Insulin-like growth factor binding protein-2 (IGFBP-2) is widely abundant in fetal life and remains highly expressed in the brain throughout life. It plays a key role in targeting IGFs to their receptors in developing organs [1]. It is also highly expressed by a broad range of aggressive cancers such that its ablation reduces cancer growth. IGFBP-2 has also recently been recognised to play a key role in metabolic regulation. We have been investigating the role and mechanisms of action of IGFBP-2, and have developed unique insights into its structure-function-relationships. Our work has mostly focused on neuroblastoma cell lines of varying aggressiveness and motility, and our manipulations of the IGFBP-2 molecule have allowed functional characterisation. We have demonstrated that the IGFBP-2 molecule contains a critical central basic region, the heparin-binding domain (HBD), which accounts for its binding to cell surface, critical in targeting IGFs to their receptors. Ablation of this domain dramatically reduces both proliferation and motility of these cancer cells, a process also involving integrin receptors [2].

This same region of the molecule also contains a Nuclear Localisation Sequence (NLS) accounting for the ability of IGFBP-2 to enter the cell nucleus. This process leads to induction of transcription of a range of cancer-promoting genes including VEGF, promoting angiogenesis in a chick embryo model, intrinsic to carcinogenesis. Ablation of the NLS blocks these processes [2,3].

Circulating IGFBP-2 is reduced in obesity and other insulin-resistant states and in animal models can enhance insulin sensitivity. It is regulated by the insulin sensitiser, leptin, and in a sheep model we have demonstrated that centrally administered leptin induces IGFBP-2 expression in skeletal muscle, via the sympathetic nervous system. Similarly, leptin applied directly to cultured skeletal muscle cells induces IGFBP-2 expression, leading to enhanced insulin sensitivity. This suggests that IGFBP-2 may mediate leptin’s insulin-sensitising effects [4]. IGFBP-2 also acts on visceral, but not subcutaneous adipose tissue, inhibiting fat accumulation, an effect not seen when the HBD region is mutated or integrin blockade is applied. Thus IGFBP-2 appears to play a beneficial role in regulating the function of visceral fat, which is critical in the pathogenesis of metabolic complications of obesity. IGFBP-2 is thus a critical player in both cancer biology and in metabolic syndrome. There is potential for targeted pharmacologic manipulation of IGFBP-2 activity in order to reduce the morbidity and mortality of these major diseases in our society.
References

O3 Weird animal genomes, sex and the evolution of new sex genes
Jennifer A. Marshall Graves
La Trobe University, Melbourne, VIC, Australia

In humans and other mammals with XX females and XY males, the Y bears a gene (SRY) that induces testis differentiation in the embryo and switches on hormones that masculinize it. The human X has more than 1500 genes, but the tiny Y is a genetic wasteland and bears only 45 protein-coding genes, most active only in testis. To discover how human sex chromosomes got to be so weird, we compared the chromosomes, genes and DNA in distinctly related mammals and even birds and reptiles (with completely different sex determining systems). Kangaroo sex chromosomes reveal the original mammal sex chromosomes, while the bizarre platypus sex chromosomes (more related to those of birds) tell us that human sex chromosomes and the SRY gene are relatively young. The human X and Y evolved from an ordinary chromosome pair as the Y degraded progressively. If Y degradation continues at this rate, it will disappear in just 5 million years. If humans don't become extinct, new sex determining genes and chromosomes must evolve, maybe leading to the evolution of new hominid species.

Where will our new sex genes and chromosomes come from? Whereas mammals (and birds) have rather rigid systems, other vertebrates (particularly reptiles) show great variation in sex determining systems, and we can find many examples of switches in sex determining systems. Using a model of dosage-dependent and temperature dependent sex determination, we can readily understand switches between temperature-dependent and chromosome-dependent sex determination, and even between XY and WZ systems. We also see many ways in which genes or gene copies (often of the same genes which seem to be particularly good at this role) have taken on a sex determining function, and defined new sex chromosome systems.

SYMPOSIA: GROWTH

O4 How databases inform clinical management – insights from ozgrow
Ian Hughes1, Andrew Cottrell2, Cathy Ooong3, Paul Hoffman3, Wayne Cutfield4, George Werther5, Maria Craig6, Christopher Covell7, Mark Harris11
1OZGROW & Mater Research, UQ Institute, Brisbane, QLD, Australia; 2Mater Children’s Hospital, Brisbane, QLD, Australia; 3Princess Margaret Hospital Perth, Perth, WA, Australia; 4School of Pediatrics and Child Health, University of Western Australia, Perth, WA, Australia; 5Liggins Institute, Auckland, New Zealand; 6University of Auckland, Auckland, New Zealand; 7The Royal Children’s Hospital, Melbourne, VIC, Australia; 8Murdoch Children’s Research Institute, Melbourne, VIC, Australia; 9Institute of Endocrinology and Diabetes, The Children’s Hospital at Westmead, Sydney, NSW, Australia; 10School of Women’s and Children’s Health, The University of Sydney Medicine, Sydney, NSW, Australia; 11Institute of Endocrinology and Diabetes, The Children’s Hospital Westmead, Sydney, NSW, Australia; 12Discipline of Paediatrics and Child Health, University of Sydney, Sydney, NSW, Australia; 13Lady Cilento Children’s Hospital, Brisbane, QLD, Australia

Recombinant human growth hormone (GH) has been used as an effective treatment for short stature since the late 1980’s. Although clinical trials were crucial in developing GH treatment strategies, database analyses have the potential to provide additional information with regard to treatment efficacy and safety. The OZGROW database was established in 1989 as an initiative of the Australasian Paediatric Endocrine Group (APEG) to allow monitoring of children receiving GH under the national Pharmaceutical Benefits Scheme (PBS). There are currently (June 2014) 1948 children receiving subsidised GH treatment in Australia and the OZGROW database contains records from 6959 individuals. This unique resource has allowed a number of clinically relevant questions to be addressed.

Defining short stature and therefore eligibility for GH treatment relies on the use of appropriate growth standards. There has been debate as to whether the World Health Organisation (WHO) or the Center for Disease Control (CDC) growth charts best describe the heights of contemporary Australian children. There appears to have been a positive secular trend for height in Australian children such that both charts underestimate the number of children eligible for growth hormone treatment.

Ascertainment bias has been proposed as an explanation for the fact that more boys than girls receive GH treatment. Analysis of the OZGROW database demonstrated that ascertainment bias did not appear to be a major factor explaining the gender discrepancy. It is possible that biological factors influencing the tempo of growth and development may contribute to the greater number of boys receiving growth hormone treatment.

Another issue that has complicated comparisons of international studies of growth hormone response has been the different dosing schedules used. A simple method for converting weight and surface area based doses was therefore developed. Further analysis suggested that the surface area based protocol used in Australia may disadvantage older children, given that the dose per kilogram reduces over time even if the dose per meter squared remains constant.

The importance of commencing GH treatment early and maximising height gain during the first year of treatment was also highlighted by analysing GH responsiveness in a number of conditions including Turner syndrome, Prader-Willi syndrome and idiopathic short stature. Ensuring that referring physicians are able to diagnose these conditions in a timely fashion therefore remains a priority.

Although the OZGROW database has allowed clinically relevant questions to be studied there remain a number of challenges, particularly with regard to long term follow up.

Acknowledgements:
Presented on behalf of OZGROW subcommittee members

O5 Growth hormone responsiveness: why does it vary and can it be predicted?
Wayne S Cutfield
Liggins Institute, University of Auckland, Auckland, New Zealand

Initial response to growth hormone (GH) varies considerably. In severe GH deficiency initial response varies across the group by almost 100%. In common non-GH deficient disorders such as idiopathic short stature (ISS) and children born small for gestational age (SGA) initial response varies by more than 100%. The explanation for the wide response to GH treatment can be clustered into three broad groups; (i) non-compliance with GH therapy, (ii) clinical characteristics associated with GH responsiveness and (iii) mutations and common gene variants in the GH-IGF-I axis.

(i) Non-compliance with GH therapy: The most common explanation for variable GH response is missed GH doses. In a national prospective study of GH compliance in New Zealand children, 34% of children missed more than one GH dose per week. Maori and Pacific children missed an additional GH dose each week than Caucasian children. Predictably, poor compliance (≥4 doses/week missed) was associated with a far poorer growth response than good compliance (height velocity SDS +0.4 vs
Even moderate compliance (2-3 doses/week missed) was associated with a poorer growth response (height velocity SDS +1.4 versus +2.8). Interestingly, paediatricians were unaware of GH non-compliance. GH response can only be maximised when more effective GH delivery devices are developed that record the date and time GH is administered to enable paediatricians to more effectively address compliance.

(ii) Clinical characteristics associated with GH responsiveness: There is a differential response to GH therapy according to the underlying disorder. GH deficient children are more responsive than those with Turner Syndrome or idiopathic short stature who are in turn more responsive than SGA children (as shown by height velocity and serum IGF-I for a given GH dose). Furthermore, across the normal birth weight range we have recently shown that progressive reduction in birth weight SDS is associated with a progressively lower IGF-I response during IGF-I generation testing. Across growth disorders; more severe GH deficiency, taller parents, shorter stature, younger age at the start of treatment and heavier children are all parameters found to be associated with greater initial and sustained response to GH treatment. Michael Ranke has pioneered individualised GH dosing through GH prediction modelling across growth disorders. GH response can be predicted by inserting common clinical characteristics into a prediction equation that includes adjusting the dose. Prediction modelling is of greatest benefit to children with adverse clinical characteristics in whom greater initial GH doses will lead to greater growth response.

(iii) Mutations and common gene variants in the GH-IGF-I axis: Downstream gene mutations in this axis (GH receptor, IGF-I and IGF-I receptor) are relatively rare causes of short stature, poor growth and GH response. Conversely common gene variants are being increasingly sought that influence stature, growth and GH responsiveness. Initial reports suggested a common GH receptor exon 3 deletion was associated with a better response to GH than the full length form in SGA and ISS children. Further studies have found little if any effect of the GH receptor deletion on initial or sustained growth response in SGA, Turner Syndrome or GH deficiency. Future studies are likely to focus on panels of common gene variants across the GH axis rather than examining individual genes to better characterise GH responsiveness.

SYMPOSIA: ADRENAL

O6 Diagnosis and management of rare forms of CAH
Taninee Sahakitrungruang
Chulalongkorn University, Bangkok, Thailand

Congenital adrenal hyperplasia (CAH) is one of the most common inherited metabolic disorders. It comprises a group of autosomal recessive disorders caused by the mutations in the genes encoding for steroidogenic enzymes that are involved in cortisol synthesis [1]. More than 90% of cases are caused by a defect in the enzyme 21-hydroxylase. Four other enzyme deficiencies (P450scC, P450c17, P450c11b, 3b(HSD) in the steroid biosynthesis pathway [2-4], along with one cholesterol transport protein defect [5], and one electron-transfer protein (P450 oxidoreductase) [6] account for the remaining cases. In these rare forms of CAH, so-called “atypical CAH”, the clinical and hormonal phenotypes can be complicated, and are not well characterized. The clinical symptoms of these different forms of CAH result from the particular hormones that are deficient and those that are produced in excess. A characteristic feature of CAH is genital ambiguity or disordered sex development (DSD), and most variants are associated with glucocorticoid deficiency. This talk will focus on the diagnosis and management of the variant forms of CAH other than 21-hydroxylase so-called “atypical CAH”, including the genetic analyses, and phenotypic correlates.

References
young children and children at risk for noncompliance with lifelong glucocorticoid and mineralocorticoid replacement. The surgical approach for removal of a PGL depends upon the location of the tumor but in selected cases can also be performed laparoscopically. Patients with unresectable malignant tumors or distant metastatic disease can usually be treated symptomatically with adrenergic blockade. Radiation therapy or radiofrequency ablation can help with symptomatic metastatic disease, and IV bisphosphonates can be considered bony metastases, particularly in patients with bone pain or lesions that increase the risk of pathological fracture. Systemic treatment modalities are only palliative in nature and include 12,13-MIBG, peptide receptor radiotherapy (PRRT) and chemotherapy. PCC/PGLs can have unpredictable behavior and metastasize late in the clinical course. In addition, children in particular are at risk for the development of metachronous tumors. This makes long-term follow-up mandatory in children with PCC/PGL.

**08 Genetic and functional study of StAR (steroidogenic acute regulatory protein) deficiency**

Chan Jong Kim
Department of Pediatrics, Chonnam National University, Medical School & Hospital, Gwangju, South Korea

Congenital lipid adrenal hyperplasia (lipoid CAH) is the most severe form of CAH, impairing adrenal and gonadal steroidogenesis. Most cases of lipoid CAH are caused by recessive mutations in the gene encoding steroidogenic acute regulatory protein (StAR), a protein that plays an essential role in cholesterol transfer from the outer to inner mitochondrial membrane, thus providing the substrate for steroid hormone biosynthesis. Affected children typically present with life-threatening adrenal insufficiency in early infancy due to a failure of glucocorticoid (cortisol) and mineralocorticoid (aldosterone) biosynthesis, and 46,XY genetic males have complete lack of androgenization and appear phenotypically female due to impaired testicular androgen secretion in utero. Previously, the Q288X mutation of StAR was shown to account for about 70% of affected alleles in most patients of Japanese and Korean ancestry. However, it is more prevalent (92.3%) in the Korean population. These results suggest that the genetic defect in the StAR gene in Korean patients with lipoid CAH is highly homogeneous, probably reflecting a founder effect. Recently, some patients have been reported that they showed late and mild clinical presentation. These cases and studies establish a new entity of ‘non-classic lipoid CAH’ showing that the phenotypic spectrum of StAR mutations is substantially broader than previously appreciated.

**09 Recent advance in FGF23 – clinical perspectives**

Toshimi Michigami
Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

Fibroblast growth factor 23 (FGF23) is a circulating factor that plays a central role in the renal reabsorption of Pi and metabolism of vitamin D. It is mainly produced by osteocytes in bone and exerts its effects on distant organs such as the kidney and parathyroid in an endocrine fashion. FGF23 increases renal Pi excretion by reducing the expression of type 2a and 2c sodium/phosphate (Na+/Pi) co-transporters in the proximal tubules. In addition, it decreases the renal production of 1,25-dihydroxyvitamin D (1,25(OH)₂D) by suppressing the expression of 25-hydroxyvitamin D-1α-hydroxilase and increasing that of 25-hydroxyvitamin D-24-hydroxilase. FGF23 requires α-Klotho as well as FGF receptor to exert its effects. FGF23 consists of 251 amino acids. Loss of function mutations in FGF23 cause familial tumoral calcinosi, which is characterized by hyperphosphatemia and increased levels of 1,25(OH)₂D. Autosomal dominant hereditary hypophosphatemic rickets (ADHR) is caused by mutations in the cleavage RXXR motif, which prevent inactivation of FGF23. Excess of FGF23 action results in renal phosphate wasting and an inappropriately low level of serum 1,25(OH)₂D. Recent studies have implicated the iron-deficiency in the late manifestation of ADHR. Tumor-induced osteomalacia is an acquired paraneoplastic syndrome of renal phosphate wasting caused by overproduction of FGF23 by tumors. Among hereditary hypophosphatemic rickets/osteomalacia, X-linked hypophosphatemic rickets (XLH) is the most common form and is caused by deletion or inactivating mutations of the phosphate-regulating gene homologous to endopeptidase on X chromosome (PHEX). Femoral recessive hypophosphatemic rickets type I and type II are caused by inactivating mutations of dentin matrix protein 1 (DMP1) and ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), respectively. In these conditions, serum FGF23 levels are increased, which is responsible for the renal phosphate wasting and impaired vitamin D metabolism. FAM20C is a secreted kinase that phosphorylates extracellular proteins including DMP1. Recently, inactivating mutations in FAM20C have been reported in patients with increased levels of FGF23 and hypophosphatemia. PHEX, DMP1 and FAM20C as well as FGF23 are highly expressed in osteocytes, indicating the critical role of osteocytes in mineral metabolism. Hypophosphatemic rickets/osteomalacia caused by the increased bioactivity of FGF23 and FGF23-mediated hypophosphatemic rickets/osteomalacia. Measurement of serum levels of FGF23 is useful for diagnosis of these conditions. Neutralization of FGF23 will be a potential treatment for XLH and other FGF23-mediated hypophosphatemic rickets/osteomalacia.

**010 Osteoporosis in children with chronic illness: lessons from natural history studies that guide clinical practice**

Leanne M. Ward
University of Ottawa, Ontario, Canada

Children with serious chronic illnesses have the potential for significant bone morbidity, particularly in the context of disorders with impaired muscle function and the need for glucocorticoid (GC) treatment. Recently, studies have shown that vertebral fractures are often the first sign of osteoporosis in this context. Longitudinal studies have taught us that vertebral fractures are most frequent in the first year of GC therapy among children with GC-treated diseases, that vertebral fractures are often asymptomatic and thereby go undetected in the absence of routine monitoring, and that even asymptomatic vertebral fractures predict an increased risk of future fractures. Other discrete clinical predictors of incident vertebral fractures are evident early in the course of GC therapy, including decreases in spine BMD Z-scores and increases in body mass index Z-scores in the first 6 months of GC therapy. Taken together, these observations highlight that the first year of GC therapy is a critical period for monitoring in order to identify bone morbidity in a timely fashion. Children with risk factors for bone morbidity other than GC therapy (such as neuromuscular disorders and immobilization) are also at increased risk for vertebral and non-vertebral fractures fractures. As such, routine surveillance for vertebral fractures (for example, with a lateral spine radiograph) is now considered a key facet of the bone health evaluation in children with chronic immobilization or GC-treated diseases. While some risk factors for osteoporosis will be permanent (such as immobilization arising from disorders such as cerebral palsy), other children will experience transient threats to bone health. This is an important distinction, since children with transient threats have the potential for vertebral body reshaping, either spontaneously or with bone-targeted treatment such as bisphosphonate therapy. Recovery from fracture-induced deformity is growth-dependent, underscoring the importance of timely diagnosis and intervention during childhood in those with limited potential for spontaneous vertebral body reshaping. Prevention begins with optimization of conservative measures, including physical activity, nutrition, treatment of co-morbid endocrinopathies and aggressive treatment of the underlying disease using the lowest effective GC dose. These measures may be insufficient to prevent first-time fractures in some, raising the need for bone-specific therapy in line with a secondary prevention approach. Secondary prevention is predicated
upon identification of early signs of osteoporosis and intervention to prevent disease progression. Since bone-targeted treatment is typically reserved for children with overt fragility, careful monitoring to avoid advanced osteoporosis presentations is paramount. Bisphosphonates are the most commonly prescribed agents in children; however, interest in the use of novel osteo-anabolic therapy is mounting given bone histomorphometric observations that osteoporosis in children with serious chronic illnesses is typically characterized by significant reductions in bone turnover.

O11 Treatment of childhood osteoporosis – current and future perspectives
Craig Munns
The Children’s Hospital at Westmead, Sydney, NSW, Australia

Bisphosphonates are the mainstay of medical therapy in the fracturing child with osteoporosis. The majority of the data in children pertains to intravenous pamidronate use in children and adolescents with osteogenesis imperfecta (OI), where pamidronate has been associated with improvements in bone mineral density, cortical thickness, vertebral shape, pain, mobility and height [1]. Side-effects of pamidronate including acute phase response to the initial dose and retardation of bone healing have also become apparent. To date, there have been no reports of osteonecrosis of the jaw. The best functional outcomes occur when bisphosphonates are given as part of a multidisciplinary approach to treatment.

More recently, bisphosphonates have been used to treat other primary and secondary osteoporotic disorders e.g. immobility and glucocorticoid. Zoledronate is a third generation bisphosphate with a potency 100-200 times that of pamidronate. Even though both pamidronate and zoledronate have a similar mechanism of action, zoledronate has potential advantages over pamidronate in the management of paediatric bone disorders due to its shorter infusion time and longer duration of action. Zoledronate has been shown to be effective in the management of osteogenesis imperfect [2] and secondary osteoporosis [3]. The optimal regimen for intravenous bisphosphonate use in both the acute and maintenance phase of treatment remains to be developed.

Oral bisphosphonates do not appear to be as beneficial as intravenous bisphosphonates in children. Although they result in increased bone density, they do not improve bone pain or alter bone histomorphometry [4]. Larger studies await publication. Further the use of bisphosphonates in primary fracture prevention in children is yet to be investigated.

Biological agents hold promise for the future. Denosumab (RANKL inhibitor) use in children has been reported but it would appear unlikely it will be used widely. Anti-sclerostin antibodies and Dickkopf-1 (DKK1), two Wnt pathway inhibitors, however are potential treatments for primary and secondary osteoporosis with their potent effects on periosteal bone formation [5].

In summary, bisphosphonates have improved the life of children with significant bone fragility. Their use in primary fracture prevention and the utility of new agents such as anti-sclerostin antibodies and DKK1 require further investigation.

References

O12 DOHAD and early pubertal timing
Ken K. Ong
MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge, UK

Age at menarche varies widely between girls, is estimated to be highly heritable and is associated with long-term health outcomes, such as obesity and type 2 diabetes. Earlier pubertal maturation in boys and girls links rapid postnatal growth weight gain to later life metabolic and cardiovascular disease [1,2]. Genome-wide association studies (GWAS), which genotype hundreds of thousands of common genetic variants located across the entire genome, have been successful in identifying many specific genetic determinants of pubertal timing and these findings have informed the mechanisms that link earlier pubertal timing to increased risks of disease. The genetic signals indicate that both obesity-related and obesity-independent mechanisms may link pubertal timing to insulin sensitivity and diabetes risk.

Our earlier findings [3] in the ReproGen international GWAS consortium identified substantial overlap between loci associated with menarche and those associated with body mass index, as had been predicted by analyses of data from twins, and in keeping with recognised associations between infancy and childhood weight gain and pubertal timing, and in turn between pubertal timing and obesity in adult life. However, the locus with the strongest individual effect size is in the gene LIN28, which regulates microRNA processing and also insulin sensitivity. Our recent larger studies indicate further mechanisms that may link puberty timing to diabetes risk, and also suggest pubertal timing as a possible postnatal development target for the evolution of genomic imprinting [4].

References

O13 Placental hormones and the control of fetal growth
Michael Freemark
Duke University Medical Center, Durham, USA

Linear growth in the postnatal period is controlled by the production, secretion, and action of pituitary growth hormone and IGF-I, IGF-I and IGF-II production and signaling are also essential for fetal growth and neural development. But the control of IGF production in the fetus is largely independent of GH.

Among the factors that control fetal IGF production, the availability and utilization of nutrients is most important. Since fetal nutrient supply ultimately derives from maternal nutrient stores, we can understand fetal growth only through analysis of the factors that control maternal nutrient utilization and transport to the fetus.

I will argue that hormones produced by the placenta, including placental lactogen, placental growth hormone, and sex steroids regulate the intake, absorption, utilization and transport of maternal nutrients to the fetus and modulate fetal and neonatal insulin production. Dysregulation of placental hormone production may be associated with fetal growth
retardation or fetal overgrowth and may predispose in later life to glucose intolerance and type 2 diabetes.

O14 Early nutrition and metabolic outcome
Veronica Mericq
Institute of Maternal and Child Research, University of Chile, Santiago, Chile

In recent years the number of extremely premature born (very low birth weight (VLBW<1500 g) children has increased as a consequence of increased survival rate. Those preterm neonates who survive have an increased risk of long-term neurological disabilities and chronic pulmonary disease. In addition, in the last two decades alterations in body composition and increased metabolic risk have been added to the list of consequences. In order to evaluate whether early patterns of infancy anthropometry and nutrition have an impact in metabolic hormonal profile and body composition we have prospectively assessed two cohorts of preterm infants and results will be presented.

SYMPOSIA: DIABETES

O15 ISPAD and its role in the management of diabetes in the young in the Indian subcontinent and the Far East
Stephen Greene
University of Dundee, Dundee, Scotland, UK

Over the last three decades, while the fundamental need for insulin replacement in Type 1 diabetes (T1D) in young people remains, the method of delivery has changed dramatically. From the “First World” view, “intensive insulin” therapy offers the best outcome, in terms of glycaemia and long-term health, and a shift to multiple injection therapy and pumps has become the approach promoted from diagnosis. A recent recognition is the sustained effect of near-normal glycaemia from diagnosis (‘metabolic memory’), achieved through strict glucose targets and dose adjustment of insulin for carbohydrate.

To use the developing technology of T1D requires considerable motivation from patients and their families and there is a need for a parallel support programme from a multidisciplinary team. The components of successful adherence to the management regimens are a matching of health beliefs, attuned communication and reciprocity between those with diabetes, the families and their health professionals.

The regions of the Indian Subcontinent and the Far East offer a significant challenge for ISPAD, an organisation dedicated to support education, science and advocacy for diabetes in the young. The heterogeneity of health care services and social standing of the component countries is significant test for ISPAD. The Society has risen to this test though a parallel support programme from a multidisciplinary team. The components of successful adherence to the management regimens are a matching of health beliefs, attuned communication and reciprocity between those with diabetes, the families and their health professionals.

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O16 Feasibility of intensive insulin therapy in a developing country – the Indian experience
Hem Chand K Prasad
Mehta Children’s Hospital, Chennai, Tamil Nadu, India

The superiority of the Intensive insulin regimen over the conventional split mix is very well established in Western centres, often considered a prelude to pump therapy. Developing countries find it a challenge to initiate Basal bolus therapy. The main problems include: lack of support systems in school environment to take up the injections and glucose monitoring at school, and difficulties in assessing carbohydrate content of native foods prepared at home (considering the variability in preparation of any given food item). The parental acceptance of five injections a day also remains a challenge. There are numerous extraneous influences and myths in minds of parents that discourage them from accepting this regimen. We present our experience in surmounting these challenges and establishing Intensive insulin therapy as a first line of insulin therapy and also share the advantages in terms of the glycemic control and growth of children on follow-up with us.

SYMPOSIA: HOT TOPICS

O18 Insights into the diagnosis and management of congenital hypothyroidism
Paul Hoffman
Liggins Institute, Auckland, New Zealand

Congenital Hypothyroidism is the commonest preventable cause of intellectual disability. Newborn screening with early identification and treatment has resulted in near normalisation of long term intellectual
All criteria require exclusion of other conditions: non-classic congenital adrenal hyperplasia, hypothyroidism, Cushing syndrome, hyperprolactinemia or androgen producing tumours which can cause a PCOS-like picture. Although diagnosis of PCOS is based on its reproductive manifestations, it is a metabolic disorder. PCOS adolescents are at a high risk of having or developing glucose tolerance abnormalities, dyslipidemia and hypertension. Insulin resistance and the consequent development of hyperinsulinaemia seem to be the central pathophysiological mechanism that links PCOS to its associated metabolic derangements; this can occur independent of weight status. Obesity, which is commonly associated with PCOS, exaggerates insulin abnormalities. Adolescents with PCOS should have evaluation of glucose homeostasis and insulin resistance at diagnosis. PCOS management should include a multidisciplinary team and should be individualized depending on the predominant complaint and weight status. Lifestyle modifications should be the first line treatment in the presence of overweight, obesity and/or insulin resistance. Metformin can also be added. Cyclic progesterone withdrawn bleed or cyclical oral contraceptive pills are used for menstrual irregularities. Antiandrogens like spironolactone and oral contraceptive pills are used for hirsutism. Permanent treatment with laser or electrolysis is usually advised after a course of antiandrogens. Various aspects of adolescent PCOS will be discussed based on illustrative cases.

**References**


### MANAGEMENT SESSIONS

**O19**

**Controversies of the assessment and management of polycystic ovary syndrome in adolescents**

Alexia Peña1, Preeti Dabadghao2

1Department of Endocrinology/Diabetes, Women’s and Children’s Hospital, The University of Adelaide, Adelaide, SA, Australia; 2Department of Endocrinology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India


The diagnosis of polycystic ovary syndrome (PCOS) in adolescents is difficult as the pathological criteria used in adults like menstrual irregularities, acne, hirsutism and polycystic ovarian morphology could be normal physiological findings during puberty; in addition the syndrome is heterogeneous and there is limited high quality evidence. [1-3] Three international conferences have been held reporting different criteria for diagnosis of PCOS in women [Table 1]. [4-6] The 2011 Australian PCOS evidence-based guideline [1], the 2012 international evidence-based workshop [2] and the 2013 Endocrine Society Clinical Practice Guideline [3] highlight the issues of applying adult criteria to diagnose PCOS in adolescents.

#### Table 1(abstract O19) Diagnostic criteria for PCOS in women

<table>
<thead>
<tr>
<th>PCOS definition</th>
<th>Clinical (modified Ferriman-Gallway score &gt;8*) or biochemical hyperandrogenemia (elevated total or free testosterone level **)</th>
<th>Oligomenorrhoea (&lt; 6-9 menstrual cycles per year) or oligo-anovulation</th>
<th>Polycystic ovaries on ultrasound (&gt;12 follicles in one ovary or volume &gt;10 cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICHID 1990 [4]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rotterdam 2003 [5]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>2 of 3 criteria</td>
<td>1 of 2 criteria</td>
<td>2 of 3 criteria</td>
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</tbody>
</table>

* Ethnicity should be considered when assessing hirsutism

**O20**

**Delayed puberty – clinical approach and management**

Pik To Cheung

The University of Hong Kong, Hong Kong, China


Delayed puberty, while not uncommonly a variant of normal pubertal physiology, could be an indicator of a wide range of less common but
important clinical disorders. Congenital pathologies may involve defective
developments of the gonads, pituitary gonadotrophs or hypothalamic
GnRH neurons. Acquired pathologies could likewise be acting at each
level. Clinical diagnostic evaluation to delineate a good range of these
disorders and the respective management will be covered in this session.

**O21**
Drilling down on the vitamin D debate: where are our priorities?
Leanne M. Ward
University of Ottawa, Ottawa, Ontario, Canada

Vitamin D deficiency remains a global, public health concern despite
intense focus in recent years. While nuanced issues such as the most
appropriate cut-offs to define degrees of vitamin D sufficiency,
isufficiency and deficiency are still unsettled, these debates occur on a
backdrop of children continuing to be diagnosed around the world with
the most devastating consequences of overt vitamin D deficiency - rickets
and hypocalcemic seizures. The fact that few, if any, countries are exempt
from new cases of vitamin D deficiency rickets underscores the potential
barriers to effective prevention, including well-publicized national policies,
education at multiple levels of the care system, access to vitamin D
supplementation and compliance. As pediatricians, the global eradication
of childhood rickets due to vitamin D deficiency is arguably our most
important mandate at the moment, one that should not be
overshadowed by the vitamin D adequacy cut-off debate. Only a small,
critical amount of vitamin D daily is required post-natally to prevent
ricks, with the optimal approach to rickets prevention targeting mother-
infant dyads. Single dose or intermittent therapy is an appealing strategy
to overcome compliance issues, although a full understanding of the risks
related to higher dose therapy during the early years is still needed.
Overall, this presentation will focus primarily on issues and strategies
related to the global eradication of vitamin D deficiency rickets, with
some discussion around the optimization of vitamin D status throughout
the pediatric years.

**ORAL SESSIONS**

**O22**
A single antenatal course of betamethasone adversely affects glucose
regulation in adulthood and the next generation in childhood
Sarah Mathai1, José Derraik, Wayne Cutfield, Stuart Dalziel, Janene Biggs,
Craig Jefferys, Jane Harding, Paul Hofman
Liggins Institute, University of Auckland, Auckland, New Zealand

**Objective:** To assess whether a single antenatal course of betamethasone
affects insulin sensitivity and other metabolic parameters in the offspring,
and whether effects are transmitted to the next generation.

**Methods:** A cohort of 52 adults (aged 35.7 years, 46% men, 23
born after steroid treatment) and their term-born children (n=61, aged
8.0 years, 52% boys, 49% from a parent born after steroid treatment),
was recruited in Auckland. Insulin sensitivity and secretion were
assessed using hyperglycaemic clamps in adults, and HOMA-IR in
children. Other assessments included DXA-derived body composition,
lipid profile, adipokines, and 24-hour ambulatory blood pressure
monitoring.

**Results:** Insulin sensitivity over the last 60 minutes of the
hyperglycaemic clamp was 31% lower in the Steroid group (p=0.048),
with a similar trend for overall insulin sensitivity (p=0.061). Steroid
adults had a compensatory increase in first-phase insulin that was 53%
higher than in controls (p=0.031), with total insulin secretion 44%
higher in the Steroid group (p=0.044). Children of parents born after
steroid treatment had higher fasting glucose (p=0.049) and insulin
(p=0.008) concentrations than controls. HOMA-IR values indicated
that children in the Steroid group were more insulin resistant than
controls (p=0.006).

**Conclusion:** This study shows that maternal treatment with a single dose
of betamethasone is associated with reduced insulin sensitivity in the
offspring in mid-adulthood. Importantly, there is indication of an inter-
generational effect, with the subsequent generation displaying increased
insulin resistance.

**O23**
Endocrine dysfunctions in patients with mitochondrial diseases
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University of Ulsan College of Medicine, Seoul, Korea; 2Medical Genetics
Center, Asan Medical Center Children's Hospital, University of Ulsan College
of Medicine, Seoul, Korea

**Aims:** Mitochondrial diseases are a heterogeneous group of genetic
disorders that result from dysfunction of the respiratory chain. The
endocrine disorders such as diabetes mellitus, hypoparathyroidism,
hypothyroidism and growth hormone deficiency have been described in
patients with mitochondrial DNA mutations. Among these, patients with
Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like
episodes (MELAS) frequently present with mitochondrial diabetes. Thus,
this study was performed to investigate endocrine dysfunctions in
patients with mitochondrial diseases.

**Methods:** A total of 106 patients (65 males and 41 females) diagnosed
with mitochondrial diseases were included. Their etiologies were
confirmed by clinical features and mitochondrial gene sequencing: Leber
Hereditary Optic Neuropathy (LHON) (56 patients, 52.8%), MELAS (33
patients, 31.1%), Leighe disease (7 patients, 6.6%), Myoclonic Epilepsy with
Ragged Red Fibers (MERRF) (7 patients, 6.6%), Pearson syndrome (2

**Table 1 (abstract O22)** Study outcomes in the offspring (adults, F1) born from mothers who were either treated with
antenatal betamethasone (Steroid) or not treated (Control), and in subsequent generation (children, F2). Data are
means and 95% CI, adjusted for confounders.

<table>
<thead>
<tr>
<th></th>
<th>Steroid</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (F1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>23</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; phase insulin (mU/l)</td>
<td>43.1 (30.9–60.2)</td>
<td>28.1 (20.9–37.8)</td>
<td>0.031</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; phase insulin (mU/l)</td>
<td>57.5 (42.6–77.8)</td>
<td>41.6 (31.8–54.4)</td>
<td>0.068</td>
</tr>
<tr>
<td>Total insulin (mU/l)</td>
<td>101.7 (74.7–138.4)</td>
<td>70.4 (53.5–92.6)</td>
<td>0.044</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>16.1 (11.0–22.4)</td>
<td>23.1 (17.3–30.2)</td>
<td>0.061</td>
</tr>
<tr>
<td>Insulin sensitivity last 60 min</td>
<td>14.3 (9.9–19.7)</td>
<td>20.6 (15.7–26.6)</td>
<td>0.048</td>
</tr>
<tr>
<td>Children (F2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>30</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>4.88 (4.69–5.12)</td>
<td>4.67 (4.50–4.85)</td>
<td>0.049</td>
</tr>
<tr>
<td>Fasting insulin (mU/l)</td>
<td>5.05 (3.98–6.41)</td>
<td>3.57 (2.79–4.58)</td>
<td>0.008</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.10 (0.85–1.43)</td>
<td>0.74 (0.57–0.98)</td>
<td>0.006</td>
</tr>
</tbody>
</table>
patients, 0.02%) and Kearns-Sayre syndrome (KSS) (1 patient, 0.9%). Clinical, auxological and endocrinological parameters such as weight, height, body mass index (BMI), serum free T4, thyroid stimulating hormone (TSH), and glycolysated hemoglobin (HbA1c) were analyzed. Their medical records were reviewed retrospectively.

**Results:** Endocrine dysfunctions were observed in 19 patients (19/33, 57.6%) with MELAS, 1 patient with KSS and Pearson disease, respectively. In patients with MELAS, mean age at diagnosis was 15.2 ± 10.7 years (range, 8 month to 36 years). Their mean height, weight, and BMI were 139.0 ± 20.1 cm (-2.54 SDS), 30.0 ± 11.6 kg (-4.43 SDS) and 15.7 ± 3.4 kg/m² (-2.18 SDS), respectively. Mean HbA1c was 6.59 ± 1.81% in 24 patients with MELAS who showed hyperglycemia in routine serum chemical tests. Thyroid functions were normal in all patients. In mitochondrial gene analysis of MELAS, mt.3243 A>G was the most common (23/33 alleles, 69.7%), followed by mt.3316A>T (1 allele), mt.13513G>A (1 allele), and mitochondrial DNA deletion (1 allele). One patient with KSS showed hypocalcemia with low parathyroid hormone level and stunted growth velocity. A Pearson correlation analysis showed a significant correlation between antibody titer and height and BMI in patients with MELAS and KSS, respectively.

**Conclusion:** Endocrine dysfunctions and growth failure are associated with mitochondrial diseases, especially in patients with MELAS. However, their growth parameters can be affected by general condition, nutrition, and other associated factors. Mitochondrial endocrinopathy should be considered as a rare cause of endocrine dysfunction and growth failure when clinically suspected.

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**O24 Criteria of radiological diagnosis for neonates with hypochondroplasia**

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Department of Pathology, Seoul National University College of Medicine, Seoul, Korea; 3Department of Anatomy, Seoul National University College of Medicine, Seoul, Korea; 4Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea; 5Department of Pathology, Seoul National University Hospital, Seoul, Korea; 6Ischemic Hypoxia Institute, Seoul National University College of Medicine, Seoul, Korea


**Introduction:** The diagnosis of hypochondroplasia (HCH) is hampered by absence of radiological criteria relevant to the age-dependent manifestations, particularly those in the neonatal period. This work deals with the radiological features in hypochondroplastic neonates with a FGFR3 mutation, including quantitative measurement that facilitates the definitive diagnosis. We propose the radiological criteria for HCH in the neonatal period.

