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13 – 15 November 2013, Brighton, UK

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Speaker Abstracts
Bone has three main components: matrix, mostly made up of type 1 collagen, mineral, which is laid down on the matrix by osteoblasts, and bone cells: osteoclasts, which are derived from haemopoietic precursors, osteocytes, which are of fibroblast precursor origin, and osteoclasts, the most numerous, which are derived from osteoblasts.

Osteoclasts operate under the influence of several humoral factors including PTH, 1,25(OH)2D and cytokines which act via specific receptors on the cell surface to stimulate osteoclast development and function with the aid of a number of other proteins such as LRP5, Sclerostin and Wnt signalling. Bone matrix formation is under genetic control by several genes including COL1A1, COL1A2, IFTM5, CRTAP, LEPR, and PPIB, mutations in any of which can cause OI. Osteoclasts are controlled by osteoblasts under the influence of RANK and its natural inhibitor osteoprotegerin which acts via the RANK ligand on the surface of osteoclasts. Bone resorption is achieved by maintaining an acid environment derived from osteoblasts.

Osteocytes play a major role in maintaining phosphate mainly via the action of phosphaturic hormone (PTH), 1,25(OH)2D and cytokines which act via specific receptors on the cell surface to stimulate osteoclast development and function with the aid of a number of other proteins such as LRP5, Sclerostin and Wnt signalling. Bone matrix formation is under genetic control by several genes including COL1A1, COL1A2, IFTM5 and PLEKHM1 (mutations cause osteoporosis), whilst cathepsin K removes demineralised matrix (mutations cause pyknodysostosis).

Osteocytes play a major role in maintaining phosphate mainly via the action of FGFR23 which is under the influence of several genes including PHEx, DMP1, GALNT3, FGFR1c, Klotho and NaP1. Mutations in any of these genes may cause either hypophosphataemic rickets or familial tumoral calcinosis.

This talk will give an overview of these processes and show how they link together and will concentrate on the newer aspects of phosphate physiology.

DOI: 10.1530/endoabs.33.CME1

Rickets is a condition only seen in growing children due to disorders that result in impaired apoptosis of hypertrophic cells and mineralisation of the growth plate and osteoid. Although there are a variety of causes of rickets vitamin D deficiency remains the commonest cause worldwide with evidence of a resurgence in some developed countries.

There are several modes of presentation of vitamin D deficiency dependent on the age and growth rate of the child. These include hypocalcaemic symptoms, progressive leg deformities and muscle weakness. A variety of aetiological factors are important in the potential development of rickets including reduced sunlight exposure, dark skin pigmentation, atmospheric pollution and prolonged exclusive breastfeeding. An additional important factor is poor dietary calcium intake with evidence suggesting this needs to be present in conjunction with vitamin D deficiency to cause the development of rickets.

This talk will review the clinical presentation of vitamin D deficiency in children and adolescents, discuss aetiological factors and subsequent treatment.

DOI: 10.1530/endoabs.33.CME2

What do we mean by ‘osteoporosis’? Essentially, bone of reduced mass that is abnormal at a micro-architectural level, with an increased propensity to fracture. The detection of such abnormality is not straightforward. Any bone will fracture given sufficient force, and it might be thought that restricting further investigation to those who fracture following mild or trivial trauma would be the way forward. Defining what level of trauma should be regarded as ‘mild’ or ‘trivial’ is difficult, however, given the anisotropie nature of bone and the problems of accurate recall in trauma settings. Clear clinical signs of osteoporosis are vertebral crush fractures and buckle fractures of the distal femur or proximal tibia. These can have particular value in the differentiation of normal from fragile bone in the pre-mobile infant.

Bone densitometry by DXA can measure bone mass, but does not distinguish between bone compartments – cortical vs trabecular bone – and the measurements are strongly influenced by size. In children with chronic disorders who are small, account needs to be taken of this confounding element.

New imaging techniques – volumetric and peripheral high resolution QCT, and MRI are still research approaches that have not entered mainstream clinical practice. Bone biopsy can provide both static and dynamic information on bone, but is site-specific. Microindentation is still a laboratory technique currently; a handheld device used in adults might damage the thinner, less mineralised cortical bone of a child’s tibia. Genetic panels for inherited bone fragility genes are improving diagnostic accuracy.

Current therapeutic interventions focus on anti-resorptive therapies, primarily bisphosphonates, as part of a multidisciplinary approach. Recent advances in the genetics of inherited bone fragility syndromes indicate alternative therapeutic targets in the canonical woll-signalling pathway. There is still a need to provide clear advice regarding nutrition and exercise in all cases.

DOI: 10.1530/endoabs.33.CME3

Growth through the pubertal progress is notoriously difficult to track and interpreting abnormal patterns is tricky. Current growth charts are unhelpful. I will present new analyses of understanding of growth patterns and the tempo of pubertal changes and how they all link together. The RCPCH has launched a specialist growth chart in June to help identify and diagnose abnormal growth patterns during puberty. These include growth centiles for extremes of stature and weight, and growth centiles for which the normal range varies according to the phase of puberty for tall, short or light children. I will present the new way of tracking puberty with stage lines which are on these new charts, and will show how they can be used to identify patterns of abnormal pubertal development.

DOI: 10.1530/endoabs.33.CME4

Abstract unavailable.

DOI: 10.1530/endoabs.33.CME5

Abstract unavailable.

DOI: 10.1530/endoabs.33.CME6

Most patients with type 1 diabetes, even children and adolescents, have residual insulin secretion at diagnosis. As long as this can be preserved blood glucose
fluctuates less, and the risk of acute and late complications decreases. Gradually the autoimmune process will destroy β-cell function unless immune intervention can stop the destructive process.

Several different interventions have been tried. The very first intervention with plasmapheresis may have had some effect, and lead to, as side effect, the discovery of the 64 kDa, later shown to be GAD. Cyclosporin proved the concept, but had, as several other broad immune suppressive agents, too serious adverse events.

Last decades the immune interventions have followed two different lines: MABs have been used to block relevant receptors. AntiCD3 seems to be the most effective and certainly can preserve residual β-cell function, but high effective doses unfortunately lead to quite common and disturbing adverse event such as anemia, bleedings, cytokine release syndrome, etc. Phase III trials have failed, but one arm in the Teplizumab study with a moderate dose had significant effect and rather mild and acceptable adverse events, which encourages to further studies. AntiCD20 had also some effect, but short and transient.

Auto-antigen treatment to create tolerance is the other main and attractive approach. GAD-vaccination gave significant preservation of C-peptide in phase II studies in children and adolescents, but phase III did not reach primary endpoint. Efficacy in several pre-specified subgroups, however, support the concept and new studies are ongoing. When vitamin D and anti-inflammatory treatment is combined to improve the vaccination effect. Experimental studies suggest the use of insulin or pro-insulin/proinsulin peptides, and clinical studies are on their way. In addition to the main stream there are several other trials made to use, e.g. TNF-blocking agents, islet neogenesis associated protein (INGAP), DNA-vaccines, IL1 blocking agents, vitamin D, and further studies are needed.

Conclusion
Preservation of residual insulin secretion is crucial. Clinical intervention studies should be encouraged. Most probably combination therapies will be needed.

DOI: 10.1530/endoabs.33.S1.1

Symposia 1 Care and controversies: present and future
S1.1
Preservation of fertility
R Anderson
Edinburgh, UK.

Fertility preservation is a rapidly advancing area of medicine. Its clinical potential in adult women was demonstrated by ovarian function and successful pregnancy following ovarian cortical tissue cryopreservation and replacement in the sheep in the 1990s with the first successful human pregnancy reported in 2004. Since then some 25 babies have been born to women who have had ovarian tissue cryopreserved and subsequently replaced, with most of these women having been treated for haematological malignancies. Much larger numbers of women have had embryo cryopreservation, which has long been a routine in IVF practice, and recent developments in oocyte vitrification have made that approach a much more viable option than was the case just a few years ago. For children however gonadal tissue storage remains the only option. Several case studies have been published showing its application to girls, and there are two reports of replacement of ovarian tissue to induce puberty in adolescent girls, although this indication is debatable. Options for boys remain experimental at present. The very first intervention with plasmapheresis may have had some effect, and lead to, as side effect, the discovery of the 64 kDa, later shown to be GAD. Cyclosporin proved the concept, but had, as several other broad immune suppressive agents, too serious adverse events.

S1.2
Cancer treatment late effects on the endocrine system
A Leiper
London, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S1.2

S1.3
SAGe: GH safety and long term concerns
J C Carel
Paris, France.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S1.3

Symposia 2 Recent advances in CAH management
S2.1
CaHASE: a UK collaborative study on CAH in adults
R Ross
Sheffield, UK.

Congenital adrenal hyperplasia (CAH) is a genetic disorder arising from defective steroidogenesis resulting in glucocorticoid deficiency; the commonest mutation is in the gene encoding 21-hydroxylase. Lifesaving glucocorticoid treatment was introduced in the 1950s and there is now an enlarging cohort of adult patients; however, there is no consensus on management. To address this issue, the Congenital adrenal Hyperplasia Adult Study Executive (CaHASE) was formed in 2003 to study the health status of CAH patients in adulthood. Seventeen specialist Endocrinology centres around the United Kingdom recruited a cohort of 203 adult patients and gathered information on medical treatment, fertility, genetic analysis and quality of life (QoL). The CaHASE study found that adult patients are prescribed a variety of glucocorticoids including hydrocortisone, prednisone, prednisolone, dexamethasone, and combinations taken in either a circadian or reverse circadian regimen. Despite this variety in personalized treatment regimens biochemical control of CAH is only achieved in approximately a third of patients. There is evidence for poor health status in some patients with an increased incidence of obesity and osteoporosis, and impaired fertility and quality of life. The evidence suggests that these poor health outcomes relate to treatment rather than genotype. Patients receiving higher doses of glucocorticoids and the more potent synthetic glucocorticoids are more likely to suffer from obesity, insulin resistance and a reduced quality of life. Further research is required to determine whether improving management and treatment in CAH patients can improve their health.

References from CaHASE Cohort study: (1–4)

DOI: 10.1530/endoabs.33.S2.1

S2.2
Paediatric surveillance for CAH: informing newborn screening policy
R Knowles
London, UK.

Congenital adrenal hyperplasia (CAH) is a recessively inherited deficiency of cortisol production affecting an estimated 1 in 10 000–20 000 live births. The salt-wasting form, which is found in over half of all children with CAH, may present with a potentially life-threatening crisis in with the newborn period while associated excess androgen production may result in girls being incorrectly assigned as boys at birth. Early detection by newborn screening, combined with

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cortisol and mineralocorticoid replacement can prevent life-threatening episodes, and ensure normal growth and sexual development in older children. Although some countries undertake screening for CAH as part of the newborn bloodspot programme, it has not been introduced in the UK, reflecting uncertainty regarding disease burden as well as the high false positive rate associated with the existing screening test. Prospective surveillance of all new diagnoses of CAH in British children was undertaken through the British Paediatric Surveillance Unit in order to determine the incidence of CAH and burden of disease, including short-term health outcomes, and to assess the potential benefit of introducing newborn screening for CAH in the UK.

Declaration funding
Department of Health – commissioned by the UK National Screening Committee.

DOI: 10.1530/endoabs.33.S2.2

Symposia 3 Present and future: novelty and goals
S3.1
Benefits of diabetes networks and beyond
F Campbell
Leeds, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S3.1

S3.2
Screening for diabetes related complications
R Amin
London, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S3.2

S3.3
What are the barriers of implementation to BPT
T Randell
Nottingham, UK.

The paediatric diabetes best practice tariff (BPT) was introduced in 2012, with the aim of standardising and improving paediatric diabetes services across England. In the first year, only about 50% of units were claiming the full tariff but this had substantially improved for 2013–2014. It is probably too early to see if there has been a positive impact on outcomes but data from the East Midlands will be presented to look at this in more detail. From 2014, the BPT will also include payment for in-patient stays and it is hoped that with more evidence we may be presented to look at this in more detail. From 2014, the BPT will also include payment for in-patient stays and it is hoped that with more evidence we may be able to apply the tariff to age 25.

DOI: 10.1530/endoabs.33.S3.3

Symposia 4 Debate: Pump vs MDI in all children with DMT1
S4.1
Pump therapy in all newly diagnosed T1DM
F Campbell
Leeds, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S4.1

Diabetes professionals Meeting Programme
DP1
NPD implications for practice
F Campbell
Leeds, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.DP1

DP2
Implementation of structured education
H Thornton
Prescot, UK.

Basic education about diabetes is a cornerstone to diabetes management but in the UK there was, until recently, no national recognised programme easily available in every Paediatric unit despite several being under development for considerable time. Children in any age group vary considerably in their ability to learn and accept new responsibilities. Diabetes education, therefore, should be adapted to the individual child’s level of development and understanding. There was a desperate need, at the time, for teams to be able to evidence this ongoing educational as part of best practice tariff.

The goals of diabetes was originally developed in 1996 in Denmark and was a nationally programme. Along with Industry partners, NovoNordisk, this programme was adapted for use in the UK in 2010–2011 and distributed to every paediatric clinic in 2012. The major key elements in its development demanded an evidence-based, structured curriculum which is flexible, quality assured, dynamic and auditable (DoH NICE 2005).

The journey of its development and implementation will be described giving delegated insight into how to utilise the materials and record sheets with practical examples of its use in clinical practice.

DOI: 10.1530/endoabs.33.DP2

DP3
Developing the role of diabetes educator in the UK
K Ross
Oxford, UK.

The multidisciplinary diabetes team consists of health care professionals (HCP) each with a profession specific role who are required to be competent to a basic level in all aspects of diabetes care. Working together, teams provide all the education required to manage this condition to children and families as they grow up. The amount and complexity of information is increasing making it difficult to deliver to all individually. Group education is a solution but introduces a range of new skills required by the HCP’s to achieve the objectives of the education. Teaching methods and teaching materials adapted from those used with individuals in diabetes education is no longer adequate. The best practice tariff requires the provision of structured education that meets rigorous standards, not least in its consistency and effectiveness for each child whilst also providing peer support and other benefits of children learning life and diabetes skills together and from each other. This requires the skills of a teacher.

In the USA, Australia, Canada and Europe children’s diabetes teams often include a diabetes educator. These professionals have a variety of backgrounds however, the majority are nurses. The training to become a Credentialed Diabetes Educator is comprehensive with teaching skills just one component. This team member is
responsible for all the education and on going support of the child and family post diagnosis. In the UK we are developing training courses to support the role of a diabetes educator which would enhance the skills of that professional and includes teaching skills. However, it will take time and further resources to fully establish this role so we need an interim approach using existing skills within the diabetes team with priority given to dedicated time to manage the structured education programme – the first responsibility of that teams ‘diabetes educator’.

DP4
Psychology: narrative theory

Abstract unavailable.

DOI: 10.1530/endoabs.33.DP4

DP5
Kids in control of food: results from the KICk-OFF randomised controlled trial
K Price
Sheffield, UK.

KICk-OFF is a 5 days structured education course for 11–16 years old with type 1 diabetes. It has been developed with input from school teachers, children and families and follows constructivist learning theory. A pilot study resulted in some changes to the curriculum.

From 2008–2013 a cluster randomised controlled trial, funded by Diabetes UK, has been undertaken, involving 396 participants from 31 UK NHS diabetes centres. Courses were randomised to deliver KICk-OFF courses or continue usual care and support. Courses were taught by three educators (two KICk-OFF employed and one from local team), to groups of up to nine young people. All educators attended a 5-day teaching skills course in advance of delivering KICk-OFF courses.

Primary outcomes are HbA1c and quality of life. Secondary outcomes include diabetic ketoacidosis, hypoglycaemia, fear of hypoglycaemia and self efficacy. Health economic analysis and modelling of future costs to the NHS has been undertaken. Courses were observed by independent educationalists to assess the standard and consistency of teaching and achievement of key learning points. Attendance at courses was very good and feedback from participants and parents was excellent. The educationalists felt that the standard of teaching was high and the curriculum was appropriate for this age group. The mathematics involved in carbohydrate counting proved challenging for many young people and the educators needed to develop particular skills in supporting them with this. Results will be presented for the primary and some of the secondary outcomes.

DOI: 10.1530/endoabs.33.DP5

DP6
Transition to adult services
H Gleeson

Abstract unavailable.

DOI: 10.1530/endoabs.33.DP6

DP7
How does the The National Paediatric Diabetes Audit help improve outcomes for CYP with diabetes?
J Warner
Cardiff, UK.

The National Paediatric Diabetes Audit (NPDA) has now been established for 9 years and collects data on standards of care as defined by the National Institute for Clinical Excellence (NICE). These include demographics of paediatric diabetes, care process completion rates and outcomes.

Since April 2011 the NPDA has been managed by the Royal College of Paediatrics and Child Health (RCPCH) which comprises a project board advised by specific working groups associated with the dataset and with experience measures and representing stakeholders.

