. The median treatment duration was 3.5 years and 1.6 years, respectively. The median age at the start of therapy was 1.5 months for the 20 mg/kg group and 3.1 months for the 40 mg/kg group. During the treatment period, 3 of the 10 patients became respiratory insufficient. They all belonged to the 20 mg/kg group, and two of the three were CRIM negative. Four of six patients in the 20 mg/kg group learned to walk, but two later lost this ability after becoming ventilator dependent. In contrast, all patients from the 40 mg/kg dose group learned to walk and maintained the ability to walk, even though their baseline motor functioning was generally worse. The decrease in left ventricular mass index and the number of infusion associated reactions was comparable in both groups.

Conclusion: The preliminary data of our study show that treatment with Myozyme at a higher dose of 40 mg/kg/week is generally well tolerated and leads to improved ventilator-free survival and motor outcomes than treatment with 20 mg/kg/eow.
Results: Out of 102 patients, six positive tests were obtained on DBS (5.9%), one of which was a false positive in a patient aged 40 years (CK>1000, symptoms from adulthood, resp. problems; ventilated at night). Five positive cases were subsequently confirmed (4.9% - plus one additional case identified as a family member). These cases will be reported in detail. If not in the audit, these patients would not have been diagnosed with Pompe disease on the basis of their symptoms.

Conclusion: Pompe disease is a progressive, debilitating and often fatal neuromuscular disorder that presents with a continuum of clinical phenotypes that vary with regards to organ involvement, age of onset, disease severity and rate of progression. Early diagnosis is key to implementing early disease modifying treatment. Whilst all these patients detected have some of the features that have been documented in Pompe disease, it is vital that clinicians are alerted to the subtle presentation that late onset Pompe can have. DBS is a rapid test that improves the time to diagnosis, and hence, time to treatment, as suggested in the International Consensus meeting [1].

Reference

Introduction: Pompe disease is a rare, metabolic, multi-system, lysosomal storage disorder with autosomal recessive inheritance, caused by a deficiency of the glycosgen-degrading lysosomal enzyme, acid alpha-glucosidase (GAA). Great phenotypic variability has led to the classification of several subtypes: infantile, late-infantile, childhood, juvenile, and adult-onset form, based on the age of onset and degree of organ involvement. In the most severe cases, disease onset is in infancy and death results from cardiac and respiratory failure along with muscle weakness within the first one or two years of life. In the milder, late-onset forms, muscle weakness is the primary symptom. Weakness of respiratory muscles is the major cause of mortality in these cases.

Results: We present the first two cases of Pompe disease in Bulgaria. The first patient is a 57-year-old female, with onset of the disease at the age of 54, and a slow progression of limb-girdle muscle weakness, restrictive-obstructive type of respiratory weakness, and liver involvement. The second patient is a 45-year-old male with clinical onset at the age of 35 with proximal muscle weakness in the lower limbs and restrictive respiratory weakness. The activity of acid alpha-glucosidase in dried blood spot samples was markedly reduced and subsequently the genetic testing proved that both patients carried the same mutations as double heterozygous for g.32-13T>G in intron 1 and c.1655T>C p.(Leu552Pro) in exon 12 of the GAA gene. The first mutation is quite common in Caucasians, while the second one is described only in Greek patients.

Conclusion: We can speculate that c.1655T>C p.(Leu552Pro) mutation in exon 12, found in the first two Bulgarian patients with adult-onset Pompe disease, may be typical for the Balkan population.

Introduction: Pompe disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of the lysosomal enzyme α-glucosidase. Clinical manifestations are dominated by progressive weakness of skeletal muscle in late-onset patients and by a combination of skeletal muscle weakness and hypertrophic cardiomyopathy in classic infantile patients.

Results: We retrospectively analyzed the prevalence of delayed motor milestones within the first 18 months of life in our Pompe cohort of 58 late-onset patients. Walking delay was recognized in 9/58 patients. In 5/9, loss of motor function was progressive and typically manifested in childhood. In 4/9 patients, initial muscle weakness was not progressive. They reached all motor milestones and were able to hold these on ERT. The phenotypic childhood-onset patients weren’t able to walk earlier than the 18th month of life, the rate of disease deterioration was faster, and they tended to have worse scores on the Walton & Gardner-Medwin scale compared to the juvenile-onset patients. Despite the expectation of severe mutations in childhood-onset patients, some of them have the c.-32-13T>G mutation, but their disease progression was less rapid.

Conclusion: This assessment confirms that childhood-onset patients’ first complaints are delayed walking and early abnormal gait. However, some patients with juvenile onset Pompe disease also present with delayed walking. Disease progression is slower in these patients compared to childhood-onset patients.

Introduction: Herein, we describe our experience with six Pompe patients in South India from September 2007 to July 2012. All patients were diagnosed at our centre by clinical exam and confirmed with enzyme assays and DNA analyses.

Results: A total of six patients (4 months to 12 months, mean 7.33 months) were diagnosed during the study period. Three presented to cardiologists for breathlessness and infiltrative hypertrophic cardiomyopathy. All had motor delay with severe hypotonia and head lag, respiratory distress, and transaminitis. Three other children presented with hypotonia and motor delay, and one of these was diagnosed during an episode of pneumonia. Novel mutations were found in some of these children. Four of six were born to consanguineous parents, and two of six were able to receive ERT. Through the INCAP programme on a compassionate basis, our patient was the first to receive ERT for Pompe disease in India. The first child started therapy at 8 months of age, and the second at 15 months. Initial improvements were noted in both; however, the first child stopped treatment and died 2 months later at 14 months due to respiratory failure. The second child received 10 infusions and died from progressive respiratory failure at 2 years of age. The other three children died within 2 months of the diagnoses, and one died at 12 months. In two families, we performed antenatal diagnoses using enzyme estimation via amniocentesis and the next pregnancies were not affected.

Conclusion: Enzyme replacement therapy started at the later ages of 8 and 15 months, respectively, was not effective in infantile onset Pompe disease. The non-availability of governmental support has made ERT virtually out of reach for Indian Pompe patients. Antenatal diagnosis is, however, effective at reducing the disease burden in this highly consanguineous population.