**Patients and methods:** Subjects included six HCH neonates with FGFR3 mutations and 30 control subjects, in whom radiological examination was available as a neonate. The following findings were evaluated: 1) short ilia, 2) squared ilia, 3) short greater sciatic notch, 4) horizontal acetabula, 5) short femora, 6) stubby femora, 7) metaphyseal flaring, 8) lumbosacral interpredicate distance narrowing, and 9) oval radiolucency in the proximal femora.

**Results:** All measurement parameters for short ilia, short greater sciatic notch, horizontal acetabula, short femora and stubby femora (parameters 1, 3, 4, 5, and 6) were statistically different between HCH and control, while the other parameters 2, 7, and 8 were not. Based on these results, we tentatively made the criteria and scoring system for the diagnosis of HCH. The major criteria that are given a score of 2 comprise parameters 1, 3, and 6, whose distribution was overlapped between HCH and control. The minor criteria that are given a score of 1 comprise parameters 2, 4 and 5, and 9, because the parameter 4 was overlapped in distribution between HCH and control, and the parameter 5 is a non-specific finding, and the parameter 9 is subjective in assessment. We presumed that a total score of 6 points or higher warrant a diagnosis of HCH.

**Conclusion:** HCH was clearly distinguishable from normal infants assessing the skeletal findings of the ilia and proximal femora on neonatal roentgenograms. We compiled a set of diagnostic criteria for the early diagnosis of hypochondroplastic neonates.

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**O25 Abundant CD4+FOXP3+ regulatory T cells fail to suppress the proliferation of T cells in patients with Turner syndrome**

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1Department of Pediatrics, Seoul National University Children's Hospital, Seoul, Korea; 2Department of Anatomy, Seoul National University College of Medicine, Seoul, Korea; 3Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea; 4Department of Pathology, Seoul National University Hospital, Seoul, Korea


**Context:** Why Turner syndrome (TS) patients are predisposed to autoimmune disease remains unclear.

**Objective:** We investigated whether the frequency, phenotype, and suppressive function of CD4+FOXP3+ regulatory T cells (Tregs) are altered in young TS patients with the 45X karyotype compared to age-matched controls.

**Methods:** Peripheral blood mononuclear cells from young TS patients (n = 24, 17.4–35.9 years) and controls (n = 29) were stained with various Treg markers to characterize their phenotypes. Tregs sorted for CD4+CD25high were co-cultured with autologous CD4+CD25+ T cell targets in the presence of anti-CD3 and CD28 antibodies to assess their suppressive function.

**Results:** TS patients exhibited a higher frequency of CD4+FOXP3+ Tregs among their lymphocytes (mean 2.06 vs. 1.52%, P = 0.005) and FOXP3+ Tregs among their CD4+ T cells (7.44 vs. 4.19%, P < 0.001) compared to controls. The expression of inhibitory CTLA-4 in the Tregs of TS patients was also significantly higher (mean fluorescence intensity = 214.1 vs. 184.6, P = 0.003). The frequency of Tregs expressing GITR, CXCR3, andCCR4/CCR6 was comparable between the two groups. However, the ability of Tregs to suppress the in vitro proliferation of autologous CD4 CD25+ T cells was significantly impaired in TS patients compared to controls (P < 0.05 at a 0.1:1 ratio of Tregs to target cells, P = 0.001 at 0.25:1, 0.5:1, and 1:1).

**Conclusions:** The presence of TS patients could not efficiently suppress the proliferation of autologous effector T cells, despite the abundance of Tregs in the peripheral circulation.
correlated with a higher daily fibre intake ($r^2 = 0.25$, Coefficient 0.20, p=0.04). Higher daily total fat intake independently correlated with worse (lower) GTN (other GTN associations in Table 1). Daily sodium intake exceeded recommendations of 1500mg, this was not significantly related to FMD/ GTN. Higher fibre and lower total fat intake, is associated with better vascular function in T1D children. This is the first evidence that diet composition may reduce the risk of CVD in children with T1D in addition to improving diabetes control.

References

Table 1(abstract O26) Independent predictors of GTN

<table>
<thead>
<tr>
<th>R² = 0.41</th>
<th>Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat</td>
<td>-0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>Vessel diameter</td>
<td>-68.15</td>
<td>0.00</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.23</td>
<td>0.04</td>
</tr>
<tr>
<td>Pump use</td>
<td>3.35</td>
<td>0.01</td>
</tr>
<tr>
<td>TID Duration</td>
<td>-1.26</td>
<td>0.04</td>
</tr>
</tbody>
</table>

O27
Height and height velocity of early/average/late maturing children and adolescents from longitudinal study of the Kangwha cohort
Hyun Wook Chae1, Ah Reum Kwon1, Jung Min Ahn2, Daeyoung Kang3, Hyun Min Kim2, Ho Hee Kim4, Ho-Seong Kim1
1Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea; 2Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, Korea; 3Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Korea; 4Seowha Children’s Hospital, Seoul, Korea. International Journal of Pediatric Endocrinology 2015. 2015(Suppl 1):O27

Aims: The timing of the growth spurt and gender differences in physical growth can vary greatly, and it may contribute to the final height. However, there are few studies about height and height velocity of early/average/late maturing children because of the requirements of a population based longitudinal study. We investigated the height and height velocity according to growth tempo from the Kangwha cohort.

Methods: The present study conducted as a part of a community-based prospective cohort study from 1986 to 1999 with 800 school children (359 males, 441 females). We calculated 2 standard deviation of peak height velocity (PHV) and the age of PHV, and then grouped the subjects into early/average/late maturing groups. We compared the results of 3 groups and investigated the differences.

Results: The age at PHV was 12 in boys and 10 in girls, and height velocity at PHV was 8.62 cm/yr in boys and 7.07 cm/yr in girls on average tempo growth. In boys, the age of PHV was 11 and PHV 9.82 cm/yr in the early maturing group, and the age of 13 and 8.97 cm/yr in late maturing group. In girls, the age of PHV was 9 and PHV 8.75 cm/yr in the early maturing group, however, in the late maturing group; the difference was not significant compared with average tempo. The final height of each group was not different.

Conclusion: Final height was similar between early/late and average tempo group. The PHV might be greater in the early than in the late maturing group, however the difference was significant only in boys. Further longitudinal studies including pubertal development are needed.

O28
Messenger ribonucleic acid expression of KISS-1 and serum level of kisspeptin in rat at different developmental stages
Jung Min Ahn1, Ah Reum Kwon1, Hyun Wook Chae2, Kyungchul Song1, Duk Hee Kim2, Hong Seong Kim1
1Department of Pediatrics, Severance Children’s Hospital, Yonsei University College of Medicine, Seoul, Korea; 2Seowha Children’s Hospital, Seoul, Korea. International Journal of Pediatric Endocrinology 2015. 2015(Suppl 1):O28

Purpose: KISS-1 and its product, kisspeptin is necessary for pubertal onset and proper adult gonadal function due to its stimulatory effect on the secretion of gonadotropin-releasing hormone (GnRH). Although the pathophysiologic importance of KISS-1 and kisspeptin is well known, the developmental patterns of expression of KISS-1 genes and serum level of kisspeptin have not been explored to date. We report herein the expression profile of KISS-1 genes and serum level of kisspeptin in the rat at different developmental stages.

Methods: Sprague-Dawley (SD) strain female rats were used. To analyze expression of KISS-1 mRNA, samples were obtained from hypothalamus, pituitary and ovaries in female rats according to developmental stages. At the same blood samples were collected for analysis of serum levels of kisspeptin and luteinizing hormone (LH). The expression of KISS-1 mRNAs was assessed by RT-PCR and the serum levels of kisspeptin and LH were analyzed by ELISA.

Results: The expressions of KISS-1 gene in hypothalamus and ovary were increased according to developmental stages and peaked at the prepubertal stage (at day 27, respectively, 0.88 ± 0.22, 0.54 ± 0.25). However, there were no significant changes or correlations between developmental stages and KISS-1 gene expression in pituitary. Serum kisspeptin level was also increased according to developmental stages. However, peak level of kisspeptin (35.43 ± 3.60 pg/mL) was in the pubertal stage at day 34. Serum LH level was also increased and peaked (23.29 ± 15.24 ng/mL) at pubertal stage (at day 38). However, an increasing pattern was little delayed than that of kisspeptin level.

Conclusion: The expressions of KISS-1 mRNA in hypothalamus and ovary, serum levels of kisspeptin and serum LH levels were increased according to developmental stages in rat in regular sequence. Therefore, serum kisspeptin levels can be an indication of KISS-1 gene expression in hypothalamus and pubertal onset.

O29
The effect and the mechanism of allo-bone marrow mesenchymal stem cells in experimental autoimmune thyroiditis
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1Department of Pediatrics, Tianjin Medical University General Hospital, Tianjin, China; 2Department of Cell Biology, Institute of Basic Medical Sciences, Beijing, China. International Journal of Pediatric Endocrinology 2015. 2015(Suppl 1):O29

Aims: To investigate the effect and the mechanism of allo-bone marrow mesenchymal stem cells (BM-MSCs) transplantation in the Experimental Autoimmune Thyroiditis (EAT) mouse model.

Methods: C57BL/6 mice were treated with porcine thyroglobulin and Freund’s adjuvant both in the simple model group and the BM-MSCs treated group. Mice in the BM-MSCs treated group were injected with homologous BM-MSCs (3×10⁶/mouse) at the beginning of model establishment. A normal control group was set as well. All mice were killed at the 28th day after primary immunity. The histopathological analysis of thyroid tissues were observed. The levels of autoantibodies, thyroid hormone, IFN-γ, IL-10 were detected.

Results: (1) A mouse model of EAT was established successfully. (2) The thyroid in the simple model group and the BM-MSCs treated group showed inflammatory response and inflammatory cell infiltration, but the response in the BM-MSCs treated group was weaker than in the simple model group. (3) Compared with the normal control group, increased autoantibodies were detected with P<0.05, an increased IFN-γ level and a decrease of IL-10 in the simple model group; Compared with the simple model group, decreased autoantibodies were detected with P<0.05 in the BM-MSCs treated group; Decreased expression of IFN-γ and increased expression of IL-10 was detected in this group with P<0.05.
Conclusion: BM-MSCs could partly restore the immunological homeostatic state through modulating the immunological dissonance of Th1/Th2, and alleviate inflammation of the thyroid. It may provide a new approach to therapy of autoimmune thyroiditis.

O30
The glycemic control has improved in Japanese patients with childhood-onset diabetes mellitus since 1995
Shin Arimori1,6, Mie Mochizuki2, Toru Kikuchi1,6, Tatsumiho Urakami1,6, Toyomori Kawamura1,6, Nobuyuki Kikuchi1,6, Nobuo Matsutani1,6, Noboru Hori1,6, Nozomi Sakai1,6, Shigetaka Shiga1,6, 1Saitama Medical University, Saitama, Japan; 2Yamanashi University, Yamanashi, Japan; 3Tohoku University, Sendai, Japan; 4Osaka University, Osaka, Japan; 5Meiyo University, Yokohama, Japan; 6Seitoku University, Chiba, Japan; 7Tokyo Women’s Medical University Medical Center East, Tokyo, Japan; 8The Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes, Japan

Purpose: The effect of basal-bolus insulin therapy on better glycemic control was documented in the DCCT study. We aimed to clarify whether the introduction of insulin analogues has improved the quality of life using basal-bolus insulin therapy without hypoglycemia to the most of pediatric and adolescent patients with type 1 diabetes mellitus (TIDM).

Methods: Glycemic control was compared between the 1st in 1995, 2nd in 2000 and 3rd in 2008 cohorts of childhood-onset TIDM in Japan, consisting of 556, 749 and 803 patients, respectively. We examined the data of HbA1c, frequency of moderately severe hypoglycemia, insulin regimen, body mass index (BMI) and the SD score each during July and October.

Results: The median values of HbA1c (% of glycemic goal <7.5%) were significantly improved between the subsequent three cohorts; 9.02% (18.6%), 8.10% (30.35) and 7.60% (44.1%), in 1st, 2nd and 3rd cohorts, respectively. In addition patients with HbA1c more than 9% were significantly decreased in that order of cohorts. The frequency of moderately severe hypoglycemia was 9 times/4 months/100 patients in 3rd cohort. The frequencies of multiple daily insulin or pump therapy were 34.5%, 59.7% and 80.7%, in that order. The daily insulin dose was higher in 3rd cohort in comparison with 1st cohort. While the height SD score significantly increased in 3rd cohort, the BMI SD scores in 2nd and 3rd cohorts were significantly higher than that in 1st cohort.

Conclusion: We conclude that the introduction of insulin analogues, especially using the long-acting analogues since 2003, resulted in better glycemic control with good quality of life with less moderately severe hypoglycemic episodes in comparison with DCCT study. On the other hand we may have to pay attention to overweight without dietary advice. On behalf of The Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes.

O31
Response to low dose growth hormone treatment in infants and toddlers with Prader-Willi Syndrome
Elly Scheermeier1, Mark Harris 2, Ian Hughes3, Patricia A Crook4, Geoffrey Ambler2,3, Charles F Verge3, Phil Bergman1, George Werther1, Maria E Craig5, Catherine S Choong2,6,7, Rie Kawakita1, Nobuyoshi Tamagawa1,2, Rie Kawaioka1, Yukiko Hashimoto1, Azumi Sakakibara1, Rika Fujimaru1, Nobuyoshi Tamagawa2,3, 1Department of Pediatric Endocrinology and Metabolism, Children’s Medical Center, Osaka City General Hospital, Japan; 2Department of Genetic Medicine, Osaka City General Hospital, Japan; 3Clinical Research Center, Osaka City General Hospital, Japan

Aim: To aimed to assess the benefits and safety of low dose growth hormone treatment (GHT, 4.5 mg/m2/week) in young children with genetically confirmed Prader-Willi Syndrome (PWS).

Methods: Data of 20 infants (2-12 months) and 24 toddlers (13-24 months) were collected from the PWS-OZGROW database. The two groups were evaluated for standard deviation scores (SDS) of height (length under age 2 years), weight and BMI using the World Health Organization standards (SDSWHO) and PWS specific BMI (SDSWS). Bone age (BA), insulin-like growth factor-1 (IGF-1) levels, hypopitonia, developmental delay, spinal curvature, sleep studies and adverse events over 2 years of GHT.

Results: At commencement of GHT infants had a reduced BMI SDSWHO (P=0.003), while toddlers had a reduced height SDSWHO (P=0.014). The height/length SDSWHO of infants increased from -1.09±1.15 at baseline to -0.26±0.89 after one year and -0.02±0.80 after two years GHT (GLM repeated measures; P <0.0001), and in toddlers increased from -2.11±1.45 to -1.11±1.1 and -0.87±0.94 (P <0.0001). BMI SDSWHO increased in both groups (data not shown), while BMI SDSWS decreased (P<0.0001, age groups P=0.005) from 0.40±0.57 at Year 1 to -0.31±0.95 Year 2 (both age groups combined). Preterm and full term children did not significantly respond in GHT, nor did children with deletion (14) and uniparental disomy (16). All children had low to very low serum IGF-1 at baseline which increased to within the normal reference range for the majority of children (61%) with the remainder modestly increased during the first 2 years of treatment. An improvement in tone, spinal curvature and developmental delay was noted in those who were more severely affected at baseline. Two children developed scoliosis. Three children ceased GHT temporaril to adjust positive airway pressure settings or for tonsilllectomy following onset or worsening of obstructive and/or central sleep apnoea. Bone age was not advanced and no other serious adverse events were reported during the two year GHT.

Conclusion: Treating young children (<2 yrs) with PWS with 4.5 mg/m2/week of GH normalises height and achieves IGF-1 levels in the normal range in the majority of patients. The risk of respiratory adverse events can be minimised by regular monitoring. The dose was sufficient to keep height and most IGF-1 values in the normal range and PWS specific BMI SDS in a negative range and may lower potential risks of long-term treatment of very young children with PWS. On behalf of the PWS and OZGROW collaboration.

O32
Molecular basis of transient neonatal diabetes mellitus in Japan: frequent KATP-TNDM and identification of a patient with a monoallelic INS mutation
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Background: It has been reported that the most common (~70%) form of transient neonatal diabetes mellitus (TNDM) is 6q24-related TNDM, followed by TNDM caused by activating mutations in the KATP channel genes (KCNJ11 and ABCC8, KATP-TNDM) which accounts for approximately 30% of TNDM. Recessive promoter mutations in the insulin (INS) gene also have been reported as rare causes of TNDM.

Aims: To elucidate the molecular basis of TNDM in Japan.

Methods: Nineteen Japanese patients with TNDM were analysed by methylation specific PCR of the differentially methylated region at chromosome 6q24 and by PCR amplification and direct sequencing of all exons and exon-intron boundaries of the KCNJ11, ABCC8, INS and gene: INS (6q24)X in 1.

Results: 6q24 abnormalities were identified in 7 (paternal duplication in 4, paternal uniparental disomy or epimutation in 3), mutations of ABCB8 (R1380C, R216C, V607M) in 3, KCNJ11 (E227K, R50Q, C42R) in 3, and INS (6q24)X in 1.
Conclusion: As compared with previous reports, the frequency of KATP channel mutations were higher in this Japanese cohort. In addition, this is the first report of a monoallelic, coding sequence mutation in the INS gene (Q62X) responsible for TNDM.

033 Continuous subcutaneous insulin infusion is associated with a reduced rate of microvascular complications
Bedowra Zabeen1, Maria E Craig2, Alison Pryke3, AlbertKF Chan4, Yoon Hi Cho5, Paul Benitez Aguile6, StephenHing7, Kim C Donaghue1
1Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Australia; 2Ophthalmology Department, The Children's Hospital at Westmead, Australia

Aim: To determine whether use of continuous subcutaneous insulin infusion (CSII) is associated with lower rates of microvascular complications than use of multiple daily injections (MDI) in adolescents with type 1 diabetes from 2000-2014.

Methods: We assessed microvascular complications in 1152 adolescents aged 12-20 years with diabetes duration ≥ 5 years. Retinopathy was detected using seven-field fundal photography, albumin excretion rate (AER) using overnight urine collections or albumin-to-creatinine ratio (ACR) and peripheral nerve function by thermal and vibration threshold.

Results: Median age was 17 years (IQR 15-18) and median diabetes duration 9.0 (7.0-12.0) years. CSII was used by 29% and MDI 72%. CSII was associated with a lower rate of retinopathy than MDI (16% vs 22%; p=0.025) across the entire study period and in the latest time period with lower rate of AER elevation (≥ 7.5 µg/min) (26% vs 37%; p=0.012); microalbuminuria (1.3% vs 5.5%; p=0.016) and peripheral nerve abnormalities (27% vs 32%; p=0.139) although the latter did not reach statistical significance.

In multivariable analysis, retinopathy was negatively associated with CSII Odds ratio (OR) 0.68 (95%CI:0.47-0.98) and positively with higher Hba1c OR 1.20 (1.08-1.32), older age at diagnosis 1.12 (1.02-1.22), longer diabetes duration 1.26 (1.15-1.38) and lower height SDS 0.78 (0.67-0.91). Early elevation of AER was associated with higher Hba1c OR 1.33 (1.20-1.47), insulin dose 1.86 (1.22-2.82) and lower socioeconomic advantage 0.66 (0.46-0.94). Microalbuminuria was associated with higher insulin dose 2.64 (1.07-6.50) and Hba1c 1.34 (1.07-1.68). A peripheral nerve abnormality was negatively associated with CSII OR 0.66 (0.44-0.97), insulin dose OR 0.50 (0.26-0.94) and positively with higher BMI SDS OR 1.31 (1.06-1.63).

Conclusion: While the benefits of CSII on glycaemic control and quality of life are recognised, this is the first study to show a beneficial association of CSII vs MDI on microvascular complications.

034 Sensory neuropathy in young people with type 1 diabetes: a systematic review
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Peripheral sensory neuropathy and its risk factors are well-described in adults with type 1 diabetes (TID). While clinically evident neuropathy is rare in young people with T1D, we and others have shown that subclinical peripheral neuropathy is common [1]. However, the prevalence of sensory neuropathies may be underestimated, due to a lack of established testing guidelines. We performed a systematic review of the epidemiology of peripheral sensory neuropathy, and diagnostic accuracy of tools used for its assessment, in young people with T1D. We searched Medline and Embase from Jan 1985 to Mar 2014. Inclusion criteria were studied in young people with diabetes duration > 1 year which tested for sensory neuropathy using nerve conduction velocity (NCV), temperature perception threshold (TPT), vibration perception threshold (VPT) and/or clinical examination.

We identified 26 eligible studies, involving 5527 young people with T1D. Only 7/26 (27%) studies were of good methodological quality (Newcastle Oottovac Scale score > 7). Clinical examination yielded a wide variation in the rates of sensory neuropathy, with pooled prevalence of 15% (95% CI 13 to 17). Abnormal VPT was more common, with pooled prevalence 33% (30 to 36), as was TPT, with pooled prevalence 32% (26 to 39). The prevalence of abnormal NCV was similar 36% (33 to 39). Overall, the pooled prevalence of sensory neuropathy, using any test, was 26% (24 to 27). We calculated sensitivity and specificity of the different diagnostic tests that were used in the included studies, in comparison with neuropathies detected by ‘gold standard’ nerve NCV testing. The sensitivity of VPT ranged from 29-62%, and specificity from 65-100%.

In conclusion, there is marked variation in reported prevalence rates of sensory neuropathy, due to lack of consensus on its definition, classification of abnormal results, and testing methodology. Clinical examination demonstrates the lowest sensitivity for detection of sensory neuropathy in young people with T1D.

Reference

035 The Australasian diabetes data network (ADDN): first steps towards a national database resource
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The Australasian Diabetes Data Network (ADDN) is a collaboration that aims to collect and centrally collate a suite of patient data across Australia and New Zealand that will be available to all diabetes researchers. ADDN will collect information prospectively, facilitating data sharing and building capacity in clinical service delivery and investigation. The central database will provide a research resource, facilitate study recruitment and be an ongoing source of data to enable benchmarking against national outcomes. By April 2015 ADDN will be populated with over 4,000 participants presenting an opportunity to analyse national data for the first time. To date ADDN holds the data of 1,136 children and adolescents. Of the T1D participants (n=1064), males and females were equally represented, with 3% (35) aged <5, 19% (200) aged 5-10, 37% (396) aged 10-15, 38% (399) aged 15-20 and 3% (34) >20 years of age. A total of 10% were treated with twice daily injections, 42% with Multiple Daily Injections and 47% with continuous subcutaneous insulin infusion (CSII). The TID group had a median Hba1c of 8% (64 nmol/mol) with 31% (330) <7.5% (58.5 nmol/mol), 42% (447) 7.5-9.0 (58.5-74.9 nmol/mol) and 27% (287) >9.0% (74.9 nmol/mol). From these preliminary results it is clear that a large proportion of participants are not meeting recommended glycaemic targets [1] despite the high uptake of intensified insulin therapy. Further analysis of the ADDN dataset is needed to understand the influence of different practices and therapies for T1D used in Australian youth, and the clinical and demographic predictors of glycaemic outcomes. This research and resource will have major implications for clinical investigation in Australasia and will provide an evidence base to inform health policy.

On behalf of the ADDN Study Group.

Reference

O36 Performance of a predictive algorithm in sensor-augmented pump therapy in the prevention of hypoglycaemia

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The Predictive Low Glucose Management (PLGM) system consists of a Medtronic Veo pump, Enlite sensor, MiniLink REAL-Time transmitter, Bluetooth-RF transmitter and a predictive algorithm operating from a Blackberry smartphone. The system suspended insulin delivery when the pre-set hypoglycaemia threshold of 4.4mmol/L was predicted to be reached in 30 minutes.

The aim of this study was to determine the plasma glucose profile with the PLGM system when hypoglycaemia was induced by (a) moderate-intensity exercise, (b) subcutaneous insulin bolus and (c) increasing the overnight basal infusion rate in individuals with type 1 diabetes. The primary outcome was the plasma glucose nadir following each hypoglycaemic stimulus with and without PLGM. Participants performed 30-60 minutes of moderate-intensity exercise or were administered a subcutaneous insulin bolus following a glucose stabilisation period on basal continuous subcutaneous insulin infusion. In participants studied with increased overnight basal rates, hypoglycaemia was induced by increasing basal rates by 180%. They were randomised and studied on 2 separate days; with PLGM off and with PLGM on. On both days, participants were observed until plasma glucose dropped to 2.8mmol/L or were symptomatic.

Results: A) PLGM suspended basal insulin in 9/13 participants who performed moderate-intensity exercise resulting in a higher glucose nadir in 6/9 participants (66%). The mean±SD glucose nadir with PLGM off and on was 3.38±0.44mmol/L and 3.5±0.56mmol/L respectively, (p=0.27).

B) PLGM suspended basal insulin in 27 participants in whom SC insulin bolus was administered resulting in a higher glucose nadir in 20 participants (74%). The mean±SD glucose nadir with PLGM off and on was 3.33±0.47mmol/L and 3.71±0.52mmol/L respectively, (p=0.003).

C) PLGM suspended basal insulin in 6/6 participants in whom overnight basal rates were increased resulting in a higher glucose nadir in 5/6 participants (83%). The mean±SD glucose nadir with PLGM off and on was 2.7±0.29mmol/L and 3.9±1.11mmol/L respectively, (p=0.05).

Sensor-augmented pump therapy with the PLGM system is likely to be effective in reducing the risk of hypoglycaemia. The system appears to be more effective when hypoglycaemia is induced by insulin bolus and increased overnight basal rates than with exercise.

O37 Childhood glycaemic control has an enduring effect on the lifetime risk of microvascular complications in type 1 diabetes mellitus

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The development of diabetes-related microvascular complications in type 1 diabetes (T1DM) is known to be related to glycaemic control, but the degree to which variations in HbA1c across the lifetime contributes to this risk is unknown. Our hypothesis was that individuals with poor control in childhood and subsequent improved control in adulthood would still have an increased risk of severe diabetes-related complications when compared with individuals who achieved good control throughout the lifespan. This study aimed to investigate this premise in a cohort for whom serial lifetime glycaemic data are available. The study population comprised children diagnosed with T1DM <18 years at The Royal Children’s Hospital (Melbourne) who transitioned to the Royal Melbourne Hospital for ongoing (adulthood) care. Data were collected through BioGrid Australia, a biorepository allowing inter-institutional data linkage, and included demographics as well as serial HbA1c and complication data. ‘Severe complications’ were defined as severe diabetes-related eye disease, renal failure, ulceration/amputation or death. Glycaemic control was categorised according to HbA1c changes over time, based on median values throughout the lifetime; “Optimal” (>8.2% throughout lifetime), “Improving” (>8.2% in childhood, ≤8.2% in adulthood), “Worsening” (≤8.2% in childhood, >8.2% in adulthood), “Poor” (>8.2% throughout lifetime). A total of 503 (male=253) individuals were identified, diagnosed 1975-2010. At the time of follow up, mean (SD) age was 27.9 (6.2) years and median (IQR) duration of diabetes was 17.8 (12.2, 23.2) years. Severe complications were documented in 26 (5.2%) and were associated with mean HbA1c at age 16-30 years (<0.05) and intra-individual lifetime glycaemic variability expressed as HbA1c SD (p=0.02). The relative risk (95% confidence interval) of developing severe complications in the improving, worsening and poor groups was 14.9 (1.7-130.9, p=0.01, n=50), 12.5 (1.4-109.4, p<0.01, n=60) and 15.4 (2.1-114.8, p<0.01, n=206) respectively when compared to the optimal group (n=187). In conclusion, the overall rate of severe complications is low in this cohort despite the lifelong poor glycaemic control demonstrated in 40.1%. Our findings demonstrate that poor glycaemic control in childhood has a lasting effect on the development of severe microvascular complications in adulthood.

O38 A randomized controlled trial on the effects of antenatal exercise on birth weight and neonatal body composition

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Aims: To determine the effects of an antenatal exercise programme on birth weight and neonatal body composition of offspring of overweight and obese women.

Methods: We are conducting a parallel arm randomized controlled clinical trial in Auckland, New Zealand (NZ). Eligible participants were enrolled to the study from March 2013 to April 2014. The intervention group participated in a 16-week home-based moderate-intensity exercise programme utilising stationary cycles and heart rate monitors. Maternal measures including weight, aerobic fitness, physical activity and diet were assessed at baseline and end of intervention. Neonatal and maternal body composition were assessed 14 days after delivery.

Results: A total of 75 participants were recruited (intervention n =37; control n =38). Participants had a mean pre-pregnancy BMI of 31.5 kg/m2; age of 30.5 years and weight of 91 kg at study entry. 57% were NZ European/other, 29% Pacific Island and 13% Maori. 25% were nulliparous. Maternal characteristics known to affect birth weight were similar between groups at baseline. To date, 42 participants (intervention n= 19, control n=23) have completed the study. The birth weight (g) of offspring in the intervention group was 3701 ± 561 compared to 3552 ± 495 in the control group. Secondary offspring outcomes in the exercise and control groups are: birth length (cm) 51.5 vs 51.6; head circumference(cm) 35.1 vs 34.8; customised birth weight centiles 59% vs 42%; neonatal lean mass (g) 3717 vs 3546; neonatal fat mass(g) 367 vs 275 and neonatal %body fat 8.8% vs 7.2%. Maternal outcomes in exercise (n=24) and control (n=26) groups are: weight gain (kg) over the intervention period 8.93 vs 8.94; postpartum maternal BMI 32.7 vs 35.5 and % body fat 46% vs 48%.

Conclusion: This is the first clinical trial exploring the effects of antenatal exercise in overweight and obese women on neonatal body composition
Adolescent obesity is associated with inflammation, insulin resistance and prediabetes. The purpose of the study was to investigate whether resistance training (RT) improves the adipokine profile, body composition and insulin sensitivity of obese adolescents. Fourteen obese adolescents (16.1±1.6 y; M/F 6:8; body mass index (BMI) SDS 2.01 ± 0.31) were recruited for a 16-week RT intervention. Thirty-one lean youth (15.6±1.3 y; M/F 19:12; BMI SDS -0.03±0.07) had baseline anthropometric measurements and blood tests for comparison. Participants completed 3 RT sessions per week with training load progressively increased from 60% to 85% of one repetition maximum (1-RM). The following parameters were examined pre- and post-intervention: 1) Height, weight, BMI; 2) High sensitivity C-reactive protein (hs-CRP) and adipokines including interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), adiponectin, soluble intercellular adhesion molecule (sICAM)-1, leptin and resistin; 3) Body composition by dual energy x-ray absorptiometry (DXA), and 4) Insulin sensitivity by homeostatic model assessment (HOMA-IR). Obese youth had significantly higher IL-1β, leptin and resistin (all p<0.0001) and lower adiponectin and sICAM-1 (both p<0.0001) at baseline compared with lean youth. Post-intervention, a reduction in IL-1β (p<0.01), IL-1β (p<0.01) and resistin (p<0.001) was observed whereas adiponectin and sICAM-1 increased (p<0.05, p<0.001 respectively) in obese adolescents. HOMA and hs-CRP remained unchanged. IL-1β and sICAM-1 levels in obese youth normalised to levels comparable to lean youth post-intervention (p = 0.1 and p=0.2), whereas TNF-α and resistin were significantly lower (p<0.05, p<0.01 respectively) post-intervention in the obese youth. Percent fat for the trunk, arm and total body (p<0.05) were reduced, while fat free mass (p<0.01) was increased after the intervention. RT is a feasible intervention to improve the adipokine profile and body composition of obese adolescents suggesting it may be a feasible intervention for improving metabolic health in obese youth at high risk of Type 2 Diabetes.

**: Supplementation with oxidised fish oil in pregnancy markedly increases neonatal mortality in male rat offspring

Introduction: Omega-3 fish oils are the most popular health supplements, taken by 15-30% of people at all stages of life, including pregnancy. These oils may improve insulin sensitivity through the recently characterized GPR120 receptor, but are chemically unstable and easily degrade into potentially toxic lipid peroxides. The health effects of oxidised fish oil are mostly unknown. We have shown that 89% of fish oil products in NZ exceed recommended oxidation limits, 36% by more than two-fold.

We hypothesised:
1. Fish oil supplementation during pregnancy of insulin-resistant mothers would prevent adverse metabolic programming of the offspring.
2. Oxidised fish oil would cause adverse metabolic and cardiovascular outcomes.

Methods: 80 female Sprague-Dawley rats were allocated to a control or high-fat diet and time-mated. Throughout pregnancy they received 1ml of unoxidised fish oil, a highly oxidised fish oil, or control (water) by daily gavage. This dose of fish oil has been shown to reverse insulin resistance in rats. Neonatal mortality was recorded. Markers of oxidative stress and inflammation will be measured in unused pups. At weaning, male offspring were fed standard chow ad libitum. At 100 days they will undergo metabolic assessment including insulin sensitivity, lipid and inflammatory profiles, blood pressure and body composition.

Results: Neonatal mortality was 8 times greater in the offspring of mothers treated with oxidised fish oil than controls (25.7 vs 3.2%, respectively; p<0.0001), with mortality from Day 2 to weaning being 1.4
times greater (p<0.042). Oxidised offspring had lower birth weight (5.4 vs 6.1 g; p=0.008), and reduced weight at weaning (36.6 vs 40.7 g; p=0.07) and adolescence (day 51: 221.6 vs 256.7 g; p=0.02). Further, puberty was delayed compared with controls (day 45.3 vs 42.7; p<0.05).

Discussion: Oxidised fish oil in pregnancy markedly increased neonatal mortality and had a powerful programming effect on the surviving offspring. Fish oils are often taken in pregnancy and are usually oxidised which may lead to adverse programming of growth and development. The long-term metabolic effects of the oxidised and fresh fish oil will be available for the ASM. As fish oils at retail are substantially oxidised, we recommend a precautionary response to these data: pregnant women should not take supplementary fish oil.

O42 Increased rates of infantile hypercalcaemia following guidelines for antenatal vitamin D3 supplementation
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Consultations for infantile hypercalcaemia (IH) have increased at Sydney Children’s Hospital since guidelines for vitamin D3 supplementation during pregnancy were introduced in 2006. Recent nationwide shortages of low-calcium formula (LCF) suggest this problem may be widespread. CYP24A1 mutations have been identified as a potential cause of IH.

To determine if IH is occurring more commonly, de-identified, first-measured serum calcium from all infants <6 months (n=5796) measured in our laboratory, were grouped by years 2005-2007 (n=1516), 2008-2010 (n=1945) and 2011-2013 (n=2335). In addition, we analysed 13 subjects treated by our department for idiopathic infantile hypercalcaemia (IH) from 2011-2013.

Rates of hypercalcaemia (>2.75mmol/L) increased from 2011 (1.1% vs 1.3% vs 8.7%, χ²P<0.001). Rates of hypocalcaemia (<2.25mmol/L) fell steadily (42.4% vs 32.3% vs 24.8%, χ²P<0.001). Twelve mothers of our 13 infants with IH received antenatal vitamin D3 supplementation. One infant also received 400 units/day Vitamin D3 post-natally. At diagnosis, median age was 13 days (range 4-50), 77% were breast-fed, 54% were symptomatic and 25% had nephrocalcinosis. Median initial calcium was 3.00mmol/L (range 2.84-4.03) and phosphate 2.04mmol/L (1.1-3.33). PTH was not elevated (median 1.0pmol/L [<0.3-3.1]), urinary calcium: creatinine ratio not suppressed (median 2.3, [0.4-9.1]), 25OHD>10 Vitamin D low-normal (median 44nmol/L [17-218]) and 1,25(OH)2D<10 elevated (median 232pmol/L [64-720]), in keeping with an abnormality in CYP24A1. In 7/10 infants with data available, treated with LCF for median 95 days (range 25-310), median PTH rose to 17.1pmol/L (8.2-49.3), P=0.02 with a trend to lower 25OHD>10 Vitamin D (median 23mmol/L [<10-108], P=0.09) despite continued high-normal calcium levels (median 2.66mmol/L [2.11-2.75]). Concurrent changes in rates of hyper and hypo-calcaemia suggest antenatal vitamin D3 supplementation as an aetiological factor. IH was associated with significant morbidity, including symptomatic hypercalcaemia and nephrocalcinosis. Treatment with LCF prevented further symptomatic hypercalcaemia, but resulted in elevated PTH. The biochemistry of our patients with IH raises variations in Vitamin D metabolism or calcium set-point as potential associated factors.

GROWTH & METABOLISM

O43 Regular, moderate intensity maternal exercise reduces birth weight but increases the risk of later childhood adiposity
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Aims: We have previously randomised primiparous mothers to either an exercise regime or normal activity between 20 and 36 weeks gestation. In this study we aimed to assess the long-term effects of exercise during pregnancy on growth parameters and body composition in the offspring over their first 6-8 years of life.

Methods: Of the initial 84 women and their offspring who participated in the RCT, follow-up data were available on 46 mothers (26 exercisers, 20 controls) and 46 children. At each follow-up visit (6 months, 1 year, 2 years, 4 years, 6-8 years) clinical assessment included measurement of mothers’ and children’s heights, weights, BMI, and waist circumference, as well as blood pressure. Body composition was assessed in both mothers and children by whole-body dual-energy X-ray absorptiometry (DXA) scans at 4-year and 7-year follow-up visits.

Results: There were no differences in anthropometry between exercise and control children in the first 2 years of life. In addition, at age 4 years there were no differences in height, BMI, percentage body fat, or waist circumference between the two groups. At a mean age of ~7.5 years, exercise and control children showed similar weight, height, BMI, and waist circumference, but the exercise group had more body fat (17.5 vs 16.0%, P=0.02) than controls. Over the course of follow-up there were no observed differences in anthropometry between exercise and control mothers.

Conclusion: While no long-term benefits of maternal exercise in the first pregnancy were noted in mothers, children exposed to maternal exercise during intrauterine life appear prone to greater fat mass accumulation in mid-childhood. Larger studies are required to confirm this important observation as exercise in pregnancy is widely recommended by obstetricians.