Under the guidance of the working groups and the project board the RCPCH have been engaging with stakeholders to improve participation and data quality. In 2010/2011 there was an increase in 23.4% of patients submitted to the audit. With the development of the regional networks in England it has been possible to express the data at individual unit level and at regional and national level allowing valuable benchmarking to take place. Risk adjusted outcomes are being developed for 2011/2012 data which will attempt to adjust for confounding factors such as deprivation, ethnicity and age.

The first national Patient/Parent Reported Experience Measure (PREM) for paediatric diabetes reported in 2013 with approximately half the paediatric diabetes population participating. There is wide unit and regional level variation in patient experience which requires careful benchmarking and evaluation. Data provided by the audit needs to be carefully reviewed by units and utilised as part of their peer review process to improve outcomes and quality of care by benchmarking against others and making changes to services where necessary.

DOI: 10.1530/endoabs.33.DP7

Endocrine Nurse Programme

EN1
Ipsen award 2012: managing children with symptomatic vitamin D deficiency; the role of the clinical nurse specialist
P Musson
Southampton, UK.

Over the past few years the number of children identified with vitamin D insufficiency/deficiency across the UK has increased. The Department of Health has recently reiterated the guidance for practitioners regarding at risk groups requiring surveillance and treatment recommendations. An audit in 2011 demonstrated that 30% of the children presenting to the paediatric orthopaedic service with musculoskeletal symptoms had vitamin D insufficiency or deficiency.

At the time management of these children was found to be inconsistent between practitioners, with children randomly being referred to the paediatric endocrine service, followed up in orthopaedic clinic or discharged to GP for management. Information given to parents by the orthopaedic service was also variable and 88% of parents were given no advice by their GP or hospital doctor on how to improve their child’s vitamin D status.

The increasing number of referrals to the paediatric endocrine service were not manageable and were increasing the waiting times for all new appointments. Following discussion with the paediatric orthopaedic team it was agreed that the patient pathway for these patients was changed. Since January 2012 children with symptomatic vitamin D deficiency referred to the paediatric endocrine service are given an appointment with the clinical nurse specialist (CNS).

A standard operational procedure for clinic appointments was agreed to inform the structure and standards for the service. The CNS has undertaken further study and supervised practice to gain the necessary skills and expertise to manage this cohort of children. Standard guidelines for the management of vitamin D deficiency are followed and information provided to families in a way they can understand that promotes concordance with the suggested treatment. Once care is complete the patient is discharged to the care of the general practitioner with advice on maintaining optimum vitamin D levels in the future.

Challenges in establishing this service, benefits to the families and outcomes will be discussed.

DOI: 10.1530/endoabs.33.EN1
The advanced nurse practitioner in paediatric endocrinology; the journey and the reality
P Laing
Liverpool, UK.

The National Health Service and Nursing are currently facing challenging times. Continuing austerity measures combined with healthcare reform and a climate of professional uncertainty often results in nurses having to justify their existence. The quality, innovation, productivity and prevention (QIPP) initiative sets out how the National Health Service is to make efficiency savings whilst improving the quality of care that patients receive. With the appropriate training, competency, professional accountability and support advanced nurse practitioners are in a unique position to work across the clinical interface and are good value for money in terms of patient safety, quality of service and efficiency, which are all high on the agenda at both government and NHS Trust level. This journey to advanced nurse practitioner presentation explores the concept of nurses developing their role in an innovative manner and explains how the step from clinical nurse specialist to advanced nurse practitioner can have a high impact effect on both personal and professional development and service delivery. The implementation of the advanced nurse practitioner role in endocrinology at Alder Hey Children’s Hospital is a new initiative and has moved from an embryonic phase to impacting positively upon service delivery and has been achieved through working collaboratively with clinicians, nursing colleagues and other members of the multidisciplinary team. DOI: 10.1530/endoabs.33.EN2

Multiple endocrine neoplasia (MEN) an overview
M Ahmed
Southampton, UK.

Multiple endocrine neoplasia type 1 (MEN1) and MEN are distinct clinical and genetic entities. This talk will cover the key clinical features and surveillance strategies for each of these conditions. DOI: 10.1530/endoabs.33.EN3

Not another blood test! Parent/patient experience of MEN
J Russell-Winter & H Russell-Winter

Not another blood test!
Living as a teenager with multiple endocrine neoplasia type 1. Brother and sister Joel (18 years) and Hope (14 years) Russell-Winter share their respective experiences of being diagnosed as teenagers with the rare condition multiple endocrine neoplasia type 1. They believe that the needs and experiences of teenagers are sometimes forgotten during hospital testing, consultations and treatment. Their presentation would like to tell you more about their condition, how it effects them, what’s it’s like trying to come to terms with it – including how friends, girl/boy friends and other people react. They also want to let you know what has been helpful (and not so helpful!) from those professionals caring for them with the condition. DOI: 10.1530/endoabs.33.EN4
Oral Communications
Oral Communications 1

OC1.1
GH testing: reducing the need for a second test for the diagnosis of GH deficiency
Zain Juma1, Angela Casey1, Juliia Prior1, Jeremy Kirk1 & Remuka Dias2
1Birmingham Children’s Hospital, Birmingham, UK; 2University of Birmingham, Birmingham, UK.

Background
The diagnosis of isolated GH deficiency (IGHD) is based on multiple factors: clinical, radiological and biochemical along with suboptimal peak GH levels demonstrated on dynamic testing. Recent guidance from the National Institute of Clinical Excellence (NICE; UK; 2010) advises that two GH stimulation tests must demonstrate a subnormal GH peak <6.7 µg/l (20 mU/l) to confirm the diagnosis of IGHD. In our centre, three different GH provocation tests are used: insulin tolerance, glucagon stimulation (1st line) and arginine stimulation (2nd line).

Objective and hypotheses
To see if other clinical and biochemical parameters can increase the sensitivity of GH provocation testing for the diagnosis of IGHD.

Methods
A retrospective case-review of all patients in a single centre from 2002 to 2012 undergoing two provocation tests, comparing those with two abnormal GH test results vs those with one abnormal result.

Results
107 children had two GH provocation tests; 41% with an abnormal 1st test had a normal GH response on retesting. Lowering the cut-off to 2.7 µg/l (~8 mU/l) to confirm the diagnosis of IGHD. In our centre, three different GH provocation tests are used: insulin tolerance, glucagon stimulation (1st line) and arginine stimulation (2nd line).

Discussion
To see if other clinical and biochemical parameters can increase the sensitivity of GH provocation testing for the diagnosis of IGHD.

GH testing: reducing the need for a second test for the diagnosis of GH deficiency
Zain Juma1, Angela Casey1, Juliia Prior1, Jeremy Kirk1 & Remuka Dias2
1Birmingham Children’s Hospital, Birmingham, UK; 2University of Birmingham, Birmingham, UK.

OC1.2
A single centre audit of the 2012 UK Newborn Screening Programme Guidelines for pre-term infants
Gemma Woods1, Shirley Langham2 & Catherine Peters2
1University of Cardiff Medical School, Wales, UK; 2Great Ormond Street Hospital, London, UK.

Newborn screening of premature infants for congenital hypothyroidism (CH) may initially be normal despite the presence of thyroid pathology and therefore repeat TSH screening is required. The 2012 revised UK Newborn Screening guidelines for premature infants state that infants born <32 weeks gestation require a repeat TSH bloodtest at 28 days postnatal age or discharge home, whichever is earlier. Prior to this, repeat testing was required at 36 weeks corrected gestation for all pre-term infants born <36 weeks.

Method
We audited pre-term referrals to our centre pre and post guideline changes. Data were collected for gestational age, birth weight, bloodspot TSH concentration, venous free T4 and TSH, age of referral and need for levothyroxine therapy.

Results
In babies born <32 weeks, we found an increase in referrals in the 1 year post policy change (17 referrals in 2012–2013 compared with an average of five referrals per year between April 2006 and 2012). The increase in referrals were mainly in infants with TSH concentrations <20 mU/l. 47 pre-term babies born at 32–36 weeks gestation were referred between 2006 and 2012. 14/47 had a venous TSH >20 mU/l and low free T4 concentrations and were commenced on levothyroxine.

Discussion
Changes to the newborn screening of premature infants has increased the number of borderline referrals born at <32 weeks. Repeat screening at 28 days may detect a TSH surge that has resolved when repeat screening occurs later at 36 weeks. These false positive referrals need to be balanced by the potential neurodevelopmental benefit of earlier commencement of levothyroxine for those babies with confirmed CH. The new standards no longer require repeat screening in babies born at 32–36 weeks gestation and would have missed the 14 babies requiring levothyroxine treatment prior to the change in standards.

OC1.3
The utility of AMH for predicting testosterone response to HCG stimulation in children with suspected DSD
Andreas Kyriakou1, Jane D McNelly2, M Guftar Shaikh1, Claudio Giacomozzi1, David Shapiro1 & S Faisal Ahmed1
1Department of Child Health, Royal Hospital For Sick Children, University of Glasgow, Glasgow, UK; 2Department of Biochemistry, Royal Hospital For Sick Children, Glasgow, UK; 3Department of Biochemistry, Glasgow Royal Infirmary, Glasgow, UK.

Introduction
In children undergoing investigation of testicular function the relationship between serum anti-Mullerian hormone (AMH) and the testosterone response to hCG stimulation test (HST) is unclear.

Methods
71 children (three females and 68 males) with a median age of 1.08 years (range: 0.003, 14.3) were investigated for suspected DSD by AMH on D1 and testosterone on D1 and D4, before and after 3-day HST. Of these children, 27 had an additional prolonged HST. Normal testosterone response to HST was defined as a testosterone greater than upper prepubertal limit or a testosterone increment (ΔT) greater than twice the baseline value. A low AMH was defined as below the 5th centile for age.

Results
The D4 testosterone response was normal in 61 with a median testosterone of 9.4 nmol/l (1.0, 40.7) and a median ΔT of 11.1 (0.8, 59.2) and abnormal in ten with a median testosterone of 0.55 nmol/l (0.5, 3.0) and a median ΔT of 1.0 (0.7, 1.9). AMH was low in 12/71 children and in 5 (42%) of these cases a low D4 testosterone was observed. An AMH >5th centile was associated with a low D4 testosterone in only 5/59 cases (8.4%) (P < 0.05). Median AMH in the two groups of patients who responded and did not respond by D4 was 708 pmol/l (97, 1926) and 107.6 pmol/l (1.5, 256) (P < 0.0001). The testosterone response after prolonged HST was normal in 23/27 children with a median testosterone of 15.0 nmol/l (0.8, 43.4) and a median ΔT of 18.2 (0.57, 62.0) and abnormal in four with a median testosterone of 0.55 nmol/l (0.5, 1.0) and a median ΔT of 1.0 (0.6, 1.2). AMH was low in six children and in 3 (50%) of these cases a low D22 testosterone was observed. An AMH >5th centile was associated with a normal D22 testosterone in 20/21 cases (95%) (P < 0.05). Median AMH in children who responded and did not respond at D4 and D22 was 420 pmol/l (100, 1664) and 2.8 pmol/l (1.5, 214) (P < 0.05). Conclusion
A normal AMH may provide valuable information on overall testicular function. However, a low AMH does not necessarily predict a sub-optimal testosterone response to HCG stimulation.

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OC1.4
Abnormal glucose homeostasis in survivors of childhood acute lymphoblastic leukaemia treated with bone marrow transplantation and total body irradiation is associated with reduced β-cell reserve and pancreatic volume
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Background
Adult survivors of childhood acute lymphoblastic leukaemia (ALL) treated with bone marrow transplantation (BMT) and total body irradiation (TBI) have increased risk of impaired glucose tolerance (IGT) and diabetes mellitus (DM). Insulin resistance (IR) has been described, but effects of TBI on pancreatic growth and β-cell function have not been previously reported.

Method
Two groups of childhood ALL survivors were studied: Group 1, treated with (n=21, 11 M) and Group 2, children (n=31, 13 M) BMT/TBI. BMT/TBI survivors received 10–14.4 Gy TBI at mean age 9.3 (1.0–10.8) years. A control Group 3, was selected of obese subjects (n=30, 10 M). All were age 16–26 years

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and had assessment of: pancreatic volume by abdominal MRI; IR by insulin composite insulin sensitivity index (ISComp) from oral glucose tolerance test (OGTT); β-cell function by acute-insulin-response (AIR) from Arginine intravenous glucose tolerance test (AIRCarg). Data were logarithmically transformed if positively skewed and analysed by ANOVA with post-hoc Scheffé’s multiple comparison tests, multiple regression and Pearson’s correlations at 5% significance. Results are reported as mean (S.D.) or geometric means (range) as appropriate.

Results

Abnormal OGTT were reported in Groups 1 (DM = 2, IGT = 7) and 3 (IGT = 1). ISComp was lower in Groups 1 (1.7 (0.35–44.7), P < 0.001) and 3 (4.8 (0.75–9.6), P = 0.003) compared with Group 2 (2.2 (0.76–7.5)). β-cell function assessed in the context of IR was significantly lower in Group 1 (60.0 (CI: 43.8–76.7)) than Groups 2 (105.4 (CI: 79.3–138.4), P = 0.003) and 3 (83.8 (CI: 69.7–100.9), P = 0.034). Absolute pancreatic volume (cm³) (PV) was lower in Group 1 (52.0 (14.2)) than Groups 2 (72.8 (23.5), P = 0.003) and 3 (72.8 (19.7), P = 0.006) and correlated with AIR (r = 0.3, P = 0.01). Pancreatic volume correlated positively with the size (represented by height) of participants (r = 0.45, P < 0.001).

Regression analysis confirmed that PV adjusted for size remained lower in Group 1 (56.4 (47.4–65.1)) than Groups 2 (71.0 (63.8–78.2), P = 0.014) or 3 (71.2 (62.3–79.3), P = 0.016). Absolute and corrected PV did not differ between Groups 2 and 3 (P = 1.0) and did not correlate with age at ALL diagnosis (P = 0.9), time from treatment (P = 0.3), age at BMT (P = 0.7), time from BMT (P = 0.3) or TBI dose (P = 0.8).

Conclusions

This study suggests that reduction in pancreatic size, and loss of β-cell compensation contribute, with increased IR, to the mechanism of abnormal glucose homeostasis in survivors of BMT/TBI in childhood.

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OC1.6

Oural bisphosphonates as prophylaxis of steroid-induced osteoporosis in Duchenne muscular dystrophy

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Background

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy, resulting in death at a young age. Corticosteroids improve muscle function and slow disease progression. However long-term steroid therapy is a significant risk factor for osteoporosis.

Aims

To assess the effect of oral bisphosphonate (risdroronate) treatment on bone mineral density in a cohort of steroid-treated children with DMD.

Method

Annual bone mineral density (DXA) scans were performed on boys with DMD treated with glucocorticoid under review at a National Muscle Centre. Data prior to bisphosphonate initiation were compared with subsequent annual DXA assessments. Lumbar spine and total body bone densities were corrected for bone volume. Information about duration of steroid treatment and fractures was also collected. All patients received vitamin D supplementation.

Results

Data on 43 patients was analysed. The median duration of steroid therapy at the initiation of bisphosphonate therapy was 33 months (range: 0–87 months). The duration of bisphosphonate therapy ranged from 1 to 4 years (average 2 years). Total body adjusted density Z score increased post bisphosphonate therapy from -0.55 at baseline to 0.62 after 3 years (P = 0.009) whilst lumbar spine adjusted density (LSAD) remained stable with a baseline value of 0.11 and 0.21 at year 3 (P = 0.97). LSAD in those with an initial Z score < -1 increased from -1.44 to -0.49 (P < 0.01). Eight patients had documented fractures following a fall whilst on bisphosphonate therapy. Three of these involved lumbar spine and these patients all had a LSAD < -1 SDS at baseline.

Conclusions

The size adjusted lumbar spine BMD of steroid treated patients with DMD on bisphosphonates remains stable and particular benefit was seen in those with an initial LSAD < -1 SDS. The relationship between fracture and baseline LSAD highlights the need to consider ways of reining bone protection in these patients with more targeted therapy.

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OC1.7

A mutation in thioredoxin reductase 2 is associated with familial glucocorticoid deficiency

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Background

Disturbances of pubertal timing affect > 4% of the population and are associated with adverse health outcomes. Studies estimate 60–80% of variation in pubertal onset is genetically determined, but few genetic factors are known. We hypothesise that causal variants will be low-frequency, intermediate-impact variants and will be enriched in populations at the extremes of normal pubertal timing. Families with constitutional delay in growth and puberty (CDGP) have pubertal onset delayed by > 2 s.d., often with an apparent autosomal dominant inheritance pattern.

Methods

Seven highly informative families from our large, accurately phenotyped CDGP cohort were selected for whole exome sequencing. Annotation and filtering of variants produced an extensive list of potential causative mutations that segregate with trait. Variants were ranked on the basis of presence in > 1 family, minor allele frequency < 5% or novel, predicted effect on the protein and conservation. Pathway analysis was performed to identify genes with action within the hypothalamic–pituitary–gonadal axis or in linkage disequilibrium (D’ > 0.8) with loci identified by genome-wide association studies (GWAS) of age-at-menarche.