O44 Pre-clinical alterations in cardiovascular phenotypes and their associations with metabolic profiles among obese youths
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Introduction: Childhood obesity and various obesity-related co-morbidities have become a serious global healthcare problem. Predictive risk stratification and early detection of high-risk obese youths can potentially help modify the outcomes of obesity before irreversible damage taking place. Newer surrogate markers for assessing pre-clinical cardiovascular alterations have good predictive values for future cardiovascular risks. However, local data regarding obesity-related arterial alterations in youth are lacking at present.

Aims: To evaluate the 1) pre-clinical cardiovascular alterations; and 2) their associations with the metabolic profiles in obese Hong Kong Chinese youths.

Study methods: A total of 56 obese subjects and 58 healthy lean controls (M: F 1:1, age 17.0 ± 2.06 years) were recruited. Clinical, biochemical and arterial (structural and functional) parameters were obtained from all participants. Structural arterial parameters were determined by assessing carotid arterial intima-media thickness with ECG-synchronized ultrasound (Vivid 7, GE Medical Systems, Norway). Cross-sectional and regional arterial functions were determined by assessing the arterial stiffness (β) of carotid arteries and pulse wave velocities of various arterial segments respectively with an automatic device (VP-2000; Colin Medical Technology, Japan). All ultrasonographic and arterial assessments were performed by a single researcher.

Results: Obese youths have worse preclinical arterial phenotypes both structurally and functionally, hence higher risks of developing cardiovascular disease in the future (p<0.0001). Important independent risk factors for preclinical arterial alterations in obese youths, including body mass indices (BMI), waist circumferences, blood pressures and plasma alanine aminotransferase (ALT) levels were demonstrated (p<0.0001). obese youths having co-morbid metabolic disturbances were associated with worse preclinical arterial phenotypes. The worst cardiovascular phenotypes were shown in obese youths with the highest triglycerides to high-density lipoproteins (Tg-to-HDL) ratios despite most
of them having normal serum triglyceride and HDL levels. Furthermore, obese subjects with higher paediatric NAFLD fibrosis index (PNFI) scores [1] have worse cross-sectional arterial stiffness.

Conclusions: Assessment of preclinical cardiovascular phenotypes in asymptomatic obese youth provides clinicians a window for early identification of those at higher risks of developing future cardiovascular events. Evaluation of lipid compositions and obesity-related liver alterations may potentially help further stratify obese youth into subgroups with different degrees of cardiovascular risks.

Reference

O45
Serum bisphenol A concentration and premature thelarche in female infants aged 4-month to 2-year old
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Aims: To estimate the association between serum bisphenol A and premature thelarche in female infants aged 4-month to 2-year old.

Methods: We set a case-control study, a total of 251 female infants (aged 4 months to 2 years) with premature thelarche and 33 healthy age-matched control subjects were enrolled. Test the serum bisphenol A (serum BPA) concentration by liquid-liquid extraction coupled with ultra-performance liquid chromatography tandem mass spectrometry.

Results: The mean serum BPA levels in the normal and premature thelarche groups were 1.70 ng/ml and 3.48 ng/ml respectively. Serum BPA concentration in the premature thelarche group was significantly greater than that in the control group. There was no correlation between age and serum BPA level. Univariate logistic regression analysis showed that serum BPA concentration positively associated with premature thelarche, and the effect of BPA falls down as the age growing.

Conclusions: This hospital-based study implies that the association between serum BPA concentrations and premature thelarche. Additionally, the serum BPA levels are much higher than we ever thought in infants, and much more concerns should be raised in infants aged 4-month to 2-year old.

O46
Gastric emptying is rapid in adolescents with type 1 diabetes and relates to gastrointestinal symptoms
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Gastric emptying is a critical determinant in postprandial glycaemic control. This study aimed to assess whether gastric emptying in adolescents with type 1 diabetes (T1D) relates to gastrointestinal symptoms and to heart rate variability (HRV) as a measure of autonomic function.

We studied 30 adolescents (age 15 ± 2.5 years, BMI 22 ± 3.1 kg/m²) with T1D. Subjects consumed a 13C labelled pancake meal. Gastric emptying was measured by 13C breath test. Blood glucose was monitored frequently over 4 hours and gastrointestinal symptoms at 30-60 minute intervals, by a visual analogue questionnaire. Chronic gastrointestinal symptoms over the previous 3 months were assessed by a validated Diabetes Bowel Symptoms Questionnaire [1]. HRV was assessed by LabChart Pro [2]. Age and sex matched controls were also studied. Gastric half emptying time was accelerated in adolescents with T1D compared to controls; 77.6 (61.4-99.3) minutes [median (IQR)] versus 109.1 (70.8-124.2), p = 0.02, independent of hyperglycaemia during the study, HbA1c, duration of diabetes, and BMI. There was no difference in the prevalence of chronic symptoms or symptoms of a severity that affected lifestyle between the two groups. The presence of nausea, vomiting, bloating and/or fullness during the study in T1D was associated with faster gastric emptying compared to asymptomatic T1D (r = 0.55; p = 0.04), and this was independent of peak glucose and glucose at 4 hours. Rate of gastric emptying in T1D did not correlate with HRV.

Adolescents with T1D have rapid gastric emptying associated with acute gastrointestinal symptoms. Symptomatology could be used as a clinical tool to determine the need for further investigation.

References

O47
Prevention of retinopathy in type 1 diabetes: a systematic review and meta-analysis
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Diabetic retinopathy (DR) is the most serious ocular complication of type 1 diabetes (T1D) and leading cause of acquired blindness in working aged adults. Although various interventions have been trialled to prevent the development or progression of DR, the evidence to support many of these remains unclear. We systematically reviewed the evidence for primary and secondary interventions, to guide the management of DR in people with T1D. Systematic searches were performed using MEDLINE, EMBASE and CENTRAL databases (from January 1990 to June 2014) to identify randomised controlled trials and controlled cohort studies reporting the incidence or progression of DR following administration of systemic interventions. English-language studies with a minimum follow-up of one year were eligible. Meta-analyses of extracted data were performed to determine pooled relative risk (RR) reduction. Twenty-three studies met the inclusion criteria. Intensive insulin therapy significantly reduced the risk of both incident DR (RR 0.44, 95% CI 0.22-0.86, p=0.02) and progression of DR (RR 0.55, 0.31-0.97, p=0.04) compared with conventional therapy. Continuous subcutaneous insulin infusion (CSII) pumps provided significantly greater protection than multiple daily injection therapy (RR 0.33, 95% CI 0.19-0.57, p<0.0001). Angiotensin-converting enzyme inhibition had no impact on DR incidence but reduced progression (RR 0.57, 95% CI 0.34-0.94, p=0.03). Conversely, angiotensin receptor blockade was effective in decreasing DR incidence (RR 0.65, 95% CI 0.49-0.83, p=0.002) but had non-significant effect on progression. Both pancreas-alone and combined pancreas-kidney transplantation retarded progression of DR (RR 0.20, 95% CI 0.10-0.41, p<0.0001). Islet cell transplantation provided no benefit compared with either intensive or conventional insulin therapy.

In people with T1D, there is strong evidence supporting intensive insulin therapy for prevention of DR. Anti-hypertensives also provide protection
against DR in normotensive, normoalbuminuric adults but their effectiveness in other populations is yet to be investigated. In patients with T1D of longer duration, pancreas transplantation slows progression of DR. There is insufficient evidence to recommend the use of anti-angiopiotic therapy or other medical interventions.

**BONE/VITAMIN D**

**O48**
High incidence of vitamin D deficiency in 2 – 17 year olds presenting with fracture to a Melbourne suburban public hospital
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To determine vitamin D deficiency risk and other lifestyle factors in children and teenagers aged 2 – 17 years presenting with fracture to Sunshine Hospital, a clinical observational study was undertaken using convenience sample data collected from children and teenagers aged 2 - 18 years of age presenting with fracture, for whom consent had been obtained to determine clinical characteristics and lifestyle factors. Recruitment was undertaken over a 4 month period from 1st February to 31st May 2014. A suburban Melbourne (latitude 38°S) teaching hospital, Sunshine Hospital provides paediatric orthopaedic services for a high proportion of children and teenagers from ethnically diverse backgrounds with an increased proportion of highly pigmented individuals, which may influence vitamin D status specifically. Proxy measures of vitamin D were used (skin pigmentation, hours spent outdoors, sunscreen use and obesity) [1] to determine patients at risk for vitamin D deficiency. Further consent was then obtained from at risk patients to take blood for 25 OH vitamin D (LIAISON®, Diasorin Assay). Of the 162 patients recruited into this study, 133 (82%) had risk factors for vitamin D deficiency. Of these 108 (81% of at risk) consented to blood testing for 25 OH vitamin D, with a median of 50nmol/l (range 14 – 110nmol/l) obtained. A total of 56 (52% at risk, 34% of total participants) were found to be vitamin D deficient and of these 45 (80% at risk) were mildly deficient (25 OH D 30 -50nmol/l) and 11 (20% at risk) had moderate deficiency (25 OH D 12.5 – 25 nmol/l). Although our study was undertaken at the end of summer, one third of the patients in our study were vitamin D deficient. Furthermore, half of those clinically deemed at risk for vitamin D deficiency were confirmed on biochemical testing. Childhood fracture incidence has been reported to be increasing, and with relatively stable genetic characteristics, any variations in childhood fracture incidence would imply environmental changes. The effect of mild to moderate vitamin D deficiency on fracture risk, healing and longer term fracture risk in children and teenagers is yet to be determined, however, based on our findings we recommend that vitamin D status be assessed in all at risk children and teenagers living in urban environments at higher latitudes presenting with fracture.

**Reference**

**O49**
The relationship of serum 25-hydroxyvitamin D with glucose homeostasis in obese children and adolescents in Zhejiang, China
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Aims: Evidence of the association between vitamin D, insulin resistance and oral disposition index (ODI) in obese children and adolescents is limited. We investigated serum 25(OH) D levels in obese children and adolescents in Zhejiang, China, and determined the relationship between serum 25(OH) D and glucose metabolism.

Method: A cross-sectional design was used. All together 348 obese and 445 non-obese children and adolescents (aged from 6-16 years old) were enrolled in this study. Obese children were divided into four subgroups: normal glucose tolerance (NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), combined IFG and IGT (IGF +IGT) according to the oral glucose tolerance test. We measured serum 25(OH)D levels and calculated the homeostasis model of insulin resistance (HOMA-IR), the whole body insulin sensitivity index (WBISI), the product of β-cell function and insulin sensitivity by the disposition index (DI).

Results: The levels of 25(OH)D in obese group were significantly lower than those of non-obese group; serum 25(OH)D level in obese with NGT group was higher than that of the other three subgroups, and it was significantly inversely with LogHOMA-IR (r=-0.114, p=0.035), positively correlated with LogWBISI, LogHOMA0DI after control for age, sex, season, puberty stage (r=0.111, p=0.040); r=0.122, p=0.024). Obese patients with vitamin D deficiency have a significantly higher risk of disturbing the glucose metabolism, such as IGF, ITG, IFG plus ITG, either IFG or ITG, for its OR 3.198(95%CI 1.467-6.97), 5.443(95%CI 1.863-15.897), 5.560(95%CI 1.212-25.502), 4.007(95%CI 2.017-7.962).

Conclusion: 25(OH) D deficiencies or insufficiency are common in obese children and adolescents in Zhejiang, China. Obese patients with 25(OH) D deficiency (<30nmol/L) are at higher risk for abnormal glucose metabolism.

**O50**
Vitamin D status in overweight and obese Malaysian school children and its relationship with metabolic syndrome
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Obesity is a rising health problem, with increasing prevalence in children and adolescents. Lower vitamin D is linked to increased adiposity and higher risk of metabolic syndrome. However, evidence from tropical Asian countries is limited, especially in children and adolescents.

To examine the relationship between vitamin D level and BMI, abnormal glucose profile, insulin resistance and metabolic syndrome markers in the overweight/ obese secondary school children. A cross sectional study in multiethnic secondary school children aged 13 -17 years was performed. Anthropometric measurements: height, weight, waist circumference and blood pressure were obtained. Blood for fasting glucose/ lipids/ insulin, and vitamin D (25 (OH)D) were taken. Oral glucose tolerance test was also performed. Insulin resistance indices were calculated based on homeostasis model assessment (HOMA) index.
A total of 543 subjects were enrolled. Forty eight percent were overweight/obese. Most of them (62%) were vitamin D deficient (<50 nmol/L), 32% were vitamin D insufficient (50 to <75 nmol/L) and only 6% were vitamin D sufficient (≥ 75 nmol/L). Mean 25(OH)D in the overweight/obese group was 44.3±15.9nmol/L and was significantly lower compared to the non overweight/obese group (47.9±19.4nmol/L); (p=0.018). Females had lower mean vitamin D level (43.2±15.9nmol/L) compared to males (53.6±19.6nmol/L) (p<0.001). The Chinese had the highest mean vitamin D level (65.9±16.4nmol/L) followed by Malays (44.2 ±16.9nmol/L) and Indians (39.5±13.3nmol/L) (p<0.001).

Among those who were overweight/obese, metabolic syndrome was present in 58 (22%) of them. No significant relationship was found between 25(OH)D level and abnormal glucose profile, insulin resistance and metabolic syndrome markers among the overweight/obese participants. The overweight/obese females had 78% prevalence of vitamin D deficiency, compared to 59% in overweight/obese males. Overweight/obese Indians had the highest prevalence of vitamin D deficiency (82%) followed by Malays (70%) and Chinese (20%). Vitamin D deficiency is highly prevalent in Malaysian adolescents despite an abundance of sunlight. Lower vitamin D levels are associated with female gender, ethnic groups with darker skin and obesity. However, no relationship was found between vitamin D deficiency and metabolic syndrome.

**OS2**

The outcomes of a standardized approach to managing metabolic bone disease of prematurity

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Metabolic bone disease (MBD) of prematurity is an increasingly well-recognized complication of pre-term birth. Despite this, there is limited evidence for the optimum method for assessing and monitoring bone health and appropriate supplementation. This study assesses the effectiveness of the MBD protocol at Monash Health nurseries (Clayton, Dandenong and Casey) in infants born under 32 weeks’ gestation between November 2012 and January 2014. Preliminary data of 91 infants (mean gestational age (GA) 29 weeks (24-3.23weeks), birth weight (BW) 1279.4g (553-2512g)) were assessed. Risk factors assessed included 8.8% IUGR infants (n=56), 12.9% maternal pre-eclampsia, 7.5% necrotising enterocolitis (NEC) episodes and exposure to medications as follows: caffeine (84.9%; mean 42 days), diuretics (23.7%; mean 13.8 days) and steroids (2.2%). Preterm infants received 14.3 days of total parenteral nutrition (TPN) on average, with the majority on intravenous expressed breast milk once enteral feeding was established. Initial MBD screen was performed for 80.6% infants (mean age 36.6 days) with only 24.7% having repeated monitoring (mean age 67.9 days). 6.5% had Alkaline phosphatase (ALP) levels >500U/I initially (range 143-827U/l), reducing to 1.1% (range 173-573U/I). Average Tubular Resorption of Phosphate (TRP) was 79.7% (n=71). The majority of infants were on Vitamin D 400units/day. 23.6%(n=22) commenced phosphate supplements (mean duration 41 days) and 15.1%(n=14) commenced calcium supplements (mean duration 53.2 days). Average birth length was 38cm (10-50th centile) with evidence of slowing growth velocity (mean follow up length 49cm (<3rd centile) at mean age 79.9 days). Five infants were identified with fractures however two were from birth trauma and two suspected non-accidental injury. One patient had an incidental finding of fractured femur with multiple risk factors for MBD including very low birth weight (700g), NEC episodes requiring prolonged antibiotic therapy (69 days), TPN (48 days), caffeine (88 days) and diuretic use (22 days).

Significant difference (p<0.001) is noted between phosphate-treatment and untreated groups for both GA and BW: Median 27weeks and 929g for treated subjects versus 29.6weeks and 1343g if untreated. In the phosphate-treatment group, ALP levels improved (mean pre-treatment 414U/l and post-treatment 264U/l, p=0.0006) and difference in phosphate levels were also significant with p=0.003. Between phosphate-treatment group versus untreated group, differences were insignificant for ALP (p=0.05) and phosphate levels (p=0.09), though this may reflect insufficient subsequent MBD screens (treatment group, n=15 versus untreated group, n=7).

Further evaluation is anticipated to help improve MBD understanding in this high-risk cohort particularly given morbidity associated with MBD occult fractures. In addition, secondary outcomes would include cost efficiency of MBD surveillance and identifying optimal supplemental therapy.
ADRENAL/DSD

O53 Novel heterozygous mutations of the SF1 gene and their functional characterization in patients with 46,XY disorders of sex development (DSD) without adrenal insufficiency

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Aims: Heterozygous mutations in SF1 have been identified in patients with 46,XY disorders of sex development (DSD) with normal adrenal function. This study was aimed to identify mutations in the SF1 gene in patients with 46,XY DSD and functional characteristics of their impact.

Methods: This study included 48 patients with 46,XY DSD without adrenal insufficiency or dysmorphic features. Genomic DNA was extracted from peripheral blood leukocytes and direct sequencing of the 6 coding exons of SF1 was performed. To evaluate the effect of SF1 mutations on transcriptional activity, transient transfection studies were performed using dual luciferase reporter assay system with cotransfection of PGL4.75 Renilla luciferase as a marker of transfection efficiency. Wild-type, or mutant SF1 expression vectors with SF1 dependent STAR and MIS promoters linked to luciferase were assayed for luciferase activity.


Conclusion: This study identified three novel loss-of- function mutations and their functional characteristics in patients with 46,XY DSD. Loss of function mutation in the SF-1 gene is one of the relatively common causes of 46, XY DSD. Therefore, genetic defect of the SF-1 gene should be considered as an etiology in 46,XY individuals without adrenal insufficiency.

O54 Response to growth hormone therapy and gonadal pathology in 45,X/46,XY females

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Turner syndrome (TS) and related sex chromosome abnormalities are associated with a variety of karyotypes and phenotypes affecting 1 in 2500 live births. Mosaicism with Y material (45,X/46,XY) and female phenotype is rare (<1 in 15,000 births) [1]. Their risk of gonadal malignancy is 10-15%, and up to 50% in those with ambiguous phenotype at birth [2]. The SHOX gene is located on both X and Y chromosomes but is more prone to deletions on the X chromosome, potentially influencing height outcomes across TS karyotypes [3]. However, children with SHOX deficiency respond similarly to TS girls when treated with the same dose of growth hormone (GH) [4]. We therefore examined height outcomes and gonadal malignancy rates in TS vs 45,X/46,XY females.

We identified 198 females aged ≤30 years with TS or mixed gonadal dysgenesis treated with GH (under TS or auxological criteria). Final height (FH) was available on 51 TS (45,X or mosaic without Y material) females. An additional 13 had 45,X/46,XY karyotype with TS phenotype, and two had non-mosaic 46,XY karyotypes with cytogenetic abnormalities consistent with TS. Of these 15 females, gonadal tissue histology was available for 11 and FH in nine. We evaluated patient records for age, height, mid-parental height (MPH), GH dose at commencement, duration of therapy and growth response at 12 months and at FH. Comparisons between TS and 45,X/46,XY groups were performed using the Mann-Whitney U test.

All 45,X/46,XY patients had a female phenotype and five had choriodomalacia at birth. Three were identified prenatally; age at diagnosis ranged from birth to 13 years, with the most common presenting features being short stature (n=5), ambiguous genitalia (n=5) and dysmorphic features (n=2). Of the 11 that underwent gonadectomy, four (none virilised at birth) had a gonadal tumor, including one yolk sac tumor in situ.

Age, height, MPH, GH dose at commencement, duration of therapy and height z-score after 12 months did not differ between groups. Median FH z-score for 45,X/46,XY was higher than TS, -1.12 [range -1.96, 0.31], vs -1.59 [-3.12, 0.01], p=0.016. Response to GH therapy (median Δ height z-score) after 12 months was similar: 0.45 [0.04, 0.84] vs 0.39 [-0.21, 1.14], p=0.81. However, height response over the total duration of therapy was better for 45,X/46,XY: 1.5 [0.72, 2.88] vs 0.87 [-0.98, 2.14], p=0.009.

45,X/46,XY females appear to respond differently to GH therapy, suggesting a possible contribution of SHOX on the Y chromosome. The rate of germ cell tumours in non-virilised females (36%) is higher than previously reported.

References:

O55 Clinical and mutational spectrum of patients with congenital lipid adrenal hyperplasia in Southeast Asia

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Aims: Mutations in Steroidogenic Acute Regulatory protein (STAR) cause congenital lipid adrenal hyperplasia (lipoid CAH), characterized by absent steroidogenesis, potentially lethal salt loss, 46,XY sex reversal and massively enlarged adrenals engorged with cholesterol esters. Nonclassic lipid CAH is a recently recognized disorder caused by STAR mutations that retain partial function. We aim to delineate the clinical and mutational spectrum of STAR mutations in patients with lipid CAH.

Methods: The entire coding regions of the STAR gene were assessed by polymerase chain reaction and sequencing analysis.

Results: There were 10 patients of lipid CAH had mutations in the STAR gene with 5 novel mutations (p.R230H>W; p.F652V, p.S561G>A, p.V533S>2Ple, p.T147R, p.Q264H). Eight patients had classic lipid CAH presenting with adrenal crisis during early infancy (range of onset 3-11 months of age). Two siblings had nonclassic, phenotypes with later onset adrenal insufficiency without disordered sex development. Adrenal enlargement by imaging was demonstrated in only 3 cases of classic lipid CAH. The functional studies of novel STAR mutations are being under investigation.

Conclusion: STAR mutations may not be rare in Southeast Asian population. There is a broad clinical spectrum of STAR mutations varying from early onset adrenal insufficiency to late onset of glucocorticoid...
In Indonesia clinical management of Disorders of Sex Development (DSD) is challenged by limited knowledge and limited diagnostic and treatment facilities. Prior to this study, most patients remained untreated and grew up with ambigious bodies and doubts about their gender. We investigated patients' experiences of being raised in ambiguity. 118 Indonesian patients, ages 6 – 41, with 46XX DSD (n=27), 46XY DSD (n=77) and chromosomal DSD (n=14) were compared to 118 control subjects matched for gender, age, and living area. Questionnaires for gender identity, gender role behavior and social stigmatization were translated or designed. The psychometric properties were satisfactory. For patient and control group comparisons, Mann-Whitney U and Fisher's Exact tests were applied. The results showed that 7% of the children, 8% of the adolescents and 44% of the adults changed gender, particularly non-diagnosed and non-treated patients with 46XX DSD (81%). 95% of the patients changed gender from female to male, including untreated patients with 46XX CAH-SV. Compared to control groups, cross-gender role behavior was seen in young girls with 46XX CAH-SV (p=0.047) and adolescent girls with different types of DSD (p=0.01). In girls with DSD, confusion with gender identity was seen (young girls p=0.004; adolescent girls p=0.01). Adult men reported past cross-gender role behavior (p=0.01) and past problems in gender identification (p=0.01) prior to female-to-male gender change. Children with genital ambiguity (p=0.006) and cross gender behavior (p<0.001) and adults with ambiguous bodies (p=0.001) and adults who changed gender (p=0.03) suffered stigmatization. Rejection or isolation elicited depression and withdrawal from social activities in girls (p=0.002), women (p=0.009) and youngsters who had changed gender (p=0.02). We conclude that a high percentage of our patients changed gender. The wish for gender change was particularly seen in patients with progressive masculinization. Patients with DSD who had visible ambiguity in physical and behavioral appearance suffered stigmatization. Teasing and rejection led to strong emotional reactions. Early clinical evaluation and treatment, patient and parent education, and teaching coping strategies will improve quality of life.

**POSTER PRESENTATIONS**

**DIABETES**

**P1**

Novel heterozygous deletion in the HNF1b gene - adolescent with antibody negative diabetes, longstanding hyperglycaemia without ketosis, cataracts, small echogenic kidneys with a cortical cyst, pancreatic atrophy, exocrine pancreatic insufficiency and a uterine anomaly

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A 13 year old pubertal Caucasian female presented with longstanding polyuria/polydipsia and weight loss of 12kg over 4 months (BMI decreased from 23 to 17.5kg/m2 despite a 5cm height gain). There was no personal / family autoimmunity history. A paternal grandparent was thought to have type 2 diabetes. She was haemodynamically stable and mildly dehydrated without clinical signs of insulin resistance. She had bilateral stellate posterior subcapsular cataracts. Plasma glucose was 57mmol/L with normal blood ketones and venous pH. HbA1c was 18.2% (175mmol/mol). Mildly elevated urea and creatinine corrected after rehydration. Liver function tests, serum magnesium and urate were normal. Ilet autoantibodies were negative. Renal ultrasound (US) identified bilaterally small kidneys (<5th centile), with echogenic parenchyma, reduced corticomedullary differentiation, normal cortical thickness and a 5mm left cortical cyst. Urinary albumin/creatinine and calcium/creatinine were normal. Further imaging (US and MRI) demonstrated severe pancreatic atrophy and a mullerian duct anomaly (arcuate / subseptate uterus). Faecal elastase 1 in a soft stool sample was low (range of severe exocrine pancreatic insufficiency). However the patient has gained weight with insulin treatment and had normal measures of fat-soluble vitamins.

**Aim:** Conduct genetic testing for the autosomal dominant Renal Cysts and Diabetes Syndrome (RCAD), also known as MODY5, caused by heterozygous mutations of the hepatocyte nuclear factor–1 beta (HNF1B) gene (chromosome 17q12).

**Methods:** Direct testing for HNF1B gene sequence variations was performed by Multiplex Ligation-dependent Probe Amplification (MLPA) and bidirectional DNA sequencing.

**Results:** A heterozygous c.390–395del (p.Gln130_Gln135del) was detected. This novel deletion results in the in-frame loss of two glutamine residues in exon 2 of the HNF1B protein. These residues are highly conserved and located in the HNF1B N-terminal domain that contains a dimerization sequence and an acidic region that may be involved in transcription activation. Parental testing has determined that this variant is likely de novo.

**Conclusion:** This de novo variant has not been previously described, hence its pathogenicity is unknown. However the phenotype is consistent with RCAD (MODY5).

**Written informed consent was obtained from the patient for publication of this Case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.**

**P2**

1,5-Anhydroglucitol, an indicator of short term glycaemic control, is the most discriminatory metabolic marker in adolescents with type 1 diabetes compared to control subjects

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**Aim:** To compare the metabolic profile of adolescents with T1D (>5 years duration) to controls using gas chromatography–mass spectrometry (GC-MS).

**Methods:** Design Case control study. Setting Tertiary paediatric hospital clinic. Population 27 (14F/13M) adolescents with T1D (age median, interquartile range) 15.5, 14.7-16.4 years; duration 7.7, 6.0-11.8 years; HbA1c 9.1, 8.1-10.1%; glucose 13.35 (7.60-17.85) and 27 (14F/13M) control participants (age 15.1, 14.4-16.8 years). BMI was <95th percentile. Measures Fasting plasma and urine metabolomes were profiled by GC-MS and compared between cohorts. Statistics Univariate comparisons.
Background: Recently Western Australia has seen a rise in African population due to both economic and refugee migration. Concurrently, a rise in the numbers of teenagers of African origin diagnosed with both type 1 and type 2 diabetes and associated complications has been noticeable. Different ethnic background is a known risk factor for poor metabolic control; this trend is reflected in studies wherein people of African origin have been found to have a high risk of developing diabetes. What is evident from health promotion literature is that parents of teenagers with a chronic health condition, when they are well informed about that condition, play a key part its management. Little is known, though, about what African migrant parents understand about diabetes and its dietary control.

Aim: To develop insight of a sample of migrant African parents now residing in Western Australia knew about, and were able to provide in relation to the dietary needs of their recently-diagnosed diabetic teenager through an exploration of family food habits.

Methods: A survey approach.

Findings: Twelve parents from five different countries of origin participated in this survey. Despite all participants having received education on the topic from a dedicated paediatric diabetes team, it was evident from their families’ food habits that either an understanding of or the capacity to accommodate the dietary requirements of their diabetic teenager was minimal.

Conclusion: It is possible that African migrant parents of diabetic teenagers’ knowledge about and capacity to support their children’s dietary needs is contributing to unplanned hospital admissions. The results of this small survey indicate a need to revise the information provided to African migrant parents of diabetic teenagers to more closely accommodate cultural preferences. Further work is necessary to determine the most effective approach to health education with this group of health care consumers.

Methods: We performed a retrospective review of all patients <15 years of age diagnosed with T1DM from our unselected complete cohort for the years 1999 to 2013. Children were included if they had type 1 diabetes as defined by clinical presentation and/or DKA and/or presence of pre-type 1 diabetes autoantibodies. DKA was classified into Mild (pH <7.3 bicarbonate <15), Mod (pH <7.2 bicarbonate <10), and severe (pH <7.1 bicarbonate <5), according to the ISPAD guidelines.

Results: For the 15-year period, there were 731 children <15 years with new-onset T1DM, 343 (47%) males, there were 195 (26.7%) cases of new-onset DKA: 51 (26%) severe, 52 (27%) moderate, and 92 (47%) with mild DKA. Average age at diagnosis was 8.6 years. The annual incidence of new-onset DKA did not differ over 15 years.

Conclusion: There has been a stable but persistent level of T1DM and in doing so, reduce the incidence of new-onset DKA.
In our cohort, the longer duration of metabolic acidosis could be evaluated in patients with T1DM. Adverse adherence to intervention in this clinical trial was unusual. Adequate adherence using MEMS was reported from 3-6 months (short-term) and from 6-12 months (long-term).

**Method:** Medication adherence was assessed in 54 T1D adolescents (age 14±2.3y, 26 males) enrolled in a 1 year RCT to receive metformin or placebo.

**Aim:** To examine the local prevalence of hypokalemia in patients with Type 1 Diabetes Melitus (T1DM) and to evaluate adherence using tablet count and prospective electronic monitoring in adolescents with Type 1 Diabetes (T1D) participating in an RCT.

**Introduction:** Treatment adherence during adolescence is challenging. Limited data exist for the rate of medication adherence in adolescents.

**Results:** Adolescents had mean T1D duration 5.9±4.2y, median HbA1c 8.5 (6.3-11.6)% and 26 used CSII. MEMS adherence data for short and long-term use was available for 53 and 48 participants respectively. Adequate adherence using MEMS was 47% (25/53) short-term and 43% (17/48) long-term. Median IQR 25-75% adherence was 79 (46.6-88.7%) short-term and 67 (43.4-86.8%) long-term. Tablet count adherence data for short and long-term use was available for 35 and 42 participants respectively. Adequate adherence using tablet count was 63% (22/35) short-term and 45% (19/42) long-term. Median (IQR 25-75%) was 84 (70.8-90.1%) short-term and 77 (61.7-86.8%) long-term.

**Conclusion:** Adolescent adherence to intervention in this clinical trial was suboptimal as shown by both electronic monitoring and tablet count. This finding reinforces the importance of parental involvement in treatment regimens in this population.

**Reference**


**P6**

**Prevalence and potential risk factors of hypokalemia in pediatric patients with diabetic ketoacidosis**

**Methods:** Retrospective review of 114 consecutive patient-episodes. Univariate analyses were performed to study any difference in mean between the group with nadir of potassium (Km) >= 3.0mmol/L from group with Km < 3.0mmol/L for predictors concerning patients' demographics, the baseline characteristics, the therapies for DKA (including average insulin infusion rate before Km), and the paced of recovery from DKA. Predictors deemed statistical significant in univariate analyses were subjected to multivariate analysis.

**Results:** The period prevalence of hypokalemia at presentation and during treatment of DKA were 13.8% and 92.5% respectively. Univariate analysis showed patients who were younger, with lower mean body weight, lower mean plasma bicarbonate at presentation, lower mean serum potassium level at presentation, higher urine output per unit body weight (in the first 24 hours of admission), higher amount of potassium supplement given before Km, shorter time lag of starting potassium supplements (as reference to time of start of insulin) and longer duration of metabolic acidosis were independently associated with risk of developing Km < 3.0mmol/L. Multivariate analysis showed that duration of metabolic acidosis was the sole risk factor for having Km < 3.0mmol/L.

**Conclusions:** In our cohort, the longer duration of metabolic acidosis predicts significant hypokalemia during DKA treatment, which could have represented a persistent accumulation of free fatty acid and an on-going stimulus for aldosterone secretion, hence kaliuresis-related hypokalemia [1-7]. Therefore, in patients with slow resolution of metabolic acidosis, the measurement of the urinary potassium might allow for better estimation of potassium requirement during DKA treatment, such that significant hypokalemia could be minimized. In our data, the average insulin infusion rate was not associated with statistically increased risk of significant hypokalemia, therefore, the strategy of lowering insulin infusion rate in patients with significant hypokalemia during DKA treatment should require further evaluation.

**References**


P9
HBa1c variability and the risk of microalbuminuria in patients with type 1 diabetes
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Aims: The higher HBa1c is a risk factor for microvascular complication in type 1 diabetes. However, it remains controversial that glycemic variability may be an additional risk factor for development of complication in diabetes. In this study we have analyzed the HBa1c variability to investigate the influence on progression of microalbuminuria in patients with type 1 diabetes.

Methods: Fifty patients (M=27, F=23) with type 1 diabetes and microalbuminuria who visited Yonsei University Severance Children’s Hospital were enrolled. In addition, ninety eight (M=51, F=47) type 1 diabetic patients without complication were enrolled for control. Microalbuminuria is defined that urinary albumin excretion rate is between 30 mg/24h and 300 mg/24h. HBa1c during 3 years (just before the development of microalbuminuria or in the past 3 years in control) were reviewed retrospectively. HBa1c variability expressed as standard deviations (SDs) of HBa1c for 3 years.

Results: There was no difference of mean age between type 1 diabetic patients with microalbuminuria and control (respectively, 22.9±5.5years and 21.6±4.8years, p=0.129). The mean duration to developed microalbuminuria was 9.9±5.1 years. Mean HBa1c was higher in patient with microalbuminuria (14.3±5.1% ) than in control (12.2±5.3%, p=0.02). HBa1c variability was also higher in patient with microalbuminuria (1.14 ±0.81) than in control (0.69±0.38, p<0.001). There were also significant trends that microalbuminuria was developed in patients with higher HBa1c SDs in shorter period (r=0.418, p=0.003).

Conclusion: This study has shown that HBa1c variability was positively correlated with mean HBa1c level and progression of microalbuminuria. In addition, higher HBa1c variability may shorten the period of development of microalbuminuria. Thus, long-term fluctuation in glycemc control seems to contribute to the development of microalbuminuria in type 1 diabetes.

P10
Reproductive health knowledge, attitudes and beliefs in young women with type 1 diabetes mellitus aged 15 – 25 years attending a tertiary centre multidisciplinary transition clinic: A descriptive study
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To assess issues related to the existing reproductive health knowledge, attitudes and beliefs in 15 – 25 year old young women with type 1 diabetes mellitus (T1DM), we administered a questionnaire as sexually active adolescents with T1DM are at high risk of unplanned pregnancies and reproductive complications. Glycaemic control during adolescence is recognised as being poorer than during any other life stage. Periconceptional poor glycaemic control is associated with increased incidence of congenital malformations. This is a descriptive study in females aged 15 – 25 years attending our Young Adult Diabetes Service (YADS) clinic, a transition clinic at Monash Medical Centre, a conception to end of life tertiary health facility. Our study was undertaken between June 2011 and June 2013, when there were 173 eligible young women on our YADS clinic database. Data was collected on a cross-sectional basis from a web-based questionnaire on a sample of 100 female adolescents who provided consent to participate (58% of those eligible), using a modified reproductive health attitudes and behaviour (RHAB) questionnaire [1]. Almost half (48%) of respondents were sexually active, with a mean age of sexual debut of 16.9±1.8years (range 13 – 21yrs). Mean HBa1c was 8.9±1.6%. HBa1c in non participants was significantly higher (9.2±1.8%), although responders and non-responders were comparable on age and SES. Responses to questions related to their personal concerns about their future health risks, revealed that respondents perceived their risk and level of concern of unplanned pregnancies (18.7%) and STDs (8.7%), to be much lower than those of weight gain (59.3%) and blindness (57.1%). Despite high perceived benefits of preconception counselling (PC) (78%), low PC delivery rates were reported by study participants (15%), although review of clinic check lists revealed documentation that 34% of study participants had received PC. Diabetic Nurse Educators (DNEs) were perceived to be the most useful source of health information (81% of respondents). We support recommendations of the National Health and Medical Research (NHMRC – 2011) that young adolescents need developmentally appropriate information from commencement of puberty, with a sensitive, proactive, preventative approach before these young women become sexually active, to enable them to make informed choices regarding reproductive health. However, engaging adolescent girls with T1DM to provide effective provision of such information remains challenging, even in an age appropriate specialised clinic setting.

Reference

P11
Neonatal diabetes as an isolated manifestation of ipex: an expanding spectrum of disease phenotype with FOXP3 mutation
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Neonatal diabetes occurs due to a genetic form of pancreatic βcell dysfunction. Mutations in a number of genes have been identified in the last decade which has helped not only in the etiological diagnosis but has also influenced medical therapy. Our proband was born at term with a birth weight of 3.99kg with no antenatal risk factors. He presented in severe diabetic ketoacidosis at 8 weeks which required intensive management. He was commenced on continuous subcutaneous insulin infusion for his ongoing management.
His initial genetic analysis for ABCC8, KCNJ11, INS gene mutations was negative. He demonstrated excellent glycaemic control with an average Hba1c of 6.5% at 2 years of age. His growth and development are appropriate for age with no associated co-morbidities. However, further targeted next generation sequencing of all known neonatal diabetes genes identified a hemizygous FOXP3 missense mutation p.R347H with his mother as a carrier. FOXP3 mutations cause IPEX syndrome, (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) and can be lethal in infancy and early childhood. Prophylactic bone marrow treatment is the only known cure for this condition.

Our proband has isolated neonatal diabetes with no other features of IPEX. His maternal grandfather aged 63 years, was also hemizygous for the mutation. He had enteropathy secondary to ulcerative colitis since childhood which was resistant to conventional treatment and required colostomy. This makes him the oldest living man with IPEX. Our proband’s maternal cousin also had eczema in infancy which has resolved.