Results

The 15 top-ranking genes identified all contained non-synonymous missense variants segregating an autosomal dominant pattern. Validation of these 15 genes through targeted re-sequencing in a further 288 CDGP individuals has identified a novel homozygous mutation, p.Y447X in TXNRD2. By Sanger sequencing of all family members. A TXNRD2-adenocortical H295R cell line was established to investigate redox homeostasis. Glutathione and thioredoxin anti-oxidant systems to detoxify mitochondrial H2O2. Knockdown human

Discussion

We describe our strategy for identification of novel causal gene variants from next-generation sequencing data in this common condition. In addition to the exciting finding of a novel gene implicated in the timing of puberty, our results highlight the significant genetic heterogeneity seen in CDGP.

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malformation and heterozygous mutations are described in humans with dilated cardiomyopathy. We find that TXNRD2 is ubiquitously expresssed in human tissues with high mRNA levels in the adrenal cortex. The predicted consequence of the mutation was premature truncation removing the seleniumcysteine residue, however RT-PCR of patient cDNA and western blotting of patient lysates revealed complete absence of TXNRD2 in patients homozygous for the mutation presumably as a result of nonsense-mediated decay of mRNA. In our affected homozygote individuals, with apparent absence of TXNRD2, we observe no evidence of cardiomyopathy or conduction disease. TXNRD2 knockdown in the H295R cell line leads to increased oxidative stress with pressure on the glutathione system and increased mitochondrial superoxide production.

Conclusion
A delicate balance of mitochondrial redox regulation controls steroidogenesis at the level of the adrenal gland. We report the first mutation in TXNRD2 associated with a predominantly adrenal phenotype, indicating the importance of the thioredoxin system in maintaining redox homeostasis in the adrenocortical environment.

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OC1.8
The repressor activity of the Wnt/β-catenin effector Tcf3/TcF7L1 is required for normal hypothalamic-pituitary development
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Aberrant development of the pituitary gland can result in the clinical manifestation of hypopituitarism. The Wnt/β-catenin pathway has been shown to be involved in normal organogenesis, terminal differentiation and the aetiology of pituitary tumours. However, the specific developmental roles during hypothalamic-pituitary development of some of the Wnt/β-catenin effectors, such as Tcf3, have been hampered due to the early lethality of null embryos for this gene. To overcome this, we have conditionally deleted Tcf3 (Tcf3flox/flox; Hesx1Cre+/−) from the Hesx1-expressing cells within the early forebrain and developing pituitary gland. A low proportion of Tcf3flox/flox; Hesx1Cre+/− animals exhibit dwarfism indicating that deficiency in Tcf3 can lead to hypopituitarism in mice. Analyses of Tcf3flox/flox; Hesx1Cre+/− mutant embryos reveals a mild hyperplasia of the pituitary gland, sometimes with the mis-location of the pituitary in the pharyngeal cavity. We show that Tcf3 has a dual function and it is required in both the ventral diencephalon (VD) and anterior pituitary gland (AP).

In the VD, absence of Tcf3 results in aberrant VD signalling with rostrally expanded Fgf10 and BMP4 expression domains, leading to a broader region of the oral ectoderm being specified into Rathke’s pouch. Within the developing AP, absence of Tcf3 results in increased mitotic index of peripluminal Rathke’s pouch progenitors, further exacerbating the AP-hyperplasia. To assess if TCF3 is required to mediate transcriptional activation or repression of Wnt/β-catenin pathway, we studied a second murine mutant (Tcf3flox/flox; Cyp11b1−/−) expressing a mutant TCF3 lacking the β-catenin interacting domain, and therefore acting as a constitutive repressor. Interestingly, Tcf3flox/flox; Cyp11b1−/− embryos exhibit normal developmental of both the prospective hypothalamus and the pituitary gland throughout all developmental stages, indicating that TCF3-repressing activity is essential for hypothalamic-pituitary development. Providing a translational impact to this research, we report the identification of a novel mutation in RTCF3 that compromises TCF3-repressing activity in a patient with septo-optic dysplasia (SOD), suggesting a contributory role of TCF3 in SOD. In summary, our research demonstrates a critical role for the Wnt/β-catenin effector Tcf3 during early development of the pituitary-hypothalamic axis in mice and humans.

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OC1.9
Genetic characterisation of short children with potential defects of GH action by single gene sequencing
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Background
GH resistance or primary IGF1 deficiency (PIGFD) presents with growth failure, low serum IGF1 and normal/elevated serum GH. PIGFD comprises a spectrum of phenotypic and biochemical abnormalities for which genetic GH-IGF1 axis defects may be causative.

Objective
Genotyping of PIGFD patients referred for sequencing of candidate genes.

Methods
From 2008 to 2013, 62 patients (42 males and 20 females), median age 6.9 years (range 0.4–17.0) with short stature (mean height SDS −3.4; range −9.4 to −1.1) were referred for genotyping. Depending on the phenotype, coding exons/intron boundaries of GHR, the GHR pseudogene, STAT3B, IGFALS, IGF1 and OBSL1 were amplified by PCR from genomic DNA and the products purified and sequenced on an automated DNA sequencer (ABI 3700).

Results
Median serum IGF1 levels were 32.9 ng/ml (range 1.4–95.0; below the normal IGF1 range for age), with 15 patient samples being below the lower limit of the assay. GH secretion was normal or elevated; median peak GH 19.0 μg/l (range 6.0–119.0). Seven patients did not have GH provocation tests, basal GH being elevated (median 45.0 μg/l, range 12.3–398.0). Seventeen patients (27%) had mutations in GH-IGF1 axis genes: homozygous GHR (n = 13; including six pseudogene and two novel IVS5s +1 G to A), homozygous IGFALS (n = 3; 1 novel c.1291delT) and a novel heterozygous STAT3B (n = 1; p.A477V). Heights in these subjects were −6.9 to −2.0 SDS. Two homozygous mutations were identified in the OBSL1 gene (height SDS −4.9 and −5.7). Two other patients had hypomethylation in imprinting control region one in 1p15 or maternal UPD for chromosome seven consistent with Silver–Russell syndrome (SRS) (height SDS −3.7 and −4.3).

Conclusions
Genotyping is advised in short children with PIGFD. In 27% of PIGFD patients, all with heights <−2.0 SDS, a genetic abnormality demonstrated a major contribution to pathogenesis. Diagnoses with similar phenotypes included SRS and 3M syndrome. In 65% (n = 41) of patients no diagnosis was defined justifying further genetic investigation.

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Oral Communications 2
OC2.1
Whole Exome Sequencing as a diagnostic tool in adrenal insufficiency
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Introduction
In recent years a growing number of gene mutations have been identified which cause a myriad of syndromes having adrenal insufficiency as a core characteristic. The evolution of each syndrome is dependent on the variant and the particular gene affected. Common practice is for candidate genes to be sequenced individually, which can be time consuming and is complicated by overlapping clinical phenotypes. The increasing availability and cost effectiveness of whole exome sequencing (WES) is proving to be a powerful alternative, especially in disorders where a large number of causative genes need to be sequenced to gain a definitive diagnosis.

Methods
WES was performed on 38 probands referred to our unit with a clinical diagnosis of familial glucocorticoid deficiency. All had been screened for mutations in MC2R, MRAP and STAR and most for mutations in GPX1 and NNT, the five genes linked to FGD.

Results
We made a genetic diagnosis in 14 probands plus two of their affected siblings, identifying mutations in the following genes: NR0B1 in four patients, CYP11A1 in five patients plus a sibling, AASS in two patients, MC2R in one patient, CYP11B1 in one patient and AIRE in a pair of brothers, most mutations were novel. Genetic diagnoses were confirmed by direct sanger sequencing of the index case and other family members.

Conclusion
A genetic diagnosis was therefore readily achieved more than a third of patients that underwent WES. It is feasible that many of the other cases are caused by novel gene defects. WES as a diagnostic tool offers rapid accurate screening for disease variants, thus reducing erroneous clinical diagnoses and enabling targeted treatment plans that should result in better long-term clinical outcomes. We believe that the evolution of WES into a diagnostic tool offers a rapid cost effective way of screening patients for monogenic diseases.

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OC2.2

Increased bone area without reduction in volumetric bone mineral density in children treated with glucocorticoids for nephrotic syndrome
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Background
Glucocorticoids are frequently used to treat childhood inflammatory disorders, and may cause increased fracture predisposition with reduced bone mineral density (BMD), particularly from trabecular bone loss. The contribution of the underlying inflammatory disease processes to these outcomes is poorly understood. Childhood nephrotic syndrome (NS) is a useful model to investigate the effects of steroids on bone, as recurrent courses are often required, but systemic inflammation is low during remission.

Methods
Children with NS were compared to age- and sex-matched controls. Body composition and areal BMD were assessed by DXA. Peripheral quantitative computed tomography (pQCT) scans were obtained at the tibial metaphysis (4%) and diaphysis (66%) to determine volumetric BMD and bone geometry. Lifetime cumulative glucocorticoid exposure was calculated from medical records.

Results
29 children with NS (55% male, age 10.7±3.1 years) were compared to 29 healthy controls (55% male, age 11.0±3.0 years). Children with NS were of similar height SDS to controls (P=0.28), but were heavier (P=0.02) with greater % body fat SDS (P=0.008). Tibial trabecular and cortical vBMD were similar between the two groups but cross-sectional area (CSA) was significantly greater in children with NS at the metaphysis (954±234 vs 817±197 mm², P=0.002) and diaphysis (555±163 vs 463±156 mm², P=0.014). Cortical thickness was lower in the children with NS (2.4±0.7 vs 2.8±0.7 mm, P=0.018), but cortical CSA was similar to controls (P=0.22). The differences in geometry were no longer significant when adjusted for weight. Cumulative steroid exposure was not associated with bone outcomes.

Conclusions
Tibial bone CSA is increased in children with NS. We speculate this is a compensatory response to increased body weight. Reductions in vBMD were not identified in this cohort of children with NS.

DOI: 10.1530/endoabs.33.OC2.2

OC2.3

Clinical phenotype of patients with MCM4 mutation suggests pubertal delay in males
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Background
We recently reported the first human mutation in mini-chromosome maintenance homologue 4 (MCM4) in a cohort of patients with adrenal failure. We now report the clinical phenotype of patients with MCM4 mutations.

Methods
Patients case notes were examined and investigations performed to fully assess adrenal function, pubertal development, gonadal function and growth.

Results
13 of 14 patients have developed isolated glucocorticoid deficiency with age of diagnosis ranging from 0.5 to 12 years. Five patients initially had normal adrenal function. All patients have undetectable DHEAS levels and low androstendione levels. Clinically all children >8 years have absent adrenarche. Renin and aldosterone levels were normal. Children had low birth weight (average –2.3 SDS) and subsequent short stature (< –2.6 SDS). Boys showed lack of a pubertal growth spurt and final height was significantly shorter than girls (males –2.8 SDS, females –1.8 SDS, P=0.01). All children who have reached final height were significantly shorter than their mid-parental height. The GH and IGFI axis was normal.

Four girls were of pubertal age; all entered and progressed through puberty normally and have normal menstrual cycles. In contrast all five boys of pubertal age had severe delay of growth and puberty and one required testosterone injections to induce puberty. Initially LH/FSH stimulation tests showed a pre-pubertal response. Subsequently two boys showed evidence of endogenous testosterone production with normal gonadotrophins and morning testosterone levels.

Conclusion
Patients with MCM4 mutations have isolated glucocorticoid deficiency with no evidence of mineralocorticoid deficiency. Both clinically and biochemically children have no evidence of adrenal androgen production suggesting failure of development of the zona reticularis. In addition boys have evidence of a significant delay in pubertal development. This potentially indicates a role for adrenal androgen priming in male puberty or a novel function of MCM4 in pubertal response. Subsequently two boys showed evidence of endogenous testosterone production with normal gonadotrophins and morning testosterone levels.

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OC2.4

FGF21 causes GH resistance in human chondrocytes through activation of SOCS2 and inhibition of IGFI1 expression
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Background
Fibroblast growth factor 21 (FGF21) is a key metabolic regulator in the adaptation to fasting. In food-restricted mice, inhibition of skeletal growth appears to be mediated by the antagonistic effect of FGF21 on GH action in the liver and in the growth plate (Kubicky et al. 2012, Yu et al. 2012). The role of FGF21 in growth regulation in humans is currently unknown.

Objective and hypothesis
To provide mechanistic insights into the reduced caloric intake associated with GH insensitivity and growth failure we hypothesized that FGF21 inhibits GH action in human chondrocytes by blocking post-receptor GH signaling.

Methods
We established chondrocyte primary cultures from costal cartilage of pediatric patients undergoing reconstructive surgery. We first assessed the integrity of the GH-receptor and IGF1 receptor signaling by western blotting, and expression of the FGF21 receptor complex by RT-PCR. Next we tested the effect of recombinant FGF21 on basal and GH-induced suppressor of cytokine signaling 2 (SOCS2) expression, basal and GH-induced IGF1 expression by qPCR, and basal and GH/IGF1-induced cell proliferation by Methylene Blue assay.

Results
Human chondrocyte cultures expressed GH-receptor and responded to recombinant to GH and IGF1 through phosphorylation of ERK1/2, AKT and STAT5, and expressed the complex FGFR1c/ KLOTHO, the preferred FGF21 receptor complex by RT-PCR. Next we tested the effect of recombinant FGF21 on basal and GH-induced suppressor of cytokine signaling 2 (SOCS2) expression, basal and GH-induced IGF1 expression by qPCR, and basal and GH/IGF1-induced cell proliferation by Methylene Blue assay.

Conclusion
FGF21 blocks GH action in human chondrocytes by inhibiting post-receptor signaling involving induction of SOCS2 and inhibition of IGF1 expression. These data provide a new mechanistic insight into GH resistance secondary to reduced caloric intake.

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OC2.5

Continuous s.c. infusion of parathyroid hormone reduces PTH requirement in patients with activating mutation of the calcium sensing receptor
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Background
Activating mutations in the calcium sensing receptor can result in severe hypohyperparathyroidism with symptomatic hypocalcaemia. Complications of treatment with calcitriol or alfacacidol include hypercalcuria, nephrocalcinosis and renal failure. The use of synthetic parathyroid hormone (PTH 1–34, teriparatide)
she was requiring 75 m daily s.c. injections of PTH. Her requirements slowly increased and after 3 years, after informed discussion, eucalcaemia was successfully achieved with twice daily s.c. injections of PTH. Her requirements slowly increased and after 3 years, she was requiring 75 μg daily in three divided injections, almost twice the recommended adult dose. To reduce the total dose of PTH and the need for multiple daily injections, CSIP was commenced using an insulin infusion pump to deliver the PTH at a constant rate throughout the day and night.

Discussion
PTH administered via CSIP significantly reduced the total daily dose, indicating that this more effective than multiple s.c. injections. She no longer required multiple injections and only needed to change her giving set every 3 days. We recommend that this is the treatment of choice in cases such as these.

Discussion
Pseudoephedrine was 2.2 mmol/l. PTH 1–34 was infused initially at a rate of 72 μg/day (equivalent to the dose being received by injection) but she rapidly became hypocalcaemic. 72 h after starting the infusion, her total dose had been reduced by 50% and her calcium stabilised.

Discussion
We report for the first time to our knowledge a novel homozygous mutation in LHX4 located at highly conserved residues. Additionally, we identified a novel heterozygous missense mutation (c.1099A>C, p.N337T) in a Caucasian female patient with isolated GHD (peak GH: 1.47 μg/l) learning difficulties, obesity and an EPP. The mutation is in the C-terminal domain, possibly affecting protein–protein interaction. DNA analysis confirmed the presence of a homozygous p.T126M mutation, located in the LIM-zinc-finger binding domain 2, predicted to alter protein–

Discussion
Objective and hypotheses
We screened 150 patients with CPHD (the vast majority having an ectopic posterior pituitary (EPP)) using PCR and direct sequencing analysis. Upon identification of any variants, 100 ethnically-matched controls were screened and control databases (1000 genomes, dbSNP) consulted.

Results
We identified a novel homozygous missense mutation (c.377C>T, p.T126M) in two deceased male patients of Pakistani origin, born to non-consanguineous parents, with panhypopituitarism. The parents also had a daughter with a depressed nasal bridge and cleft palate. The second son had panhypopituitarism and was born small for gestational age with a micrognathia, underdeveloped scrotum, and mid-facial hypoplasia. In spite of rapid commencement of hydrocortisone and thyroxine, all three children died within the first week of life. DNA analysis confirmed the presence of a homozygous p.T126M mutation, located in the LIM-zinc-finger binding domain 2, predicted to alter protein–protein interaction. Additionally, we identified a novel heterozygous missense mutation (c.1099A>C, p.N337T) in a Caucasian female patient with isolated GHD (peak GH: 1.47 μg/l) learning difficulties, obesity and an EPP. The mutation is in the C-terminal domain, possibly affecting protein–protein interaction. Both mutations are located at highly conserved residues.

Discussion
Objective and hypotheses
To investigate a cohort of patients with congenital hypopituitarism for mutations in LHX4.

Method
We screened 150 patients with CPHD (the vast majority having an ectopic posterior pituitary (EPP)) using PCR and direct sequencing analysis. Upon identification of any variants, 100 ethnically-matched controls were screened and control databases (1000 genomes, dbSNP) consulted.

Results
We identified a novel homozygous missense mutation (c.377C>T, p.T126M) in two deceased male patients of Pakistani origin, born to non-consanguineous parents, with panhypopituitarism. The parents also had a daughter with a depressed nasal bridge and cleft palate. The second son had panhypopituitarism and was born small for gestational age with a micrognathia, underdeveloped scrotum, and mid-facial hypoplasia. In spite of rapid commencement of hydrocortisone and thyroxine, all three children died within the first week of life. DNA analysis confirmed the presence of a homozygous p.T126M mutation, located in the LIM-zinc-finger binding domain 2, predicted to alter protein–protein interaction. Additionally, we identified a novel heterozygous missense mutation (c.1099A>C, p.N337T) in a Caucasian female patient with isolated GHD (peak GH: 1.47 μg/l) learning difficulties, obesity and an EPP. The mutation is in the C-terminal domain, possibly affecting protein–protein interaction. Both mutations are located at highly conserved residues.

Discussion
Objective and hypotheses
To evaluate the utility of four published clinical scoring systems for genetic testing in a cohort of patients referred to a clinical service laboratory.

Methods
Individuals with suspected SRS referred for molecular genetic testing of H19 methylation status or mUPD7 were scored according to published criteria. Anthropometric measures and clinical features were requested from the referring clinician using a custom-designed questionnaire.

Results
36 of 139 (25.9%) patients referred for testing had a genetic abnormality identified. Comparison of four published clinical scoring systems demonstrated that all included subjective criteria that could be difficult for the general clinician to assess. We developed a novel, simplified, scoring system utilising four objective, easily measured parameters (low birthweight, postnatal growth failure, relative macrocephaly and asymmetry) that performed similarly to the most sensitive and specific published scoring system (~80%).

Conclusions
Effective utilisation of genetic testing by clinicians without specialist genetic expertise will be facilitated by the development of targeted testing protocols of PTH (CSIP) that are based on robust objective clinical features and that are designed for use in a busy clinical practice rather than a research setting.

Discussion

OC2.7
Novel lethal form of hypopituitarism associated with the first recessive LHX4 mutation
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Background
LHX4 encodes a member of the LIM-homeodomain transcription factor protein family that is required for development of the pituitary gland. To date, only incompletely penetrant heterozygous mutations in LHX4 have been described in patients with variable combined pituitary hormone deficiencies (CPHD).

Objective/hypothesis
To investigate a cohort of patients with congenital hypopituitarism for mutations in LHX4.

Method
We screened 150 patients with CPHD (the vast majority having an ectopic posterior pituitary (EPP)) using PCR and direct sequencing analysis. Upon identification of any variants, 100 ethnically-matched controls were screened and control databases (1000 genomes, dbSNP) consulted.

Results
We identified a novel homozygous missense mutation (c.377C>T, p.T126M) in two deceased male patients of Pakistani origin, born to non-consanguineous parents, with panhypopituitarism. The parents also had a daughter with a depressed nasal bridge and cleft palate. The second son had panhypopituitarism and was born small for gestational age with a micrognathia, underdeveloped scrotum, and mid-facial hypoplasia. In spite of rapid commencement of hydrocortisone and thyroxine, all three children died within the first week of life. DNA analysis confirmed the presence of a homozygous p.T126M mutation, located in the LIM-zinc-finger binding domain 2, predicted to alter protein–protein interaction. Additionally, we identified a novel heterozygous missense mutation (c.1099A>C, p.N337T) in a Caucasian female patient with isolated GHD (peak GH: 1.47 μg/l) learning difficulties, obesity and an EPP. The mutation is in the C-terminal domain, possibly affecting protein–protein interaction. Both mutations are located at highly conserved residues.

Discussion
Objective and hypotheses
To evaluate the utility of four published clinical scoring systems for genetic testing in a cohort of patients referred to a clinical service laboratory.

Methods
Individuals with suspected SRS referred for molecular genetic testing of H19 methylation status or mUPD7 were scored according to published criteria. Anthropometric measures and clinical features were requested from the referring clinician using a custom-designed questionnaire.

Results
36 of 139 (25.9%) patients referred for testing had a genetic abnormality identified. Comparison of four published clinical scoring systems demonstrated that all included subjective criteria that could be difficult for the general clinician to assess. We developed a novel, simplified, scoring system utilising four objective, easily measured parameters (low birthweight, postnatal growth failure, relative macrocephaly and asymmetry) that performed similarly to the most sensitive and specific published scoring system (~80%).

Conclusions
Effective utilisation of genetic testing by clinicians without specialist genetic expertise will be facilitated by the development of targeted testing protocols of PTH (CSIP) that are based on robust objective clinical features and that are designed for use in a busy clinical practice rather than a research setting.

Discussion

OC2.8
Establishing a national audit of paediatric GH prescribing
Emma-Jane Gauld1, Sheila Shepherd2 & Nick Shaw
1University of Glasgow, Glasgow, UK; 2NHS Greater Glasgow and Clyde, Glasgow, UK; 3Birmingham Children’s Hospital, Birmingham, UK.

Introduction
GH therapy is prescribed to UK children for a variety of indications. However, no central record exists, making follow-up studies difficult.

Aim
To establish an ongoing audit of UK children and adolescents newly-prescribed GH in order to i) monitor trends in prescribing practice and ii) facilitate future long-term follow-up.

Patient population
UK children aged ≤16.0 years newly starting GH therapy.

Methods
Consultants prescribing paediatric GH (BSPED members/non-members) can participate. The following anonymised data are recorded: partial postcode, diagnostic category, sex, month/year of birth, age, GH dose, injections per week, ongoing prescription (GP/hospital). Data are submitted and collated centrally quarterly. Audit ID numbers are allocated and sent to participating centres for local linkage to NHS, CHI or H&C numbers.

Results
Eighty-four centres are participating; for the first quarter (Jan/Feb/Mar 2013, 75 submitted returns (89%), of which 22 had no patients to report. The remaining 53 centres reported 250 patients (M/F: 138/112) treated at a median (range) age of 8.2 (0.2–22.6) years for the following indications.

Discussion

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Most treatment is for a licensed indication and initiated at all paediatric ages. (248) receive daily injections and most ongoing prescribing is via the GP (152 vs both 90), with mg/kg per week less common (68; Table 1). The majority

Table 1 Indication for GH therapy (n).

<table>
<thead>
<tr>
<th>Indication</th>
<th>GHD</th>
<th>TS</th>
<th>PWS</th>
<th>CRl</th>
<th>SGA</th>
<th>SHOX</th>
<th>Other</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>134</td>
<td>23</td>
<td>9</td>
<td>7</td>
<td>39</td>
<td>4</td>
<td>34</td>
</tr>
</tbody>
</table>

Conclusion
Early indications are that a national audit of paediatric GH prescribing is feasible. Most treatment is for a licensed indication and initiated at all paediatric ages. Ongoing challenges include maintaining the initial high return rate and auditing local data linkage; fundamental to future follow-up studies.

DOI: 10.1530/endoabs.33.OC2.8

OC2.9

A comprehensive next generation sequencing-based strategy for genetic diagnosis in congenital hypothyroidism

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Introduction
Less than 20% of congenital hypothyroidism (CH) has a known genetic aetiology; thyroid transcription factor mutations (PAX8, Nkx2.1, Nkx2.5, FOXE1) or biallelic TSHR mutations cause <5% of thyroid dysgenesis (TD), whereas mutations in genes mediating thyroid hormone biosynthesis (TPO, TG, DUOX2, DUOX2, IYD, SLC5A5, SLC26A4) account for most dysmorphogenesis cases. Increased CH frequency in consanguineous populations, relatives of TD cases, and in conjunction with extrathyroidal anomalies suggests involvement of hitherto unidentified genes. Although genetic diagnosis is not routinely undertaken, establishing the molecular basis of CH may inform treatment, anticipate extrathyroidal features and confirm recurrence risk to facilitate genetic counselling. Prediction of genetic basis from clinical phenotype is unreliable, precluding implementation of selective candidate gene analysis; accordingly, a comprehensive genetic screening strategy has been developed.

Method
Compared to conventional sequencing, next generation sequencing (NGS) technologies increase sequencing capacity and speed, with molecular ‘barcodes’ enabling multiplex analysis of samples, to improve throughput and efficiency. 11 known and 20 putative CH-associated genes were screened using NGS in 49 families. This genetic diagnostic strategy aimed to identify mutations in known and predicted CH-associated genes and to delineate a ‘mutation-negative’ cohort in whom novel genetic causes can be sought.

Results
Ten families harboured mutations in known causative genes, of which five were known (DUOX2: Q686X, R354W, TPO: R665Q, R491H, TG R277X) and six were novel (DUOX2: Q570L, TG: S509X, R140X W1031L, C707Y, T1397RfsX30, c.638+5 G>A); two families harboured compound TG mutations.

Conclusion
NGS enables efficient screening of multiple genes simultaneously, facilitating genetic diagnosis in CH. Such comprehensive screening will identify mutations in known genes associated with atypical clinical phenotypes, and in putative CH-associated genes identified from animal models. Identification of ‘mutation-negative’ cases defines a population in whom whole exome sequencing may identify novel genetic aetiologies for CH, elucidating novel pathways in thyroid development and physiology.

DOI: 10.1530/endoabs.33.OC2.9

OC2.10

A new approach to the definition and diagnosis of adrenal insufficiency during inhaled corticosteroid therapy for asthma

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1Alder Hey Children’s NHS Foundation Trust, Liverpool, UK; 2Lancaster University, Lancaster, UK.

Background
Up to 50% of children treated with inhaled corticosteroids (ICS) have biochemical evidence of adrenal insufficiency (AI). Episodes of adrenal crisis (AC) are extremely rare.

To address the discordance between the prevalence of biochemical AI and AC, we re-examined the biochemical definition of AI during ICS therapy. We then investigated the utility of early morning salivary cortisol (EMSC) and cortisone (EMSCn) for the identification of patients with AI using standard and revised diagnostic criteria.

Patients and methods
Cases of AC during ICS therapy in childhood were identified on PubMed. Data from these cases were used to inform a revised definition of AI on the LDSST. Fifty cases of AC were identified in PubMed. Dynamic function tests were re-examined the biochemical definition of AI during ICS therapy. We then investigated the utility of early morning salivary cortisol (EMSC) and cortisone (EMSCn) for the identification of patients with AI using standard and revised diagnostic criteria.

Introduction
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Patients and methods
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Results
Thirty-five cases of AI were identified in PubMed. Dynamic function tests were re-examined the biochemical definition of AI during ICS therapy. We then investigated the utility of early morning salivary cortisol (EMSC) and cortisone (EMSCn) for the identification of patients with AI using standard and revised diagnostic criteria.

Discussion
Screening subjects using EMSCn, followed by a LDSST using PC concentration. The relationship between EMSC and EMSCn and peak cortisol (PC) on the LDSST was determined.

Conclusions
A new approach to the definition and diagnosis of adrenal insufficiency during inhaled corticosteroid therapy for asthma.

DOI: 10.1530/endoabs.33.OC2.10
**OC3.1**

**Catch up growth and insulin sensitivity in adolescent children born preterm**

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1 Newcastle Neonatal Service, Newcastle Hospitals NHS Foundation Trust, Newcastle, UK; 2 Institute of Health and Society, University of Newcastle, Newcastle, UK; 3 Institute of Genetic Medicine, University of Newcastle, Newcastle, UK.

**Background**

Preterm infants represent around 10% of births worldwide and have increased risk of adverse metabolic outcomes in later life. The approach to feeding preterms must balance the need to promote brain growth by providing adequate nutrients whilst avoiding potentially harmful excess nutrition.

**Objective**

To investigate the association between patterns of weight gain in infancy and childhood with later insulin sensitivity in adolescents who were born preterm. Design, setting and participants Growth was assessed at regular intervals during the neonatal period, and early childhood. Subjects were reassessed in adolescence and underwent a short oral glucose tolerance test and assessment of fat mass using dual X-ray absorbmetry. Earlier growth parameters were compared with body compositional data and insulin sensitivity derived using the homeostatic model assessment.

**Results**

153 children were reviewed, 102 consented to venepuncture at a median age of 11.5 years. Median birthweight was 1365 g and mean gestation was 30.8 ± 2.2 weeks. Neither gestation nor birthweight SDS were associated with adolescent insulin sensitivity. Increase in weight SDS between birth and discharge was positively associated and increase in weight SDS between discharge and term negatively associated with later insulin sensitivity. In both periods, the association only remained significant for those born small for gestational age (SGA). Increase in childhood weight SDS and current fat mass index were negatively associated with subsequent insulin sensitivity.

**Conclusions**

Enhanced weight gain at a critical stage in early life may improve insulin sensitivity in adolescence. Although higher rates of pre-discharge weight gain do not appear harmful in SGA infants, rapid weight catch-up immediately following hospital discharge is associated with decreased later insulin sensitivity. The interactions between fetal, neonatal and infant weight gain and subsequent markers of the metabolic syndrome are complex, but suggest the potential for early nutritional care to modify later chronic disease risk.

DOI: 10.1530/endoabs.33.OC3.1

**OC3.2**

**GAD and IA2 autoantibody positivity is associated with a requirement for insulin treatment: results of the UK national paediatric Type 2 Diabetes cohort**

Zoe Gray 1, Emma Ilesley 1, Catherine Cotter 2, Lydiah Makusha 3, Anna Ford 4, Kelly Turner 5, James Heywood 6, Kyla Chandler 7, Polly Bingley 8, Anthony Barnett 9, David Dunger 10, Julian Shield 11, Jeremy Wale 12 & Timothy Barrett 1

1 University of Birmingham, Birmingham, UK; 2 Birmingham Children’s Hospital, Birmingham, UK; 3 Sheffield Children’s Hospital, Sheffield, UK; 4 Royal London Hospital, London, UK; 5 University of Cambridge, Cambridge, UK; 6 University of Bristol, Bristol, UK; 7 University of Sheffield, Sheffield, UK.

**Objectives**

To establish the frequency of islet cell autoimmunity in children with a clinical diagnosis of type 2 diabetes (T2DM) and describe associated clinical and laboratory findings.

**Methods**

We recruited children with paediatrician diagnosis of T2DM; BMI above 85th centile for age and sex; children with other confirmed diagnoses such as monogenic and type 1 diabetes (T1DM) were excluded. Clinical data was collected into a national database. Blood was taken for diabetes auto-antibody status to exclude diagnoses of T1DM. Autoantibodies were measured using standardised radio-binding assays; GADA and IA-2A with 35-S labelled antigens and IAA with I-125 labelled insulin in the reference laboratory in Bristol.

**Results**

Of the 130 recruited to the UK national cohort who have had antibody testing to date, 14 (11%) were positive for either GAD2 or IA2 antibodies (AAb positive). Of these, 8 (6%) were positive for a single antibody, and 6 (5%) were positive for both antibodies. Children were not classified as AAb positive if they were only positive for insulin autoantibodies, as this is likely an indicator of previous insulin treatment. Diabetes autoantibody positivity was significantly associated with a reduced pooled C-peptide (median 530 vs 1270 P = 0.016), and previous insulin treatment (86 vs 31% P < 0.001). There was a trend towards differences in sex, BMI-SDS and HbA1c between the groups, with more girls being antibody negative, the AAb positive group having a lower BMI-SDS, and higher HbA1c. Conclusion Approximately 11% of patients presenting with T2DM are in fact autoantibody positive, suggesting a masked diagnosis of T1DM. This is associated with insulin treatment and a reduced C-peptide. This suggests the need to do autoantibody testing on all children with a diagnosis of diabetes, even if it suspected T2DM, and predicts the need for insulin treatment 2 years after diagnosis in AAb positive patients.

DOI: 10.1530/endoabs.33.OC3.2

**OC3.3**

**Successful treatment of four patients with severe hyperinsulinaemic hypoglycaemia with a novel therapy using mTOR inhibitor**

Senthil Senniappan 1, Sanda Alexandrescu 1, Nina Tatevian 1, Pratik Shah 1, Ved Arya 2, Sarah Flanagan 3, Sian Ellard 4, Dyanne Rampling 5, Michael Ashworth 6, Robert Brown 7 & Khalid Hussain 8

1 Great Ormond Street Hospital, London, UK; 2 University of Exeter Medical School, Exeter, UK; 3 University of Texas Medical School, Houston, Texas, USA.