This case highlights the impact of genetic diagnosis on the management of neonatal diabetes. A lethal condition with no cure other than bone marrow transplant has now been shown to have atypical manifestations with the availability of genetic testing. The management in our patient is challenging given the poor genotype – phenotype correlation and the dearth of information regarding milder forms limited to a few case reports with similar mutation. We have decided against prophylactic bone marrow transplant and will consider it in the event of enteropathy or another autoimmune manifestation.

Written informed Consent for this patient has been taken including results of the genetic analyses according to the Institutional Ethics Committee procedures of our health service.

P12
Phenotype, genotype of neonatal diabetes mellitus due to insulin gene mutation
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Insulin (INS) gene mutations that cause permanent neonatal diabetes mellitus change single protein building blocks (amino acids) in the protein sequence. These mutations are believed to disrupt the cleavage of the proinsulin chain or the binding of the A and B chains to form insulin, leading to impaired blood sugar control. At least 10 mutations in the INS gene have been identified in people with permanent neonatal diabetes mellitus.

Objective: To describe clinical features and laboratory manifestations of patients with INS gene mutation and to evaluate outcome of management.

Subject and methods: Clinical features, biochemical finding, mutation analysis and management outcome of 3 cases from 3 unrelated families were studied. All exons of INS gene were amplified from genomic DNA and directly sequenced.

Results: 3 cases (one girl and two boys) onset at 126.6 ±56.7 days of age with gestation age of 38.0 ± 1.4 weeks, birth weight of 2850 ± 494.9 g. All of them admitted with the feature of diabetic ketoacidosis with pH of 6.94 ±0.16; HCO₃⁻ 2.63 ±0.85 mmol/l; BE 26.05±4.03 mmol/l, plasma glucose levels were 37.57±15.2 mmol/l, Hba1c of 9.9 ±2.5%. Mutations in the INS gene showed: heterozygous for a novel missense mutation (c.127T>A; C43S) in exon 2 of INS gene in one case; heterozygous for a novel INS splicing mutation, c.188-31G>A of the INS gene in two cases. After 8 months of insulin treatment, two patients with c.188-31G>A mutation have normal development with Hba1c of 6.85 ±0.49%, quite normal blood glucose levels. The case with c.127T>A mutation treated with insulin for 8 years has physical development delay, poor blood glucose control with Hba1c of 11.4%.

Conclusions: It is important to perform screening gene mutation for patients with diabetes diagnosed before 6 months of age to control blood glucose and follow up the patients.

P13
Clinical, para-clinical and outcomes of diabetes ketoacidosis in Vietnam national hospital pediatrics
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Diabetic ketoacidosis (DKA) is a serious complication of diabetes mellitus that occurs when your body produces high levels of blood acids called ketones.

Objective: This study aimed at describing some characteristics of clinical and commenting outcomes of the treatment for DKA in children with diabetes mellitus type 1 (DM1) in Vietnam National Hospital of Pediatrics from 2007 to 2012.

Methods: Description retrospective and prospective on all patients previously diagnosed of DM1 or newly diagnosed of DM1 with DKA.

Results: On average: each year, patients with DKA were admitted. 72% of these cases were first presentation with diabetes. Up to 36% of cases had misdiagnosis for other diseases. Clinical: dehydration 100%, 92% altered consciousness; vomiting 72%; thirsty 72%; weight loss 78%. The clinical presentation of DKA in patients who newly diagnosed of DM1 was more severe than that in previously diagnosed patients. The risk factors: 64% infection for all; 57.1% non-compliance with treatment for patients being treated insulin before. Laboratory: Blood glucose 36.8 ± 13.5 mmol/l (from 14 to70 mol/l). Severe and moderate acidosis was seen in 56%. Abnormality of sodium levels were found in 11/25 patients (44%), of which only 3/25 patients actually decreased serum sodium (adjusted sodium); hyperkalemia in 6/25 patients (24%). The time of infusion insulin was 18.9 ± 27.56 hours. Average time replacing fluid was 37.7±21.1 hours. The duration of ketonuria was 37.9 ± 17.5 hours. Patients were alert after 12.04 ± 11.52 hours.

Conclusion: DKA is a complex disordered metabolic state characterized by hyperglycemia, ketoadipsis, and ketonuria. The goal of treatment is to correct the high blood glucose level with insulin. Another goal is to replace fluids lost through urination, loss of appetite, and vomiting.

P14
Cyclical variation in the national incidence of childhood type 1 diabetes in Australia (2000 - 2011)
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To determine the incidence and incidence rate trends of type 1 diabetes in children aged 0-14 years Australia-wide using all available data from 2000 to 2011, and to examine the temporal trends for non-linear, cyclical variation.

Cases were identified from the National Diabetes Register (NDR) which was established in 1999 and contains data on patients with insulin-treated diabetes Australia-wide. For 0-14 year olds with type 1 diabetes the NDR is estimated to be 97.7% complete [1]. Population data published by the Australian Bureau of Statistics were used as the denominator data. Annual age-standardised as well as gender and age specific incidence rates were calculated. Poisson regression was used to analyse the incidence by calendar year, gender, and age at diagnosis. To analyse the incidence for non-linear variation, sine and cosine functions
were applied to Poisson regression models for 3-, 4-, 5-, 6-, and 7-year cycles and the Akaie Information Criterion (AIC) used to assess goodness-of-fit [2].

Between 2000 and 2011, 11,575 (6,049 M, 5,526 F) cases of childhood type 1 diabetes were identified from the NDR. The mean incidence of childhood type 1 diabetes in Australia over this time period was 23.6 (95%CI:23.2 – 24.0) per 100,000 person years. The mean incidence was 4.9% (95%CI:1.1% - 8.8%) higher in boys compared to girls. Compared to 0-4 year olds, the mean incidence was 65% higher in 5-9 year olds, and 208% higher in 10-14 year olds. No significant linear increase in the incidence rate trend was observed overall (Incidence rate ratio 1.003 (95%CI:0.997 – 1.008), or by gender. An average annual increase in incidence was only observed in the 10-14 year old age group (1.2% per year (95%CI:0.4% - 2.1%)). When analysed for non-linear variation in the temporal trends, a 5-year cyclical variation of 6% was observed in the overall incidence rate trend. A 5-year cyclical variation in incidence was observed in both genders and all age groups.

From 2000 to 2011, no linear increase in the annual overall incidence of childhood Type 1 diabetes was observed in Australia. Of interest, a sinusoidal pattern in the incidence rate trend was observed, with a 5-year cyclical pattern. The cyclical pattern of incidence rate trends observed Australia-wide corroborates findings reported in Western Australia [3] and provides further evidence supporting a key role of environmental factors in the aetiology or clinical onset of childhood type 1 diabetes – further investigation is required.

References
1. AIHW: Diabetes series no. 13. Cat. no. CV0 2010, 51.

P15
D-buddy peer support for better health outcomes in adolescents with diabetes mellitus
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Aim: Diabetes can be demanding and burdensome causing emotional distress. Non-adherence to treatment and self-care management can affect diabetes outcomes and quality of life. Peer support can play an important role in better psychological adjustment to diabetes. The aim of this study is to evaluate improvement in Quality of Life (QOL), Problem Areas in Diabetes (PAID) and glycaemic control in adolescents with diabetes.

Methods: Adolescents age 12-18 years with Type 1 or Type 2 diabetes on insulin were recruited between October 2012 to December 2013 and paired with a buddy of same age, gender and type of diabetes to provide peer support. They were instructed to contact peer buddy via telephone, SMS, Facebook, WhatsApp, or face-to-face for 6 months. QOL, PAID scores and HbA1c were measured before and after 6 months. The adolescents who refused enrolment were treated as control group and HbA1c compared at 6 months with the study group.

Results: A total of 66 patients (33 buddy pairs) were recruited in peer support group and 100 in control group. There were more females in peer support group (72.7%) than in the control group (49%).

In peer support group, mean number of contact episodes was 1.3 ±1.4, and most common mode of contact was via SMS (43.9%), WhatsApp (27.3%) and Facebook (21.2%). There was slight improvement in mean QOL score (67.2 ±14.3 vs. 69.1 ±13.8; p=0.1) and also a marginal reduction in mean PAID score (25.2 ±19.3 vs. 23.4 ±18.6; p=0.3) indicating less negative emotions related to diabetes. From baseline to 6 months, there was no improvement in mean HbA1c for peer support group (9.3 ±3.2 vs. 9.3 ±2.4; p=1.0) and control group (9.4 ±2.2 vs. 9.3 ±2.3; p=0.5).

Conclusions: Our findings showed that there were no significant improvement in glycaemic control, quality of life and problem areas in diabetes of adolescents receiving peer support. Therefore, we need to develop other methods engaging adolescents sustain improvement in health outcomes.

P16
A risk of association between vitamin D-binding protein and 25-hydroxyvitamin D concentrations in pediatric type 1 diabetes without microalbuminuria
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The risk of vitamin D deficiency might increase along with the increased urinary loss of vitamin D binding protein (VDBP) consequent to impaired 25-hydroxyvitaminD (25-OHD) circulation. We aimed to evaluate the possible increased urinary loss of VDBP, a correlation between VDBP and circulating 25-OHD levels, and the risk factors influencing low vitamin D levels in pediatric type 1 diabetes patients without microalbuminuria. Subjects with T1DM without microalbuminuria (n=45) and age-matched healthy control subjects (n=29), aged 9–14 yr, residing in Seoul and the Gyeonggi-Do in Korea (37°N) were studied. Height, weight and pubertal stage were evaluated. The percentage of body fat was measured by bioelectrical impedance analysis (inbody). A questionnaire was used to assess the amount of daylight outdoor activity and vitamin D intake. Serum levels of calcium, phosphorus, intact parathyroid hormone, 25-OHD, 1,25 dihydroxyvitamin D and VDBP, as well as urinary levels of VDBP, microalbumin and creatinine (Cr) were measured. 25-OHD deficiency was defined as ≤20 ng/mL. The urinary VDBP to Cr ratio (VDBP/CR) in type 1 diabetes patients was higher than that in the control group (P = 0.016) and correlated positively with the urinary microalbumin to Cr ratio in both groups (P <0.001). The serum 25-OHD levels did not correlate with the serum VDBP or urinary VDBPCR. A multivariate regression analysis including known vitamin D deficiency risk factors (age, gender, body fat percentage, vitamin D intake, daylight outdoor hours, and urinary VDBPCR) revealed that daylight outdoor hours (β = 2.881, P = 0.009) and vitamin D intake (β = 2.342, P = 0.050) affected the 25-OHD levels in type 1 diabetes patients.

In pediatric type 1 diabetes patients without microalbuminuria, the urinary VDBP loss was increased proportionally with the urinary mACR. However, the urinary VDBPCR did not correlate with the serum 25-OHD levels. The factors associated with 25-OHD levels during winter periods were daylight outdoor hours and vitamin D intake.

P17
Analysis of insulin pump settings in children and adolescents with type 1 diabetes mellitus
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Aim: To characterise current insulin pump settings used in young patients with type 1 diabetes mellitus (T1DM) and their relationship to glycaemic and weight control.

Methods: This retrospective study included patients aged ≤18 years old with T1DM duration >1 year who were using the Medtronic pump device. Data from the insulin pumps including number of blood glucose (BG) tests per day, basal and bolus insulin parameters, carbohydrate ratio (CR) and insulin sensitivity factors (ISF) were averaged over 14 days for statistical analyses. Anthropometric data and recent HbA1c was also recorded.
Results: 292 patients (144 males, 148 females) were included in the study. Participants had a median age (IQR) of 12.9 (10.0-15.1) years and pump duration of 2.8 (1.5-4.2) years. No significant differences in median HbA1c (IQR) were observed in preschool (n=14; HbA1c 8.0% (7.0 to 8.0%)), prepubertal (n=105; HbA1c 8.0% (8.0 to 9.0%)) and adolescent subtypes (n=173; HbA1c 8.0% (8.0 to 9.0%) ). Adolescents took significantly fewer boluses and BG tests per day compared to younger children (p<0.05). Age specific diurnal variation in basal insulin doses was noted. Additionally, stronger carbohydrate cover was used in real-life compared to the theoretical 500 rule while weaker corrections were used in real-life compared to the rule 100. Predictors of lower HbA1c values included higher number of daily boluses, greater number of blood glucose testing per day, lower average CR/500 rule ratio and higher average ISF/100 rule ratio adjusted for age (R2 =0.22; p<0.01). Predictors of favourable weight (lower BMI-SDS) included lower total daily dose (units/day), lower percentage of basal to total daily insulin dose, weaker average CR and higher number of different CR adjusted for age (R2 = 0.33; p<0.05), although age was the strongest predictor (older age associated with lower BMI-SDS).

Conclusion: Insulin pump therapy requires continuous adjustments and glycaemic targets are achieved only by a minority. This study provided additional information on real life carbohydrate ratio and insulin sensitivity factor, which may be helpful in optimising pump therapy in the future.

P18
Body composition in Indian children and adolescents with type 1 diabetes
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Studies suggest that children and adolescents with type 1 diabetes (T1DM) have suboptimal body composition with higher fat mass and lower bone mass. Aim of our study was to compare body composition of Indian children with type 1 diabetes with age gender matched healthy controls.

In a cross-sectional study, body composition parameters were measured by DXA (Lunar DPX PRO, Total Body Densitometer) in 160 (74 boys) children with T1DM (attending type 1 diabetes clinic) and age gender matched healthy controls. Z scores for bone mineral content (TBBMC) for age, bone area for age (TBA), TBBMC for TBB, TBB in height, lean body mass (LBM) for height, TBMC for LBM [1] and fat and lean mass [2] were computed using Indian reference data. Anthropometry and Tanner staging (TS) was assessed for all children. The height (HAZ), weight (WAZ) and BMI (BAZ) were converted to Z scores using contemporary Indian references [3].

Mean ages of boys and girls were 11.4±3.3y and 10.9±3.4y respectively. For both genders HAZ (boys -0.5 vs 0.3, girls -0.5 vs 0.1) and WAZ (boys -0.6 vs 0.0 and girls -0.5 vs -0.1) were significantly lower in diabetics, though BAZ scores were comparable. Similarly, mean Z scores were significantly lower for fat mass (boys -0.1 vs 0.2, girls -0.1 vs 0.1) and higher for lean mass (boys -0.4 vs -1.1, girls -0.3 vs -0.6) in diabetics for both genders. Diabetic boys and girls had lower android fat percent (boys 20 vs 25, girls 28 vs 32, P<0.05) when compared with controls. Mean Z scores for bone parameters showed TBB2A for age (boys -0.1 vs 0.5, girls -0.1 vs 0.3), TBBMC for age (boys -0.1 vs 0.6, girls -0.1 vs 0.3) and TBBMC for LBM (boys -0.4 vs 0.0, girls -0.5 vs -0.2) were significantly lower in diabetics while all other bone parameters were comparable. Indian children with type 1 diabetes had lower fat mass (including android fat) and higher muscle mass than controls; however, diabetics need special attention to optimize their bone health.

References
status and choose a proper treatment modality using the body composition chart.

Methods: Fourteen type 1 diabetic adolescent girls (age 12.6±3.3 years) and 16 type 2 diabetic adolescent girls (age 14.2±2.6 years) were included. Height, weight and body compartment of fat mass, fat-free mass were measured in each patient. Body mass index (BMI), fat mass index (FMI), fat free mass index (FFMI) and percent body fat (PBF) were calculated. FFMI and FMI were plotted on body composition chart and traced the coordinate during follow-up period.

Results: BMI difference between diabetes types was explained with the difference in FFMI as well as FMI. Body composition chart presented that type 2 diabetes girls showed marked elevation in FMI and PBF. And FFMI was lower in type 1 diabetes girls. Superimposed effect of obesity on type 1 diabetes was expressed on body composition chart with marked increment of FMI and the adequate effect of lifestyle intervention in type 2 diabetes was showed marked decrease in FMI and sustained FFMI during follow up period.

Conclusion: Body composition chart might be useful in adequate growth and glucose control monitoring in diabetes children and adolescents. Early adjustment of diabetes management strategy on the basis of body composition during growing period will improve glucose control and promote adequate growth.

Table 1 (abstract P21)

<table>
<thead>
<tr>
<th></th>
<th>At presentation</th>
<th>At last visit</th>
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<td>11.79 years old (7-17)</td>
<td>15.3 years old (8-9-22)</td>
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<tr>
<td>Mean Weight:</td>
<td>61kg</td>
<td>70.4kg</td>
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<td>Mean BMI (SDS):</td>
<td>28kg/m^2 (+2.62)</td>
<td>28.5kg/m^2 (+1.91)</td>
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<td>Mean WC:</td>
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<td>94.3 cm</td>
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<tr>
<td>Mean HbA1c:</td>
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<td>9.7% (5.4-14.4%)</td>
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<tr>
<td>Metformin:</td>
<td>56% (21/37)</td>
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<td>Insulin:</td>
<td>32% (12/37)</td>
<td>32% (12/37)</td>
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<td><strong>mainly due to ketosis at diagnosis</strong></td>
<td><strong>mainly due to poor BG control</strong></td>
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<td>Dyslipidemia:</td>
<td>92% (22/24 screened)</td>
<td>87% (21/24 screened)</td>
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<tr>
<td>Fatty Liver:</td>
<td>Not screened at diagnosis</td>
<td>80% (8/10 screened)</td>
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<tr>
<td>Nephropathy:</td>
<td>Not screened at diagnosis</td>
<td>24% (9/37)</td>
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<tr>
<td>Hypertension:</td>
<td>24% (9/37)</td>
<td>8% (3/37)</td>
</tr>
<tr>
<td>Retinopathy:</td>
<td>Not screened at diagnosis</td>
<td>1 had early changes of diabetes retinopathy</td>
</tr>
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Conclusion: Glucose fluctuations were positively associated with oxidative stress inpatients in different phases of T1DM. Glucose fluctuations may have a stronger effect than sustained chronic hyperglycemia on triggering oxidative stress, but coexisting high levels of blood glucose are required.

P23
Eye and renal compiliation in pediatric patients with diabetes mellitus type 1
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Management and life expectancy for patients with diabetes mellitus type 1 (DM 1) is significantly improved. Long-term complication of the disease such as eye and renal compiliation have been paid much attention because it is an important cause of blindness and renal failure.

Aims: We studied status of eye and renal compiliation and its relationship with HbA1c in 81 patients diagnosed of DM 1.

Method: Observational, random collection.

Results: Eye compiliation was seen in 23.5% of patients. Renal compiliation was seen in 22.2% of patients. 13.6% of patients had both kinds of compiliation. The longer duration of DM 1 the patients had, the more eye and renal compiliation was detected. In groups with eye and renal compiliation, HbA1c was significantly higher than that in groups without compiliation. Probability of having renal compiliation in a poor glucose control group was higher than that in a good glucose control group with OR ratio of 2.2. For eye compiliation, the figure was 3.7.

Conclusion: The best thing to postpone eye and renal compiliation is glucose control.

P24
SNPs in the exons of toll-like receptors are associated with susceptibility to type 1 diabetes in Chinese population
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Objective: Toll-like receptors (TLRs) recognize a wide range of pathogen-associated molecular patterns (PAMP) and mount the initiation of immune response. Single nucleotide polymorphisms (SNPs) in exons of genes encoding TLRs might be responsible for the generation of an abnormal immune response which could lead to autoimmune diseases. In this study, we investigated the SNPs in TLRs in a Chinese population, and we hypothesized that SNPs in TLRs are associated with type 1 diabetes (T1D), an autoimmune disease caused by destruction of insulin producing pancreatic β-cells, in the studied population.

Research design and methods: We selected 28 SNPs in exons of TLRs with an aim to identify those that might have a direct correlation with T1D etiology and many have not been included in previous GWAS studies. Genotyping of those SNPs in TLRs was performed in 429 T1D patients and 300 age and gender-matched healthy controls in Chinese Han population. The earlier GWAS studies did not include samples from China.

Results: Among the SNPs genotyped, the T allele of TLR1-626 was found to be positively associated with T1D (OR=1.98, P=0.01). We identified another T1D associated locus in TLR6, the homozygous AA genotype of TLR6-1329 was negatively and heterozygous GA was positively associated with T1D (OR=0.54, PC=0.02 and OR=1.70, PC=0.03). We also identified the haplotype T-G-A in TLR1 gene to be positively associated with T1D (OR=2.22, PC=0.03). Additional haplotypes in TLR-6 also showed significant positive and negative association. In addition, our haplotype analysis and conditional analysis showed that these two SNPs are the primary T1D associated loci among the SNPs tested in our cohort in each TLR gene.

Conclusion: SNPs and haplotypes in TLR1 and TLR6 gene were associated with T1D in Chinese Han population. Our study, for the first time, indicates that TLR1 and TLR6 gene might play important roles in the etiology of T1D.

P25
Novel mutation in the hepatocyte nuclear factor 1B/maturity – onset diabetes of the young type 5 gene – unreported Vietnamese case
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Maturity-onset diabetes of the young type 5 (MODY5), a type of dominantly inherited diabetes mellitus and nephropathy, has been associated with mutations of the hepatocyte nuclear factor-1 (HNF-1β) gene, mostly generating truncated protein. Various phenotypes are related to HNF-1β mutations. Our aim to describe clinical and genetic findings in the unreported Vietnamese case identified with HNF-1β mutations. The proband with kidney failure from 7.5 years of age and diabetes diagnosed at 13.5 years of age who were described. Case report included information: characteristics of diabetes, renal function and structure, pancreas structure. Genomic DNA were extracted from WBC of whole blood and HNF-1β mutation was performed using PCR and direct sequencing. The proband is heterozygous for a novel HNF1B missense mutation (c.505T>C; p.Y169H). This mutation results in the substitution of the amino acid histidine (charged polar) for tyrosine (uncharged polar) at codon 169. The tyrosine residue is conserved across species and it is therefore likely that the p.Y169H mutation is pathogenic. This result is consistent with a diagnosis of renal cysts and diabetes syndrome (RCAD). Testing was done for proband’s parents and no mutation was found in HNF1B. It is therefore likely that the p.Y169H mutation has arisen de novo. Kidney MRI showed right kidney atrophy and pancreas MRI showed only tissue of head of pancreas. Investigations at 14.5 years of age – diagnosed diabetes showed: plasma urea 10.1 mmol/l; creatinine 250 micrommol/l; HbA1C 13.6%. He was given insulin of 0.8 U/kg/day and HbA1C was 6.8% after one year of treatment with insulin injection. Maturity-onset diabetes of the young type 5 encompasses a wide clinical spectrum. Analysis for mutations of HNF-1β is warranted, even without a family history of diabetes, in non obese patients with diabetes and slowly progressive non diabetic nephropathy, particularly when pancreatic atrophy.

Written informed consent was obtained from the patient for publication of this Case report (and any accompanying images). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

P26
Day and night glucose control using a hybrid closed loop system for the management of type 1 diabetes
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Achieving tight glycemic control for the management of type 1 diabetes is often associated with a heavy burden of care, and frequent hypoglycemia. Closed loop insulin delivery, or an ”artificial pancreas”, represents a new technological frontier for the management of type 1 diabetes which aims to overcome these difficulties. Rapid advancement and improvement in the components of closed loop systems (continuous glucose monitors, insulin pumps, and mathematical algorithms) has been translated into numerous published reports demonstrating effective
glucose control in hospital studies, camps, hotels, and most recently – in home studies. Most studies to date have focused on overnight control due to the difficulties in managing glucose excursions from carbohydrate intake and exercise. We investigated the capability of the Medtronic Hybrid Closed Loop (HCL) System in managing glucose levels during both day and night. The Medtronic HCL system consists of a Medtronic MiniMed insulin pump, Medtronic MiniMed Enlite II glucose sensor, Medtronic MiniMed Minilink REAL time sensor, Medtronic MiniMed Translator, and an Android mobile device with the HCL algorithm (proportional integrative derivative minus insulin feedback and additional safety parameters) software application installed. When using the HCL meal boluses are delivered manually using the Android mobile device. All basal insulin delivery is controlled by the algorithm. We present in-clinic pilot data from 3 individuals with type 1 diabetes, incorporating 140 hours of closed loop management, over 5 days and nights. A free living environment was simulated, with free access to food, and exercise encouraged. For the three participants, percent of time spent in target glucose range (4 – 10mmol/L) was 81%, 62% and 73% respectively. Including all data, the mean glucose was 8.74mmol/L, which corresponds to an HbA1c of approximately 7%. There were no hypoglycemic or adverse events. We conclude that the Medtronic HCL system is potentially effective and safe for the management of type 1 diabetes.

Outpatient studies, with comparisons to sensor augmented pump therapy with low glucose suspend in a randomized cross-over trial are ongoing.

P27 Comparison of alternating home telemedicine consultations with regular face to face consultations in type 1 diabetes

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Aims: To compare a model of alternate home videoconference consultations/faceto face consultations with regular face to face consultations in young rural patients with Type 1 Diabetes Mellitus (T1DM).

Methods: A 12 month non randomized controlled trial was performed in 2013 comprising a cohort of children, adolescents and young adults with T1DM from the immediate local region compared with a similar cohort from a region greater than 70 Km away. The local cohort continued with 3 monthly appointments and extra visits as required between appointments. The distant cohort had 6 monthly face to face consultations, alternating with 6 monthly formal videoconference consultations to their homes. Extra visits were also managed via videoconference.

Outcome was measured by comparison of Hba1c between the two groups before during and after the intervention. Missed or rescheduled visits were compared. A patient satisfaction survey was performed and logistic issues were described from both the patient and medical team perspective.

Results: 20 patients (mean age 18.3 years) in the control group (mean Hba1c 8.4%) were matched with 29 patients (mean age 17.2 years) in the intervention group (mean Hba1c 8.3%) (NS). During the intervention period, the glycaemic control in both groups deteriorated slightly (control 8.7%, intervention 8.5%) (p=0.31). Upon return to regular 3 monthly appointments, Hba1c was 8.4% (control) and 8.6% (intervention). Missed or rescheduled appointments occurred more in the telemedicine group. Patient satisfaction was strong for 4 measures of convenience (time of day, home location, accessibility to other parent/partner and time off school/work) but with major inconvenience accessing Hba1c testing. The major disincentives were lack of personal interaction and more difficulty discussing issues. The major issues for the medical team were reduced ability to read patient’s and parent’s emotions because of technology. System to appointments by some families.

Conclusion: Telemedicine consultations to home are well accepted and convenient for rural families and young adults with T1DM but are associated with more difficulty accessing Hba1c tests, more missed appointments and more difficulty reading emotional cues during consultations. Glycaemic control did not improve. Catch up videoconferences between appointments were very well accepted.

Replacing face to face consultations with direct home videoconference should be done with caution.

P28 Development of diabetes mellitus after hematopoietic stem cell transplantation for childhood leukemia

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Aims: We investigated clinical features of newly diagnosed diabetes mellitus (DM) after hematopoietic stem cell transplantation (HSCT) for treatment of childhood leukemia.

Methods: Between April 2009 and March 2014, total 124 patients (73 males, 51 females) were visited the clinic of pediatric endocrinology for routine follow-up check after HSCT for leukemia. Among them, five patients developed DM (4 males, 1 female). We retrospectively reviewed medical charts including laboratory findings.

Results: Three patients were diagnosed as acute lymphoblastic leukemia who received total body irradiation and chemotherapy. The other two patients were diagnosed as acute myeloblastic leukemia. The mean age at HbA1c was 8.0 ± 4.2 years. Four out of five patients developed chronic graft-versus-host disease (GVHD) and treated with steroid more than 2 years. The mean age at diagnosis of DM was 15.8 ± 1.8 years and the time interval between HSCT and DM was 7.8 ± 4.4 years. Three patients showed obesity depend on body mass index (>95th percentile for sex and age). No one showed antibodies related with pancreatic β-cell. All five patients showed hypereutininaemia with mean fasting insulin levels at diagnosis of DM was 13.3 ± 9.2 μIU/mL. The mean homeostasis model assessment of insulin resistance index (HOMA-IR) of patients was 4.39 ± 2.01.

Conclusion: GVHD, long-term steroid treatment and insulin resistance seem to be close related to develop of DM after HSCT for treatment of childhood leukemia.

P29 Permanent neonatal diabetes due to a heterozygous INS mutation

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Permanent Neonatal Diabetes Mellitus (PNDM) is a rare disorder where patient presents with diabetes within the first few months of life without autoantibodies associated with type 1 diabetes. The majority of PNDM cases have INS, ABCB8 or KCNJ11 mutations. We present a PNDM case with INS mutation. The proband is a second child of three siblings without family history of diabetes. She was born at term via emergency lower segment caesarean section with good APGAR score. Her birth weight was 2.0kg (<3rd percentile), length 49cm (50th percentile), and head circumference 34cm (50th percentile). She was discharged well at day 3 of life, but readmitted at day 17 of life with hyperglycaemia, sepsis and severe metabolic acidosis, requiring insulin infusion. Despite clinical improvement and resolving sepsis, she remained hyperglycaemic and hence neonatal diabetes was suspected. Her GAD-65 and ICA-512 antibodies were negative. Hba1c and c-peptide at diagnosis were 7.9% and 38 pmol/L (normal range: 297.9–1324) respectively. She was still hyperglycaemic despite receiving total daily insulin (TDI) of 1.5U/kg/day, but not ketotic. She was discharged after 20 days of hospitalization with insulinard administered three times daily (TDI 1.2U/kg/day). During the first 8 months of diagnosis, her metabolic control was good (Hba1c 6.7 - 7.6%) despite low insulin requirement, as low as 0.4U/kg/day. Her metabolic control deteriorated since then (Hba1c 11.9 - 13.2%), with TDI doses ranging 0.7 - 0.9 U/kg/day. Rapid acting insulin was not used due to episodes of hypoglycaemia and unpredictable eating habit and activity levels during her toddler years. Direct DNA sequencing revealed she is
PFOS, PFOA, PFNA, and PFDA were detected in >90% of the serum samples. The number of chemicals above median concentrations among these 5 PFCs were graded on a scale of 0 to 5, and classified into exposure (0) (n = 97), exposure (1-2) (n = 88), and exposure (≥3) groups. After adjusting for sex, birth weight, MPH, and BA, log-transformed PFHxS, PFOS, PFOA, and PFDA were associated with a 1.60, 1.35, 1.57, 1.29 cm decrease in height (all P < 0.005). Log-transformed PFOS, PFOA, PFNA, and PFDA were negatively related to weight gain (all P < 0.05). Change in weight Z-scores decreased progressively from exposure (0), to exposure (1-2), and to exposure (≥3) (mean ±0.43 vs. ±0.29 vs. ±0.10, P = 0.012).

Conclusions: Increased concentrations of PFOS, PFOA, PFNA, and PFDA were associated with short stature and failure to weight gain in 2-year-old children. The more PFCs detected above median concentrations, the shorter and the poorer weight gain. Further prospective studies are needed to clarify causal relationship.

**GROWTH**

**P30**

Disease-specific growth charts of Marfan syndrome in Korea

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Aims: Understanding the growth pattern in Marfan syndrome (MFS) is useful for predicting adult height and for planning the timing of growth reduction therapy. We have reviewed the growth parameters of patients with MFS in Korea and generated the Korean MFS-specific growth curve for understanding the growth pattern in MFS.

Methods: Anthropometric data were available from 187 males and 152 females with MFS through a retrospective review of medical records. The standardized growth curves were constructed for weight and height according to gender. Comparisons between MFS patients and the general population were performed using a one-sample T-test.

Results: Korean MFS patients had similar height and weight compared with the general population at birth. However, linear growth curve of Korean MFS after two years of age showed that the 50th percentile of MFS is above the 97th percentile of normal in both genders. Regarding body mass, although the mean body weight of MFS patients was larger than that of the general population in males and females, the gap of the mean weight curve was small. In the Korean MFS growth curve, the growth pattern and final adult height were nearly analogous to those of the United States (US).

Conclusions: Korean MFS-specific growth charts showed that an excessive growth pattern began in the early infant period, which was prominent in terms of linear growth compared to body mass. There were no ethnic differences in the growth pattern compared with Western MFS patients.

**P31**

Association of serum concentrations of perfluoroalkyl compounds with poor growth and failure to weight gain in 2-year-old children

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Backgrounds: Potential health concerns of perfluoroalkyl compounds (PFCs) have been raised.

Objectives: We investigated the relationship between exposure to PFCs and growth parameters in Korean 2-year-old children.

Methods: Three hundred sixty children (189 boys, 19.0 to 2.2 years) born as appropriate gestational age infants were enrolled. Height and weight at visit, birth height, midparental height (MPH) and bone age (BA) were evaluated.

Results: Among fifteen PFCs analyzed, perfluorohexane sulfonic acid (PFHxS), and perfluorooctanoic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) were detected in >90% of the serum samples. The number of chemicals above median concentrations among these 5 PFCs were graded on a scale of 0 to 5, and classified into exposure (0) (n = 97), exposure (1-2) (n = 88), and exposure (≥3) groups. After adjusting for sex, birth weight, MPH, and BA, log-transformed PFHxS, PFOS, PFOA, and PFDA were associated with a 1.60, 1.35, 1.57, 1.29 cm decrease in height (all P < 0.005). Log-transformed PFOS, PFOA, PFNA, and PFDA were negatively related to weight gain (all P < 0.05). Change in weight Z-scores decreased progressively from exposure (0), to exposure (1-2), and to exposure (≥3) (mean ±0.43 vs. ±0.29 vs. ±0.10, P = 0.012).

Conclusions: Increased concentrations of PFOS, PFOA, PFNA, and PFDA were associated with short stature and failure to weight gain in 2-year-old children. The more PFCs detected above median concentrations, the shorter and the poorer weight gain. Further prospective studies are needed to clarify causal relationship.

**P32**

Growth effect of TKI treatment in childhood CML


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Aim: Childhood chronic myeloid leukemia (CML) is rare myelo proliferative disorder, and diagnosed mostly in adult, representing for 10% of all CML, and accounts for up to 2-3% of all childhood leukemia. Tyrosine kinase inhibitor (TKI), mostly Imatinib mesylate, is now used in the frontline standard treatment of CML in chronic phase. The aim of this study is to investigate the growth effect of TKI treatment in childhood CML.

Methods: This retrospective study consisted of 20 pediatric CML patients (13 males and 7 females) received TKI treatment at Seoul and Yeouido St. Mary hospital from January 2001 to January 2014. Patients with chronic-phase CML, received TKI treatment for more than 6 months were included. Height and weight data were obtained from the patient’s medical records. The differences (Δ) of height and weight standard deviation scores (SDS) at before and after treatment were calculated and associations of factors that influence the growth were analyzed.

Result: Seventeen patients (85.0%) had reduction in height SDS was observed. Mean age at the start of TKI was 10 years, and median follow-up was 53 months. When the mean levels of Δ height and weight SDS were analyzed, we observed significant reduction in height SDS (mean ±SE, -0.35±0.33, P=0.000), but not in weight SDS (mean±SE, -0.04±0.54, P=0.723). Growth deceleration was seen predominantly in patients who started TKI at a prepubertal age compared with those who started at pubertal age or started at prepubertal age but enter puberty on treatment (mean±SE, -0.59 ±0.32 vs. -0.21±0.28, P=0.015). But no significant difference of height SDS were observed between two group depend on the TKI type. After adjusting for type of puberty, significant linear correlations with the reduction of height SDS after treatment was found for age at onset treatment (r²=0.81, P=0.005).

Conclusion: After received TKI treatment in childhood CML patients, a significant number of patients experience growth deceleration. Initiation of TKI treatment in prepubertal age and age of begin treatment are associated with growth impairment. Continuous follow-up and monitoring growth after received TKI treatment in childhood CML is important for improving quality of life.

**P33**

Growth status of small for gestational age (SGA) Indian children from two socioeconomic strata

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Aims: To assess growth and factors associated with growth in children born SGA from two socio economic strata in comparison to age and gender matched healthy controls.

Methods: Retrospective study conducted at two hospitals in Pune, 0.5 to 5 years old 618 children – 189 SGA from Upper Socio-economic Strata (USS), 217 SGA from Lower Socio-economic Strata (LSS) and 212 appropriate for gestational age (AGA) healthy controls were randomly selected. Birth history, maternal history, socio-economic status, length/ height and weight of children were recorded. Anthropometric data were converted to Z scores (HAZ, WAZ) using WHO AnthroPlus software [1]. Data on neonatal morbidity and feeding history of children were recorded (analysis in progress).

Results: Mean ages of all 3 groups were similar (2.7 years for USS, 2.8 for LSS and 2.9 for controls). The HAZ and WAZ of the SGA group were significantly lower as compared to the controls (p < 0.05), and that of the LSS SGA were lower than that of the USS SGA (p<0.05). The percentage of children who were stunted (HAZ < -2.0) were 32% in USS and 49% in LSS (p< 0.05 for all). The percentage of stunted children in the USS SGA group at 2 years was 29% and at 5 years was 17% while in the LSS SGA group, 54% of children were found to be stunted at 2 years and 46% at 5 years. To determine factors associated with stunting in SGA children, general linear model (GLM) was used. GLM revealed that a normal vaginal delivery (l = 0.625) and mother’s age (l = 0.072) were positively associated with risk of stunting, high SES (l = -0.830), absence of major illness (l = -1.01), higher birth weight (l = -1.34) were negatively associated (p for all <0.05).

Conclusion: Children born SGA showed relatively poor growth as compared to healthy controls. Special attention to growth is necessary especially in children from the lower socio economic strata, very low birth weight babies and those with major illnesses during early years of life.

Reference

P34
Influence of growth hormone receptor exon 3 polymorphism on growth hormone deficiency in children with growth hormone deficiency
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International Journal of Pediatric Endocrinology 2015, 2015(Suppl 1)P34

Aims: Pharmacogenetic effects of recombinant human growth hormone according to growth hormone receptor (GHR) exon 3 polymorphism (fl vs. d3) were controversial. We investigated growth hormone response in children with growth hormone deficiency (GHD).

Methods: Total 56 prepubertal children (31 boys and 27 girls) with GHD were enrolled in this study. Subjects were divided to 2 groups according polymorphism (fl/fl, n=48; fl/d3 and d3/d3, n=10), and compared baseline phenotypes and the first year growth response to growth hormone treatment.