**Introduction**

Hyperinsulinaemic hypoglycaemia (HH) is the most common cause of severe and persistent hypoglycaemia in neonates. The treatment of diazoxide unresponsive HH involves pancreatectomy. Mammalian target of rapamycin (mTOR) is a protein kinase that regulates cellular proliferation. We aimed to evaluate the efficacy of mTOR inhibitor Sirolimus and assess mTOR expression in the pancreas of infants with severe HH.

**Methods**

Four infants with severe, persistent HH were recruited. Treatment with maximal doses of diazoxide and octreotide (35 μg/kg per day) was unsuccessful in all infants who required high concentrations of intravenous dextrose and intravenous glucagon to maintain normoglycaemia. We commenced treatment with Sirolimus and the dose was gradually increased based on serum concentration. Morphoproteomic analysis was performed on the tissue from two patients with diffuse HH to understand the role of mTOR in the pathogenesis of HH.

**Results**

Genetic testing suggested diffuse disease in three infants due to homozygous or maternally inherited heterozygous ABCC8 mutations, but no mutation was identified in the fourth case. Following treatment with Sirolimus, all patients showed good glycaemic response over the following weeks. Intravenous dextrose and intravenous glucagon were weaned and the dose was gradually reduced. Octreotide treatment was ceased in all children. Sirolimus treatment was well tolerated, and no major side effects were reported. Conclusion We report, for the first time, the successful use of mTOR inhibitor Sirolimus in four infants with severe HH. Morphotropomic analysis performed on the tissue from two patients with diffuse HH to understand the role of mTOR in the pathogenesis of HH.

**DOI**: 10.1530/endoabs.33.OC3.3

**OC3.4**

**Successful Use of Long Acting Octreotide in Treatment of Congenital Hyperinsulinism**

Pratik Shah, Clare Gilbert, Kate Morgan, Louise Hinches, Senthil Senniappan, Ved Arya, Hannah Levy & Khalid Hussain

Great Ormond Street Hospital NHS Foundation Trust, London, UK.

**Introduction/Aim**

Congenital hyperinsulinism (CHI) is a cause of severe hyperglycaemia in infancy. Treatment of diazoxide unresponsive patients includes the use of somatostatin...
analouges (octreotide given either as four s.c. injections daily or via a pump). We aimed to evaluate the use of a long acting somatostatin analogue (Lanreotide) in children with CHI, switching them from daily oral diazoxide or s.c. Octreotide injections to 4 weekly Lanreotide injections.

Methods
Children with diffuse CHI on high dose diazoxide or daily octreotide injection were recruited. Lanreotide 30 mg was injected by deep s.c. route and the daily diazoxide/octreotide was weaned after the first dose of Lanreotide as per standard protocol. Each patient had height/weight, baseline USS abdomen, TFT, IGF1/IGFBP3, liver function, HbA1c and continuous glucose monitoring pre and post-Lanreotide therapy. Quality of life questionnaire was completed. Lanreotide levels for all the patients were measured.

Results
Four boys and four girls have been started on Lanreotide in the ongoing study. The mean age is 6.4 years (3.5–14 years). Three of them are currently being weaned off their continuous overnight feeds. Results as below.

Conclusion
Lanreotide is a safe and effective alternative to octreotide/diazoxide therapy in patients with CHI, offering an improved quality of life. Long term follow up is required. The preliminary data on quality of life does suggest that both parents and children are very satisfied with the response.

DOI: 10.1530/endoabs.33.OC3.4

OC3.36
A feasibility study of intra-gastric balloons (supported by a lifestyle programme) for the treatment of severe adolescent obesity – the (BOB) Study.

Pooja Sachdev1, Lindsey Reece2, Rob Copeland2, Jerry Wales2 & Neil Wright3
1University of Sheffield, Sheffield, UK; 2Sheffield Hallam University, Sheffield, UK; 3Sheffield Children’s Hospital, Sheffield, UK.

Rationale
Although many adolescents meet the NICE criteria for bariatric surgery there is a reluctance to undertake or commission such irreversible procedures in young people. Balloons are temporary, reversible, safer and more acceptable and in adults have been shown to promote a clinically significant change in BMI of 4.0–9.0 kg/m² But due to subsequent weight regain, bypass surgery is preferred. This is a feasibility study of endoscopic intra-gastric balloon placement for 6 months supported by a lifestyle management programme.

Objectives
i) To assess the efficacy of the intragastric balloon s supported by a lifestyle intervention to promote weight loss in severely obese adolescents.
ii) To assess the effect of the weight loss on biomedical outcomes such as glucose metabolism, lipid profiles, bone density and architecture and psychosocial health.

Methodology
A cohort study of 12 adolescents (BMI > 3.5 s.d., Tanner stage 4 or above) with a 2-year follow-up. All the young people took part in a comprehensive medical assessment including OGTT’s, measurement of basal and stimulated inretnins, bone turnover markers, DEXA scans and high resolution peripheral quantitative CT scans.

Results
Nine young people (four girls) currently recruited. Average age, weight, BMI and BMI SDS are 15.5 years, 139.8 kg, 47 kg/m² and +4.0 respectively. Average weight loss at 4, 8 and 12 weeks is 6.3, 7.7 and 8.4 kg (Figure 1). First balloon removals are in August 2013.

Figure 1 Graph depicting percentage weight loss over time.

Conclusion
Interim data suggests that the young people will experience clinically significant weight loss. The balloon has been well tolerated. Some data on impact of weight

OC3.5
Loss of the tumour suppressor micro-RNA 34a, and anti tumour cellular immunity in paediatric obesity – is obesity increasing the future risk of cancer in children?

Eirin Carolan1, Andrew Hogan1, Michelle Corrigan1, Jean O’Connell1, Niamh Foley1, Luke O’Neill1, Declan Cody2 & Donal O’Shea3
1University of Sheffield, Sheffield, UK; 2Sheffield Children’s Hospital, Sheffield, UK; 3Sheffield Biomedical Sciences Institute, Sheffield, UK.

There is strong epidemiological data linking obesity to an increased risk of various cancers. It is associated with immune dysregulation and chronic low grade inflammation, however little is known about its impact on anti-tumour immunity. Whether childhood obesity is an independent risk factor for future malignancy is not fully established. We hypothesized that alterations in key immunity anti-tumour mechanisms begin prior to adulthood in paediatric obesity. MicroRNA-34a (miR-34a) is a transcriptional target of p53 that is down-regulated in cancer cell lines. Natural killer cells and cytotoxic T cells are vital to tumour rejection. Invariant natural killer T cells are important bridging cells between the innate and adaptive immune system.

Peripheral blood mononuclear cells were isolated from 61 patients aged 6–18 years. The expression of microRNA 34a (miR34a), a target for tumour suppressor gene p53 was quantitatively measured. Cytotoxicity assays determining natural killer (NK) cell activity and immunophenotyping were performed.

The age and BMI Z-score of obese participants were 12.9 ± 3.0 years and 3.3 ± 0.4 respectively and non-obese participants were 12.2 ± 2.9 years and 0.4 ± 0.9.

A reduction in cytotoxic cell capacity and targets of potent tumour suppressor gene expression occurs from an early age in obese children and may be contributing to future cancer risk in this population.

DOI: 10.1530/endoabs.33.OC3.5

OC3.6
A feasibility study of intra-gastric balloons (supported by a lifestyle programme) for the treatment of severe adolescent obesity – the (BOB) Study.

Eirin Carolan1, Andrew Hogan1, Michelle Corrigan1, Jean O’Connell1, Niamh Foley1, Luke O’Neill1, Declan Cody2 & Donal O’Shea3
1University of Sheffield, Sheffield, UK; 2Sheffield Hallam University, Sheffield, UK; 3Sheffield Children’s Hospital, Sheffield, UK.

Parameter | Obese (n=40) | Non-obese (n=21) | P value
---|---|---|---
CD8 cytotoxic T cells (%CD3+T cells) | 26.3 ± 7.3 | 30.3 ± 6.6 | 0.03
Invariant natural killer T cell (%CD3+T cells) | 0.32 ± 0.03 | 0.54 ± 0.02 | < 0.001
NK cytotoxicity (K562 tumour cell death) | 201 ± 86 | 615 ± 122 | 0.01
miR-34a expression (relative quantification) | 0.72 ± 0.1 | 18 ± 2 | < 0.001

Data expressed as mean ± s.d. P values calculated using independent-samples t test.

Conclusion
Interim data suggests that the young people will experience clinically significant weight loss. The balloon has been well tolerated. Some data on impact of weight
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**Oral Communications 4**

**OC4.1**  
**Risk factors for emergency hospital admission for diabetic ketoacidosis in children and young people: national cross-sectional analysis**  
Swarna Khare1, Michael Solij1, Justin Warner2, Rakesh Amin1, Sonia Saxena1, Russell Vine2, Azemem Majeed1 & Neena Modi1  
1Imperial College London, London, UK; 2Noah’s Ark Children’s Hospital for Wales, Cardiff, UK; 3UCL Institute of Child Health, London, UK.

Objectives  
To identify patient and clinical factors associated with emergency hospital admission with diabetic ketoacidosis (DKA) in children and young people with type 1 diabetes attending specialist NHS outpatient clinics in England and Wales.  

Design  
Cross-sectional observational analysis of linked data from the National Paediatric Diabetes Audits (NPDAs) in England and Wales, and Hospital Episode Statistics and Patient Episode Database for Wales. We selected 12 potential independent variables from NPDAs including patient, care process and metabolic control factors. We imputed missing data and fitted Poisson Generalized Linear Multilevel Models with the Paediatric Diabetes Unit (PDU) of treatment as the random effects level.

Setting  
PDUs in England and Wales.

Participants  
2944 children and young people with type 1 diabetes with at least one DKA hospital admission between 2008 and 2010.

Interventions  
Regular diabetes care provided by PDUs.

Main outcome measures  
DKA hospital admissions between 2008 and 2010.

Results  
In all age groups girls had a higher average number of DKA admissions over the 3 years than boys. Boys and girls aged 15–19 years had the highest DKA admission rates of any age group (342.3 and 627.3 per 1000 respectively). In the multivariate regression model, deprivation (quintile 5 IRR 1.20, 95% CIs 1.09–1.32), Black/Black Caribbean ethnicity (IRR 1.20, 95% CIs 1.02–1.41), female sex (IRR 1.11, 95% CIs 1.04–1.18), haemoglobin A1c (IRR 1.07, 95% CIs 1.05–1.09), and age (incidence rate ratio (IRR) 1.03, 95% CIs 1.01–1.04) were associated with significantly higher DKA admission rates.

Conclusions  
Children from Black/Black Caribbean ethnic groups, those residing in deprived areas, young people aged 15–19 years and those diagnosed with diabetes at an earlier age are at greater risk of being admitted with DKA. The strong association of admission rate with HbA1c level, but not other intermediate outcomes, shows the impact of HbA1c on short-term as well as chronic complications in diabetes. Our analysis points to the need to understand the determinants of the health inequalities identified and to explore interventions to reduce DKA admissions in these groups.

**OC4.2**  
**Maturity-onset diabetes of young 5 (MODY5) with gallbladder duplication cyst: a novel case**  
Anbezhil Subbarayan1,2 & Deborah Kendall1,2  
1Imperial College London, London, UK; 2Noah’s Ark Children’s Hospital for Wales, Cardiff, UK; 3UCL Institute of Child Health, London, UK.

Introduction  
Maturity-onset diabetes of young 5 (MODY5) is caused by a heterozygous whole gene duplication of HNF-1β and was diagnosed with MODY5. She was antenatally diagnosed with gallbladder duplication cyst, which could now be explained by the same genetic defect, as HNF-1β is expressed in the liver and biliary system and conditional HNF-1β knockout mouse showed similar features. She also had developmental delay, learning difficulties and autistic spectrum disorder. Interestingly these features could be explained by the contiguous gene deletion in the long arm of chromosome 17 within band q12 which included the HNF-1β gene found by further Microarray analysis. Following her genetic diagnosis, she was screened for other known associated features and was noted to have renal cyst and bicornuate uterus. She was treated with Metformin initially but soon she needed insulin treatment to maintain normoglycaemia.

We report this first case of MODYS5 with gallbladder duplication cyst and to our knowledge this association has not been reported in the literature so far. This case highlights the importance of genetic testing which was very useful in finding an explanation for all of the problems and to plan the management appropriately. Although the biochemical features and the initial management might be similar to patients with type 2 diabetes, it is very important to understand the need for insulin treatment earlier in the course of the disease and to screen for other associated problems.

**OC4.3**  
**The incentive trial: do financial rewards improve glycaemic control in teenagers with poorly controlled type 1 diabetes?**  
Carley Freerichs, Douglas Thomas & Tabitha Randell  
Nottingham Children’s Hospital, Nottingham, UK.

Introduction  
Adolescence is recognised as a period where compliance to diabetes treatment is challenging and adolescents assume increasing responsibility for their diabetes self-management. In this study we investigated whether giving modest financial rewards motivated teenagers with type 1 diabetes to improve glycaemic control.

Methods  
Population: young people with type 1 diabetes, age 13–16 years at entry, duration of diabetes of >2 years and sustained HbA1c level of >9% for >6 months. Retinal screening and an educational refresher on hypoglycaemia was provided. At each clinic visit patients received a £10 gift voucher for every 0.5% drop in HbA1c. This reward was summative until an HbA1c of 7.5% was achieved. A maintenance voucher of £10 was given if HbA1c continued to be <8.0%. If the HbA1c increased patients were only eligible for further financial rewards after they returned to their previous best HbA1c level. The patients were eligible for payments for one year and data was collected over the following year to assess for sustained improvements.

Results  
The study included 17 participants (ten males and seven females) aged 13–15 years (median 14 years). Mean HbA1c at the start of the study 10.4% (range 9–12.1%) and at 2 years 10.4% (range 7.7–14.9%). At 9 months the cohort reached the lowest mean HbA1c (9.6%, P=0.03) however this was not sustained. No patients received a maintenance payment. Receivers of vouchers (n=11) showed an overall fall in HbA1c (10.8–9.8%) and for non-receivers (n=6) the HbA1c increased (9.6–11.6%).

Conclusions  
In this cohort financial incentive did not improve HbA1c. In current practice good education at diagnosis and throughout is important as when glycaemic control deteriorates it can be difficult to instigate behaviour change.

**OC4.4**  
**Special features of neonatal diabetes in a series of Arab patients from the Gulf region**  
Asma Deeb1, Mohamed Abiary2, Salima Attia1, Amani Osman3, Sarah Flanagan2 & Sian Ellard3  
1Paediatric Endocrinology Department, Mafraq Hospital, Abu Dhabi, United Arab Emirates; 2Paediatric Endocrinology Department, Shaikh Khalifa Medical Center, Abu Dhabi, United Arab Emirates; 3Paediatric Endocrinology, Al Ain Hospital, Al Ain, United Arab Emirates; 4Medical School, University of Exeter, Exeter, UK.

Introduction  
Advances in molecular genetics revealed various causes for neonatal diabetes (ND) wider clinical awareness led to recognition of different phenotypes. In areas like the Gulf, it is expected that the incidence of ND to be higher due to the high frequency of consanguinity. The different ethnic background might result in different causes and phenotypes of ND compared to data reported from the west.
We report 19 patients from 11 families with ND. All patients were pancreatic autoantibody negative and 16 presented before 6 months of age. All patients were born at term and were small for gestational age. All were born to first degree relatives parents. 12 patients were on multiple daily injections and seven on insulin pump therapy. Eight had liver impairment, five skeletal dysplasia and one had pancreatic agenesis. Four patients died at ages 3, 6, 7 and 15 years and one had liver failure requiring transplant.

Genetic analysis was carried out in all patients. KCNJ11, ABCC8, INS genes were sequenced in all patients while EIF2AK3, GCK, IFG1, PTF1A, GATA6, RXF6 were done based on specific clinical features. Ten patients (five families) had Wolcott Rallison syndrome due to mutations in the EIF2AK3 gene; W430X, G956E, E524X, deletion exon 9–13, and H650T (novel). All parents were confirmed to be heterozygous carriers. Four siblings were homozygous to a novel mutation in insulin gene; INS c-331C>G. The same mutation was later found in another unrelated patient. One child had a kATP mutation and was successfully switched to sulphonylurea and one patient had a novel heterozygous H410Y ABCC8 variant.

ND is an important cause of diabetes in areas like the Gulf countries. The main causes of ND vary in different ethnic groups. Phenotype related to age at presentation, organ involvement and disease severity may vary within the same family of affected children.

– WRS as the commonest cause of neonatal diabetes in this cohort with various ages at presentation of liver impairment.
– Death due to liver failure occurs regardless of age of presentation of liver disease.
– First patient reported to undergo liver transplant due to liver failure of WRS.
– Different phenotype and age at diabetes presentation in siblings of the same family with insulin gene mutation (6 weeks, 3 months, 13 years, 18 years).

– Relative difficulty to switch from insulin to sulphonylurea in a previously reported kATP channel mutation.

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**OC4.5**

**Peer Review: A tool to improve Paediatric Diabetes services**

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Peer Review programmes (PRP) help organisations to improve the quality of clinical services in a developmental and supportive way. The West Midlands Paediatric diabetes network (WMPDN) consists of 15 National Health Service (NHS) Trusts looking after 2800 children (aged 0–18 years). 2010/2011 National Paediatric diabetes audit (NPDA) data showed that the median HBA1c achieved in the region was 69 mmol/mol. In order to improve the metabolic control and quality of care, the network embarked on a PRP.

**Method**

Following development of network quality standards and formal training of members of the diabetes multidisciplinary team, parents and commissioners as reviewers, all the NHS Trusts carried out a self-assessment of compliance against the quality standards. This was followed by review visits (September 2012–March 2013) assessing all aspects of the patient journey. During the visit of facilities, patients, parents, medical, nursing, dietetic are interviewed. Results of visits are sent to Trust chief executives and will be made public.

**Results**

14/15 Trusts have had visits. 48 reviewers trained. The median level of compliance following visits was significantly lower than self-assessment of compliance (61 vs 81%) (P < 0.001). The level of compliance amongst the Trusts varied from 38 to 86%. There was a significant positive correlation between level of compliance following peer review (CPR) and percentage of children in the unit with HBA1C < 58 mmol/l (r = 0.63, P = 0.028). 64% did not have adequate specialist nursing/dietetic staff for the number of children in their caseload. 65% did not offer regular robust structured group patient education on an ongoing basis. 57% did not have robust arrangements for ensuring all children received all care processes as defined by NPDA. Transition arrangements were judged inadequate in 50%.

**Conclusion**

PRP has enabled the network to identify areas of service that need improvement. 88% of reviewers report using the experience to improve their services.

DOI: 10.1530/endoabs.33.OC4.5

**OC4.6**

Increased urinary megalin and cubulin excretion in children with type 1 diabetes mellitus: an association with low molecular weight protein loss

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Nephropathy remains a major diabetes related complication despite improvements in metabolic control. Current interventions are based on the appearance of albuminuria. Whether earlier detection and treatment might be beneficial is unclear. The reabsorption of low molecular weight (< 170 kDa) plasma proteins in the renal proximal tubule is mediated by an endocytic receptor, megalin, and its coreceptor, cubulin.

Using label free quantitative proteomics we measured megalin, cubulin, vitamin-D binding protein, retinal binding protein and albumin in the urine of ten children with type 1 diabetes mellitus (T1DM) and ten controls. The T1DM children displayed normal glomerular filtration rates with no evidence of microalbuminuria. Urinary megalin (T1DM 300 pmol/mmol creatinine; controls 110 pmol/mmol creatinine) and cubulin (450 vs 50 pmol/mmol creatinine; P = 0.05) values were elevated compared to controls. Excretion of vitamin-D binding protein and retinal binding protein were increased in T1DM (100 and 6.2 pmol/mmol creatinine respectively) compared to controls (40 and 1.0 pmol/mmol creatinine respectively; P = 0.05). Albumin excretion was not increased significantly. No correlation with HbA1c was observed.

Increased urinary excretion of low molecular weight proteins such as megalin and cubulin in children with T1DM may presage microalbuminuria.

DOI: 10.1530/endoabs.33.OC4.6

**OC5.1**

**Joint BPSU-CAPSS Surveillance Study of Childhood Gender Identity Disorder**

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¹UCL Institute of Child Health, London, UK; ²Tavistock and Portman NHS Foundation Trust, London UK; ³National Children’s Hospital, Dublin, Ireland.

**Aims**

The incidence of childhood/adolescent gender identity disorder (GID) is unknown. GID is an important condition where gender identity differs from biological sex. It is associated with significant distress, particularly with puberty, with much controversy internationally over the optimal timing of hormonal treatment. We examine the incidence and clinical presentation in UK/Irish children and adolescents.

**Methods**

Study population: UK/Irish children/adolescents aged 4–15.9 years. Design: Joint British Paediatric Surveillance Unit (BPSU) and Child and Adolescent Psychiatry Surveillance System (CAPSS) study. New cases of GID reported by clinicians over a 19-month reporting period (01 November 2011–01 June 2013) are validated against the authoritative DSM-IV-TR (2000). Exclusions include disorders of sexual differentiation and major psychosis. Primary outcome: incidence of childhood/adolescent GID, calculated by dividing the number of validated cases by the base population of children/adolescents aged 4–15.9 years. Sources of denominator data: UK Office of National Statistics and the Central Statistics Office in Ireland. Statistical analysis: descriptive statistics and comparisons using two-sample Z-tests/Mann–Whitney U tests for continuous data and χ²/Fisher’s exact tests for categorical data.

**Results**

Preliminary data from the first 15 months’ surveillance (n = 138 cases, 69 males) indicate that similar numbers of males/females are affected by this condition. Early estimates suggest UK and Irish incidences of 1:80 000 and <1:200 000.

There is a substantial lag between median (inter-quartile range) onset of symptoms (7 years (4–12 years)) and presentation to Paediatricians or Psychiatrists (14.5 years (11.9–15.2 years)). Only 25% of cases (n = 35) were <12 years old at reporting. There are high levels of psychiatric co-morbidity at presentation, with ≥1 other mental health diagnosis in 45%, and ≥2 other diagnoses in adolescents aged ≥12 years.

**Conclusions**

We present the first ever population-level data on the incidence, clinical features and presentation of childhood/adolescent GID. These data will inform clinical management, including the highly controversial debate around early puberty suppression in this group.

DOI: 10.1530/endoabs.33.OC5.1
OC5.2
Clinical, biochemical and neuroradiological characterization of a cohort of patients with septo-optic dysplasia and multiple pituitary hormone deficiencies
Manuela Cerbone, Maria Guemes & Mehal Dattani
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Introduction
Septo-optic dysplasia (SOD) is characterized by a combination of midline forebrain, pituitary and eye abnormalities. We aimed to evaluate the clinical, neuroradiological and endocrine features of patients with SOD and multiple pituitary hormone deficiencies (MPHD).

Design
Retrospective data were collected from 76 patients with SOD and 26 with MPHD, followed at a single centre. SOD patients were divided into two groups: i) with pituitary hormone deficiencies (SOD +, n = 64) and ii) with normal pituitary function (SOD −, n = 12).

Results
Mean age of diagnosis was similar in all three groups (Table 1). Onset of first pituitary hormone deficiency was similar in both groups. The most prevalent deficiency in SOD + was GH deficiency, whilst TSH deficiency was the most prevalent deficiency in MPHD. Of patients with ACTH deficiency, pituitary stalk abnormalities were more frequent in patients with hormone deficiencies. Other brain abnormalities were more frequently identified in SOD patients.

Table 1
Clinical, biochemical and radiological features of patients with: i) septo-optic dysplasia (SOD) with pituitary hormone deficiencies (SOD +), ii) SOD with normal pituitary function (SOD −) and iii) multiple pituitary hormonal deficiencies (MPHD).

<table>
<thead>
<tr>
<th>Clinical details</th>
<th>SOD + (n=64)</th>
<th>SOD − (n=12)</th>
<th>MPHD (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>34/30</td>
<td>7/5</td>
<td>12/12</td>
</tr>
<tr>
<td>CA at SOD/MPHD diagnosis (years)</td>
<td>2.1 ± 0.4</td>
<td>3.7 ± 1.5</td>
<td>2.2 ± 0.7</td>
</tr>
<tr>
<td>CA at first pituitary deficiency diagnosis (years)</td>
<td>2.6 ± 0.4</td>
<td>–</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>Undervirilised external genitalia (%)</td>
<td>29.7</td>
<td>33.3</td>
<td>65.4</td>
</tr>
<tr>
<td>Spontaneous puberty (%)</td>
<td>83.3 (n=6)</td>
<td>100 (n=1)</td>
<td>57.1 (n=7)</td>
</tr>
<tr>
<td>DI (%)</td>
<td>18.75</td>
<td>–</td>
<td>11.58</td>
</tr>
<tr>
<td>CA at DI diagnosis (years)</td>
<td>2.5 ± 1.1</td>
<td>–</td>
<td>0.1 ± 0.0</td>
</tr>
<tr>
<td>CA at GHD diagnosis (years)</td>
<td>3.4 ± 0.4</td>
<td>–</td>
<td>3.1 ± 0.6</td>
</tr>
<tr>
<td>CA at TSHD diagnosis (years)</td>
<td>1.9 ± 0.4</td>
<td>–</td>
<td>3.1 ± 0.9</td>
</tr>
<tr>
<td>CA at ACTHDI diagnosis (years)</td>
<td>2.1 ± 0.5</td>
<td>–</td>
<td>3.4 ± 1.0</td>
</tr>
</tbody>
</table>

Associated clinical features
Hypoplasia (H) | 9.4 | 33.3 | 3.9 |
Neurodevelopmental delay (%) | 60.9 | 66.7 | 15.4 |
Autism (%) | 32.8 | 8.3 | 7.7 |
Sleep disturbances (%) | 40.6 | 16.7 | 15.4 |
Neuromaging
Anterior pituitary hypoplasia (%) | 78.1 | 75.0 | 80.8 |
Ectopic posterior pituitary (%) | 35.9 | – | 65.4 |
Pituitary stalk abnormalities (%) | 50 | 16.7 | 42.3 |

M, males; F, females; CA, chronological age; DI, diabetes insipidus; GHD, GH deficiency; TSHD, TSH deficiency; ACTHDI, ACTH deficiency.

MPHD patients, whereas spontaneous puberty and diabetes insipidus (DI) were more frequent in the SOD + cohort. In three SOD + patients, DI evolved after the age of 7.3 years.

OC5.3
Hypoglycaemia success during the insulin tolerance test: a two centre comparison
Rachel Besser1, Suet Ching Chen1, Emma Knight1, Ethel MelNeil1, Pauline Musson2, Victoria Fisher2, Stephanie Kerr1, Malcolm Donaldson2, Nikki Davies1, Faisal Ahmed1, M Gürar Shaikh1 & Justin Davies2
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Introduction
The insulin tolerance test (ITT) is the gold standard method to assess GH and/or ACTH deficiency. Safety concerns with the use of this test were raised more than 20 years ago from overtreatment of hypoglycaemia and consequent cerebral oedema, resulting in some centres using alternative tests. We have re-appraised the use of the ITT in a contemporary setting and evaluated: i) timing of the glucose nadir, ii) time to resolution of hypoglycaemia, iii) adverse events and iv) staffing levels.

Methods
Data from ITTs in two regional UK paediatric endocrinology centres (A and B) were collected retrospectively during 2012. Both centres use 0.1 unit/kg i.v. actrapid with samples taken at 20, 45 and 75 min whereas B samples at 15 and 120 min. Successful hypoglycaemia was defined as laboratory glucose <2.2 mmol/l and/or >50% reduction from baseline.

Results
49 patients (A, n = 23 and B, n = 26; 80% male) aged median (interquartile range) 14.8 (11.2–15.6) years were included. Patients from Centre A were older (median 15.0 vs 12.3 years, P = 0.04) but had a similar BMI SDS (P = 0.19) and gender distribution. Hypoglycaemia occurred in 100% (23/23) patients in Centre A and 73% (19/26) in Centre B, P = 0.01. The 7/26 patients from Centre B who did not become hypoglycaemic tended to be older, although this did not reach significance (median 14.0 vs 11.6 years, P = 0.59). The glucose nadir was lower in Centre A (1.5 vs 1.9 mmol/l, P = 0.007), occurred later (20 vs 15 min, P = 0.04) and resolved more quickly (time to BM > 4 mmol/l: 45 vs 60 min, P = 0.006). None of the patients required i.v. treatment or hospital admission. Two healthcare professionals were present during each ITT. Centre A had two specialist endocrine nurses (EN) for the majority (87%) of the ITTs, whereas B always had one EN and one doctor present.

Conclusions
Successful hypoglycaemia was more likely if samples were taken at 20 min. The ITT is safe when performed under specialist endocrine nurse supervision. This has important resource and safety implications.

DOI: 10.1530/endoabs.33.OC5.3
Poster Presentations
Introduction
The incidence of adrenal insufficiency in cases of unexplained death in young children is unclear. It is also unclear whether there is a relationship between adrenal size and plasma cortisol concentration.

Methods
All post-mortem (PM) reports of sudden deaths in children in the West of Scotland between 2010 and 2012 were retrospectively analysed. Combined adrenal weight (g) was recorded and expressed as the percentage of total body weight (%TBW). Plasma cortisol was measured by immunoassay using a sample from the right atrium.

Results
Of 153 cases during the study period, 106 had data on adrenal weight and plasma cortisol. The median (5th, 95th) age was 5 months (3 days, 11 years) with 70 cases (63%) under the age of 1 year. Median time to PM was 60 h (20, 144). There was no correlation between plasma cortisol and time to PM \((r = -0.06, P = 0.6)\). The median %TBW was 0.058 (0.025, 0.27) and the median plasma cortisol was 232 nmol/l (28, 1300). There was a positive correlation between total body weight and combined adrenal weight \((r = 0.4, P < 0.0001)\). There was a weak positive correlation between %TBW and plasma cortisol levels \((r = 0.2, P = 0.03)\), with a stronger correlation seen in children over 1-year-old \((r = 0.5, P = 0.003)\). The lowest and highest plasma cortisol quartile had a median of 52 nmol/l (28, 95) and 946 nmol/l (477, 1973), respectively. In the lowest quartile, conditions associated with death included 17 cases (65%) of sudden unexpected death in infancy, three cases (12%) of drowning and two cases of seizure (8%). In the highest quartile cases included infection (six cases, 23%), sudden unexpected death in childhood (five cases, 19%) and hypoxic ischaemic encephalopathy (four cases, 15%) \((P < 0.0001)\).

Discussion
Although there is a relationship between circulating cortisol and relative adrenal size, there is substantial inter-individual variability. Cortisol levels are often low at PM but this is a less frequent finding in cases of infection.

Conclusions
Spectrum of CAH in Sri Lanka is similar to other countries. The prevalence is lower than in Kuwait (1.1/10 000) and other Arabian countries and is higher than the in West (0.06/10 000). Great Britain.

DOI: 10.1530/endoabs.33.P2

P3
Diagnosing congenital adrenal hyperplasia. Radiologist rather than biochemist.
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Introduction
The male child with congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency classically presents with salt-wasting and the female with genital ambiguity. 17-OHP measurement is a key investigation but the assay takes time to perform and is not usually available at weekends. We have examined the role of renal/adrenal ultrasonography in the above clinical scenarios.

Method
An abdominal ultrasound focussing on adrenal anatomy was performed following the presentation of a baby with suspected CAH (March–June 2013). The images were viewed jointly by radiologist and paediatric endocrinologist. The radiological diagnosis (CAH or not) was compared with the final diagnosis made on the basis of a range of indices including 17-OHP values.

Results
There were four babies with suspected CAH. Cases 1–3 were male infants, 2–5 weeks of age, with a salt wasting picture (sodium 119, 120 and 128 mmol/l, potassium 6.7, 7.2 and 6.5 mmol/l). Case 4 had genital ambiguity noted at birth. A diagnosis of CAH was made in infants 1, 2, and 3 on the day of presentation on the basis of a normal renal tract but characteristically enlarged, irregular, echogenic adrenal glands. Grossly elevated 17-OHP concentrations were identified 2–5 days after the initial presentation (2681, 2882, and 2159 nmol/l). Imaging was normal in infant 3 and 17-OHP concentrations were age appropriate. He was diagnosed with pseudohypoaldosteronism on the basis of his biochemistry and urine steroid profile.

Conclusion
Adrenal ultrasonography is a key diagnostic tool when investigating suspected CAH with high sensitivity/specificity. It can be undertaken in the first hours following presentation, the images are easy to interpret and the test means that CAH can be diagnosed promptly out of hours. In two of the above cases the diagnosis was made at the weekend. UK guidance should highlight the role of adrenal ultrasonography in greater detail.

DOI: 10.1530/endoabs.33.P3

P4
Subnormal Synacthen testing in infants <6 months age: a review of diagnoses and outcomes
Timothy Shao Ern Tan1, Rajesh Chidanandaswamy2, Fiona Ivison3, Mars Skae4, Raji Padidela5, Sarah Eltisham6, Peter Clayton7, Indi Banerjee6 & Leena Patel7
1Manchester Medical School, The University of Manchester, Manchester, UK; 2Department of Paediatric Endocrinology, Royal Manchester Children’s Hospital, Manchester, UK; 3Department of Clinical Biochemistry, Royal Manchester Children’s Hospital, Manchester, UK; 4Faculty of Human and Medical Sciences, The University of Manchester, Manchester, UK.