Results: The distribution of GHR exon 3 isoforms in children with GHD demonstrated that the frequency of fl/fl (82.8%) is higher than that in most of European studies. There was no significant difference in baseline height SDS between 2 groups. Height velocity during the first year of growth hormone replacement therapy tended to be higher in subjects who have d3 allele (fl/d3 and d3/d3), but there was no statistical difference according to genotyoe.

Conclusion: It seemed that d3 allele of GHR exon 3 had no impact on the baseline phenotype and growth hormone response in patients with GHD. Relationship between GH dose and IGF-1% to help fully elucidate the value of IGF-1 testing in GH treatment.

P35
Growth status of first grader children in elementary schools in Watu Alo, Manggarai, East Nusa Tenggara
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Background: East Nusa Tenggara (NTT) had the highest number of children under five with mild to severe malnutrition in Indonesia, happened mostly in Manggarai Regency, with the highest number of cases found in Watu Alo Primary Health Care Supervision Area, with 5 out of all 19 cases in Manggarai, NTT (RISKESDAS, 2010). Nevertheless the method to classify the growth status was unclear.

Objective: To determine growth status of first grader children in Watu Alo, Manggarai, NTT using the WHO and CDC growth charts and comparing the results.

Method: A cross-sectional descriptive study. The data was taken from 19 to 22 August 2013 and 24 August 2013 in 5 elementary school under the supervision of Watu Alo Primary Health Care, Manggarai Regency, East Nusa Tenggara. Data interpretation with CDC and WHO growth chart.

Results: CDC: the children are 74% short; 26% normal stature (median: 109 cm), 21.9% underweight; 69.4% normal weight; 6.1% overweight; and 2.6% obese (median: 18 kg). WHO: 72.4% of the children are normal stature; 20.9% stunted; 6.6% severely stunted, 84.7% normal weight; 6.6% risk of overweight; 6.6% wasted; 1% overweight; 0.5% obese; 0.5% severe wasted.

Conclusions: To interpret the growth status, clinical judgement is also needed to be considered. Children growth status should be monitored continuously. Standardized national growth chart for Indonesian children should be made.

P36
Successful treatment with two siblings affected classic Bartter syndrome
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Classic Bartter syndrome is a salt-wasting tubulopathy caused by mutations in the CLCNKB (chloride channel Kb) gene. Classic Bartter syndrome is characterized by early childhood onset. Herein, we report two Vietnamese siblings affected classic Bartter syndrome.

Case presentation: Two siblings were admitted to National Hospital of Pediatrics with chief complaints of motor-development delay, growth retardation and failure of thrive. The 1st child - a 39 month old boy with his birth weight of 1.9 kg presented with his height of 69 cm (-7.5 SD), his weight of 7.5 kg (-4.4 SD). The 2nd child – an 18 months old girl presented with her height of 58 cm (-7.8 SD), her weight of 5.8 kg (-3.4 SD). They both derived polypurina (6ml/kg/hour), polydipsia, chronic dehydration and motor delay that they could not stand and walk but had normal intelligence. The investigations revealed hypokalemia metabolic alkalosis (PH: 7.5 – 7.51; pCO2: 45.9 - 56.8 mmHg; HCO3: 36.6 - 45.7 mmol/l; serum potassium levels: 1.8 - 2.1 mmol/l), hyponatremia (125 – 128 mmol/l), hypochloremia (67 – 84 mmol/l), normal calcium, and normal sugar. They were treated with potassium supplement, indomethacin (2.5 mg/kg/ day). After 15 months of treatment: height, weight of the 1st boy and 2nd girl were 94 cm (increasing 25cm; -3 SD), 12kg (increasing 4.5kg; -3 SD) and 84 cm (increasing 26 cm; -2.4 SD), 11 kg (increasing 5.2 kg; -1.3 SD), respectively. Their plasma electrolyte became normal after 2 weeks of treatment.

Conclusions: Classic Bartter syndrome will have good prognosis if treated early. This is one cause that can result in growth retardation. Written informed consent was obtained from the patient for publication of this Case report (and any accompanying images). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

P37
Turner syndrome and growth hormone therapy: a review on growth response
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Aims: Turner syndrome (TS) is a sex-chromosome abnormality in females resulting from partial or complete absence of one of the X chromosomes
One of the main features of TS is short stature. Final height in short girls with TS improves with growth hormone treatment [2]. The aim of this study was to assess the effectiveness of growth hormone therapy in a cohort of Malaysian patients with TS.

Methods: Data from the electronic medical records of 20 patients with TS treated with growth hormone in Putrajaya Hospital, Malaysia from the year 2005 to 2014 was analysed.

Results: The mean age of initiation of therapy was 11.5 ± 3.4 and 55.0% were started after the age of 12 years. The mean height standard deviation score (SDS) increased from -3.84 (±0.94) SD at study entry to -3.47 (±0.97) SD at the end of the first year. This improvement was seen with both frequent year of treatment, though the degree of change in height SDS reduced with time. Age of initiation of therapy had a bearing on treatment response as those who had received growth hormone at an earlier age experienced better growth response. 75.0% of patients who achieved final height were able to achieve the final height within the target height. Of the patients who achieved final height, mean age of puberty was 16 ± 1.5 years and mean height SDS at onset of puberty was -3.35. There were no reported adverse events.

Conclusion: Growth hormone therapy improved growth profile of Malaysian children with TS and the importance of early initiation of therapy is demonstrated in this study.

References:

P38 Insulin-like Growth Factor 1 (IGF-1) measurements recorded in the OZGROW database and their relation to growth response in children currently being treated with growth hormone

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Aims: IGF-1 is produced in a GH dependent fashion and measurement of IGF-1 has become increasingly common for both diagnosis of GH deficiency and to guide GH therapy. The OZGROW database records the results of IGF-1 tests performed on patients receiving GH or being assessed for GH treatment. The OZGROW database was used to determine the extent to which IGF-1 testing is performed in this population and to assess the relationship between IGF-1 levels and growth rate.

Methods: Records were obtained for children entering the OZGROW database since 2009 and who were currently receiving GH. Number of patients, visits, and frequency of IGF-1 tests was determined. The nature of IGF-1 tests, such as the units used and whether a reference range was provided was noted. Patients with at least one IGF-1 test result were selected for further analysis. IGF-1 results were standardized (where a reference range was available) by expressing them as a % of the reference range. %x = ((x-U)/L-U), where x is the test result and U and L are the upper and lower values of the reference range. Growth was measured as either growth velocity (GV, cm/year) or height SDS/year over either a 6month (+/- 10 weeks but adjusted to 6m) or 1 year (+/-13weeks adjusted to 1y). Regressions (coefficient=b and correlations (r) were performed.

Results: 829 patients were assessed representing 7573 clinic visits. 577 (69%) did not have any IGF-1 tests recorded. 25% had one test recorded, 4% had two tests, and 1% had three tests. Another 21 IGF-1 tests were noted but not used in analyses as no reference range was given. Units used were nmol/L, mmol/L, U/ml, mg/l, mgf, and ‘other’. 11 results had a reference range but no units. Overall a moderate but significant relationship was found between IGF-1% and growth: 6month GV-b=0.014cm/y,%IGF-1, r=0.31, P<0.001; 1Y GV-b=0.016, r=0.14, P=0.03; 1Y SDS-b=0.0033, r=0.31, P<0.001. More detailed analyses stratified by indication and gender will be presented.

Discussion and conclusions: IGF-1 has been recommended to titrate GH dose. We found significant variation between IGF-1% and growth response although the correlation was significant. There was also great variation in measurement units used and references ranges stated. Further analyses will focus on the relationship between GH dose and IGF-1% to help fully elucidate the value of IGF-1 testing in GH treatment.

ADRENAL

P39 High incidence of adrenal suppression in children with Kawasaki disease treated with intravenous immunoglobulin plus prednisolone

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Context: Combination treatment with intravenous immunoglobulin (IVIG) plus prednisolone, newly designed for children with severe Kawasaki disease (KD), significantly reduces coronary artery abnormalities [1]. Prednisolone is administered for approximately 20 days in this regimen.

Objective: Our aim was to examine whether adrenal function of the treated patients is suppressed by glucocorticoid administration in this regimen.

Design/setting: This was a prospective study at one medical institution.

Patients: We analyzed data from 21 children with KD who were treated with IVIG plus prednisolone between February and June, 2012.

Main outcome measures: The main outcome measures were cortisol and ACTH values in the morning after the cessation of prednisolone administration and peak cortisol and ACTH values at CRH stimulation test repeated 0, 2, and 6 months after the treatment.

Results: Morning cortisol and ACTH values after the cessation of prednisolone treatment were suppressed. Peak cortisol values at the first CRH stimulation test ranged from 5.1 to 25.4 mcg/dL and were less than 20 mcg/dL in 17 of 21 patients, but were restored to more than 14.6 mcg/dL in all of them by 6 months after the prednisolone treatment. A significant positive correlation was observed between cortisol values at 09:00 after the prednisolone treatment and peak cortisol values at the following CRH stimulation test (r = 0.770, p < 0.0001).

Conclusions: Adrenal suppression can occur in a high proportion of children with KD treated with IVIG plus prednisolone, despite rather short duration and low administered dose of glucocorticoids.

Reference:

P40 Addison’s disease in a child: a case report

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Addison’s disease is chronic primary adrenal insufficiency, a rare disorder which is characterized by adrenocortical insufficiency. The sign and symptom in Addison’s disease is nonspecific. This paper is to report Addison’s disease in a child focusing in diagnostic approach. Method is case report. Girl, 4 years old suffered from general weakness without paresthesia, fatigue, salt craving and hyperpigmentation including skin, lips, gum, buccal mucosa, hard palate and plantar cresae. Tanner stage was prepubertal condition. Basal cortisol plasma level in the morning was 94.8 (50-250) µg/mL and 14.3 (25-125) µg/mL in the evening. This patient was performed ACTH stimulation test. The result revealed declining cortisol plasma level before (20.83) and 30’, 120’ after the test (16.53, 4.31) µg/mL respectively.
An infant with Cushing syndrome
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Background: Infantile Cushing syndrome is rare. We report an 8-month-old infant who developed growth failure and hypertension from an apparently innocuous topical steroid application.

Case Presentation: An 8-month-old boy was referred to the endocrinology clinic for concerns of growth failure since 3 months of age. He was born full term with a birth weight of 2.67kg and a length of 45cm. His parents noticed that he was not growing well from 3 months of age. However, his weight gain remained more than satisfactory and he gained 700g in the past month. This infant was otherwise in good health, apart from atop dermatitis, for which the parents had been applying a daily cream with good effect. He was breast fed until 2 months of age and weaned onto solids at 6 months of age.

On examination, the infant had a moon face with hypertrichosis, facial telangiectasia and prominent supraclavicular fat pads. His recumbent length was 62cm (<3rd percentile), his weight was 7.74 kg (25th percentile), and his head circumference was 41.0 cm (3rd percentile). There was no hyperpigmentation or lentigens, but he was hypertensive with a blood pressure of 140/90 mmHg (95th percentile for age is 99/55 mm Hg) with a heart rate of 140 beats/minute. His apex beat was not displaced and his heart sounds were normal with no murmurs. A random steroid profile demonstrated a depressed serum cortisol level of 30 nmol/L and an unmeasurably low serum ACTH level of <1.1 pmol/L. This was consistent with exogenous Cushing syndrome. An ECG showed biventricular hypertrophy and a 2-D echocardiogram confirmed severe biventricular hypertrophy with good ventricular function.

On further questioning, he had been receiving twice daily applications of a topical cream for atopic dermatitis, which had been obtained over the counter, without a prescription. Subsequent analysis of the topical agent revealed the contents to be betametasone dipropionate, a high potency corticosteroid.

On establishing the diagnosis of exogenous Cushing syndrome, the offending topical steroid cream was discontinued. Since he was at risk of primary adrenal failure from sudden withdrawal of steroid cream, he was started on a weaning regimen of hydrocortisone. He was also commenced on captopril which achieved good blood pressure control.

Conclusion: Continuous use of high potency topical corticosteroids over several months can lead to Cushing syndrome. Physiologic dosing of hydrocortisone should be prescribed to prevent an adrenal crisis until hypothalamic-pituitary-adrenal axis recovery is confirmed.

Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

P42
A case report of neonatal adrenocortical carcinoma
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Adrenocortical carcinoma is rarely seen in a neonatal period. Adrenocortical carcinoma usually causes virilisation, precocious puberty, Cushingoid syndrome.

Aims: Describe a case of neonatal adrenocortical carcinoma diagnosed and treated in Vietnam National Hospital of Pediatrics.

Method: A case report of neonatal adrenocortical carcinoma with Cushingoid syndrome and persistent hypertension.

Results: A boy was admitted to hospital at the age of 23 days because of vomiting, poor feeding and abdominal distension, and edema on both legs. On examination we found the child had Cushingoid syndrome, but not precocious puberty, edema on both legs, and hypertension. Blood pressure was 150/90 mmHg, required IV Loxen to maintain BP. Investigation showed cortisol 8AM was high of 4473 nmol/l; cortisol 24AM 3971 nmol/l. Electrolyte, renal function, glucose, urine VMA/HMA were normal. Abdominal ultrasound found a hypo-enhancing mass in the left adrenal area with calcification and dimension of 37x32 mm. Dilated left renal pelvis was also observed. Cardiac ultrasound found ventricular hypertrophy, suspected cardiomyopathy. Neck MRI detected abnormal connection between lymphatic vessels and venous vessels. Abdominal CT showed a heterogeneous mass of 40x41x50 mm with calcification in the left adrenal area. Operation was done to remove the mass. No metastase was noticed during operation. Histology confirmed a diagnosis of adrenocortical carcinoma. Cortical was normal after operation. However, hypertension was still present a week after operation and IV Loxen was indicated to maintain normal BP.

Conclusion: Post-operation hypertension was persistent in a neonatal adrenocortical carcinoma patient.

Written informed consent was obtained from the patient for publication of this Case report (and any accompanying images). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

P43
Clinical and molecular characterization of patients with classic 3β-hydroxysteroid dehydrogenase deficiency
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Background: 3β-Hydroxysteroid dehydrogenase type 2 (3βHSD2) is the key enzyme converting Δ5-steroids to Δ4-keotosteroids in adrenal and gonadal steroidogenesis. Severe loss-of-function mutations of HSD3B2 gene encoding for this enzyme cause the rare form of congenital adrenal hyperplasia, “3βHSD deficiency”. Affected individuals have salt losing, adrenal insufficiency and ambiguous genitalia in both sexes. Patients with 3βHSD deficiency may have elevated 17α-hydroxyprogesterone (17OHP) levels due to normal peripheral type 1, 3βHSD.

Aims: To describe two unrelated patients with 3β-hydroxysteroid dehydrogenase deficiency and perform mutation analysis of the HSD3B2 gene.

Patients and Methods: Patient 1 (Thai) and 2 (Indian) are 46,XY male newborns with ambiguous genitalia (microgenis, penoscrotal hypospadias) who developed salt-losing since early infancy. They were stabilized with normal saline resuscitation and high dose hydrocortisone replacement. Patient 2 was initially misdiagnosed as 21-hydroxylase deficiency due to elevated 17OHP until he was referred for genitoplasty at the age of 2.5 years and the patient were re-evaluated. The ACTH tests revealed low cortisol response, moderately elevated 17OHP, elevated Δ5-D4 steroids, suggestive of blockage at the level of enzyme 3βHSD. Patients’ leukocyte genomic DNA was extracted and the entire coding regions of the HSD3B2 gene were assessed by polymerase chain reaction (PCR) and sequencing analysis.

Results: Patient 1 was homozygous for T259M (c.776C>T) mutation in the HSD3B2 gene. Patient 2 was homozygous for the novel nonsense mutation Y180X (c.540C>A) and his parents were heterozygous carrier.

Conclusion: We report the mutations of HSD3B2 gene, T259M and Y180X (novel) responsible for classic 3βHSD deficiency. The clinical and hormonal phenotypes can be complicated in this disorder. These cases emphasize the importance of confirming the specific enzyme deficiency with molecular genetic analysis.
P44
17-hydroxyprogesterone quantification in dried blood spots by high performance liquid chromatography-tandem mass spectroscopy
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Measurement of 17-hydroxyprogesterone (17-OHP) in daily dried blood spots via radioimmunoassay is a convenient and accepted method for monitoring of glucocorticoid toxicity in Congenital Adrenal Hyperplasia. Characteristics of this method that serve to limit its clinical usefulness include its lack of specificity for 17-OHP, and a relatively high limit of detection. Mass Spectroscopy is the gold standard method for steroid quantification. We aim to establish a High Performance Liquid Chromatography-Tandem Mass Spectroscopy (HPLC-MS/MS) method for dried blood spot 17-OHP quantification and develop normative age- and Tanner-stage specific, as well as Congenital Adrenal Hyperplasia genotype-phenotype correlated reference ranges to guide glucocorticoid therapy.

Four 3mm blood spots were punched from patient dried blood spot filter papers. 17-OHP was eluted into solvent and concentrated using liquid nitrogen. Steroids were separated using high performance liquid chromatography and quantitated by Tandem Mass Spectrometry. For the radioimmunoassay / HPLC-MS/MS correlations, measurements were performed by both methods on 49 samples from children with glucocorticoid-dependent Congenital Adrenal Hyperplasia, as well as children undergoing dynamic endocrine function testing at The Mater Children’s Hospital. Reference samples for HPLC-MS/MS calibration, and determination of sensitivity, precision, and recovery were prepared using whole blood samples spiked with 17-OHP spotted onto filter paper. Concentrations were expressed as mean (nmol/L), standard deviation, and coefficient of variation (%). There was excellent correlation between HPLC-MS/MS and radioimmunoassay methods (r²=0.9610). For the radioimmunoassay method, the lower limit of quantification has been established at <5 nmol/L while LC-MS/MS allows detection to 1.0 nmol/L (1.2nmol/L, 0.26, 22%) with a proposed lower limit of quantification of 1.5 nmol/L (1.3 nmol/L, 1.3%, 13%). We have established an accurate, reliable, and specific method for quantifying 17-OHP concentrations from dried blood spot using HPLC-MS/MS. This will allow for the establishment of clinically relevant and time-specific reference ranges to guide glucocorticoid dose adjustment in children with Congenital Adrenal Hyperplasia.

P45
An infantile exogenous Cushing syndrome caused by topical steroid
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Corticosteroids are widely used for the treatment of various diseases. Long-term use of corticosteroids may lead to development of Cushing syndrome and hypothalamic pituitary adrenal axis suppression. However, iatrogenic Cushing syndrome from absorption of topical steroids to systemic circulation is less common comparing to parenteral or oral use. Infantile age group have greater risks for systemic side effects of the drugs because their skin has poorly developed barrier function and large surface area. We reported a 5-month-old female child was admitted to our hospital with puffiness of face and excessive weight gain after 4 months old. She was born at term with an uneventful pregnancy with a birth weight of 3.4 kg. Her body weight was 8.2 kg (+2SDS), height was 63.5 cm (+2SDS). Physical examination showed her face was moon face appearance, generalized obesity, hirsutism and buffalo hump. There were few erythema and weeping present at skin fold areas. Blood pressure was 105/68 mmHg (>95th percentile). Past history revealed that the child had diaper dermatitis at 3.5 month of age. She was prescribed a topical combination drug containing nystatin, neomycin, gramicidin and trimcinolone acetonide from private pediatric clinic. Since then she was applying the drug 3-4 times daily on neck, axilla, diaper area and all skin fold areas. Totally drug usage was 30 g in 6 weeks. Investigations showed hemoglobin of 15 g/dL, white blood cell count 18,240/mm³, platelet count 471,000/mm³, blood glucose 74 mg/dL and normal electrolyte, renal and liver function. Ultrasonography of whole abdomen revealed no abnormality. Random PM cortisol was low (0.2 mcg/dL). Secondary adrenal insufficiency was suspected. 1-mcg ACTH stimulation test was done and the peak cortisol was 1.9 mcg/dL. Therefore, exogenous Cushing syndrome and secondary adrenal insufficiency due to overuse of topical combination drug which containing moderate potency steroid was diagnosed. She was promptly treatment by discontinued applying the drug and administered steroid during stress. This report highlights the importance of prolonged use of moderate potency topical steroids can causes hypothalamic pituitary adrenal axis suppression and Cushing syndrome, especially during infantile period. Therefore, limiting the use of moderate- to high-potency topical steroids in children and provide information about potential adverse effects to the caregivers are crucial.

Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

P46
Leydig cell tumor in a boy with undiagnosed precocious puberty due to congenital adrenal hyperplasia
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Aims: To describe the clinical presentation and sequelae of undiagnosed congenital adrenal hyperplasia (CAH).
Methods: Case report.
Results: A 5-year-old boy presented with penis and testicular enlargement for 1 year. The past medical history had no severe vomiting or failure to thrive. His height was 120 cm (> 95th percentile). His penis was 7 cm and asymmetric testicles. Scrotal ultrasound detected his left testicle was 1.5x0.9 cm and his right testicle was 3.0 x 2.0 cm with a heterogeneous hypechoic mass 1.8 x 2.0 cm at inferior pole with sheath thickness, clearly margin. His bone age was 14 years. His serum 17-hydroxypregnenolone and testosterone levels were elevated to 1768 ng/dL and 694.3 ng/dL, respectively. His serum hCG was below 1.2 IU/L and DHEA-S < 0.001 mcg/ml. An absent LH response after GnRH stimulation was recorded. He was diagnosed with CAH and treated with hydrocortisone. After one month of treatment, his serum 17-hydroxypregnenolone and testosterone levels decreased to 11 ng/dL and 20.75 ng/dL, respectively. Then, he underwent an open testis biopsy for further evaluating the mass of his right testicle. Histological examination of the testicle demonstrated large, polygonal, and eosinophilic cells with round nuclei and prominent nucleoli, which are consistent findings with Leydig cell tumors. Thereafter, the child underwent radical orchietomy of his right testicle.
Conclusion: Undiagnosed congenital adrenal hyperplasia can affect normal development. Universal newborn screening is recommended for congenital adrenal hyperplasia.
Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

P47
Long term follow up of growth in children with Congenital Adrenal Hyperplasia 21-Hydroxylase deficiency
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Obesity and decreased final height are described in children with CAH 210HD. Of 119 children (50 M, 69F; 79 Salt Wasters(SW), 40 Simple
Viralizers (SVI) diagnosed over 24 years, various growth parameters were studied in 43 children with regular follow up for 5 years or more. Clinical data, anthropometry, genotype, hormonal and biochemical profile were evaluated at presentation. On follow up, growth and clinical characteristics, metabolic control (8am 17OH-Progesterone), bone age and replacement doses of gluco-corticoid (GC) and mineralo-corticoid (MC) were studied. Growth parameters were expressed as SDS. Obesity, defined as BMI SDS >/= 2 and short stature, defined as Ht SDS </= -2 were correlated with all the variables, using Unpaired T Test, Pearson Correlation and One way ANOVA Test.

43 children (16M, 27F, 325W, 115W; 36 mutations proven) had a mean duration of follow up of 11 +/- 4.14 years. At last follow up, Ht SDS was </= -2 in 27.9% cases (N=12/43: 4M, 8F; 95W, 35V). Age at onset of puberty (p=0.035), higher GC dose at presentation (>40mg/m2) (p=0.034) and at 3 years of age (p=0.047) and use of Hydrocortisone and/or Prednisolone (p=0.002) had a negative correlation with Ht SDS. 6 (13.95%) children (1M, 5F; 65W) had achieved Adult Height (AH) SDS of >2.36 and 2 (4.6%) had SDS – TH SDS (Target Height) was -0.11 +/- 1.23. BMI SDS >/=2 found in 32.6% cases (N=14/43: 2M, 12F; 85W; 65V) correlated positively with 17 OHP values (p=0.013). Girls were heavier than boys (p=0.006). Adiposity rebound occurred at 4 years for both the genders. At the time of study analysis, HT SDS showed a distinct shift to the left and BMI SDS, a distinct shift to the right of mean of the reference population as cited [1].

In the present series, there was a higher incidence of obesity (32.6%) but short stature was noted in 27.9% only. Aggressive lifestyle management, dietary control, optimizing dose of therapy (GC) and regular monitoring should be an integral part of long term management of patients with CAH 210HD.

Reference
mutation has been found in the other Vietnamese family. The 46,XY newborn referred at 3th month of life with severe dehydration associated with hypernatremia (93 mmol/L) and hyperpigmentation. The tests were palpable in the scrotum but associated with a severe hypospadias (microepis 0.5 cm; posterior). Clinical presentation and increased 17OHP- Progesterone (9.7 ng/ml) in this 46, XY DSD suggest the diagnosis of 3|β- HSD deficiency. The sequencing of HSD3B2 also confirms the diagnosis because he is homozygous for a missense mutation, p.Ala161Pro. The severity of this mutation correlates well with the phenotype in these patients. Parents of two unrelated pedigrees are not consanguinity. This study contributes to a better understanding of the molecular defects of 3|β-HSD and of the phenotypic heterogeneity of CAH related to 3|β-HSD deficiency. Written informed consent was obtained from the patient for publication of this Case report (and any accompanying images). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

P51
Adrenocortical tumor in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency
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Adrenocortical tumour have been described in patients with 21-hydroxylase deficiency. These tumours are usually considered to be ACTH – dependent, as diffuse adrenal cortical hyperplasia is commonly seen. We report adrenal cortical tissue tumours developed in three patients with untreated congenital adrenal hyperplasia due to 21-hydroxylase deficiency. All of them had symptoms of adrenogenital virilizing syndrome. A diagnosis of adrenocortical tumour was established by the symptoms, hormonal profile, ultrasonography, and adrenal CT scan. Two of the tumours were located in the right side, all the patients were performed surgery before hormonal replacement therapy because of evidence of secreated adrenal tumors, and the histological diagnosis indicated an adrenocortical adenoma. After removal of the tumours, the size of adrenal gland was monitored by serial ultrasonography, and the congenital adrenal hyperplasia was confirmed by extremely high levels of basal serum testosterone, 17-OHP levels, increasing virilizing syndrome after surgery, diffuse hyperplasia of adrenal gland and identified mutations in CYP21A2 gene.

P52
Phenotype of patients with congenital adrenal hyperplasia due to 11β-hydroxylase deficiency
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Congenital adrenal hyperplasia (CAH) is one of the most common metabolic diseases. It is caused by a severe or partial impairment of adrenal steroidogenesis affecting cortisol biosynthesis. Approximately 5–8% of all cases are due to steroid 11β-hydroxylase deficiency (11OHD; OMIM +202010), which occurs in approximately 1:100,000 to 1:200,000 live births in non-consanguineous populations. Mutations in the CYP11B1 gene, causing 11b-hydroxylase deficiency in the zona fasciculate in the adrenal cortex, have been identified. Our aim is to describe clinical and biochemical features in patients with CAH due to 11β-hydroxylase deficiency. The current series report included 9 patients (6 male and 3 female) from 7 unrelated families who was identified novel and/or reported homozygous or compound heterozygous mutations in CYP11B1 gene. Diagnosed age was from 2 to 11 years old. All three female cases presented with ambiguous genitalia at birth. Other clinical features were hypertension (6/7 cases); hyperpigmentation (5/7 cases); pseudo-precocious puberty (5/5 cases). Hypokalemia was noted in 3/7 cases. Three cases need antihypertensive drug associated with hydrocortisone replacement therapy. In conclusions, the clinical hallmark of 11β-hydroxylase deficiency is variable and virilization and hypertension are the prominent clinical features of 11b hydroxylase deficiency. Biochemical identification of elevated precursor metabolites is not usually available and mutation analysis of CYP11B1 will held confirmation of diagnosis.

P53
Evaluation of parental knowledge after establishing CAH clubs in Vietnam & Indonesia
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The incidence of Congenital Adrenal Hyperplasia (CAH) in some Asian countries is far higher than in Australia, (eg 1:6000 as per the Filipino Newborn Screening Program). For many families in low and middle-income countries in Asia resources are limited, affordable and reliable access to essential medicines is problematic, and families living remotely are required to travel long distances for medical care [1]. CAH is associated with significant physical & psychosocial consequences for affected children & their families where treatment is suboptimal, so there are important equity implications for the global CAH and paediatric endocrinology communities to consider. Health education is an integral component of health care in any setting. “CAHPepTalk” is an educational resource that was developed initially for CAH families in Australia. This validated educational resource has been produced in DVD format and can be facilitated by one health professional. The program includes a translated validated CAH Knowledge Assessment Questionnaire (CAHKAQ) [2], to enable staff to assess patient knowledge in order to evaluate educational needs. In collaboration with CLAN (Caring Living As Neighbours), an Australian NGO committed to optimal quality of life for all children living with chronic health conditions), translation of “CAHPepTalk” into Vietnamese & Indonesian was undertaken, & distributed to CAH Communities in the Asia-Pacific region, was supported by CLAN.

Knowledge of parents of children with CAH in Vietnam and Indonesia was assessed prior to families attending education programs run at CAH Club meetings supported by CLAN, in 3 settings: Hanoi, Ho Chi Minh City & Jakarta. 260 questionnaires have been completed by parents. The results to be presented will include knowledge, management & demographics. Using the CAHKAQ is the first step in the education process in order to improve health outcomes for families in any setting, within Australia, Vietnam or Indonesia.

References
PS4
Evolution of a website: CAHPePtalk.com & the development of the emergency hydrocortisone mobile app
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A comprehensive, validated psychosocial education program (PEP) titled ‘The CAH Family Workshop’ was developed a decade ago to meet the needs of families with Congenital Adrenal Hyperplasia (CAH). Engaging professionals experienced in the field of endocrinology, together with information from parent interviews, was key to development of the program’s content. Validation of the program was conducted with the families participating in the program, from one of the three tertiary Children’s Hospitals in NSW Australia. The PEP provides families with essential information to assist in understanding and managing the condition. An awareness of a lack of CAH resources for families living in rural and remote regions of NSW and Australia led to the development of the program into a DVD format. This enabled these families access to the program which covers all aspects of care. The DVD format was designed to be facilitated by one experienced health professional thus reducing the need for a team of specialists to travel to country areas, which was logistically difficult and costly.

The need for CAH resources was further identified in the neighbouring South-East Asian countries of Vietnam and Indonesia where there is a higher incidence of CAH. Through the support of volunteer medical professionals and health services interpreters, the program was translated into these languages. The provision of this valuable resource for families and health professionals in these countries was supported by Caring Living As Neighbours (CLAN) and the CAH Support Group of Australia (CAHSGA).

The most recent stage of this project is the development of the CAHPePtalk.com website, which provides easy access to the English, Vietnamese and Indonesian translations of the program and relevant resources. This presentation will discuss the process of developing this patient-focused education website together with a new Hydrocortisone Emergency Injection App for iPhones & android devices.

PS5
Congenital adrenal hyperplasia with cholestatic jaundice: a case report
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Congenital adrenal hyperplasia (CAH) describes a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both. Classic CAH is rare, affecting 1 in 16,000 population. However CAH with cholestatic jaundice is extremely rare.

A 23 days old boy presented with vomiting, persistent jaundice. He was born at term, and his birth weight was 3 kg. In family history, no liver or endocrine disease was reported.

On examination, his weight was 3 kg; his height was 51 cm; jaundice, hyperpigmentation, dehydration, no hepatomegaly. Strength of his pennis was 3 cm; 2 testis were in the scrotum with volume of 1 ml. Investigation showed: electrolyte imbalance Na+ 110 mmol/l, K+ 7.3 mmol/l, Cl- 80mmol/l, 17 OHP 111 ng/ml, Testosteron 36.36 nmol/l, cholestatic jaundice : total bilirubin 114.6 mcml/dl, direct bilirubin 75.5 mcml/l, GOT 40 UI/l, GPT 25UI/l, GGT 142.76 UI/l. The markers for viral hepatitis were negative. Abdominal ultrasound was normal. He was diagnosed of CAH and treated with hydrocortisone and fludrocortisone. After 1 month of treatment, jaundice disappears and electrolyte is normalized.

Written informed consent was obtained from the patient for publication of this Case report (and any accompanying images). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

PS6
Pamidronate therapy for hypercalcemia of childhood malignancy
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Background: Hypercalcemia is a common complication of adult malignancies, but uncommon in childhood cancers. The mechanism leading to hypercalcemia varies with the primary tumour and can include the following: 1) Increased osteoclastic activity at the site of the tumour in the bone marrow 2) A paraneoplastic phenomenon secondary to PTH-related peptide (PTHrP) secretion or 1.25dihydroxyvitamin D by the tumour. Patients with serum calcium above 3.5 mmol/L tend to be symptomatic and require prompt treatment. The symptoms are generally non-specific and include lethargy, nausea, vomiting, constipation and abdominal pain. Left untreated, hypercalcemia can progress to stupor and coma.

Case Presentation: A 3-year-old girl presented with prolonged fever, hepatosplenomegaly, pancytopenia and multiple osteolytic lesions. She experienced significant weight loss of 5 kg over the past one month associated with anorexia and began to develop persistent daily fever up to 39.5°C with severe pruritus, constipation and irritability.

She was diagnosed to have Ebstein Barr Virus (EBV)-induced T-cell Lymphoproliferative disorder. However, she developed severe symptomatic hypercalcemia of 3.76 mmol/L associated with the paraneoplastic syndrome of an elevated PTH-related peptide, which was successfully treated with intravenous pamidronate (0.5 mg/kg administered as 2 doses), after conventional therapy with hydration and forced saline diuresis failed. Her serum calcium began to normalize to 2.3 mmol/L 2 days after pamidronate administration, with improvement in her symptoms of pruritis and temperament. She tolerated the infusion of pamidronate well with no adverse side effects.

Conclusion: We have demonstrated the effective use of pamidronate as a single agent at a total dose of 1mg/kg to lower serum calcium levels in a patient with severe hypercalcemia of malignancy. In such cases of severe hypercalcemia, we recommend the early use of pamidronate since hydration with saline diuresis is unlikely to normalize serum calcium levels effectively.

Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

CALCIUM/BONE
PS7
Incidence and characteristics of vitamin D deficiency rickets in New Zealand children: a prospective New Zealand paediatric surveillance unit study
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Vitamin D deficiency rickets is the most significant manifestation of vitamin D deficiency in growing children. Concerns have been raised in New Zealand (NZ), and worldwide, that cases continue to present, and may be possibly increasing. We undertook a prospective study to investigate the incidence and characteristics of vitamin D deficiency rickets in NZ children.

Prospective surveillance of Vitamin D Deficiency Rickets was conducted by the NZ Paediatric Surveillance Unit (NZPSU), for 36 months, from July 2010 – June 2013 inclusive. Inclusion criteria were: children aged <15 years with vitamin D deficiency rickets (defined by low 25-hydroxyvitamin D and elevated alkaline phosphatase levels, and/or radiological rickets).
58 children with confirmed vitamin D deficiency rickets were identified. Median age was 1.4 years (range 0.3 – 11), male gender 47%, 95% of children were born in NZ, as opposed to 22% of mothers. Overall annual incidence in those aged <15 years was 2.2/100,000, while incidence in the south of NZ peaked at 6.8/100,000. Overall NZ incidence in children aged <5 years was higher at 6.6/100,000. Skeletal abnormalities, poor growth and developmental delay were the most common presenting features, with hypocalcaemic convulsion in 16%. Key risk factors identified were: dark skin pigment, Indian/South Asian and African ethnicity, age ≤2 years, exclusive breast feeding, and southern latitude, particularly when combined with a winter/spring. Vitamin D deficiency rickets remains a health problem for New Zealand children, with significant associated morbidity. Public health policy, utilising infant supplementation, for at minimum the above identified risk factors, should be considered to reduce the incidence of this disease among those at high risk.

PS58
Idiopathic calcinosis cutis universalis
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Background: Calcinosis cutis is an uncommon disorder characterized by deposition of crystals of calcium phosphate (hydroxyapatite) in the skin in various areas of the body. Medical and surgical treatments are options to cure calcinosis cutis. Because calcinosis cutis are not always well defined, a recurrence of the lesions may occur.

Case: A 12-year-old girl with complaints of multiple lumps on her body since 1 year prior to admission. Two years prior to admission patient complained of movement limitation due to pain when doing leg lifting, squatting and standing up. One year prior to admission patient got bilateral symmetrical lumps on hip, corn size and getting bigger. Two months prior to admission the lumps got ruptured and patient felt pain. From past history no calcium supplementation, no allergy.

In physical examination patient vital sign are within normal limits, moderate malnourished. From head and neck no enlargement of lymph nodes. Heart and lungs are normal. Abdomen is normal and no sign of edema on extremities. On the extremities multiple bilateral and symmetrical lumps, corn size and coin size. On the hip multiple bilateral and symmetrical lumps. The laboratory investigations revealed within normal limits. Biochemical examinations gave normal results for complete blood picture, electrolyte, liver function and kidney function tests. Serum calcium 1.2 (normal 1.2 – 1.48 mg/dl), phosphorus 4.2 (normal 2.4-5.1 mg/dl), 25-hydroxyvitamin D 18.7 (normal 17-54 ng/dl), parathormone (PTH) 29.46 (normal 15-65 pg/ml), and magnesium 2.0 mg/dl (normal 1.3-2.7 mg/dl). On radiologic findings there are multiple calcification in soft tissue layer on humeral, antebrachial, femoral and crural bilateral. On tissue biopsy there are cystic space containing calcified material separated by fibrous tissue. Patient underwent treatment with bisphosphonate using zolendronate and surgical excision.