Background
The standard dose Synacthen test (SDST) is commonly used to identify glucocorticoid deficiency. A subnormal SDST in young infants raises the possibility of adrenal insufficiency (AI) due to pathology such as congenital adrenal hyperplasia (CAH). A physiological delay in maturation of adrenal glucocorticoid secretion may be another explanation especially in asymptomatic infants with a transiently subnormal SDST.

Aims
To review the diagnoses and outcomes of infants <6 months who had a subnormal SDST at a single regional centre.

Methods
Data from 45 infants <6 months age who had a SDST over a 2-year period was reviewed. A SDST with cortisol level <550 nmol/l at 30 min was defined as subnormal. Hyponatraemia and requirement for fludrocortisone indicated salt-wasting form of 21 hydroxylase deficiency.
wasting AI. Clinical outcomes were reviewed at 6 months after presentation.

Results
The SDST was normal in 23 (51%) and subnormal in 22 (49%) (15 males) infants. Among the latter, the subnormal SDST was associated with hypopituitarism (3/22), 21-hydroxylase CAH (1/22), salt-wasting primary AI of unknown aetiology (1/22), persistent glucocorticoid deficiency necessitating replacement with hydrocortisone but aetiology not identified (9/22, 41%) and transiently impaired SDST (6/22, 36%). Of the eight infants with a transient abnormality, two were born small-for-gestational-age, three were premature and none received steroid treatment antenatally. Their median (range) 30 min cortisol at initial SDST was 416 (266; 431) nmol/l which normalised by age 4 (1; 9) months. They were asymptomatic until follow-up SDST results normalized. No infant presented with an adrenal crisis.

Conclusion
A significant proportion of infants <6 months age have persistent AI, the aetiology of which can be primary, secondary or unascertained. A third of infants are asymptomatic and have a transiently subnormal SDST. This is suggestive of a physiological delay in maturation of adrenal glucocorticoid secretion.

DOI: 10.1530/endoabs.33.P4

P5
Primary glucocorticoid deficiency presenting as cholestatic jaundice in a neonate
Manjusha Hira, Amar Wahid & Vasanta Nanduri
Watford General Hospital, Watford, Hertfordshire, UK.

Introduction
We report the case of a term neonate born with dark skin to Caucasian parents, who presented with severe hypoglycaemia on the postnatal ward. He went on to develop prolonged cholestatic jaundice, hypertransaminasaemia, pale stool and hepatosplenomegaly.

Case report
Thorough investigation led to a diagnosis of primary glucocorticoid deficiency. Hydrocortisone replacement therapy resulted in resolution of the cholestasis, improvement in liver function and pigmentation suggesting a causal relationship between cortisol deficiency and cholestasis.

Conclusion
On literature review we find several case reports of neonates presenting with cholestasis as a result of hypopituitarism, however in this case pituitary function was intact. Primary adrenal insufficiency as a cause for neonatal cholestatic jaundice is rarely reported in Caucasian populations. We explore potential pathological mechanisms from experimental models linking cortisol levels with bile synthesis, transport and flow rate. We conclude with the recommendation that neonates with unexpected hyperpigmentation, hypoglycaemia and cholestasis should alert paediatricians to the possibility of cortisol deficiency. Prompt investigation of adrenal function should be undertaken as this is a completely reversible cause of cholestasis.

DOI: 10.1530/endoabs.33.P5

P6
Severe 21-hydroxylase deficiency congenital adrenal hyperplasia and congenital hypothyroidism due to thyroglobulin mutations in a single family: two distinct genetic disorders with phenotypic variability within a single family
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1Great Ormond Street Hospital, London, UK; 2University of Cambridge, Cambridge, UK; 3University College London Hospital, London, UK.

Background
21-Hydroxylase deficiency due to mutations in CYP21A2 represents the commonest form of congenital adrenal hyperplasia (CAH). Dsynormonogenetic congenital hypothyroidism (CH) may be due to TPO, TG, DUOX2, DUOX2A, IHD, SLC5A5 and SLC26A4 mutations.

Case report
Two of six children born to unrelated parents presented in the neonatal period with salt-losing CAH due to compound heterozygosity in CYP21A2 (maternally derived intron two splice mutation, paternally derived p.Bel172Asn). Congenital hypothyroidism was diagnosed in both by neonatal screening. Next generation sequencing recently demonstrated compound mutations in the thyroglobulin gene (TG): p.R277X and p.T1397Rfs+30. A third sibling presented with pubic hair and body odour since 7 years of age, and had a simple virilising form of CAH (normal plasma renin, aldosterone and thyroid function; genetic analysis awaited), treated with hydrocortisone.

The oldest sibling, a female now aged 17, has learning difficulties and is short (height SDS = −2.60) with severe obesity (BMI 52.5), insulin insensitivity, severe virilisation with marked hirsutism, primary amenorrhoea and voice changes, and polycystic ovarian disease, due to poor compliance with medication (currently on dexamethasone, 9-a-fludrocortisone, metformin, flutamide and thyroxine). Pelvic ultrasound and abdominal MRI revealed bilaterally enlarged adrenals with a probable right adrenal adenoma, probably due to chronic ACTH stimulation. Her 13-year-old brother is currently on hydrocortisone, fludrocortisone and thyroxine (height SDS = −0.90, weight SDS = +1.39, and BMI SDS = +2.63). His compliance is also erratic, and he is being treated with GnRH analogue for gonadotrophin-dependent precocious puberty.

Conclusions
In this unusual pedigree, three siblings manifested two different forms of CAH, and the older siblings show inheritance of two distinct genetic disorders, namely CAH and CH due to TG mutations. Finally, this case illustrates the importance of optimal disease control in CAH; poor compliance with chronically elevated ACTH concentrations may have resulted in an adrenal adenoma in the older sibling.

DOI: 10.1530/endoabs.33.P6

P7
Audit on the characteristics and management of patients in a large tertiary hospital paediatric adrenal clinic
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1Royal Manchester Childrens Hospital, Manchester, UK; 2University of Manchester, Manchester, UK.

Adrenal insufficiency (Adr-I) and congenital adrenal hyperplasia (CAH) are important conditions requiring specialist attention and management. Recent CAH genotype-phenotype studies have linked mutations with enzyme functioning and disease severity. Accurate diagnosis for the cause of adrenal insufficiency and the genetic cause of CAH is vital as it impacts management and prognosis.

Methods
We audited patients with Adr-I and CAH seen in outpatients from January 2011 to May 2013. Data was collected on diagnosis, auxology and treatment from clinic letters and the specialist nurse database. Genetic reports were obtained from the Molecular Genetics Department.

Results
Of 129 patients with CAH (45% males), 119 had 21-hydroxylase deficiency. 22 patients (18%) were simple virilising and 97 (82%) salt wasting. 14 patients presented late (M=4 years, range 1–13). There were 184 patients with Adr-I which resolved in 47 during the audit period. 22 patients had primary Adr-I (13 Addison’s, 1 AAA syndrome, four adrenalneokystodystrophy). 74 patients had Adr-I secondary to exogenous steroid treatment (44 oral, 26 inhaled, four topical), 16 due to CNS pathology (four septo-optic dysplasia, eight CNS tumours, two hypopituitarism, one hypothalamic hamartoma, one meningiitus), four had congenital adrenal hyperplasia, three pseudohypoaldosteronism, 19 were associated with prematurity and in 45 the cause was unclear. There was no adverse effect of steroid treatment on height (CAH mean HSDS = −0.01 ± 1.96, Adr-I = 0.85 ± 1.96) but it was associated with an increased BMI (CAH BMIDS mean = 1.14 ± 1.42, Adr-I = 0.89 ± 2.00). The distribution of genetic mutations for patients with CAH closely mirrored that found in other European studies. Hydrocortisone and fludrocortisone doses correlated with the severity of the genetic mutations (P<0.02) but BMI did not (I=0.178).

Conclusion
The patient cohort characteristics including genetic characteristics largely mirrored other European cohorts. Increased severity of CAH correlated with higher doses of hydrocortisone and fludrocortisone but had no effect on height or BMI.

DOI: 10.1530/endoabs.33.P7
P8
Reliability of diagnostic tests for paediatric Cushing’s syndrome
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1Great Ormond Street Hospital for Children, London, UK; 2University College London Hospital, London, UK; *Institute for Child Health, London, UK.

Introduction
Cushing’s syndrome is a rare and life-threatening paediatric disease, the diagnosis of which can be challenging given its heterogeneous clinical presentation and the investigation results which are frequently inconclusive.

Aim
To assess the reliability of the tests used for screening and for establishing the aetiology of Cushing’s syndrome.

Design
We conducted a retrospective study analyzing cases of Cushing’s syndrome that presented between 1983 and 2013 at two tertiary hospitals. Clinical, biochemical and radiological features are described.

Results
The study cohort included 30 patients (14 females) with a median age at presentation of 8.9 years (range 0.2–15.5) and a delay between onset of symptoms and diagnosis of 1.0 year (range 0.04–6). The most common presenting manifestations were weight gain (23/30), hirsutism (17/30) and acne (15/30). Other clinical features included psychological symptoms (13/30), weakness (12/30), growth retardation (11/30) and systolic hypertension (8/30). Median BMI SDS at presentation was +2.27 (range −6.5 to +4.6).

The table lists the investigations undertaken and their performance.

<table>
<thead>
<tr>
<th>Test</th>
<th>Abnormal n (%)</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine free cortisol</td>
<td>17/18 (94)</td>
<td>Suppression means cortisol &lt; 50 nmol/l at 48 h</td>
</tr>
<tr>
<td>(nmol/24h)</td>
<td>(71.6)</td>
<td></td>
</tr>
<tr>
<td>0800 h cortisol (nmol/l)</td>
<td>10/27 (37)</td>
<td></td>
</tr>
<tr>
<td>480 h ACTH (ng/l)</td>
<td>2/3 (67)</td>
<td></td>
</tr>
<tr>
<td>Pituitary tumours</td>
<td>1/1 (100)</td>
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<tr>
<td>Adrenal tumours</td>
<td>2/10 (20)</td>
<td></td>
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<tr>
<td>Ectopic ACTH</td>
<td>1/10 (10)</td>
<td></td>
</tr>
<tr>
<td>Midnight cortisol (nmol/l)</td>
<td>2/27 (100)</td>
<td></td>
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<tr>
<td>Midnight ACTH (ng/l)</td>
<td>5/5 (100)</td>
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<tr>
<td>24-h cortisol profile</td>
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</tr>
<tr>
<td>(mean value nmol/l)</td>
<td>620 (369)</td>
<td></td>
</tr>
<tr>
<td>LDSS + 48 h cortisol (nmol/l)</td>
<td>20/20 (100)</td>
<td></td>
</tr>
<tr>
<td>(20 μg/kg per day only)</td>
<td>620 (369)</td>
<td></td>
</tr>
<tr>
<td>HDDS + 48 h cortisol (nmol/l)</td>
<td>20/20 (100)</td>
<td>Failure of suppression:</td>
</tr>
<tr>
<td>(80 μg/kg per day only)</td>
<td>620 (369)</td>
<td>Suppression means cortisol &lt; 50 nmol/l at 48 h</td>
</tr>
<tr>
<td>Pituitary tumours</td>
<td>1/10 (10)</td>
<td>Response if: cortisol ↑ &gt; 20% &amp; ACTH ↑ &gt; 50%</td>
</tr>
<tr>
<td>Adrenal tumours</td>
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<td></td>
</tr>
<tr>
<td>Ectopic ACTH</td>
<td>1/2 (50)</td>
<td></td>
</tr>
<tr>
<td>CRH test</td>
<td>Rise in ACTH of cortisol</td>
<td></td>
</tr>
</tbody>
</table>

Urine Steroid Profile showed increased output of glucocorticoid metabolites in 20/30 (67%) patients and BIPPS was useful in the diagnosis of five cases of Cushing’s disease and in one ectopic tumour.

All of the patients underwent surgery and final diagnosis were: 16 pituitary ACTH secreting adenomas, 11 primary adrenal diseases, two ectopic ACTH secretion and in one case the aetiology remains unknown. Complications included hormone deficiencies (28/30; including transient and persistent), incomplete resection (4/30), deep venous thrombosis (1/30), septic shock (1/30), CSF leak (1/30), chylos effusion (1/30), relapse (5/30) and second tumour (1/30).

Conclusion
Screening tests showed high sensitivity, with Urine Free cortisol, midnight cortisol and LDLDS presenting the best performances. HDDS and CRH test reliably distinguished between pituitary and adrenal disease but performed less well in cases of ectopic ACTH secretion.

DOI: 10.1530/endo2013.P8

P9
Enzyme-replacement therapy in life-threatening perinatal hypophosphatasia in a premature infant
Raja Paddidela, Robert Yates, Elaine Chan & Zulf Mughal
Royal Manchester Children’s Hospital, Manchester, UK.

Hypophosphatasia (HP) is a rare inborn error of metabolism resulting from inactivating mutations in the gene for the tissue-nonspecific isozyme of alkaline phosphatase (TNSALP). Deficiency of alkaline phosphatase (ALK) activity leads to severe rickets. The perinatal form presents with extreme skeletal hypomineralisation at birth, and was a fatal condition until recently. We describe an 11-month-old infant who is one of the few surviving cases of a preterm infant with the perinatal form (homozygous mutation in TNSALP c.1336G>A) of HP. She has been treated with the recombinant TNSALP (Asfotase alfa) provided on a compassionate basis by Alexion (352 Knott, CT 06410, United States).

A female infant was born preterm at 34 weeks of gestational age to consanguineous parents of Pakistani descent and required ventilatory support from birth for respiratory insufficiency. She was noted to have short limbs and hypotonia. Radiographs revealed severe skeletal hypomineralisation with features of rickets. Her serum ALK was low however, urinary phosphoethanolamine, serum calcium and serum inorganic pyrophosphatase (iPP) were elevated as expected in patients with HP.

Treatment with Asfotase alfa was commenced at 4 weeks of age. Infant remains on ventilatory support however, treatment has resulted in dramatic improvement in growth and mineralisation of bones, healing of rickets, normalisation of serum calcium and serum iPP, improved developmental milestones and pulmonary function.

Management of this infant has brought about unique challenges which have not been previously reported in medical literature. The dose of Asfotase alfa has been increased steadily (6 mg/kg per dose, three times a week) beyond the usual dose (2 mg/kg per dose) to allow adequate mineralisation of bones and normalisation of serum calcium concentration. Combination of lung disease of prematurity and respiratory comprise from HP has required on going ventilatory support. Nevertheless she is making good developmental progress and plans are underway to discharge her home ventilatory support.

DOI: 10.1530/endo2013.P9

P10
Case report: a novel PHEX mutation in a female with X-linked hypo-phosphataemic rickets
Julia Phillips1, Anthony Hulse1, Sian Ellard2 & Victoria Moye3
1 Evelina Children’s Hospital, London, UK; 2Royal Devon and Exeter NHS Foundation Trust, Devon and Exeter, UK.

Introduction
X-linked hypo-phosphataemic rickets is characterized by hypophosphataemia, vitamin D deficiency, poor bone and dental mineralization. Mutations occur within the PHEX gene. Currently 329 mutations have been sequenced1. We report a novel PHEX mutation in a female with hypo-phosphataemic rickets.

Case report
A 12-year-old girl presented with genu varum, short stature and a previous dental abscess. Investigations showed hypophosphataemia with a high urinary phosphate level, vitamin D deficiency, elevated parathyroid hormone, elevated alkaline phosphatase and normal calcium levels. Knee X-rays showed bilateral lunate lines and tibial growth plate defects. DEXA scan results were at the extreme lower limit of the expected range. The PHEX gene was analysed by Sanger sequence analysis of the coding and flanking intron regions by multiplex ligation-dependent probe amplification. Databases cross-referenced were: dbSNP, Exon Variant Server and locus specific database http://www.phebx.mcgill.ca. DNA analysis of both parents was also performed. The patient was heterozygous for a novel, de novo PHEX mutation in the gene location c1501_1502ins24, exon 14 of PHEX gene.

This resulted in an in-frame insertion of 8 novel amino acids in the protein. This resulted in a novel PHEX mutation in a female with hypo-phosphataemic rickets.

Discussion
A 12-year-old girl presented with genu varum, short stature and a previous dental abscess. Investigations showed hypophosphataemia with a high urinary phosphate level, vitamin D deficiency, elevated parathyroid hormone, elevated alkaline phosphatase and normal calcium levels. Knee X-rays showed bilateral lunate lines and tibial growth plate defects. DEXA scan results were at the extreme lower limit of the expected range. The PHEX gene was analysed by Sanger sequence analysis of the coding and flanking intron regions by multiplex ligation-dependent probe amplification. Databases cross-referenced were: dbSNP, Exon Variant Server and locus specific database http://www.phebx.mcgill.ca. DNA analysis of both parents was also performed. The patient was heterozygous for a novel, de novo PHEX mutation in the gene location c1501_1502ins24, exon 14 of PHEX gene.