Conclusions: Calcinosis cutis is an uncommon disorder which results in progressive deposition of insoluble calcium salts (crystals of calcium phosphate, hydroxyapatite) in the skin. Medical and surgical treatment are options to cure calcinosis cutis. Medical treatment using bisphosphonate. A better understanding of the process of calcinosis cutis will lead to therapies to improve patient morbidity. Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

PS60
Parathyroid adenomas – a cluster of boys
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Primary hyperparathyroidism is rare in children and adolescents, representing 1% of all cases, with a slight female preponderance [1-3]. 3-5% of cases are hereditary and may represent the initial clinical manifestation of multiple endocrine neoplasia type 1 (MEN1). Over the last 30 years, ten cases of primary hyperparathyroidism have presented to our hospital, all aged 11-14 years, with nine cases being male, and eight cases over the last six years. Presenting features included headache and blurred vision in five patients, abdominal pain and nausea (in three), renal calculi (in four), generalized bone pain (in three) and two asymptomtamic. One patient had received radiation for acute lymphoblastic leukaemia. Other history included ADHD (in one patient), mild developmental delay (in one), depression (in one) and fine motor difficulties (in one). No patients had a significant family history. Peak corrected calcium level ranged between 3.12-3.65 mmol/L (2.1-2.65), peak PTH level 6.9-154 pmol/L (1-7), and urine calcium creatinine ratio
To evaluate the effect of bisphosphonates treatment showed no serious adverse effects.

### References


### P61

**Effect of bisphosphonate treatment in osteogenesis imperfecta children in Cipto Mangunkusumo Hospital Jakarta**

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**Background:** Bisphosphonates are the mainstay of pharmacologic fracture-prevention therapy for most forms of osteogenesis imperfecta (OI). Studies suggest that bisphosphonate treatment may significantly improve the natural history of all type of OI, particularly by decreasing the rate of fracture, increasing bone mineral density, decreasing bone pain, and significantly increasing height.

**Objective:** To evaluate the effect of bisphosphonate treatment in OI children treated in Cipto Mangunkusumo Hospital (CMH) Jakarta.

**Method:** We retrospectively studied the data of age, gender, age at diagnosis, bisphosphonate treatment, and its effects in OI patients in CMH from Indonesian OI children registry, which is documented from January 2012 to May 2014.

**Results:** Seventy-seven OI cases (39 male), which were diagnosed at the age of 1 - 9 years old were recorded. Five patients underwent surgery and three patients died before commencing treatment. Nine patients received intravenous pamidronate and sixteen patients received zoledronic acid therapy. Liver and renal functions, as well as serum electrolyte levels were evaluated before and after treatment. Eight patients reported hyperthermia and others experienced fatigue, bone pain, and abdominal pain within 24 hours of therapy. Serum calcium level decreased in eight patients. No serious adverse effects were documented.

**Conclusions:** All registered OI cases that received bisphosphonates treatment showed no serious adverse effects.

### P62

**Vitamin D status of healthy adolescents from two states in Malaysia**

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Hypovitaminosis D is a widespread disorder across all age groups in developing countries. The prevalence of hypovitaminosis D varies from 30-90% depending on the cut off level used to define hypovitaminosis D. In Malaysia, Khor et al found 35.3% of 402 primary school children aged 7-12 years to have 25(OH)D level < 37.5nmol/L and 37.1% have the level between 37.5-50nmol/L. If a broader definition of hypovitaminosis < 50nmol/L is used then, the prevalence was as high as 74.6%. The risk factors associated with hypovitaminosis D in developing countries are the same as in western countries. The most consistently reported risk factors are female gender, increased skin pigmentation, seasons/latitudes, obesity, concealing clothing style and vulnerable groups (neonates, preschool, elderly).

A total of 469 adolescents (107 PJ, 362 KB) participated in the study. The mean age was 15.6+/-.14 years. Female gender contributed about 61.0% compared to male gender, 39.1%. As for the race distribution, the proportion of Malay was 79.3%, Chinese 17.7% and Indian 3.0%. Teenagers from KB with family income < RM 1000 was higher (37.8% cf 10.3%; P <0.001). Adolescents from PJ was taller (160.6cm cf 156.3cm; P = 0.02). The mean BMI was 21.0+/-.4.4 kg/m2. The mean 25(OH)D was19.9+/-.8.1, in which PJ had a higher level(21.0 cf 19.6) but the mean differences was not statistically significant. More than half (58%) of adolescents had 25(OH)D < 50nmol/L. The proportion of subjects with 25(OH)D < 50nmol/L was 60.2% in KB and 56.4% in PJ.

### P63

**Sun exposure, ultraviolet (UV) irradiance and serum 25 hydroxycholecalciferol (25OHDL) in pregnant women in rural North India**

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Vitamin D deficiency is rampant in India despite abundant sunshine. We aimed to estimate the amount of cutaneous vitamin D synthesis in pregnant village women (n=100) in different seasons in conjunction with serum 25OHDL. We also correlated variations in surface UV energy with the presence of environmental pollution and crowding.

**Methods:** The measurements of UVB radiation energy were obtained using UV spectrometer at different times of the day between 9 am and 4 pm, in different seasons. The instrument was calibrated to denote 13 microWatt/cm² of irradiance per mVolt of deflection. Measurements were taken at our institution (situated in the countryside), at crowded inner city areas and the villages where our subjects resided. The clothing, outdoor activity pattern, and dietary calcium intake were prospectively measured.
Vitamin D deficiency is not expected in prepubertal schoolgoing children in a sunny country like India since they should have good sunshine exposure in conjunction with school activities. However, data from India in this age group are scant.

Aims: To evaluate the vitamin D status of apparently healthy prepubertal vs pubertal schoolchildren and to examine the influence of gender and socioeconomic status on serum 25 hydroxyvitamin D (25OHD).

Methods: Children referred to the pediatric endocrinology clinic for growth evaluation, interpretation of thyroid functions, concern regarding delayed puberty, etc. and found to be normal were enrolled, as were their healthy siblings. Pubertal assessment, a food frequency questionnaire for calcium, sunlight exposure (minutes of sunshine exposure from 10 AM - 4PM) and percentage of skin exposed were recorded. Serum calcium, albumin, creatinine, alkaline phosphatase (ALP), 25OHD and iPTH were assayed.

Results: 118 children (69% prepubertal) were enrolled. Vitamin D deficiency (25OHD < 20 ng/ml) was present in 71.6% of prepubertal and 87.8% of pubertal children. Mean 25OHD was significantly higher in the prepubertal as compared to the pubertal group (16.0 ± 7.9 versus 10.6 ± 7.5 ng/ml, p = 0.001). Their calcium intake and sunlight exposure was also significantly higher. Girls had lower mean 25OHD as compared with boys (12.9 ± 7.6 vs 16.0 ± 8.4, p=0.02), lower calcium intake (569 ± 270 vs 715 ± 334 mg, p=0.02) and less sunlight exposure (46.7 ± 45.8 vs 75.1 ± 39.1 minutes, p=0.001) than their male counterparts. There was no significant difference in 25OHD of upper, middle and lower socioeconomic classes. We found a significant correlation between serum 25OHD and calcium intake (r=0.238, p=0.02), duration of sunlight exposure (r=0.235, p=0.02) and body surface area exposed (r=0.28, p=0.003). There was a significant negative correlation between 25OHD and iPTH levels (r=-0.45, p<0.001).

Conclusions: Pubertal children have lower 25OHD than prepubertal children, probably due to limitation of outdoor activities on the background of high demand. There is significant gender bias against girls for both calcium intake and sun exposure, resulting in lower serum 25OHD than in boys.
Conclusions: Vitamin D deficiency was not significantly associated with long term AED use in children with epilepsy. Being on polytherapy over monotherapy or being on carbamazepin over sodium Valproate was not associated with Vitamin D deficiency. However a significantly higher than normal levels of ALP was associated with long term use of AED which needs further evaluation.

P67 Bisphosphonates as treatment of secondary osteoporosis in children: a case series
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Background: Secondary osteoporosis due to chronic disease is a major pediatric health concern and has certain unique diagnostic with various clinical challenges. Bisphosphonates has been used in small numbers of pediatric patients to treat secondary osteoporosis resulted in significantly fewer fractures and improved mobility.

Objective: To present case series of secondary osteoporosis due to chronic disease treated with bisphosphonate.

Case Series: We included 6 patients (2 boys, 4 girls), 7–15 years of age with secondary osteoporosis who were treated with bisphosphonate. Two patients were diagnosed acute lymphoblastic leukemia, two patients with systemic lupus erythematosus and others with juvenile rheumatoid arthritis. Two patients received methotrexate and dexamethasone; one patient was treated with methotrexate and prednisone; two patients with methylprednisolone; and rest with only methotrexate. Four of them suffered back pain due to trauma and from radiographic examination showed multiple compression fracture on the vertebrae. Lumbal BMD Z-score was ranging from -2.8 to -5.1 in patients who had fracture, while in patients without fracture -2.6 to -3.1. We used zoledronic acid 0.05 mg/kgBW. Two patients already received pamidronate as previous treatment. In 6 - 12 months of follow-up, there were evidence of reduced pain, improved mobility and BMD Z-score, also no evidence of new fractures in radiographic evaluation.

Conclusion: Bisphosphonates appears to be safe and effective as treatment for children with secondary osteoporosis.

P68 Hearing loss in osteogenesis imperfecta patients
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Osteogenesis imperfecta (OI) is an inherited bone and connective tissue disorder associated with the lifelong occurrence of frequent fractures following even mild trauma. Hearing loss is frequently reported in patients with OI. Objective: to examine the ratio of hearing loss in children with OI, and the relationship between audiological findings and CT images of temporal bone in children with OI. Subject and methods: forty – two children aged 5 to 17 years with OI were included in the study. The patients have type A of tympano and were measured threshold of hearing by play audiometry. CT imaging was performed in 8 cases as well. Imaging abnormalities were correlated with clinical phenotypes and severity of hearing loss deduced from audiograms. Results: Hearing loss of all etiologies was observed in 28.05 % of ears in studied OI patients. Sensorineural and mixed hearing loss was observed in 4.88% and conductive hearing loss was detected in 23.17% of ears. CT revealed bone - bridge image in the middle ear (10/16 ears), hypodense foci in the fissa ante fenestram (4/16 ears) and coellear (2/16 ears), abnormal stape ( 5/16 ears). Conclusion: hearing loss in children with osteogenesis imperfecta is quite frequent. We have all type of hearing loss, but the conductive of hearing loss have highest ratio. The site of abnormal on temporal bone CT images in OI corresponds to presence and type of hearing loss determined by audiometry.

OBESITY/METABOLIC SYNDROME

P69 Correlation between C-reactive protein levels and affecting factors for adiposity in apparently healthy Korean adolescents
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Aims: Recent studies have shown that C-reactive protein is not just an indicator of cardiovascular disease (CVD) incidence and mortality. Thus, early detection of a continuous increase in CRP concentrations may be useful in predicting subsequent development of CVD or metabolic syndrome.

The objective of this study was to analyze high sensitivity C-reactive protein (hs-CRP) in apparently healthy young Korean adolescents and determine confounding factors for high hs-CRP in this population.

Methods: We enrolled 197 middle school students (93 boys and 104 girls) who participated in a general health check-up at a tertiary hospital in Seoul. We measured height, weight, waist circumference and blood pressure and investigated hs-CRP concentrations, insulin levels, insulin resistance and lipid profiles. HS-CRP levels were measured using the Behring BN II nephelometer (Dade Boering, Marburg, Germany) and log-transformed for analysis.

Results: hs-CRP concentration was significantly higher in boys than in girls (P=0.012). Pearson’s correlation coefficients revealed a significant correlation between log-transformed hs-CRP and BMI (r=-0.24, P=0.0008), waist circumference (r=-0.24, P=0.0007), systolic (r=-0.17, P=0.019) and diastolic blood pressure (r=0.23, P=0.014), and ALT (r=0.16, P=0.023). In stepwise multivariate linear regression analysis, sex (male gender), waist circumference, and diastolic blood pressure were positively and fasting serum HDL-cholesterol level was negatively associated with log-transformed hs-CRP.

Conclusions: We found that there exists a gender difference in hs-CRP concentrations in apparently healthy adolescents and that log-transformed hs-CRP concentrations were positively associated with male, waist circumference and diastolic blood pressure and negatively associated with HDL-cholesterol level. The gender difference and the contributing factors for hs-CRP found in these healthy adolescents suggests a possibly relevant pathophysiological mechanism involved in the increase of cardiovascular risk associated with childhood obesity.

P70 Association of serum 25-hydroxyvitamin D concentration and metabolic syndrome in Korean children and adolescents
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Aims: Vitamin D is required not only for bone health but also has been reported to play a role in a range of ailments such as autoimmune disease, cardiovascular disease, type 2 diabetes, hypertension, depression, and certain types of cancer. Several studies have reported that poor vitamin D status during childhood and adolescence is related to obesity and metabolic syndrome. Vitamin D deficiency has been associated with hypertension and increased risk of cardiovascular disease while 25(OH)D concentration is known to be independently associated with both insulin sensitivity and beta cell function. A recent study reported that low serum 25(OH)D to be associated with obesity and metabolic syndrome in Korean children. We investigated the association between serum 25(OH)D
concentrations and the presence of metabolic syndrome components in Korean children and adolescents. We also compared the components of metabolic syndrome according to vitamin D status in Korean children and adolescents.

Methods: The study included 141 Korean children and adolescents who were aged 6 to 18 in Kangdong Sacred Heart Hospital. Anthropometric measurements, including height, weight, body mass index (BMI, kg/m²), waist circumference, and blood pressure were performed. Serum lipid, fasting plasma glucose (FPG), insulin, and 25(OH)D levels were measured. HOMA-IR (homeostasis model assessment for insulin resistance) = (glucose [mmol/L] x insulin)/22.5 was calculated. Metabolic syndrome defined by modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).

Results: Among total 141 subjects, 26 (18.4%) children and adolescents had metabolic syndrome. Children and adolescents who have metabolic syndrome have significantly lower serum 25(OH)D concentration than those who do not have (12.35 ± 4.65 vs. 14.81 ± 4.63 ng/mL; p=0.015). Waist circumference, SBP, fasting plasma glucose, insulin, HOMA-IR are significantly correlated with serum 25(OH)D concentration (p<0.05). Only LDL-cholesterol is significantly different according to tertile groups of serum 25(OH)D concentration. The odds ratio of group I (25(OH)D <11.50 ng/mL) is 1.826 compared to group III (25(OH)D >16.30 ng/mL).

Conclusion: Children and adolescents who have metabolic syndrome have lower serum 25(OH)D concentration. The prevalence of metabolic syndrome may be higher in children and adolescents with severe 25(OH)D deficiency. Further investigation will be needed to identify the influence of 25(OH)D on metabolic syndrome.

P71
The association between bone age advancement and insulin in prepubertal children with obesity
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Aims: Obesity is associated with bone age (BA) advancement of unclear etiology. In animal study, insulin may directly modulate skeletal growth. Our objective was to investigate the association with BA maturation and insulin levels in children with overweight and obesity.

Methods: In this cross-sectional study of 103 prepubertal children, anthropometric data and hormonal values during oral glucose tolerance test were measured. Subjects were divided into two groups by the difference between BA and chronological age (CA) (noted as BA-CA). Results: The study population included 49 (47.6%) males and 54 (52.4%) females with a mean age of 7.6 ± 1.6 years. The advanced bone age group defined as BA-CA>1 year (n=53) had significantly higher HOMA-IR, fasting insulin levels and lower quantitative insulin sensitivity check index (QUICKI). Also, BA-CA was significantly correlated with fasting insulin (r=0.315, P<0.001), HOMA-IR (r=0.288, P<0.001), and QUICKI (r=-0.353, P<0.001). In multiple regression analysis, fasting insulin was identified as significant independent predictors for BA-CA.

Conclusion: Skeletal age is more advanced in overweight and obese children with hyperinsulinemia and insulin resistance. These findings suggest that insulin may modulate skeletal growth.

P72
Autosomal dominant Kenny-Caffey syndrome with congenital hypoparathyroidism, short stature and normal intellect: a case report
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Kenny-Caffey syndrome (KCS) is characterized by proportionate short stature, cortical thickening and medullary stenosis of tubular bones, delayed closure of anterior fontanelle, eye abnormalities, and hypoparathyroidism. The autosomal dominant form (KCS Type 2) caused by mutations in FAM111A is distinguished from the autosomal recessive form (KCS Type 1), caused by mutations in TBCE gene, by the absence of mental retardation. Our proband presented on day 8 of life with hypocalcaemic seizures secondary to hypoparathyroidism. Normocalcaemia was achieved with IV calcium gluconate and maintained by oral calcium carbonate 100mg BD and calcitriol 0.1mcg BD for the first 2 years of life while serum PTH remained low at <0.3pmol/L. There has been no evidence of nephrocalcinosis on follow up. The dose of supplemental calcium and calcitriol is being gradually reduced. She also has persistent mild microcytic anaemia with normal iron stores. Her phenotype included small hands and feet, triangular hypoplastic nails, hypoplastic mid-face, macrocrania and large persistent fontanelles. Karotype and FISH for 22q11 deletion were normal. Initial investigations included a normal ECHO, renal ultrasound and MRI brain. Her neurodevelopment is normal but her growth is compromised. At 1 year, her length was 65.5cms (SDS -2.9) and at 3 years, her height was 80cms (SDS -3.8). There is no family history of short stature or hypoparathyroidism. She is growth hormone sufficient on pharmacological testing; however she has been commenced on growth hormone treatment based on her poor growth velocity and short stature. It is currently too early to determine response.

A skeletal survey performed at 2 years of age was suggestive of KCS. Genetic testing revealed a heterozygous mutation c.1622C>A (p.Ser541Tyr) in FAM111A. However, the unusual nails, the reducing calcium requirement and the unexplained microcytic anaemia are unique to our patient.

Written informed Consent for this patient has been taken including results of the genetic analyses and images according to the Institutional Ethics Committee procedures of our health service.

P73
Association of fat mass and obesity-associated gene rs9399609 variant with early onset obesity among batakense and Chinese children in Indonesia
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Background: Obesity is becoming a worldwide epidemic in modern society, it is prevalent in individuals of both genders and of all ages, socio-economic strata, and ethnic group. Several studies have reported an association between rs9399609 polymorphisms of the FTO gene and obesity. However, this association has not yet been studied among the Indonesian children.

Aims: This is the first study in Indonesia to investigate the association between fat mass and obesity-associated gene rs9399609 variant with early onset obesity among Batakense (n=94) and Chinese (n=60) children in Medan, North Sumatera, Indonesia.

Methods: We conducted a case control study in ten elementary schools in Medan, North Sumatera, Indonesia. Case group (n=105) were children with early onset obesity and control group (n=55) were normal weight children. The inclusion criteria were Batakense and Chinese children, aged 6-12 years with early onset obesity. We examined body weight and
height, body mass index, waist circumference. Genotyping was performed using a TaqMan assay for rs9939609 polymorphism.

Results: A total of 160 children between 6 and 12 years old were recruited in this study. The distribution of genotypes and alleles was significantly different among ethnicities (P<0.004), but no association was found for early onset obesity, related anthropometric measurements and gender. FTO rs9939609 allele was not associated with central obesity.

Conclusion: Our study showed there were no associations between fat mass and obesity-associated gene rs9939609 variant with early onset obesity. However, the prevalence of genotypes for FTO rs9939609 in our study were similar with other study in China and Malaysia.

P74
Study of serum visfatin and blood glucose and lipid metabolism, nafld in simple obese children
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Aims: To investigate the relationships between serum visfatin and blood glucose and lipid metabolism, nonalcoholic fatty liver disease (NAFLD) in simple obese children.

Methods: Eighty-six children (57 boys and 29 girls) including 40 obese children, 22 overweight children and 24 healthy children were recruited with ages ranged 7-15 years. The serum visfatin levels were determined by ELISA.

Results: (1) As compared with normal and overweight children, serum visfatin levels increased 49.80% (P<0.05) and 35.88% (P<0.05); (2) There were no differences of serum visfatin levels between the healthy and overweight children. (2) The body mass index, TC, TG, LDL-c, FPG, FINS and insulin resistance index of the obese children were higher than the healthy children (P<0.05 or P<0.01); the HDL-c and insulin sensitivity index of the obese children were lower than the healthy group (P=0.01 or P<0.05). The body mass index, the fasting insulin and the insulin resistance index of the obese children were higher than the overweight children (P<0.01). The ALT and AST levels of the obese children were higher than the healthy group (P<0.05). There was significant difference between the obese children and healthy children on the no-alcoholic fatty liver disease (P<0.01) with the prevalence of 23.3% and 5.26%, respectively. (3) Correlation analysis: Body mass index, TG and ALT were positively correlated serum visfatin (r=0.218, P<0.05; r=0.500, P<0.01; r=0.426, P<0.01, respectively).

Conclusions: The serum visfatin level is correlated with obesity and it is related with the disorder of lipid metabolism and the occurrence of fatty liver in obese children. Serum visfatin levels can be used as a new indicator to evaluate the trend of childhood obesity and evaluate the risk of fatty liver, diabetes and cardiovascular of the obese children in the future.

P75
Genetic testing in Indian patients with Prader-Willi syndrome using methylation specific multiplex ligation dependent probe amplification (MS-MLPA)

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Aims: Obesity is a risk factor for vitamin D deficiency (VDD), because the lipid soluble vitamin D can be sequestered in adipose tissue. Although it was suggested that higher dose of vitamin D might be required to treat VDD in obese individuals, little is known about treatment responses in overweight children. We investigated the response to vitamin D replacement in normal weight and overweight children.

Methods: This is a prospective study including 66 Korean children between 8 and 15 years of age diagnosed with VDD between Dec 2013 and Feb 2014. VDD was defined as serum 25OHD < 20 ng/mL, and vitamin D sufficiency as ≥30 ng/mL. Overweight was defined as body mass index (BMI) >85th percentile (n = 25), and normal weight as BMI between 5th and 85th percentile (n = 41). All participants received vitamin D supplementation (2000 IU/d) for 8 weeks. The level of serum 25OHD, PTH, and biochemical parameters were measured before and after treatment.

Results: The mean age was 9.9 ± 1.4 years in normal weight children and 10.0 ± 2.1 years in overweight children (n=ns). Baseline serum 25OHD level was lower in normal weight children (13.2 ± 3.2 ng/mL) than in overweight children (14.2 ± 2.1 ng/mL, P=0.011). Baseline PTH level was 32.3 ± 9.5 and 39.5 ± 18.0 pg/mL in normal weight and overweight children, respectively (P=0.027). After 8 weeks of treatment, 28 (68.3%) normal weight children and 10 (40%) overweight children achieved vitamin D sufficiency (P=0.023). The mean serum 25OHD level was 33.7 and 28.6 ng/mL in normal weight and overweight children, respectively (P=0.04). The increase of serum 25OHD levels without supplementation was significantly higher in normal weight children than in overweight children (20.6 ± 7.2 vs. 14.4 ± 7.9 ng/mL, P=0.002). However, the decrease in PTH levels seemed to be slightly larger in overweight children compared to normal weight children (3.2 ± 2.08 vs. -1.1 ± 1.11 ng/mL, P=0.05). In multiple regression analysis, overweight was significantly related to the 25OHD increase after vitamin D replacement (β=0.523, P=0.01).
Conclusion: The response to vitamin D replacement can be influenced by adiposity, and overweight children require larger doses of vitamin D to achieve vitamin D sufficiency.

P77

Familial lipoprotein lipase deficiency – neonatal presentation
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A baby girl, born by normal spontaneous vaginal delivery with birth weight 3.845kg, was admitted for neonatal jaundice on day 2 of life. Her mother had maternal gestational diabetes on diet control. Her father was newly diagnosed with hyperlipidaemia on health screen and was put on diet control. There was no consanguinity. Her serum bilirubin level on admission was 186mmol/L with normal liver function test. However, the serum was noted to be very lipaemic when checking with bedside bilirubin machine and it persisted for few blood samples. The baby girl was on exclusive breastfeeding. In view of lipaemic serum, random lipid profile was checked and showed hypertriglyceridaemia (TG) 10.6mmol/L (<1.7mmol/L) and cholesterol (TC) 3.1mmol/L (<5.2mmol/L). Repeated fasting sample showed persistent elevated triglyceride level 8.5mmol/L. Other blood parameters including amylase and liver enzymes were unremarkable. Physical examination showed no dysmorphic features. There was no hepatosplenomegaly or xanthoma. Ophthalmologically examination did not show any lipaemia retinialis.

In view of elevated serum triglyceride, further workup included lipoprotein electrophoresis and genetic analysis for lipoprotein lipase (LPL) gene were performed. Dietitian was consulted and the baby girl was given a therapeutic trial with commercially available special milk formula, Monogen (85% medium-chain triglyceride oil). The pretreatment lipid profile were TG 8.5mmol/L, TC 4.8mmol/L and HDL 0.6mmol/L (<1.3mmol/L) while TG 6.0mmol/L, TC 3.9mmol/L and HDL 0.6mmol/L after 2 weeks of special milk. She otherwise tolerated the special formula well. Parents’ fasting lipid profiles were also checked. Mother showed hypertriglyceridaemia 3.0mmol/L, and father had elevated TG 3.57mmol/L, TC 7.14mmol/L and LDL 4.65mmol/L (<2.6mmol/L). Lipid electrophoresis of baby girl detected a chylomicron band and a dense VLDL band, which was occasionally found in lipoprotein lipase (LPL) deficiency. Genetic analysis of LPL exon 6 by direct sequencing showed a heterozygous LPL NM_000237.2:c.836T>G mutation. The patient was confirmed to be compound heterozygous LPL NM_000237.2:c.835C>G mutation while mother carried heterozygous LPL NM_000237.2:c.836T>G mutation. The patient was confirmed to be compound heterozygous lipoprotein lipase deficiency.

On monthly follow-up evaluations 10 months after hospital admission, the patient remained asymptomatic, maintained adequate growth, and had triglyceride levels gradually on downward trend 4.7mmol/L.

Conclusion: This was a case of neonatal presentation of familial lipoprotein lipase deficiency, presenting with serum lipaemia. Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

P78

Insulin resistance and adverse lipid profile in obese pre-pubertal South Indian children
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High prevalence of obesity, type 2 diabetes mellitus (T2DM) and the metabolic syndrome (MS) are evident among children and adults in India. [1,2] Strong evidence exists for the higher risk for insulin resistance (IR) syndrome in South Asians compared to other ethnicities, thereby demonstrating the higher risk for MS in this population. [3] MS is a risk factor for cardiovascular disease (CVD) and T2DM. [4,5] Adverse metabolic features such as dyslipidaemia are seen even in childhood and persist into adulthood with important long term implications. [6,7] Lipid profile data from pre-pubertal obese children from India is sparse and hence this has been addressed for the first time in this study, along with the relationship between lipid profile and IR in south Indian children. Heights and weights of healthy pre-pubertal children aged 4-10 years of age were measured and body mass index (BMI) was calculated. Subjects were classified as overweight (BMI ≥85% to <95%) and obese (BMI ≥ 95%) for age and sex. Complete lipid profile as well as plasma glucose and insulin were measured in fasting venous blood samples, LDL/HDL (low & high density lipoprotein cholesterol), TC (total cholesterol)/HDL and IR by HOMA-IR (Homeostatic model assessment) were analysed. Tests used for analysing differences between groups included: unpaired t-test for quantitative variables; comparison between groups by the non-parametric Mann-Whitney test; ANOVA for quantitative variables; Pearson coefficient of correlation for relationship between the variables and the chi square test for differences in categorical variables between groups. "P" value of <0.05 using a two-tailed test was considered significant. Data were analysed with the statistical software SPSS version 16.0.

Among the 100 participants, 98 were obese and two were overweight (M: F 51:49). Insulin resistance was observed to be higher with increased weight and BMI. A significant positive correlation was present between HOMA-IR and BMI (r = 0.291), triglycerides (r = 0.214) & TC/HDL (r = 0.225). A negative trend in correlation was found with HDL (r = -0.023). Obese south Indian children were found to have IR and dyslipidaemia during their pre-pubertal years. Long term studies on this population and intervention measures are necessary to analyse and reduce the risk for the MS and CVD in later years.

References

OTHER/MISCELLANEOUS

P79

A case series of intracranial hypertension in patients with Turner syndrome, with and without growth hormone therapy
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Intracranial Hypertension (IH) is a known side effect of GH therapy [1], but has many other aetologies. Turner syndrome patients have growth failure related to loss of the SHOX transcription factor and so respond to high dose GH therapy. Turner patients also have a high incidence of middle ear disease that can cause intracranial hypertension via mastoiditis and
venous sinus thrombosis. IH has been reported in Turner syndrome with no predisposing cause. 

Aim: To describe a case series of 4 patients with Turner syndrome who developed IH. 

Methods: Turner syndrome patients were identified prospectively from the Paediatric Endocrine Database (PED) in a University teaching hospital. All patients had routine ophthalmological and ENT assessments prior to GH therapy. Ocular Coherence Tomography (OCT) scanning was done if papilloedema found. MRI and MRV scans were performed. 

Results: 26 active patients with Turner Syndrome, age range 2 to 20 years, were identified and four noted to have co-existent IH. Case 1, age 15 years was referred by a neurologist with pre-existing IH and had never received GH therapy. No cause was found. Case 2, age 14 years was asymptomatic and papilloedema found on fundoscopy as part of pre-GH ophthalmology assessment. The patient had severe middle ear disease and had a mastoidectomy. CSF pressure > 35 mmHg. MRV showed abnormal venous drainage and GH therapy was not started. Both patients were treated with Diamox. Case 3, age 14 yrs and Case 4, age 10 yrs, commenced GH at 9.2 mg/m²/day (having had normal fundi) and developed headaches and papilloedema, which resolved when GH treatment was ceased. Case 3; CSF pressure 20 mmHg and MRV abnormal sagittal sinus flow. In both patients, GH was successfully restarted at low dose with slow upward titration. 

Conclusions: Intracranial hypertension may be seen in Turner syndrome independently from GH therapy. An ophthalmological consultation prior to starting GH therapy is important as some patients have asymptomatic papilloedema. Having significant middle ear disease may add to the risk. 

Reference 


P80 

Endocrine complications in survivors of childhood medulloblastoma 

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Introduction: Medulloblastoma is the most common malignancy of the central nervous system in childhood. With the current combined treatment with surgery, chemotherapy and radiotherapy, the survival rates had improved dramatically in recent years. However, these survivors are prone to develop various late sequelae secondary to treatment. 

Objectives: The aim of this study is to assess the rate and the nature of endocrine complications among medulloblastoma survivors in a single center. 

Patients and methods: A retrospective chart review of patients with medulloblastoma managed in the department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Hong Kong, between January 1994 to June 2012 was performed. Patients who had follow-up of less than 2 years were excluded from the study. 

Results: Thirty-four patients were included in the study. The median age at diagnosis was 7.5 years (range = 0.8 - 17.2 years) and the median follow-up time was 10.45 years (range = 2 – 18.3 years). Hypothyroidism was diagnosed in 16 patients (Primary hypothyroidism = 5 patients; compensated hypothyroidism = 10 patients; central hypothyroidism = 1 patients) and it was the commonest endocrine complication among this group of patients. The median time to develop hypothyroidism was 50 months (range = 15-155 months) from diagnosis. Male sex was the only risk factor that was found to be associated with the development of hypothyroidism (OR = 3.14; p = 0.031). Eight patients developed growth hormone deficiency and eight patients developed gonadal dysfunction. 

Age at diagnosis and dose and fractions of radiotherapy, chemotherapy regimen and duration of follow-up were all not associated with the development of these complications. 

Conclusions: Hypothyroidism is a common late complication among medulloblastoma survivors. Patients could present with minimal symptoms but it could be easily screened and treated. Therefore, thyroid function test should be regularly monitored among this group of patients. 

P81 

Siroliimus therapy following subtotal pancreatectomy in neonatal hyperinsulinism: a case report 

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Hyperinsulinemic hypoglycaemia (HH) occurs due to an unregulated insulin production from the pancreatic β-cells in the presence of low blood glucose. Mutations in ABCC8 and KCNJ11 are associated with severe HH that is unresponsive to conventional medical treatment. The only treatment for patients with medically unresponsive diffuse HH is a subtotal pancreatectomy. However, following surgery, hypoglycaemia may persist and some patients develop diabetes and malabsorption. Overexpression of the mTOR pathway is contributory to HH. Sirolimus, an mTOR inhibitor, is currently used in the treatment of congenital hemangiomatos and in post renal transplant. Senniappan et al [1] recently reported efficacy of sirolimus in four surgically naïve patients with diffuse HH unresponsive to diazoxide and octreotide. We present a patient who was treated with sirolimus due to persistent hypoglycaemia following subtotal pancreatectomy. 

A term neonate with a birth weight of 4.67kg had persistent hypoglycaemia since birth secondary to hyperinsulinism and was unresponsive to treatment with maximal doses of diazoxide and octreotide with a glucose infusion requirement (GIR) of 38mg/kg/min. Genetic testing revealed a homozygous ABC8 nonsense mutation, p. Gln1020Ter. A subtotal pancreatectomy was performed on day 40. Post-surgery, he had a GIR of 20mg/kg/min and was recommenced on daily subcutaneous (SC) octreotide, with monthly long acting (LA) octreotide. At 3 months, he was commenced on oral sirolimus. The dose was adjusted to maintain serum trough levels between 5 and 15ng/ml. Parenteral fluids and SC octreotide were weaned over a month. He was discharged home at 4.5 months on sirolimus (2.5mg/m²/day) and LA octreotide. He was monitored with capillary blood glucose testing twice a day with the aim to maintain levels above 3.5mmol/L. Further surgery has been deferred. His growth and development are appropriate at 6 months of age with no side effects from sirolimus. 

The clinical response in our patient supports sirolimus as a new therapeutic strategy in patients with HH which may facilitate deferment of surgery. Written informed Consent for this patient has been taken including results of the genetic analyses and histopathological images according to the Institutional Ethics Committee procedures of our health service. 

Reference 


P82 

A study of arterial stiffness in turner syndrome patients using cardio-ankle vascular index 

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A large proportion of the increased mortality in Turner syndrome (TS) is related to cardiovascular complications. Increased arterial stiffness may be an important predictor related to cardiovascular complications in TS patients. A novel method of evaluating arterial stiffness, which is
relatively independent of changes in blood pressure (BP), is the cardio-ankle vascular index (CAVI). The aim of this study was to compare arterial stiffness using CAVI between TS patients and healthy controls and to evaluate for possible factors affecting arterial stiffness within the patient group. Known TS patients (n=24) with confirmed karyotypes were recruited from the outpatient clinic of Seoul National University Children’s Hospital between August, 2010 and June, 2013. Patients with type 2 diabetes and/or hypertension requiring medication were excluded. There were 5 patients with one or more combined congenital heart anomalies (aortic coarctation (n=2), bicuspid aortic valve (n=2)), aortic stenosis (n=3). Anthropometric data, fasting blood lab and measurements of CAVI and pulse wave velocity were collected. A healthy control group (n=23) matched for age and body mass index (BMI) were recruited for comparison. The mean age and BMI of the TS patients were 27.0 years and 22.8 kg/m² respectively while that of the control were 28.2 years and 22.04 kg/m². CAVI was significantly higher in the TS patients compared to controls (6.05 vs. 6.65, P < 0.001), while there was no significant difference in pulse wave velocity. Univariate analysis for factors affecting CAVI within the TS patient group showed that CAVI was associated with waist circumference (P = 0.04) and systolic BP (P = 0.045). There were no significant factors related to CAVI using multivariate regression analysis including age, systolic BP, waist circumference, HOMA-IR and presence of cardiac anomalies. TS patients showed an increased arterial stiffness compared to age- and BMI-matched controls using CAVI measurement. Further prospective studies in larger TS patient group are mandatory in order to find significant factors related to increased arterial stiffness.

**P83**

The role of community development in improving awareness, diagnosis and management of childhood non-communicable diseases (NCDs) in Indonesia

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**Background:** NCDs are now recognised as a major public health problem globally. In Indonesia, WHO estimates that 63% of all deaths are caused by NCDs. Lack of community awareness and health systems ill-equipped to deal with NCDs contribute to misdiagnosis, underdiagnosis, and increased preventable morbidity and mortality, particularly for children and adolescents.

**Objective:** To raise awareness and improve the diagnosis and management of childhood NCDs in Indonesia.

**Method:** Established NCD Family Communities: IKADAR (Type-1 Diabetes) in 2003, YTI (Turner’s Syndrome) in 2003, KAHAKI (Congenital Adrenal Hyperplasia) in 2008 and FOSTEO (Osteogenisis Imperflecta/OI) in 2013. Community development approach, with focus on education, research (collation of data from IIPS registries at Cipto Mangunkusumo Hospital), advocacy and health systems strengthening.

**Results:** Establishment of clubs and registers increased known prevalence across Indonesia: a 4.5 fold increase in CAH, from 65 patients (2008) to 293 (2014); 2 fold increase in OI, from 35 patients (2013) to 70 (2014); 5 fold increase in Diabetes, from 156 patients (2009) to 960 (2014). Access to medicines improved: donations of hydrocortisone (oral and injectable) to medicines improved: donations of hydrocortisone (oral and injectable) 

**Written informed consent was obtained from the patients for publication of this abstract. A copy of the written consent is available for review by the Editor of this journal.**

**P84**

Pseudohyopoparathyroidism: phenotypic spectrum in kindred

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Pseudohyopoparathyroidism (PHP) encompasses a heterogeneous group of disorders due to an inactivating mutation in the GNAS gene which encodes the α subunit of Gs proteins (Gsα). Gsα plays a crucial role in intracellular signal transduction of peptides, hormones and neurotransmitter receptors in multiple tissues. Key features of PHP include Albright Hereditary Osteodystrophy (AHO) and biochemical evidence of multiple hormone resistances. There are several conflicting mechanisms for its heterogeneity; a possible explanation is a tissue-specific differential imprinting of Gsα protein. PHP type 1a has AHO with multiple hormone resistance and is inherited as maternal imprinting defect. PHP type 1b presents with hormone resistance but no AHO features and is probably due to epigenetic methylation defects. Pseudohypoparathyroidism is another subtype with AHO but absence of hormone resistance and is inherited as paternal inactivating mutation. We describe a family with female members having PHP with variable clinical and biochemical features. Two female siblings from non-consanguineous parents, patient A (15 year) & patient B (13 year) presented at birth with raised TSH levels and were diagnosed to have congenital hypothyroidism and treated with thyroxine replacement. Patient A was noted to have infantile obesity with short stature and evolving phenotypic features consistent with AHO. Further history revealed that her sister patient B has similar phenotypic appearance and was confirmed on clinical exam. Biochemical evaluation for Patient A showed a borderline low calcium and normal phosphate level with elevated PTH while Patient B had normal calcium and phosphate levels with high PTH. Both patients entered puberty at 11 years and patient A progressed to breast Tanner 4 but has no menarche at 15 years despite pubertal gonadotropin levels (Table 1), advanced bone age (18 years) & mature uterus. Patient B is currently 12.5 years old and has progressed to Tanner 3 breasts with no menarche. Mother exhibits features of AHO without hormone resistance. The father and younger brother do not have any features of AHO. The two patients with PHP described above had an interesting presentation as congenital hypothyroidism with features of AHO evolving later in life. They exhibit clinical evidence of maternal transmission with end-organ resistance. This family illustrates heterogeneity of presentation of GNAS mutation.

**A multicenter study of endocrine abnormalities in septo-optic dysplasia (SOD) in Asean countries**

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1ASEAN Study group, Thailand; 2ASEAN Study group, Indonesia; 3ASEAN Study group, Philippines; 4ASEAN Study group, Malaysia; 5ASEAN Study group, Vietnam


**Background:** Septo-optic dysplasia (SOD) is a heterogeneous malformation condition consisting of optic nerve hypoplasia, various types of forebrain defects and hormonal deficiencies. This study aims to expand knowledge about endocrine abnormalities in patients with SOD in Asean countries.

**Material and method:** Forty-eight patients (27 male, 21 female) who has been diagnosed as having SOD in ASEAN countries were clinically reviewed from medical records.

**Results:** Clinical manifestations and endocrine abnormalities of the patients are shown in Table 1.
Conclusion: This multicenter and multinational study shows that about 20-35% of SOD patients have endocrine abnormalities. Hypothyroidism and GH insufficiency are the most common endocrine problems associated with this condition.

P86
Diazoxide-unresponsive congenital hyperinsulinism associated with ABCC8 nonsense mutation
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International Journal of Pediatric Endocrinology 2015, Volume 2015 Suppl 1

Background: Congenital hyperinsulinism is a dysregulated insulin secretion that results in persistent hypoglycemia. It is a heterogenous condition but common to all is the inappropriately high insulin during hypoglycemia with absence ketone bodies and reduced free fatty acids.

Table 1(abstract P84)

<table>
<thead>
<tr>
<th>AHO Features</th>
<th>Patient A</th>
<th>Patient B</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachydactyly</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Short stature</td>
<td>(136cm, -4.05 SDS)</td>
<td>(134cm, -2.84 SDS)</td>
<td>(145cm, -2.79 SDS)</td>
</tr>
<tr>
<td>Obesity</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Round face</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Ectopic ossification</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cognitive dysfunction with need for special school</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Table 1(abstract P85) Clinical manifestation of SOD patients

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Clinical manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation (months) mean ± SD</td>
<td>MRI findings</td>
</tr>
<tr>
<td>33 ± 39 months (range 20 - 178)</td>
<td>Absence of septum pellucidum (%) 62</td>
</tr>
<tr>
<td>Ht SDS, mean ± SD</td>
<td>Pituitary hypoplasia (%) 33</td>
</tr>
<tr>
<td>0.97 ± 1.97</td>
<td>Abnormal of corpus callosum (%) 16</td>
</tr>
<tr>
<td>Wt SDS, mean ± SD</td>
<td>Cortical dysplasia (%) 8</td>
</tr>
<tr>
<td>0.02 ± 2.35</td>
<td>Endocrine abnormalities</td>
</tr>
<tr>
<td>Eye presentation</td>
<td>Hypothyroid (%) 35</td>
</tr>
<tr>
<td>Nystagmus (%) 54</td>
<td>GH insufficiency (%) 29</td>
</tr>
<tr>
<td>Squint (%) 3</td>
<td>Delayed/arrested puberty/suspected HG (%) 23</td>
</tr>
<tr>
<td>Poor vision (%) 35</td>
<td>Cortical insufficiency (%) 17</td>
</tr>
<tr>
<td>Delayed development (%) 16.2</td>
<td>Diabetes insipidus (%) 19</td>
</tr>
<tr>
<td>Seizure (%) 7.9</td>
<td>Hypoglycemia (%) 8.1</td>
</tr>
<tr>
<td>Neonatal jaundice (%) 2.7</td>
<td>Bilateral ON hypoplasia 84</td>
</tr>
<tr>
<td>Undescended testes (%) (boys) 5.4</td>
<td>Microcornea 3</td>
</tr>
<tr>
<td>Micropenis (%) (boys) 21</td>
<td></td>
</tr>
</tbody>
</table>

HG = Hypogonadism, ON = Optic nerve

Case presentation: A baby boy with birth weight of 2.4kg at 35 weeks was born via Caesarian section. The boy was allowed feeding on demand, however he had the first episode of hypoglycemia at 2 hours of life. His blood sugar ranged from low reading to 2.5 mmol/L. The patient was treated with boluses of intravenous dextrose D10% followed by maintenance dextrose with its increasing strength in order to treat the refractory hypoglycemia. In addition to that intravenous hydrocortisone and glucagon infusion were started. The patient’s blood sugar could only be maintained > 3.0mmol/L after a glucose load of 30mg/kg/min and a glucagon infusion of 50mcg/kg/hour. During hypoglycemia, the insulin level was 19.6 pmol/L (17.8-173.0) and blood ketone was negative. Oral diazoxide was started at 5.0mg/kg/day in divided doses combined with chlorothiazide 7.0 mg/kg/day. Diazoxide was titrated up to 20.0mg/kg/day as he had a poor response even after 1 week of the treatment. Apart from that oral nifidipine 2.5 mg/kg/day in divided doses was also started after a few days with the combination therapy. Only after starting
octreotide infusion a good rise of blood sugar was seen within 1 hour and the glucose load could be brought down and the other drugs were off. The boy was discharged with subcutaneous octreotide infusion at 2mcg/hour via portable insulin pump.

Results: The boy is heterozygous for an ABCC8 nonsense mutation, p. R934*. A second ABCC8 mutation has not been found and sequencing of the KCNJ11 gene failed to detect a change from the normal sequence. He has inherited the mutation from his father; a focal lesion is therefore identified and surgically resected, microsatellite analysis of the DNA can be undertaken to confirm loss of heterozygosity.

Conclusion: KATP mutation is the commonest cause for diazoxide resistant congenital hyperinsulinism. Continuous subcutaneous octreotide infusion is a feasible alternative to pancreatic surgery.

Written informed consent was obtained from the patient’s parent or guardian for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

P87
A custom next generation sequencing panel to identify the cause of monogenic disorders of insulin secretion, disorders of sexual development and noonan syndrome
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Next generation sequencing (NGS), using massive parallel sequencing, is increasingly being used in the clinical setting. It is a high throughput technique that offers a fast and cost-effective testing solution for genetic disorders with a number of candidate genes. In this study we have employed NGS to sequence 48 samples that had been referred to the Molecular Genetics Department for the investigation of Monogenic Disorders of Insulin Secretion (MDOIS), Disorders of Sexual Development (DSD) and Noonan Syndrome (NS). All samples had previously been genotyped using Sanger sequencing.

Next Generation Sequencing was performed on an Illumina MiSeq using an Illumina Nextera Rapid Capture Custom Enrichment Kit. This custom assay contained capture probes for the coding regions (including +5 bases of intronic sequence) for 66 genes: 34 for DSD; 19 for MDOIS; and 13 for NS. Sequence data generated by the MiSeq was aligned to hg19 and variants detected using CLC Genomics Workbench. Genetic variants were annotated using Cartagenia BENCHlab NGS.

Thirty mutations associated with DSD (SRD5A2, HSD17B3, NR5A1, AR), MDOIS (ABCC8, GCK, GLUD1, INS, HNF1A, HNF4A, HNF1B) and NS (PTPN11, RAF1) were detected. This was concordant with genotypes detected by Sanger sequencing.

Next generation sequencing has proven to be an accurate and efficient method of generating monogenic disorders with multiple candidate genes, and is an ideal technique for the clinical laboratory.

P88
Severe neonatal hyperparathyroidism: a case report
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Aims: To report case presenting with neonatal severe hyperparathyroidism. Methods: A severe neonatal hyperparathyroidism was reviewed including demographic and clinical data.

Results: A 6 day-old girl was referred from province hospital due to lethargy, poor feeding and irritability. On examination, there were no dysmorphic features and apart from mild tachypnea, systemic examinations were normal. Her chest X-ray was also normal. Calcium and parathyroid hormone (PTH) levels at presentation were 17.3 mg/dL and 1,776 pg/mL, respectively. Firstly, she was managed with ceftotaxime for treatment of sepsis. She received intravenous hydration, diuresis, hydrocortisone but calcium and PTH levels were persistent high. Furthermore, pamidronate was introduced and calcium level was decreased to normal range. Unfortunately, 7-10 days after stop pamidronate, calcium and PTH levels were gradually increased. A sestamibi nuclear scan was performed and showed hyperfunction parathyroid nodule at upper portion of both thyroid lobes. At age of 60 days, this girl went to have operation with a total parathyroidectomy and autotransplantation, using one half of gland placed into the right groin. Serum calcium and PTH were return to normal after operation.

Conclusions: Neonatal severe hyperparathyroidism is managed effectively with total parathyroidectomy and autotransplantation. Written informed consent was obtained from the patient’s parent or guardian for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

P89
Treatment of central precocious puberty using low dose GnRH analogs (GnRHa)
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Aims: 1. To study the efficacy of lower dose GnRHa in pubertal suppression and bone age advancement. 2. To study if low dose of GnRHa avoided the need for concomitant use of GH therapy while causing adequate pubertal suppression.

Methods: Clinical Records of 17 children (16 girls and 1 boy) were retrospectively analyzed over a period of 24 months (Mar 2012 to Mar 2014). All children satisfied the criteria for precocity based on clinical features, radiological assessment and GnRHa stimulation test. All 16 girls had idiopathic precocious puberty and the only boy had hypothyroidism.

The mean age of presentation was 6.9 years.

All children received GnRHa as monthly injection in an average dose of 190 µg/m²/month and were regularly followed for evaluation of pubertal suppression, height gain and Bone age advancement.

Results: Over a 24 month study period, children showed good pubertal suppression with a comparatively low dose of GnRHa (190 µg/m²/month). Mean LH post stimulation while on therapy was 2.31 mIU/ml suggesting adequate suppression, average annual growth velocity was 5.1 cm. Advancement in bone age was 1.4 years over a period of 2 years. Conclusion: 1. Children with CPP could be managed with a lower dose of GnRHa to achieve adequate pubertal suppression (190 µg/m²/month) as opposed to the standard recommended dose of 300 - 750 µg/m²/month).
2. While adequately suppressing puberty and controlling bone age advancement, lower dose of GnRHa seems to allow normal height gain thus negating the need for concomitant GH therapy in an economically challenging situation.

P90
Outcome of girls with central precocious puberty (CPP)
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Due to non-affordability of GnRH analogues (GnRHa), Medroxyprogesterone Acetate (MPA) is still used as a treatment option in girls with CPP in India. The aim here is to study the clinical features of girls with CPP in respect to the age at presentation, etiology and outcome as per the medication used for their treatment (GnRHa vs MPA).

Retrospective study of 38 girls with CPP (19 idiopathic) treated with either MPA or GnRHa (Lupreolein or Triptorelin) were followed up for period
varying from 1 to 8 years. The progression of growth parameters in relation to their age, etiology and medication used for the treatment was studied. Statistical analysis was done using one way ANOVA, unpaired t-test and Pearson correlation tests.

Mean age at onset of puberty in girls with idiopathic (ICP(n=19), neurogenic NCP(n=12) and hypothalamic hamartoma(HH)(n=7) were 4.68 ±2.83, 5.32±2.20 and 1.76±1.44 years, respectively(P=0.003). Mean height sds at presentation of all girls was higher (0.51±1.80) with comparison to MPH sds (0.90±1.19)(P=0.0201). 70% of the girls presented with SMR stage 3. Bone age was more advanced as compared to height age in all (P=0.001)(0.001) and this trend continued till last follow up. At presentation, girls with ICP were significantly heavier and taller as compared to NCPP and HH (P=0.002 for weight SDS and 0.022 for height SDS). Mean baseline LH, FSH and estradiol were 3.05±2.49 mIU/ml, 4.75±2.29 mIU/ml and 29.43 pg/ml respectively. At presentation, bone age was more advanced in HH(8A/CA P=0.001 with BA/HA P=0.03) and LH levels significantly higher(5.6 ±2.26; P=0.02). At last follow up, there was no significant difference in weight sds(p=0.285), height sds(p=0.074) and PAH sds(p=0.056) in girls of different age groups and etiologies. After 4 years of follow up, height sds was better with GnRHa(1.80±0.98) as compared to MPA(0=0.01) but height sds with MPA was also good(0.49±0.81).

Due to prevalence of CNS infections, the proportion of NCPP(31.57%) is higher in our set up, as compared to industrialized countries. With financial constraints, MPA can be considered as a treatment option for CPP.

**P91**

Test on kisspeptin levels in girls with idiopathic central precocious puberty and its significance

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Aims: This paper is aimed to explore the significance of plasma kisspeptin level in diagnosis and therapeutic evaluation through the detection of kisspeptin level of girls diagnosed with idiopathic central precocious puberty (ICPP) before treatment and after 6-months of treatment and girls with simple premature thelarche (PT).

Methods: A total of 70 girls including 24 girls diagnosed with ICPP, 21 girls with PT and 25 normal girls were enrolled. ELISA was adopted to detect plasma kisspeptin level.

Results: The kisspeptin level of ICPP group before treatment (1.80 ±0.13ng/ml) was higher than those of other groups with significantly statistic difference. The kisspeptin level of ICPP group after 6-months of treatment (1.49±0.21ng/ml) was significantly lower than those before treatment (P<0.05).

Conclusions: We can conclude that plasma kisspeptin level is related with initiation of pubertal development, and it can be served as important parameter in ICPP diagnosis and therapeutic effect evaluation.

**P92**

Effect of triptorelin 3.75 mg subcutaneously injection every 6 weeks on adult height in girls with idiopathic central precocious puberty

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Aims: To evaluate the long-term efficacy of triptorelin 3.75 mg subcutaneously injection every 6 weeks on final height in girls with idiopathic central precocious puberty.

Methods: Forty females with ICPP received triptorelin 3.75 mg every 6 weeks subcutaneously injection in our hospital from 2002 to December 2010 and reached final height were collected. These patients were divided into two groups according to whether there was presence of growth deceleration and rhGH used concomitantly during the treatment. Group A: triptorelin alone, n=17; group B: triptorelin + rhGH, n=23. During the treatment, height, weight, annual GV, sexual development, PAH and adverse effects were observed. BA and height SDS were monitored yearly. After discontinuation of treatment, follow-up was continued for 4–9 years till final height was attained, and age of menarche, time of menarche from discontinuation were recorded.

Results: FAs were 159.8±4.95 cm and 161.0±4.89 cm respectively in the two groups, the excess the genetic target height (THT), about the 50th percentile of normal female height. FAH increased by 1.5±4.30 cm, 4.86 ±4.49 cm from THT respectively. The values of (FAH-THT) showed significant difference between the two groups (P<0.05). FAH was less than the predicted adult height (PAH) before and after treatment in group A, and greater than that of group B. The value of (FAH-PAH post-treatment) showed significant difference between the two groups (P<0.05). FAH was positively correlated with HT SDS-BH at the end of treatment, THT, course of rhGH treatment and age of menarche (r2=0.66). BMI increased after treatment compared with that before treatment in both groups, however, compared with healthy children at the same age, there was no significant tendency of increase. Ages of menarche were 11.7±0.66 years and 12.18 ±0.69 years respectively. Times of menarche from discontinuation were 17.4±6.96 months and 14.7±4.77 months respectively.

Conclusion: The final adult height in patients with ICPP was improved effectively by triptorelin 3.75 mg subcutaneously injection every 6 weeks, and more height gain will be achieved when rhGH was used concomitantly to refrain from growth deceleration during the treatment. BMI maintained steadily and ovarian function restored quickly after discontinuation of the treatment with the age of menarche similar to that of normal children. Neither significant adverse effect nor polycystic ovary syndrome was observed.

**P93**

Mixed embryonal carcinoma – teratoma cause early puberty: a case report

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Results: A 3 year 7 month old boy presented with enlargement of penis, acnes, pubic hair, deep voice. He admitted with his height of +2.3SDS, penis length of 6cm, testes volum 4ml, pubic hair P2 (tanner). Abdomen ultrasound and CT scan showed adrenal tumor. Serum laboratory showed: 17 OHP 3.8 ng/ml, testosterone 32.3 nmol/l, cortisol 8h 433.9 nmol/l, cortisol 22h 39.2 nmol/l, glucose 3,7 mmol/l, FP 3945,9 u/l, electrolyte normal; urine VMA 15.5 µmol/24h; bone age 5 years. Surgical showed the tumor did not originate from the adrenal. Histological showed mixed embryonal carcinoma – teratoma. After surgeon, the signs of virilization reduce, serum testosterone become normal.

Conclusion: Mixed embryonal carcinoma – teratoma can be caused testosterone excretion and early puberty.

Written informed consent was obtained from the patient’s parent or guardian for publication of this case report (and any accompanying images). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**P94**

Risk factors for idiopathic central precocious puberty of girls in Fujian province

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Objective: This study aimed to investigate the potential risk factors of idiopathic central precocious puberty (ICPP) girls in Fujian province.

Methods: A case-control study was conducted in 566 girls who were diagnosed with ICPP at endocrinology department and 547 healthy girls for routine physical examination in Fuzhou Children’s Hospital of Fujian from October 2011 to October 2013. Parents were asked to fulfill the questionnaires on children’s diets, behaviors, parents and family conditions, and Logistic regression analysis was conducted for risk factors.

Results: Chi-square test showed that 23 variables had significant statistically difference. Logistic regression analysis indicated that some variables were entered the final model: mother’s age at menarche were older than 13 years, BMI, parental income, and heavy study burden. The mean age at the start of treatment was 8.11 ± 0.70 years in group 1, 8.28 ± 0.75 years in group 2, and 8.95 ± 0.72 years in group 3. Intaking organic fruit and doing more exercise for a long time were associated with lower FH at 18 years of age.

Conclusion: There were many factors related to ICPP girls in Fujian province, such as mother’s age at menarche, diet and behaviors, BMI, parental income, and heavy study burden.

P95
Final height after gonadotropin-releasing hormone agonists with or without growth hormone in Korean girls with central precocious puberty and early puberty
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Aims: We investigated the final height (FH) in GnRHa treatment with or without GH in Korean girls with CPP or CP.

Methods: The forty-one patients were divided retrospectively into three groups: group 1 subjects with CPP (n=20) received GnRHa. Group 2 with early puberty (n=12) received only GnRHa. Group 3 with early puberty (n=9) received combined treatment with GH and GnRHa.

Results: The mean age at the start of treatment was 8.11 ± 0.70 years in group 1, 8.98 ± 0.38 years in group 2 and 9.46 ± 0.46 years in group 3, respectively. The mean predicted adult height (PAH) SDS at the start of treatment was -1.29 ± 1.16 in group 1, -1.14 ± 0.88 in group 2 and -1.87 ± 1.09 in group 3, respectively. Rate of growth during treatment with GnRHa combined with GH was higher significantly in group 3 (6.89 ± 1.45 cm) than in group 1 (5.27 ± 0.89 cm, p = 0.001) and in group 2 (5.64 ± 0.72 cm, p = 0.022). The mean FH SDS was -0.60 ± 0.88 in group 1, -0.40 ± 1.03 in group 2 and -0.92 ± 0.72, respectively and significantly higher than initial height prediction. For the girls received GnRHa alone, FH SDS was correlated significantly with TH SDS, PAH at the start of treatment.

Conclusion: After GnRHa treatment in girls with CPP or EP, FH is significantly higher than initial height prediction. GnRHa treatment combined with GH resulted in higher growth rate.

P96
Bedding types affect pubertal progression in rat
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Aims: Recently, many experimental animal studies have demonstrated several adverse effects of endocrine disrupting agent, such as reduced reproductive behavior, altered estrous cycle, and decreased slow-wave sleep. The purpose of this study was to compare the pubertal progression in wild type female rats according to different bedding types.

Methods: Twenty female Sprague Dawley rat (SD rat) were randomly divided into two groups according to their bedding types. The 1st group was raised in wood shaving bedding as a control and 2nd one was in corncob bedding as an endocrine disrupting agent. Each group was checked daily for the first day of vaginal opening, and their vaginal smears were collected to determine estrous cyclicity after vaginal opening. The interval between vaginal opening and the first normal estrous cycle was recorded for determining sexual maturation. The phases of normal estrous cycles were as follows, proestrus, estrus, metestrus and diestrus.

Conclusion: We compared the proportion of normal estrous cycles in each group. The onset of vaginal opening was earlier, and the irregularity of estrous cycles was increased in corncob bedding groups. Endocrine disrupting agents in corncob bedding were considered to be associated with early vaginal opening and the irregularity of estrous cycles. Therefore, the bedding type can be an affecting factor in pubertal progression in rodents.

P97
The characteristics of familial precocious puberty
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Aims: Precocious puberty is defined as the precocious onset of pubertal manifestations. The cause of precocious puberty is unknown despite numerous attempts to find it. Despite most precocious puberty is sporadic disease, some patients have familial tendency. Recently specific gene mutation has proven to cause precocious puberty and the existence of familial precocious puberty is emerging. This study was performed to compare the characteristics of familial precocious puberty and sporadic precocious puberty.

Methods: We studied 32 girls diagnosed with central precocious puberty (CPP) at Ajou University Hospital from 1st Jan 2007 to 31th May 2014. All girls have sisters diagnosed with CPP and the other 16 children have no family history of CPP. We divided these subjects to two groups, familial CPP and sporadic CPP. All subjects had been treated with GnRH agonist. We reviewed their auxological data, Tanner stage, laboratory findings, and bone age retrospectively.

Results: The onset of precocious puberty was not available. Baseline characteristics including mid parental height (MHP), bone age, height SD, the bone age advancement, body mass index, Tanner stage and LH peak on GnRH stimulation test revealed no significant difference between familial CPP and sporadic CPP. Age at diagnosis (yr) was 8.54 ± 0.48 and 8.11 ± 0.68 respectively (p = 0.049). The GnRH agonist treatment period (yr) was 3.26 ± 0.39 and 2.96 ± 0.79 respectively (p > 0.05). The growth velocity (cm / yr) during the treatment was 5.36 ± 0.55 and 5.34 ± 0.85 respectively (p > 0.05). After the GnRH agonist treatment was finished, the increment of PAH (cm) was 12.14 ± 4.42 and 10.63 ± 4.98 respectively (p > 0.05). The difference between PAH and MHP was not significant (p > 0.01) in familial CPP and 1.13 ± 4.18 in sporadic CPP (p > 0.05).

Conclusion: The clinical manifestation of familial precocious puberty is similar with sporadic precocious puberty. GnRH agonist treatment increases the predicted adult height above the mid parental height in familial precocious puberty.
THYROID

P98
A case of 3 months old Japanese boy with sporadic congenital none-autoimmune hyperthyroidism
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Sporadic congenital none-autoimmune hyperthyroidism is rare disease. It causes the gain of function with TSH receptor gene mutation. We report 3 months old Japanese boy with sporadic congenital none-autoimmune hyperthyroidism. Our case was born in the 34th week of gestation with a birth weight 1830g, his length 42.0cm, his head circumference 29.5 cm as low birth weight baby between non consanguineous parents. Oligohydramnios was pointed out his perinatal period. There was no history of thyroid disease in other family members. He showed failure to thrive after the age of one month in spite of increasing nutrition. At the age of 3 months, His weight was 3.5kg, his length 54.6cm. He presented with tachycardia (170–180/min), severe sweating, mild exophthalmos and no goiter. We examined carefully and found he was suffered from hyperthyroidism. The thyroid function showed TSH<0.005 μIU/mL, FT3 20.55 pg/mL, FT4 7.43 ng/dl, Tg603 ng/mL with tests for anti-thyroid antibodies negative. His thyroid ultrasonography showed enlarged as his age, 99mTcO4- scintiscan of thyroid gland showed a homogeneous uptake. His bone age was advanced to 2 years old. Brain MRI showed normal image for his age. His mother had no goiter and had not showed symptoms of hyperthyroidism. Tests for anti-thyroid antibodies were negative with her. We detected TSH receptor gene mutation with our case. The mutation is heterozygous and shows c842G>A,p.Ser281Asn that had been reported before. The boy was treated with amount of 0.8 mg/kg/day of methimazole, his irritability disappears and his heart rate is down. Now his weight gains slowly and his development is appropriate for his age. We conclude that careful examination and follow up need for his development and growth because the severity of sporadic congenital none-autoimmune hyperthyroidism is variety and most reported case were recurrent.

Written informed consent was obtained from the patient’s parent or guardian for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

P99
Permanent and transient congenital hypothyroidism in Korea: analysis of patients in a single center
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Background: Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation. Neonatal screening programs allow for the early detection and treatment of CH. Transient CH reverts later to normal, which may or may not require replacement therapy. The aim of this study was to determine the prevalence and manifestations of permanent and transient CH in Korea.

Methods: We retrospectively reviewed 610 patients who were diagnosed with CH from January 2001 to January 2011 in Sunchon University Hospital. They all underwent clinical re-evaluation after the age of 2-3, based on the thyroid function testing after levothyroxine therapy withdrawal.

Results: Of the 610 patients diagnosed primarily with CH; 554 (89.1%) patients were diagnosed to have permanent CH, and 66 (10.8%) patients were diagnosed to have transient CH. The median TSH levels before treatment were significantly higher in patients with permanent CH than transient CH (median 58.1μIU/mL vs. 1 μIU/mL). Male to female ratio was 1.12 (53:31) in transient CH. Of the 66 children diagnosed with transient CH, children discontinued levothyroxine replacement therapy at the age of 25±13.2 months. These patients received relatively low dose hormone replacement (initial and at the time of trial of discontinuation).

Conclusion: We concluded that the incidence of CH as well as the transient form similar to the worldwide reported ones.

P100
Pediatric thyroid cancer presenting aggressive pathologic characteristics shows persistently high rates of recurrence during the last 35 years in Korea
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Objective: Clinicopathological characteristics at diagnosis and long-term outcomes of pediatric thyroid cancer were analyzed. Predictors for poor outcome or recurrence were investigated among pediatric papillary thyroid cancer (PTC) patients. Whether young age at diagnosis (<20 years) was independently predictive for recurrence was investigated among PTC patients of all ages.

Methods: We evaluated 153 patients (28males) diagnosed younger than 20 years, managed during 1980 through 2013 (median 7.0 years of duration). Good or poor outcome (persistence or recurrence) was analyzed in 126 patients followed for at least 12 months. Predictors for recurrence were analyzed among 108 pediatric PTC patients. Adult PTC patients (n = 3093) were finally included in Cox proportional hazards models to find predictors for recur-free survival among PTC patients of all ages.

Results: At the time of diagnosis (papillary (86.9%), follicular (7.9%), medullary (3.9%) and poorly differentiated (1.3%), 38.6% of multiplicity, 57.8% of extrathyroidal extension, and 66.7% of lymph node (LN) and 13.9% of lung metastasis were found. The proportions of PTC, multiplicity, extrathyroidal extension, LN metastasis (all for P< 0.05), and distant metastasis (P< 0.001) were significantly higher in younger patients at diagnosis. Forty-four of 126 patients (34.9%) showed poor outcome. Recurrence rates at 5 and 10 years were 13.9% and 33.8% respectively. In an analysis of 108 pediatric PTC patients, the poor outcome group showed larger tumors (2.7cm vs. 2.0cm), higher rates of multiplicity (66.7% vs. 30.6%) and distant metastasis (27.0% vs. 7.7%) than the good outcome group (all P< 0.01). After adjusting for sex, age at diagnosis, primary tumor size and LN metastasis, both multiplicity and primary tumor ≥4cm (all P< 0.01) were independent predictors for recurrence among pediatric PTC patients. Male sex, multiplicity, LN metastasis (all P< 0.001), primary tumor ≥4cm (vs. 1.0-1.9cm), and extrathyroidal extension (P< 0.01 for both) rather than age at diagnosis (<20, 20-39, 40-59, ≥60 years) were independent predictors for a poor recur-free survival among PTC patients of all ages.

Conclusions: Pediatric thyroid cancer presented aggressive pathologic characteristics and showed persistently high rates of recurrence during the past 35 years in Korea. The younger onset, the more aggressive was the pathologic presentation. Among pediatric PTC patients, large tumors (≥4cm) and multiplicity were predictive for recurrence. Among PTC patients of all ages, aggressive pathologic presentations at a young age rather than young age itself were decisive factors for recurrence.
screening and early diagnosis of thyroid disorders, particularly hypothyroidism, is essential for early intervention.

**Objective:** To determine the prevalence of thyroid disorders among children with Down Syndrome (DS) seen in the outpatient clinics of the Philippine General Hospital from January 2007 to December 2011.

**Secondary objectives:** To classify the thyroid disorders present; to describe the clinical profiles and genotype of the children with Down syndrome.

**Methodology:** A Retrospective chart review of all patients with Down syndrome seen in the Out-patient Clinics of the Philippine General Hospital from January 2007 to December 2011.

**Results:** Eighty-nine patients were included, 60% males and 40% females. Fifty-six percent had thyroid disorders. Of these, eighty percent had subclinical hypothyroidism, 12% had overt hypothyroidism, while 8% had hyperthyroidism. The mean age for the diagnosis of thyroid disorder was 3.33 (±0.52) years old. The mean age on initial consult was 2.38 (±3.14) years. The mean age of mothers at childbirth was 34.23 (±6.77) years. The most common co-morbid illness was congenital heart disease (46%, 41/89). The most common chromosomal abnormality was full trisomy 21 (95.51%, 85/89).

**Conclusion:** Fifty-six percent of children with Down syndrome in this study have thyroid disorders, with subclinical hypothyroidism being the most common. This study provides evidence for the need of regular monitoring of thyroid function test among children with DS.

**References**

**P102**

**Graves' disease in children less than 8 years of age: review of clinical features and treatment outcome**

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**Background:** Graves' disease is the most common cause of thyrotoxicosis in children. Prepubertal children are the most difficult to treat with remission attained in less than 15% [1,2].

**Objective:** To characterise clinical features and review treatment outcome among children with very early onset Graves' disease.

**Methodology:** Retrospective medical record review of patients diagnosed with Graves' disease at age less than 8 years, who received treatment in our department in the last 14 years.

**Results:** Sixteen patients (2 males) were identified with median age at diagnosis of 4.96 years (range 2.5-7.83). Presenting symptoms were hyperactivity, weight loss, poor sleep and diarrhoea. They had predominant non-Anglo-Saxon ethnicity. Significant co-morbidities were: Down syndrome [1], juvenile idiopathic arthritis [1], situs inversus with extrahaepatic biliary atresia ie EHBA [1].
Two had family history of Graves' disease. All had goitre, increased serum Free T4 (median 53.65 pmol/l, range 35-94), increased serum Free T3 (median 33.5 pmol/l, range 19.3-46) and suppressed TSH levels. All were positive for TSI (thyroid stimulating immunoglobulin) or TRAb (thyrotropin receptor antibody). Anti thyroid peroxidase was positive in 83.3% (10/12) and anti thyroglobulin in 80% (8/10). Anti-thyroid drugs (ATD) alone were used in 9 patients, 4 received one dose each of radio-active iodine ablation (10-15 mCi) and 3 underwent thyroidectomy. Our cohort tolerated the ATD's. Growth monitoring showed decline in median weight sds from 0.41 at diagnosis to 0.29 at follow up and height sds from 1.35 to 0.69. Of the sixteen patients 2 girls were followed through their puberty till 16 years of age and both are in remission (1 underwent thyroidectomy and other received Neomercaloze).

**Conclusion:** Our cohort had 16 patients diagnosed with Graves' at a median age of 4.96 years. Overall remission for those with more than 30 months follow-up is 58.3% (7/12), at a median age of 10.13 years. Thyroidectomy had a remission rate of 100%; ATD's alone of 33.3% and one dose of radioactive iodine ablation of 25%.

**References**

**P103**

**Hypertensive encephalopathy in untreated congenital hypothyroidism: a case report**

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Hypothyroidism is a well-known cause of poor linear growth in children. In long standing untreated congenital hypothyroidism, short stature, mental retardation and myxedema are common. Sexual precocity associated with bone age advancement can occur, but hypertensive encephalopathy is rare. This case highlights an uncommon finding of hypertensive encephalopathy in a 10 year old Filipina girl who was diagnosed to have hypothyroidism at 18 months old with presenting symptoms of short stature and constipation. She was treated with levothyroxine but with poor compliance. Because of a 2-week history of vomiting, headache, blurring of vision, and increased sleeping time, she was admitted. She was noted to have short stature (height for age Z score -3.62) and obesity (BMI = 26.3, Z score +2.55, WHO) with myxedematous appearance, stubby fingers and toes, and SMR IV. While in the hospital she had seizures, and developed hypertensive encephalopathy. She was noted to have elevated TSH levels (12.5 mIU/L) with normal FT4 and FT3 consistent with subclinical hypothyroidism. Cranial CT scan revealed hypodense foci on the occipital area with cerebral edema. She was given levothyroxine, mannitol and antihypertensive drugs. Her blood pressure was controlled and edema subsided. Prolonged untreated hypothyroidism with elevation of thyroid stimulating hormone leads to mental retardation, short stature, sexual precocity, and hypertension. TSH and gonadotropin hormones have some regions of identical structures in common and may cross react to the same receptors. Prolonged increase in TSH and early rise in gonadotropin have led to ovarian follicles to secrete estrogen, and consequently, breast development, menarche and skeletal maturation. The hypertension related to hypothyroidism is a result of increased peripheral resistance, changes in renal hemodynamics and hormones. Early recognition of symptoms and treatment as well as adherence to levothyroxine therapy is essential in preventing complications of hypothyroidism.

Written informed consent was obtained from the parent of the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

**P104**

**Follicular thyroid carcinoma in a child presenting as autonomously functioning thyroid nodule**

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Despite being born oversized at birth, LGA infants displayed longer if unstable control. Since 2010, werome and MEN2 are also possible, 2015(Suppl 1):e (AGA). In addition, we aimed to nodule with no radiotracer uptake in the rest of h can include a hamartoma/tumour to titration regimen (TIT), after the Cochrane review showed that changed the anti-thyroid treatment protocol from block and replacement medication for 2 years. Among the 10 patients (4 males, 6 females, age 8-16 years) analysed, no significant drug side effect was experienced during both treatment periods. While on TIT, patients required longer duration of treatment (average 23% longer, p=0.005) with more clinic visits (average 50% increase, p=0.003) and thyroid function tests (average 85% increase, p=0.002). They needed more frequent clinic visits (average 22% increase, p=0.04) and thyroid function tests (average 50% increase, p=0.007) per year. They had higher number of abnormal free thyroxine levels per year (average 28% more frequent, p=0.023). The percentage of abnormal free thyroxine levels dropped insignificantly by 2.6% (p=0.645).

The estimated drug cost for 2 year's B&R was ~397 HKD (51.2 USD / 54.6 AUD), while 2 years' TIT cost ~177 HKD (22.8 USD / 24.3 AUD).

Conclusion: Both B&R and TIT are safe without significant adverse effect. B&R seems more cost effective with shorter treatment duration and less frequent clinical and biochemical monitoring, even drug cost is slightly higher.

**DEVELOPMENTAL ORIGINS OF HEALTH AND ADULT DISEASE**

**P106**

**LGA infants display early catch down growth in length and weight without epigenetic changes**

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**Aims:** To evaluate the growth patterns of infants born large-for-gestational-age (LGA) from birth to age 1 year compared to those born appropriate-for-gestational-age (AGA). In addition, we aimed to investigate possible epigenetic changes associated with being born LGA.

**Methods:** Seventy-one singleton infants born at term were classified by birth weight as AGA (10th-90th percentile; n=42) and as LGA (>90th percentile; n=29). Post-natal follow-up until age 1 year was performed with clinical assessments at 3, 6, and 12 months. Assessments included measurement of infants’ weight, length, ponderal index, BMI, as well as head, chest, and abdominal circumference. A subgroup of 38 infants (17 AGA and 21 LGA) was selected for genome-wide DNA methylation analysis. Umbilical cord was collected at birth, and methylation profile on umbilical tissue was analysed using the Illumina Infinium 450K methylation array.

**Results:** At birth, the LGA group had greater birth weight (P<0.0001), length (P<0.0001), head circumference (P<0.0001), ponderal index (P=0.02), BMI (P<0.0001), chest and abdominal circumferences (P=0.04 and P=0.007, respectively) than AGA newborns. At the age of 3 months, LGA infants still presented greater weight (P<0.0001), length (P=0.006), BMI (P=0.02), as well as head (P=0.004) and abdominal (P=0.04) circumferences than AGA peers. However, by age 6 months there were no more anthropometric differences between the two groups. This was due to higher length increment in AGA than LGA infants between 0-6 months (18.3 vs 15.1 cm; P<0.0001), whereas length increment was identical in both groups between 6-12 months (7.7 vs 7.7 cm; P=0.96). For the genome-wide analysis, more than 485,000 DNA methylation sites covering 99% of human NCBI Reference Sequence (RefSeq) genes were examined at birth, but no differences were found between LGA and AGA infants.

**Conclusion:** Despite being born oversized at birth, LGA infants displayed early catch-down growth (i.e. slower length velocity), so that by the age of 6 months LGA infants were of similar length and BMI as AGA infants.
In addition, no epigenetic differences in genome-wide methylation were found in those born LGA.

**P107**

First borns and offspring of younger parents have increased metabolic risk

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Introduction: Perinatal factors such as SGA, LGA, and twin birth are known to adversely program metabolism, increasing the risk of metabolic and cardiovascular disease in adulthood. Birth order and parental age at childbirth have recently been associated with metabolic alterations in childhood. First-born children have poorer insulin sensitivity than second-borns, and lower parental age at childbirth is associated with reduced insulin sensitivity in girls. It is unknown whether the effects of these perinatal factors persist into adulthood increasing the risk of diabetes and heart disease.

Methods: Participants were recruited for two clinical trials investigating metabolic effects of dietary supplements. Overweight middle-aged (35-55 years) men born singleton at term were eligible. Exclusion criteria were diabetes, hypertension, known dyslipidaemia, tobacco use, and use of medications likely to affect blood pressure, lipid profile or insulin sensitivity. Insulin sensitivity was assessed using the Matsuda method. Additional assessments included DXA-derived body composition, 24-hour ambulatory blood pressure (BP) monitoring, carotid artery intima-media thickness (CIMT), physical activity (IPAQ), and diet (3-day food diary).

Results: 73 participants were included in the parental age study, while 50 first- and second-borns men were included in the birth order analysis. As maternal and paternal ages were highly correlated, mid-paternal age at childbirth (MPAC) was used in analyses. Decreasing MPAC was associated with a continuous decrease in insulin sensitivity (p=0.008), increased nocturnal systolic (p=0.020) and diastolic (p=0.047) BP, as well as poorer nocturnal diastolic dipping (p=0.046). Decreasing MPAC tended to be associated with a subtle increase in CIMT (p=0.068). First-born men were 6.9 kg heavier (p=0.013) and had BMI that was 1.6 kg/m² greater (p=0.004) than second-borns. Insulin sensitivity in first-born men was 33% lower than in second-borns (p=0.014), despite adjustment for fat mass, physical activity, and diet. The first born effect was independent of parental age.

Discussion: Among overweight middle-aged men, first-borns had lower insulin sensitivity and greater adiposity than second-borns. Those who have younger parents also had adverse metabolic risk. These data provide evidence that the effects of birth order and parental age on metabolism seen in childhood persist into mid-adulthood and are likely to influence long term cardiovascular and metabolic disease. Further studies should examine sibling pairs and the offspring of parents with disparate ages.

**P108**

Clinical characteristics and imprinting analysis of Chinese Silver Russell Syndrome

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Aims: To study clinical characteristics and imprinting defects in Chinese children with SRS.

Methods: Forty-nine SRS cases were studied retrospectively. Out of these 49 cases, 36 were available to be detected chromosome 11p15 imprinting defects and 21 cases were detected uniparental disomy of maternal chromosome 7 (UPD[7] mat).

Results: There were 32 boys and 17 girls whose ages ranged from 3 m to 12 y. The main clinical characteristics of these SRS were: i) SGA and postnatal growth retardation (mean height standard deviation score (HT SDS) was 2.25; ii) Skeletal malformation including triangular-shaped face, small chin, irregular/crowded teeth, limbs asymmetry and fifth finger clinodactyly. Genetic analysis showed that ICR1 hypomethylation were 22/36 (61.1%) which were following: Ten had hypomethylation in chromosome 11p15 imprinting control region 1 (ICR1) of the paternal allele; seven had both hypomethylation in ICR1 and ICR2; five had hypomethylation in ICR1 and hypermethylation in ICR2. And UPD7 (mat) positive is 1/2(48%). Six patients had been treated with growth hormone (GH) for 3 to 24 months. Growth rates ranged from 4 to 10.8 cm/year.

Conclusions: This study demonstrated that Chinese children with SRS had more growth retardation than bone retardation and had classical skeletal malformation such as triangular faces, and limb asymmetry. Chromosome 11p15 imprinting defects contributed to over 60% of these cases and UPD7 (mat) positive is 4.8%.

**P109**

Shorter mothers have shorter pregnancies

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Objective: Studies have shown that shorter women are at a greater risk of preterm birth. In light of these previous findings, we aimed to assess whether maternal height was associated with gestational age in a cohort of children born at term.

Methods: Subjects were a control cohort of 294 children of New Zealand European ethnicity, high socioeconomic status, normally conceived, born appropriate-for-gestational-age of singleton pregnancies at 37–41 weeks of gestation. Gestational age was determined by ultrasound scans performed <20 weeks. Maternal and paternal heights were measured using a Harpenden stadiometer. Associations with maternal height were assessed using linear regression mixed models, accounting for infant’s gender, birth order, maternal age, and paternal height, with family number added as a random factor.

Results: Mothers were 167.5 (SD=6.2) cm tall (range 151.4–183.0 cm). Increasing maternal height was associated with longer gestation (p=0.002). Stratified analyses showed that the main effect appears to occur among shorter mothers (<165 cm tall), who experienced gestation that was ~0.6 weeks shorter than that of mothers 165–170 cm (p=0.001) and >170 cm (p=0.0002) tall (Figure 1). There was also a progressive increase in birth weight standard deviation scores with increasing maternal height (p<0.0001). Paternal height was not associated with study outcomes.

Conclusions: This study shows that maternal height is positively associated with gestational length across the term window. An association between shorter mothers and preterm birth has been previously shown. We have extended this observation showing that maternal short stature is associated with shorter pregnancies within the term window. The breakdown of term pregnancies into early term (37 0/7 ~ 38 6/7 weeks of gestation), full term (39 0/7 ~ 40 6/7 weeks), and late term (41 0/7 ~ 41 6/7 weeks) has recently been proposed, in light of differences in neonatal morbidity and mortality as well as in neurocognitive outcomes later in life. Maternal stature seems to be a factor determining offspring outcomes, with proposed underpinning mechanisms including socioeconomic factors, undernutrition in utero, and anatomical constraints on pelvis during birth. In our study, socioeconomic factors were not at play in light of the homogeneity of our cohort. Lastly, our findings also support the lack of a paternal height effect on length of gestation.

**P110**

Decreasing birth weight is associated with adverse metabolic profile and lower stature in childhood and adolescence

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Objective: We aimed to evaluate the association of birth weight SDS (BWSDS) with insulin resistance, blood pressure, and auxology in children and adolescents born 23–42 weeks of gestation.

Methods: We studied 143 singleton children and adolescents aged 9.3 ± 3.3 years (range 2.0 – 17.9 years). Clinical assessments included auxology, insulin resistance measured by the HOMA2-IR, and blood pressure from sphygmomanometer measurements. Continuous associations were
examed and stratified analyses carried out. For the latter, participants were divided into those of below-average birth weight (BBW, <0 SDS) and above-average birth weight (ABW, ≥0 SDS).

**Results:** Irrespective of gestational age, lower BWSDS was associated with progressive insulin resistance (p<0.0001) and fasting insulin concentrations (p<0.0001). Decreasing BWSDS was associated with higher systolic (p=0.011) and diastolic (p=0.006) blood pressure. Lower BWSDS was also associated with decreasing stature (p<0.010). The BW group was ~40% more insulin resistant than ABW participants (p<0.004), with the former also displaying fasting insulin concentrations 37% higher (p<0.004). BBW participants were 0.34 SDS shorter than those of higher birth weight (p<0.002). On average, ABW participants failed to meet their genetic potential, tending to be shorter than their parents (p=0.065). As a result, when corrected for parents' heights, BBW participants were 0.6 SDS shorter than those of born higher birth weight (p<0.001). Sub-group analyses on participants born appropriate-for-gestational-age (n=128) showed that associations of BWSDS with both insulin resistance and stature remained (although attenuated).

**Conclusion:** Decreasing BWSDS (even within the normal range) is associated with adverse metabolic profile and lower stature in children and adolescents.

**P111**
**Anthropometrics of neonates born to mothers with diabetes in pregnancy in the Northern Territory**

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Type 2 diabetes (T2DM) is increasing in prevalence in Indigenous Australian children and adolescents. High rates of diabetes in pregnancy (DIP) in Indigenous Australians increases the risk of diabetes for the next generation. DIP is associated with neonatal adiposity, which correlates with long-term risk of obesity and diabetes. Indigenous Australians have high rates of low birth weight and increasingly, large for gestational age associated with DIP. The aims are: 1. To evaluate adiposity in babies born to Indigenous mothers and those of European background with DIP in the Northern Territory; 2. To evaluate the relationship between maternal factors and neonatal birth weight and body composition. Thus far 266 mothers and neonates from the PANDORA cohort (Pregnancy and Neonatal Outcomes in Remote Australia) have been assessed. Neonatal anthropometrics were performed on all neonates, including skin fold measures. Calculations of fat mass were made using a validated equation (fat mass=0.39055*(birth weight)+0.0453*(flank skinfold)−0.03237*(length)+0.54657). Significant differences were found in maternal characteristics between Indigenous and European background participants, including diabetes type (T2DM 14.7% vs 1.1%, p<0.001), smoking in pregnancy (26.5% vs 9.1%, p<0.001) and location of residence (regional/remote 41.4% vs 9.8%, p<0.001). Gestational age at birth was significantly different (38.2 vs 39 weeks, p<0.001), however birth weight was not significantly different (3380 vs 3428g). Indigenous neonates had greater subscapular (4.69 vs 4.20mm, p=0.003) triceps (4.75 vs 4.22mm, p=0.004) and skin fold thickness (4.08 vs 3.60mm, p=0.006). This difference remained significant for the skin fold fold only, after adjustment for diabetes type and maternal body mass index (BMI). There was no significant difference in calculated fat mass. On regression analysis, maternal BMI, smoking, nulliparity and T2DM were each independently associated with birth-weight z-score. Recruitment to PANDORA is ongoing. Preliminary data reveals higher skin fold measures, indicative of adiposity, in Indigenous neonates. There was no significant difference in fat mass. Smoking, BMI, nulliparity and T2DM were independently associated with birth-weight z-score. Ethnicity was not independently associated.

**DISORDERS OF SEXUAL DIFFERENTIATION**

**P112**
**Phenotype and genotype of patients with disorder of sex development due to 5α-reductase deficiency**

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A rare form of the 46,XY disorders of sex development (DSD), 5α-reductase deficiency was first described in patients with pseudovaginal perineoscrotal hypospadias, microphallus, and cryptorchid testes in 1974 by Imperato. This undervirilization in the male is due to an alteration in the 5α-reductase type 2 gene (SRD5A2), which encodes for 5α-reductase activity. Our registry of 750 patients with DSD showed no definitive diagnosis in 80% of cases with 46,XY DSD. Our aim is to identify mutations in SRD5A2 gene and to describe phenotype of detected mutational cases. Mutation analysis was performed for genomic DNA extracted from WBC of 10 patients with 46,XY DSD using PCR and direct sequencing. We identified mutations of SRD5A2 gene in two cases. The first case presented with isolated micropenis at birth, two palpable testes in the normal scrotum. Pelvic ultrasound showed no ovaries and uterus, karyotype was 46,XY and SRY was positive. Serum FSH level was 2.4 IU/L; LM level was 0.9 IU/L and testosterone level was 0.4 nmol/L at 8 years of age. A homozygous missense mutation (p.R237G) was identified in the SRD5A2 gene. The second case presented with micropenis, penoscrotal hypospadia, gonad bilateral in labioscrotal folds. No uterus and ovaries were found by pelvic ultrasound. Karyotype was 46,XY and SRY was positive. A novel homozygous missense mutation (c.659C>T; p.S220L) was identified in the SRD5A2 gene. Mutation analysis of SRD5A2 gene helps to make definitive diagnosis for patients with 46,XY DSD.

The Wilms’ tumor suppressor gene (WT1) is a transcription factor that plays a major role in development of the gonads and kidneys. It is expressed even earlier than sex-determining region of the Y chromosome in the urogenital ridge from which the gonads and kidneys are derived. WT1 mutations will impair gonadal and urinary tract development and have been demonstrated to cause syndromes of WAGR, Denys-Drash and Fanconi. In this study, our aim is to identify mutation in WT1 gene and to describe clinical features of a Vietnamese patient with 46,XY disorder of sex development (DSD) associated with Wilms’ tumor. DNA was extracted from WBC and mutation analysis of WT1 gene was performed using PCR and direct sequencing. A 5 days newborn presented with penoscrotal hypospadia, microphallus, right testis in the right inguinal and no left testis was found. Karyotype was 46,XY and no ovaries and uterus were found using pelvic ultrasound. Wilms’ tumor was detected at 13 months of age by abdominal ultrasound and CT scan. Mutation analysis was identified a heterozygous missense mutation (c.1390G>A; p.D464N) in exon 9 of WT1 gene. In conclusions, WT1 analysis should be performed in newborns with complex hypospadias with at least one cryptorchid testis and in isolated 46,XY partial to complete gonadal dysgenesis. WT1 analysis is mandatory in all 46,XY DSD with associated kidney disease. Patients with WT1 mutations should be followed up closely because the risk of developing a Wilms’ tumor, nephropathy.

Written informed consent was obtained from the patient’s parent or guardian for publication of this Case report (and any accompanying
images). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

P114
Clinical, endocrinological, and molecular genetic characterization of Kallmann syndrome and normosomic idiopathic hypogonadotropic hypogonadism in childhood and adolescence
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Aims: Isolated gonadotropin-releasing hormone (GnRH) deficiency (IGD) is characterized by delayed or absent sexual development associated with low gonadotropin and sex steroid levels. IGD is classified as Kallmann syndrome (KS) with anosmia and normosomic idiopathic hypogonadotropic hypogonadism (nHH). This study was undertaken to investigate clinical and endocrinological profiles in patients with KS and nHH during childhood and adolescence in Korea.
Methods: Twenty nine patients (24 males and 5 females) were included. Their clinical, endocrinological, and radiologic findings were analyzed by retrospective medical record review. In all patients, all exons and intronic flanking regions of the GNRH1, GNRHR, KISS1, KISS1R, PROK2, PROKR2, TAC3, TACR3, FGFR8, FGFR1, KAL1, CHD7, and SOX10 genes were amplified by PCR with specific primers and directly sequenced.
Results: Of 29 patients, 14 were KS and 15 were nHH. At diagnosis, mean chronologic age was 16.55 ± 3.76 years; height SDS was -0.92 ± 1.53; testis volume was 2.10 ± 1.25 mL; and Tanner stage was 1.45. There were associated anomalies in some KS patients: 6 patients with hearing loss, 4 patients with congenital heart disease, and 2 patients with cryptorchidism. Absence or hypoplasia of the olfactory bulb or sulci was found in 9 (82.8%) KS patients. Peak LH and FSH levels were 5.64 ± 5.83 and 5.11 ± 4.61 mIU/mL after GnRH stimulation. Baseline testosterone levels were 0.46 ± 0.62 ng/mL. Twenty four patients (20 males, 4 females) received hormone replacement therapy for 51.1 months of duration. During the follow-up period, all patients reached final adult height of 173.29 ± 8.07 cm (0.27 ± 1.03 SDS). Of 29 patients from 28 unrelated families, molecular defects were found in 10 (34.4%). Two male siblings with KS harbored a novel heterozygous mutation of p.W380* in KAL1. Two unrelated female patients with typical and partial/incomplete CHARGE syndrome were heterozygous for frameshift (p.A608GF*4) and nonsense (p.W983*) mutations in CHD7, respectively. A 31-year-old male with KS and deafness harbored a heterozygous p.M112I mutation in SOX10.
Conclusion: This study described clinical, endocrinological, and molecular genetic features in relatively large cohort of IGD patients. Although the mutation screening was performed in ten genes responsible for causing IGD, molecular defects were identified in relatively small proportions of cohort.

P116
A case of congenital combined pituitary hormone deficiency who showed respiratory distress and hypoglycemia soon after birth
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Congenital combined pituitary hormone deficiency (CCHPD) is a rare disease, presenting with respiratory distress, hypoglycemia and jaundice soon after birth. It is caused by a pituitary aplasia or hypoplasia or abnormality of transcription factor which related to pituitary development. We describe a Japanese patient with CCHPD, who presented with respiratory distress, hypoglycemia and jaundice soon after birth. The patient is now 13 months old Japanese girl. She was born by cesarean section because of fetal distress with 39 weeks and 4 days gestation after an uneventful pregnancy. Her parents were unrelated. Birth length and weight were 43.8cm (-2.2SD) and 2,100g and Apgar scores were 8 at both of 1 and 5 min. She had showed tachypnea and cyanosis since soon after birth and taken nasal-CPAP. However respiratory distress had not improved. She had also showed jaundice and hypoglycemia and was treated with phototherapy and infusion therapy. At 6 days old, we found her FT4 level was 0.4 pg/ml and TSH level was below 0.01 mIU/ml. She was suspected CPHD and anterior pituitary hormone levels were assessed. All of anterior pituitary hormones were undetectable. Anterior pituitary was not visible, posterior pituitary was detected at normal position and there were no other abnormality on brain magnetic resonance imaging. We diagnosed her as CCHPD and hydrocortisone was started since 6 days old and levotheroxine since 8 days old. After that respiratory distress and jaundice had improved rapidly. But hypoglycemia had appeared again after interrupting infusion therapy. GH level after arginine stimulation was also undetectable. She had also started growth hormone therapy since 25 days old and she has had no hypoglycemic episodes after that. Her length and weight were 70.3cm (-1.25D) and 8,485g at 1 year old. GH replacement therapy that was started soon after diagnosis was able to prevent the severe growth retardation. She has no gene abnormalities of transcription factors, HESX1, LHK4 and OTX2, that involves pituitary development. Further studies are needed for investigating genetic basis of this patient.
Written informed consent was obtained from the patient's parent or guardian for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.
**P117** Bone mineral content in growth hormone deficient children treated with growth hormone after withdrawal of 1 year of supplementation with calcium, vitamin D and zinc

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Supplementation with calcium (Ca), vitamin D (vit D), zinc has been shown to have a positive effect on bone mineral content (BMC) gain in growth hormone deficient (GHD) children on GH therapy [1]. It is unknown if this gain is sustained after supplement withdrawal. We aimed to investigate the influence of prior supplementation with Ca, vitD and zinc on BMC accretion after supplement withdrawal.

31 prepubertal GHD children were randomly allocated to receive A) calcium (500mg/d), vitamin d (30,000 IU/3 months) and B) calcium (500mg/d), vitamin D (30,000 IU/3 months) & zinc (8 mg) for 1 year with GH. Ht measurement, bone mineralization by dual energy x-ray absorptiometry, Tanner staging were performed at 4 timepoints, baseline, post 1 year of supplementation and 1 & 2 years after withdrawal of supplementation. Height for age z-scores (HAZ) were calculated from ethnic growth references.

At baseline, children (18 boys, 9.6±2.8 years) from group A & B were similar in their HAZ (-4 ±1.5, -4 ±1.3) and BMC (702±15 9, 740±167g). 1 year post supplementation, 40% & 36% children and by the end of 2nd year of supplementation withdrawal, 47% & 80% from group A & B respectively had entered puberty. Since Ht has strong correlation with BMC, % change in height adjusted BMC was analyzed. The gain in BMC was greater (p < 0.05) in group B (51 %) children than in group A (49 %) children. However, after the withdrawal of the supplementation, the % gain in ht as well as height adjusted BMC was similar in both groups. The % gain in height adjusted BMC was lower (p < 0.05) in the 1st year of supplement withdrawal (22 %). In 2nd year, the height adjusted BMC showed a significantly greater (53 %, p < 0.05) gain than the supplementation year and first year after withdrawal supplementation.

Effect of short term supplementation with calcium, vit D & zinc in GH treated GHD children may not continue after the withdrawal of supplementation. However, the greater gain in the 2nd year after supplementation withdrawal was possibly due to the effect of puberty.

**Reference**


**P118** Hypopituitarism due to central nervous system germinoma: a case report

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Germ cell tumors in the central nervous system affect children and adults, the peak incidence is from 10 -19 years of age. Clinical presentation is mainly involving to the location and size of the tumor and the patient age. Endocrine abnormalities are the most common symptom.

We presented a case who had hypopituitarism due to central nervous system Germinoma. A 10 years old girl was admitted to our hospital due to polyuria. Past history: she was diagnosed with diabetes insipidus and treated with oral minirin ( desmopressin ) 3 years ago. But she did not taken oral minirin for 2 years ago.

Physical examination showed: polyuria ( 8 ml/kg/h ), polydipsia, no dehydration, no weight gain. Her height was 131 cm ( -0.5 SD ). Her weight was 41 kg. Her BMI was 23.9 (> 97th ) . She had no manifestation of puberty. Laboratory evaluation revealed: blood osmotic pressure: 304 mosm/kg ( normal range : 275 mosm/kg – 295 mosm/kg ), urinary osmotic pressure : 80 mosm/kg ( normal range : 500 – 1200 mosm/kg);

serum cortisol at 8 a.m : 9.2 nmol/l ( normal range : 200 – 600 mol/l ); plasma glucose level and electrolyte were normal; T4 : 38.8 nmol/l ( normal : 50 -150 nmol/l ); T3 : 2.35 nmol/l ( normal range : 1 – 3 nmol/l ), TSH : 4.1 mcU/ml ( normal range : 1 – 5 mcU/ml ); LH : 0.16 UI/ ml (normal range : 0.5 – 9.9 UI/l ), FSH : 0.9 UI/ml (normal range : 1.4 – 5.6 UI/l), Estradiol < 43.3 pmol/l ( normal range : 97 – 169 pmol/l ). An MRI of brain showed: an under hypothalamic mass measuring 14 × 20 mm, suspected Germinoma.

She was treated with hormone replacement (desmopressin, levothyroxine, hydrocortisone) and radiation therapy.

Written informed consent was obtained from the patient’s parent or guardian for publication of this Case report (and any accompanying images). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**P119** Multiple endocrine glands insufficiency due to langerhans cell histiocytosis (LCH): a case report

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LCH is the rare disease involving clonal proliferation of Langerhans cells, abnormal cells deriving from bone marrow and capable of migrating from skin to lymph nodes. The clinical presentation of LCH may occur in multiple organs: bone, skin, lymph nodes or pituitary gland, but clinical presentation of LCH rarely occurs in multiple endocrine systems.

We presented a special case who was diagnosed with LCH and presentation of LCH occurred in multiple systems: pituitary gland, thyroid, adrenal gland. A 11 years old girl was hospitalized for lump on the neck. Past history: one year ago, she was diagnosed with autoimmune polyendocrine syndromes and treated with hormone replacement (levothyroxine 3mcg/kg/day, desmopressin 4 mcg/kg/day, hydrocortisone 10 mcg/kg/day).

Physical examination showed: she had a swollen lump on her neck, she had a temperature of 38 °C. She had no polyuria, no polydipsia. Her height was 141cm (-0.29 SD); her weight was 37 kg; her BMI was 18.5 (50th – 70th ).She had normal growth velocity and normal pubertal development. Laboratory evaluation revealed: WBC : 10.3 × 109 /l (normal range : 4×10 9 /l – 10 × 109 /l ); CRP : 105.78 mg/l ( normal range : < 10 mg/l ); serum cortisol at 8 a.m : 16.3 nmol/l ( normal range : 200 – 600 nmol/l ); T3 : 1.8 nmol/l ( normal range : 1 – 3 nmol/l ), T4 : 135.9 nmol/l ( normal range : 50 – 150 nmol/l ), TSH : 0.002 mU/ml ( normal range : 1 – 5 mU/ml ); blood osmotic pressure : 279 mosms/kg, urinary osmotic pressure : 127 mosms/kg; plasma glucose level and electrolyte were normal. An MRI of brain showed: thickened pituitary stalk. A biopsy of the lump on her neck showed: features of Langerhans Cell; skeletal and long bone radiograph showed no osteolytic lesion.

She was treated with hormone replacement and chemotherapy.

Written informed consent was obtained from the patient’s parent or guardian for publication of this Case report (and any accompanying images). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**P120** Variations of amino acid, free carnitine and acylcarnitine profiles analysed by tandem mass spectrometry in newborns during their first four weeks of life

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Aims: Electrospray ionization-tandem mass spectrometry (MS/MS) has increasingly been advocated for expanded newborn screening and for the early diagnosis of amino acidemias, fatty acid oxidation disorders, and
organic acidurias. Here, we characterized amino acid, free carnitine, and acylcarnitine status with respect to postnatal ages in 158,730 newborns over the last two years.

**Methods:** Six age groups were defined: 3-4 d (Group A), 5-7 d (Group B), 8-10 d (Group C), 11-15 d (Group D), 16-20 d (Group E), and 21-28 d (Group F). Amino acid, free carnitine, and acylcarnitine concentrations of dried whole blood spots were obtained from the MS/MS analysis. Linear regression analyses of all results of highly disease-related analytes were carried out to identify covariates associated with sampling time in Matlab. For the respective regression coefficients (RC), plus represents the analyte levels elevate as the sampling time prolongs, and vice versa for minus.

**Results:** Except for PHE, ALA and GLY, values of the remaining amino acids increased with postnatal age as the regression coefficients were plus. In addition, most amino acids levels during days 5-10 were distinctly higher with the exceptions of ALA, ORN and GLY. For free carnitine and short-chain ACs, C0, C3 and C5OH elevated slightly with sampling time (RC<0.05), while analytes decreased along with age especially for C2 and C3 (RC for C3 was 0.01). For medium- and long-chain ACs, all analytes concentrations decreased with specimen collection time. C14, C16, C18, and C18:1 turned out to remain only half of their primary levels; and the level of C16 varied from 2.73 μmol/L in Day 3-4 to 0.84 μmol/L in Day 21-28. Our results indicate that most amino acids and acylcarnitines had no obvious age-dependent varieties in concentration levels during neonatal period with exceptions of C2, C3, C14, C16, C18, C18:1 and C16.

**Conclusions:** Although the risk of underdiagnosis of IEM with the use of some parameters the use of age-related reference values may have a potential impact on the diagnosis and management of inherited errors of metabolism.

**P122**

Congenital central hypoventilation syndrome with hyperinsulinemia in an infant

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Congenital central hypopventilation syndrome (CHHS) is a rare disorder that typically presents in the newborn period and is characterized by alveolar hypventilation and symptoms of autonomic nervous system dysregulation. We describe an infant with CCHS who developed hyperinsulinism, which is an uncommon association. She was born by semi-elective Caesarean section at 37 weeks of gestation after a pregnancy complicated by polyhydramnios. Apgar scores were 7and 9 (at 1 and 5 min) and birth weight was 3550 g. She was intubated and ventilated within 24 hours for frequent apnoea’s and desaturations. Multiple extubation attempts on the following days failed because of progressive respiratory acidosis. She underwent tracheostomy at 2 months of age. CCHS was diagnosed in the first month of life, after a polyanaline repeat expansion of the PHOX2B gene (20/26genotype) was detected. At 7 months of age, she was admitted to hospital with seizures associated with hypoglycaemia. A critical sample (glucose 2.5mmol/L) revealed an inappropriate raised plasma insulin of 3.0 μIU/L, growth hormone 7μIU/L, cortisol 470 mmol/L, and serum ketones <0.1g/L. Urine and serum metabolic screen was normal, as was an EEG. Diazoxide was commenced at 5 mg/kg/day along with hydrochlorothiazide at 1mg/kg/day. These relatively low doses were used in view of parental concerns of potential drug side effect of hirsutism. The dose had to be increased to 7.5mg/kg/day as hypoglycaemic episodes persisted. Capillary blood glucose testing and continuous glucose monitoring showed no further hypoglycaemia at this dose. Sequence analysis of the KCNJ11 and ABCB8 genes implicated in congenital hyperinsulinism was undertaken and no pathogenic mutation was found. The mechanisms underlying abnormal glycaemia in CCHS are not fully understood. Multiple hypotheses have been postulated including the co-expression of the dopamine beta hydroxylase gene mutation with PHOX2B mutation. Further, disordered autonomic homeostasis as seen in PHOX2B mutations is thought to impact the regulation of insulin and glucagon secretion. Our case highlights the importance of considering hyperinsulinism in the differential diagnosis of hypoglycaemia in infants with CCHS.

**P123**

Sirolimus treatment of severe congenital hyperinsulinism

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Sirolimus treatment reduced dependence on octreotide and frequent feeding in 4 infants with CHI in a recent study [1]. We report our experience in a 1 year-old boy with presumed diffuse disease due to a de novo heterozygous ABCB8 missense mutation (p.D1506E). This neonate had a birth weight of 2.99 kg (1st centile, normal weight was 3550 g). She was intubated and ventilated within 24 hours for frequent apnoea’s and desaturations. Multiple extubation attempts on the following days failed because of progressive respiratory acidosis. She underwent tracheostomy at 2 months of age. CCHS was diagnosed in the first month of life, after a polyanaline repeat expansion of the PHOX2B gene (20/26genotype) was detected. At 7 months of age, she was admitted to hospital with seizures associated with hypoglycaemia. A critical sample (glucose 2.5mmol/L) revealed an inappropriate raised plasma insulin of 3.0 μIU/L, growth hormone 7μIU/L, cortisol 470 mmol/L, and serum ketones <0.1g/L. Urine and serum metabolic screen was normal, as was an EEG. Diazoxide was commenced at 5 mg/kg/day along with hydrochlorothiazide at 1mg/kg/day. These relatively low doses were used in view of parental concerns of potential drug side effect of hirsutism. The dose had to be increased to 7.5mg/kg/day as hypoglycaemic episodes persisted. Capillary blood glucose testing and continuous glucose monitoring showed no further hypoglycaemia at this dose. Sequence analysis of the KCNJ11 and ABCB8 genes implicated in congenital hyperinsulinism was undertaken and no pathogenic mutation was found. The mechanisms underlying abnormal glycaemia in CCHS are not fully understood. Multiple hypotheses have been postulated including the co-expression of the dopamine beta hydroxylase gene mutation with PHOX2B mutation. Further, disordered autonomic homeostasis as seen in PHOX2B mutations is thought to impact the regulation of insulin and glucagon secretion. Our case highlights the importance of considering hyperinsulinism in the differential diagnosis of hypoglycaemia in infants with CCHS.

**Written informed consent was obtained from the patient’s parent or guardian for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.**
No ABCB8 missense mutation was identified in either parent or his second cousin.

Initial management included intravenous glucose (12 mg/kg/min) and glucagon infusions. Maximal dose diazoxide (20 mg/kg/day for 5 days) was ineffective so subcutaneous octreotide infusion was initiated (26 mcg/kg/day). At discharge from hospital (age 10 weeks) he was overweight (height SDS 1.11, weight SDS 3.1), receiving octreotide 27 mcg/kg/day, nocturnal gastrostomy Polyjoule® feeds (equivalent to 11 mg/kg/min glucose) plus 3-hourly bolus feeds.

Sirolimus (0.5 mg/m2/day) was added at age 7 months because of continued weight gain and intermittent mild hyperglycaemia while receiving octreotide 37 mcg/kg/day. The dose was increased to 6 mcg/m2/day, aiming for trough levels 15-20 ng/mL. After 3 months, the octreotide dose had stabilised (36 mcg/kg/day) and the intensity of feeds has been reduced (3.5 mg/kg/minute glucose overnight), resulting in weight loss; however, he has also developed linear growth failure (height velocity 0.6 cm/year over 3 months). At 1 year of age his length and weight SDS are 0.48 and 1.21 respectively, and he is developmentally appropriate for age.

Apart from one mild episode of respiratory syncytial virus, he has had no significant illnesses during sirolimus treatment.

In conclusion, treatment with sirolimus has improved our patient’s blood glucose concentrations, decreased his dependence on hypercaloric nocturnal continuous feeds and decreased his weight gain; however, the burden of care remains more significant than reported in the 4 published cases, 2 of whom had heterozygous mutations in ABCB8. The combination of high-dose octreotide and sirolimus may not be sustainable long-term in view of their likely combined contribution to his growth failure and the potential for immunosuppression due to sirolimus. Written informed consent was obtained from the patient’s parents for the publication of this Case report (and any accompanying images). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Reference


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Primary hyperlipidemia in children: clinical, biochemistry characteristics and outcome

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Background: Primary hyperlipidemia is genetic dyslipoproteinemia. Without any intervention, cardiovascular diseases and acute pancreatitis may be occurred. The detection and appropriate management of pediatric hyperlipidemia can have a significant impact upon the disease course and can prevent complications.

Objectives: to describe the clinical and biochemical characteristics of hyperlipidemia in Vietnamese children and to evaluate outcome of treatment.

Patients and methods: From 2007 to 2013, 30 children with primary hyperlipidemia were recruited and were treated with diet and/or lipid-lowering drug therapy at the National Hospital of Pediatrics, Hanoi, Vietnam. Clinical symptoms and biochemical finding, outcome of treatment were studied. Results: Among 30 cases from 28 families, 8 patients were mixed hyperlipidemia (MHL), 13 patients were hypertriglyceridemia (HT) and 9 patients were hypercholesterolemia (HC). Mean age of diagnosis was 5.5 years (1 month – 16 years). The rate of male/female was 13/17. Clinical manifestations included hepatomegaly (4 cases), xanthemata in the knees and elbows (5 cases), “creamy” blood (21 cases). Twenty cases were clinical asymptomatic. 8/28 patients had family history with hyperlipidemia and cardiovascular diseases. Serum cholesterol levels of HC group was 9.2 ± 4.4 mmol/L. Serum triglyceride level of HT group was 23.6 ± 9.9 mmol/L. MHL group had hypercholesterolemia (12.1 ± 4.5 mmol/L) and hypertriglyceridemia (20.3 ± 10.5 mmol/L). After interventions, HT group had the best outcome with serum triglyceride level was 10.1 ± 4.6 mmol/L, next to MHL group with serum cholesterol level was 5.8 ± 1.8 mmol/L, and serum triglyceride level was 9.5 ± 5.2 mmol/L; finally, serum cholesterol level of HC group was 12.4 ± 5.5 mmol/L. Five infants with HT had the best outcome of treatment: serum triglyceride level decreased from 19 - 57.6 mmol/L to 5 - 10 mmol/L. Two patients with HC had the worse results (unchanged blood lipid level).

Conclusions: Primary hyperlipidemia had poor clinical manifestations and good results of treatment. Screening for primary hyperlipidemia help to prevent premature cardiovascular diseases.

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Molecular genetics, correlation between genotype and phenotype of 65 Vietnamese patients with congenital hyperinsulinism

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Hyperinsulinemic hypoglycaemia (HH) is a consequence of unregulated insulin secretion by pancreatic β-cells. Congenital HH is caused by mutations in genes involved in regulation of insulin secretion (ABCB8, KCNJ11, GLUD1, CGK, HADH, SLC16A1, HNF4A and UCP2). Severe forms of congenital HH are caused by inactivating mutations in ABCB8 and KCNJ11, which encode the two components of the pancreatic β-cell ATP-sensitive potassium channel. Our aim is to identify mutations in the ABCB8 and KCNJ11, HNF4A and GLUD genes, and to describe genotype and phenotype correlations of Vietnamese children with congenital hyperinsulinism. A prospective study was conducted on 65 cases with congenital hyperinsulinism diagnosed and treated at the National Hospital of Pediatric from January 2007 to April 2014. Patients were selected by using inclusion criteria of Hussain K (2008). Mutations were identified in 32 cases (49.2%) including mutations of ABCB8 gene (28 cases; 43.1%), KCNJ11 (3 cases; 4.6%), HNF4A (1 case; 1.5%). 100% of cases with homozygous/compound heterozygous recessive mutations or one paternal dominant mutation of ABCB8 gene did not respond to diazoxide treatment and required 95% pancreatectomy. Molecular analysis using pancreas tissue after surgery from cases with one mutation of ABCB8 gene inherited from father confirmed focal lesion type. Other cases without identified mutations usually responded to diazoxide. In conclusions, children with congenital hyperinsulinism should be performed mutation analysis which helps in making diagnosis and treatment decision. Families of children with congenital hyperinsulinism should be given genetic counseling. Prenatal diagnosis should be performed as well as follow - up and treatment should be given to children with congenital hyperinsulinism immediately after birth.

WATER/ELECTROLYTES

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Challenges in the diagnosis and management of Pseudohyposalenosteronism Type 1

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Autosomal recessive Pseudohyposalenosteronism Type 1 (PHA-I, MIM#264350), is a rare disease with a severe clinical phenotype [1,2] and generally no improvement with age [3]. It results from mutations in the amiloride-sensitive epithelial sodium channel causing mineralocorticoid-resistant (ENAc), systemic salt wasting, and is lethal without ongoing supra-physiological sodium supplementation and management of hyperkalaemia [4,5].

Other manifestations of systemic PHA-I include decreased sodium-dependent clearance of alveolar fluid causing recurrent chest congestion, cough and wheeze, but no airway infection by bacterial pathogens.
typhifying cystic fibrosis [6,7]; and skin rashes from inflammation of sodium-blocked sweat glands [8] with recurrent Staphylococcal skin infections described [9].

Our patient, now nearly four years old, presented as a day 6 neonate with vomiting, apnoea and florppiness. She was shocked and dehydrated with hyponatraemia, marked hyperkalaemia with runs of ventricular tachycardia.

PHA-1 was diagnosed with high cortisol, renin and aldosterone, normal 17-hydroxyprogesterone, inappropriately high spot urine sodium with low potassium, and normal renal ultrasound. Diagnosis was genetically confirmed with the finding of two inherited, distinct, disease causing mutations in the SCNN1A gene. Increased sweat sodium confirmed systemic salt-wasting. Initial management included a high-sodium, low-potassium formula (Kinderrgen) supplemented with 22 mmol/Kg/day of enteral sodium, the use of daily potassium binding resin (Resonium), and trial of Fluorocortisone.

Requirement for daily large doses of sodium 16 mmol/Kg/day, provided as a mix of sodium citrate and sodium chloride, and daily Resonium continues. Significant oral aversion remains an issue with good growth achieved on calorie-concentrated Kinderrgen. Gastromotony was changed to percutaneous jejunal continual feeding due to persistent gastric emptying problems. Central venous access established early has posed ongoing challenges, with intermittent Staphylococcal infections. Our patient has also been hypertensive requiring medical management from 6 months age. She has a recurrent moist cough with past Haemophilus inection.

Minimising inpatient management is vital for establishing ‘normality’ and optimising development. The need for frequent electrolyte monitoring and adjustment of sodium intake is managed creatively between home and hospital in close liaison with her paediatric endocrinologist and community-based supports. Clear emergency management plans involving early symptom recognition and rapid hospital-access are instituted to manage salt-wasting episodes. We shall discuss the challenges and pitfalls of managing this rare, life-threatening disease with sparse long-term prognostic information, in the Australian health care context.

Written informed consent was obtained from the parent of the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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