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URL: http://www.phebx.mcgill.ca. DNA analysis of both parents was also performed. The patient was heterozygous for a novel, de novo PHEX mutation in the gene location c1501_1502ins24, exon 14 of PHEX gene.

Nevertheless she is making good developmental progress and plans are underway to discharge her home ventilatory support.

DOI: 10.1530/endo2013.P9

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dependent phosphate transporters within the renal proximal tubules to reduce phosphate reabsorption\(^1\). FGF23 also inhibits 1α-hydroxylase activity causing vitamin D deficiency\(^2\). PHEX mutations result in failure to cleave FGF23 to an inactive form, resulting in renal phosphate leak and low vitamin D levels\(^3\). FGF23 is considered a hormone, under the influence of PHEX as part of the bone-renal axis of phosphate homeostasis.

References:

DOI: 10.1530/endoabs.33.P10

**P11**

**Successfully modified intermittent i.v. calcium treatment in a patient with hereditary vitamin D resistant rickets with alopecia: presence of nonsense mutation in ligand binding domain of vitamin D receptor**

**Celal Bayar University, School of Medicine, Manisa, Turkey; 2Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.**

Hereditary vitamin D-resistant rickets (HVDRR) is a rare recessive genetic disorder caused by mutations in the VDR that result in end organ resistance to 1,25(OH)\(\_2\)D\(\_3\), action. Here, we describe a patient with HVDRR with severe alopecia and rickets. Patient was 3 years old male presenting with gait disorder. He had hypocalcemia (8 mg/dl), secondary hyperparathyroidism (1232 pg/ml), alopecia and rickets. Patient was 3 years old male presenting with gait disorder.

**Case 1**

Date 12/3/13 16/4/13 15/4/13 5/6/13

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**Case 2**

Date 12/3/13 16/4/13 15/4/13 5/6/13

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**P12**

**Brown tumours caused by severe vitamin D deficiency: a report of two cases**

**Loveline Ayuk, Wolfgang Hogler & Nick Shaw**

**Birmingham Children’s Hospital, Birmingham, UK.**

Brown tumours are benign osteolytic lesions of bone caused by high levels of serum parathyroid hormone (PTH). They are now rarely seen as a feature of primary hyperparathyroidism. We report two cases of brown tumour in adolescent girls caused by secondary hyperparathyroidism due to severe vitamin D and dietary calcium deficiency.

**Case 1**

14.5-year-old South Asian girl referred with a 1 year history of right hip pain. She had presented to the orthopaedic team with a low trauma fracture of her right fibula. X-ray and MRI scan showed a Looser’s zone (insufficiency fracture) in the right distal femur and a 2.1 cm brown tumour in the right proximal tibia. Both girls had low calcium intake and presented in Spring.

**Case 2**

13.6 year old South Asian girl referred by the orthopaedic team with a 2 year history of gradually worsening pain of the right knee but no history of trauma. X-rays and MRI scans showed a Looser’s zone (insufficiency fracture) in the right distal femur and a 2.1 cm brown tumour in the right proximal tibia.

**P13**

**In unexplained hypoglycaemia, is the presence of ketones (beta-hydroxybutyrate) a reliable indicator that insulin is suppressed, excluding hyperinsulinism and avoiding the need to assay insulin directly**

**Raghad Sabbagh1, Neil Wright2 & Camilla Scott2**

1Sheffield Medical School, Sheffield, UK; 2Sheffield Children’s Hospital, Sheffield, UK.

Introduction

In the majority of patients presenting to A&E with hypoglycaemia it is secondary to infection or stress and individuals exhibit a ketogenic response. A minority who first present with hypoglycaemia may have endocrine or metabolic disorders. For this reason a full “hypoglycaemia screen” is undertaken. It is recommended by mhetobinet that before glucose administration, the following are measured: intermediary metabolites (glucose, b-OHB, free fatty acids, lactate), insulin, cortisol, GH, amino acids and acylcarnitines.

Insulin suppresses lipolysis and ketogenesis, thus in the presence of ketones, it would be expected that insulin should be appropriately suppressed.

Aims

To investigate whether the presence of ketones in unexplained hypoglycaemia is always associated with insulin suppression and whether specific measurement of insulin is required. If not, there is a modest potential cost saving.

Methods

Results were reviewed retrospectively on all patients that presented with unexplained hypoglycaemia over a 6-month period between 2012 and 2013.

**Table 1:** Date 12/3/13 16/4/13 15/4/13 5/6/13

<table>
<thead>
<tr>
<th>Date</th>
<th>Calcium</th>
<th>Alkaline phosphate</th>
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**DOIs:** P12: 10.1530/endoabs.33.P12
The nationally accepted methionine criteria was used for the definition of hypoglycaemia $<2.6$ mmol/l to select the samples. In addition, similar data from a historical study carried out between March 2006 and May 2008, were included. Intermediate insulin at the time of hypoglycaemia was defined as $>30$ pmol/l.

### Results
The study viewed 127 patients with glucose of $\leq 2.6$ mmol/l. Two patients had insulin $>30$ pmol/l. Of the two patients, one had complex pituitary dysfunction; this patient had very high insulin (60.3 pmol/l) and low B-OHB (0.1 mmol/l). The second patient was a 1-month-old baby with high insulin (34.6 pmol/l) and high B-OHB (2.5 mmol/l); interestingly the plasma amino acids were also low indicating an anabolic (hypoglycaeminaemic) state.

### Conclusion
The study illustrates that suppressed levels of insulin cannot be inferred from the presence of intermediary metabolites. If insulin was only assayed if ketones are absent, complex and rare disorders may be missed.

DOI: 10.1530/endoabs.33.P14

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**P14**

**Design and validation of a severity scale for use in congenital hyperinsulinism**

Jessica Most1, Zainab Mohamed1, Hima Bindu Avatapalle1, Sarah Elhisham1, Peter Foster2, Adam Stevens3, Karen E Cosgrove4, Mark J Dunne1, Indaneel Banerjee1 & Peter E Clayton1

1Department of Paediatric Endocrinology, Royal Manchester Children’s Hospital, Manchester, UK; 2School of Mathematics, University of Manchester, Manchester, UK; 3Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK; 4Faculty of Life Sciences, University of Manchester, Manchester, UK.

### Introduction
Congenital hyperinsulinism (CHI) is an important cause of hypoglycaemia in infancy requiring intensive medical and surgical support. Carbohydrate requirement (CHO) represents a simple index of severity but does not predict the failure of medical treatment and hence the requirement for pancreatectomy.

### Aims
To design and validate a severity tool for use in early onset CHI patients.

### Methods
To design the Manchester CHI severity score (M-CHISS), frequency of blood glucose levels $<3.5$ mmol/l over 72 h (hypo), maximum dose of glucagon (max-glucagon) (mg/kg per day) as putative markers of severity, were tested for correlation with CHO (mg/kg per min) in a cohort ($n=9$) with early onset CHI. M-CHISS was validated in an independent cohort ($n=29$) with 4 years follow-up data, in whom 13 (43%) children had CHI-related mutations and 10 (35%) children underwent pancreatic surgery.

### Results
Max-glucagon (standardised coefficient 0.9, $R^2=0.8$, $<0.001$) but not hypo or max-diazoxide correlated positively with CHO in the design cohort. To derive the M-CHISS tool, CHO and max-glucagon were each categorised into scores of one, two and three, and added together to form a composite score. In the validation cohort, M-CHISS, ranging between one and six, correlated positively with CHO in an independent cohort ($R=0.6, P<0.001$) in a logistic regression model controlling for age, gender and prematurity. For M-CHISS $=6$, the probability for requiring surgery was 80% (with a 75% probability of not needing surgery if M-CHISS $<6$). In contrast, for M-CHISS $\geq 3$, the probability of not requiring surgery was 100% (with a 53% probability of requiring surgery for M-CHISS $\geq 2$).

### Conclusions
M-CHISS is a simple and practical tool to assess the severity of hypoglycaemia in early presenting CHI. Further validation is required in prospective cohorts to test the prognostic value of M-CHISS.

DOI: 10.1530/endoabs.33.P14

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**P15**

**18F-DOPA PET MRI as a new imaging modality for the precise localisation of focal congenital hyperinsulinism**

Senthil Senniappan1, Pratik Shah1, Marguerite du Preez2, Raymond Endozo1, Celia O’Meara3, Caroline Townsend1, Clare Gilbert1, Kate Morgan1, Louise Hinchey1, Agostino Pierro1, Lorenzo Biassoni1, Oystein Olsen1, Jamshed Bomanji2 & Khalid Hussain

1Great Ormond Street Hospital, London, UK; 2University College London Hospital, London, UK.

### Introduction
Congenital hyperinsulinism (CHI) includes two major histological subtypes; diffuse and focal. Fluorine-18-L-dihydroxyphenylalanine positron emission tomography ($^{18F}$-DOPA PET/CT) has been established as a novel imaging technique to differentiate focal from diffuse CHI. However CT provides only limited soft tissue contrast and exposes the patient to a significant radiation dose.

### PET/MRI
PET/MRI could provide images with an excellent soft tissue contrast, very good spatial resolution of the anatomy and very accurate temporal and spatial image fusion with no additional radiation exposure. We aimed to evaluate the feasibility of using $^{18F}$-DOPA PET/MRI for the diagnosis focal CHI.

### Methods
Five children with severe CHI underwent simultaneous $^{18F}$-DOPA PET/CT and PET/MRI imaging. All medications including octreotide and glucagon were discontinued 48 h before the scan. The $^{18F}$-DOPA was administered intravenously at a dose of 4 MBq/kg and iodine contrast media at a dosage of 1.5 ml/kg.

### Results
PET/MRI in 4 children revealed diffuse CHI (SUV $<1.3$) and one child had focal CHI (SUV $>1.5$). The focal lesion was delineated clearly in accordance with the results from PET/CT images. In addition PET/MRI provided soft tissue and anatomical information of the adjacent structures that aided the precise surgical resection of the lesion.

### Conclusions
In this preliminary study, we have demonstrated the feasibility of using PET/MRI as a novel imaging modality for diagnosing focal CHI. Further studies are needed to establish the accuracy and validity of PET/MRI. Given the potential of less radiation exposure and higher soft tissue clarity, PET/MRI is likely to become a preferred imaging modality for CHI management.

DOI: 10.1530/endoabs.33.P15

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**P16**

**Increasing weight in children with congenital hyperinsulinism is linked to KATP channel gene mutations**

Zainaba Mohamed1, Rajesh Chidannadasswamy1, Abigail Swancott1, Caroline Steele1, Philip Murray1, Lindsay Rigby1, Raja Padidela1, Sarah Elhisham1, Mars Skae1, Leepa Patel1, Sian Ellard1, Mohammed Didi2, Karen E Cosgrove4, Mark Dunne1, Indaneel Banerjee1 & Peter E Clayton1

1Department of Paediatric Endocrinology, Royal Manchester Children’s Hospital, Manchester, UK; 2Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK; 3Faculty of Life Sciences, University of Manchester, Manchester, UK; 4Molecular Genetics, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK; 5Department of Paediatric Endocrinology, Alder Hey Children’s NHS Foundation Trust, Liverpool, UK.

### Introduction
Congenital hyperinsulinism (CHI) is a cause of severe hypoglycaemia due to insulin over-secretion. The medical management of CHI involves supplementary glucose, which combined with insulin excess, may be obeseogenic. However, increased weight in CHI patients has not been reported. We have investigated if children with CHI increase in weight and if genetic or treatment factors influence the weight trajectory.

### Methods
Weights were measured and expressed as SDS in children with CHI at birth ($n=70$) and at ages 1 ($n=51$), 2 ($n=44$), 3 ($n=30$) and 4 ($n=23$) years. Weight SDS at follow-up was tested for correlation with ATP-sensitive K$^+$ channel ($K_{ATP}$) gene mutation status ($n=65$) and with treatment variables, which included medical/surgical treatment, resolution of CHI, supplemental glucose and response to diazoxide, in a backward regression model.

### Results
Weight SDS increased from birth (median range) $-0.2$ (−4.4; 5.7)) to ages 2 ($+0.1$ (−2.7; +5.0)), 3 ($+0.5$ (−2.2; +2.9)) and 4 ($+0.5$ (−3.3; +3.1)) years. The weight increment was most significant at age 2 years ($P=0.02$). $K_{ATP}$ channel mutations, either heterozygous or homozygous, were present in 25 (39%) children. Children with mutations were heavier at birth ($P<0.001$) and remained so at 2 years ($P=0.002$). Mutation status, but not treatment variables were correlated with weight SDS at 2 years ($R^2=0.5, p=0.004$) implying that genetic factors alone may associate with an increased weight trajectory in CHI.

### Conclusions
Weight SDS may increase in the first 2 years of life, which is correlated with $K_{ATP}$ channel mutation status but not to the treatment of CHI. Further follow-up is required to assess if weight trajectory in later childhood leads to obesity.

DOI: 10.1530/endoabs.33.P16
P17

Frequency of focal and diffuse congenital hyperinsulinism with paternally inherited mutations in ABCC8 and KCNJ11
Jaya Sujatha Gopal1, Zainaba Mohamed1, Raja Padidela2, Leena Patel1, Mars Skae1, Mohammed Didi1, Jackie James1, Louise Caine2, Lindsay Rigby3, Karen E Cosgrove3, Mark Dunne4, Sian Ellard3, Indi Banerjee5 & Peter Clayton1

1Department of Paediatric Endocrinology, Royal Manchester Children’s Hospital, Manchester, UK; 2Department of Paediatric Endocrinology, Alder Hey Children’s NHS Foundation Trust, Liverpool, UK; 3Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK; 4Faculty of Life Sciences, University of Manchester, Manchester, UK; 5Molecular Genetics, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK.

Introduction
Congenital hyperinsulinism (CHI) causes severe hypoglycaemia, which can be either focal or diffuse in aetiology. Both forms are associated with paternally inherited mutations in ABCC8/KCNJ11. Lymphocytic DNA analysis alone is inadequate to diagnose focal CHI, as pancreatic maternal allelic silencing cannot be tested prior to surgery. Additional 18-fluorodopa PET–CT scanning (PET–CT) is required for definitive diagnosis; in this study, we have reviewed the diagnostic outcomes of scanning in children with paternally inherited ABCC8/KCNJ11 mutations.

Methods
The diagnosis of focal/diffuse CHI was reviewed in children with paternally inherited mutations in ABCC8/KCNJ11 (n=23) following PET–CT and confirmation by histology in those undergoing surgery. Severity of the CHI phenotype was assessed by maximum glucose requirement, maximum dose of glucagon and maximum dose of diazoxide at presentation.

Results
CHI was diagnosed with a mean (interquartile range) serum insulin 86.7 (110.2) mU/l and blood glucose 0.8 (1.4) mmol/l. The majority carried mutations in ABCC8 (n=17, 74%). Focal CHI was present in 17 (74%) children, and was successfully treated surgically. Diffuse CHI was present in 6 (26%) children where a maternal allelic mutation was not identified. In this group, only two required subtotal pancreatectomy to achieve glycaemic stability. Three children were medically managed and one child achieved spontaneous resolution. The severity phenotype did not correlate with the diagnosis of focal or diffuse CHI following PET–CT.

Conclusions
A paternally inherited mutation in ABCC8/KCNJ11 is associated with focal CHI in 74% children with CHI, requiring surgery. In those with diffuse CHI, the majority can be medically managed.

DOI: 10.1530/endoabs.33.P17

P18

Altered plasma incretin concentrations in patients with non-typical forms of congenital hyperinsulinism
Yanqin Shi1, Hisa B Avatapulle2, Mars S Skae3, Raja Padidela1, Melanie Newbould1, Lindsey Rigby1, Sarah E Flanagan2, Sian Ellard1, Jacques Rahier5, Peter E Clayton2, Indraneel Banerjee3, Mark J Dunne4 & Karen E Cosgrove1

1Faculty of Life Sciences, University of Manchester, Manchester, UK; 2Department of Paediatric Endocrinology, Royal Manchester Children’s Hospital, Manchester, UK; 3Department of Paediatric Histopathology, Royal Manchester Children’s Hospital, Manchester, UK; 4Royal Devon and Exeter NHS Foundation Trust, Peninsula College of Medicine and Dentistry, Exeter, UK; 5Department of Pathology, Cliniques Universitaires Saint Luc, Brussels, Belgium.

Introduction
Congenital hyperinsulinism (CHI) may arise due to loss-of-function mutations in ABCC8 and KCNJ11 genes which encode subunits of ATP-sensitive potassium (KATP) channels. KATP channels couple nutrient metabolism with insulin secretion in pancreatic β-cells but are also located in enteroendocrine L- and K-cells and may play a role in the control of GLP-1 and GIP secretion respectively. More than 70% of patients with CHI have no identified mutations in known CHI-associated genes and this includes many patients with transient CHI which spontaneously resolves.

Aims
We hypothesized that CHI patients with KATP channel gene mutations may have altered plasma profiles of GLP-1 (7–36) and GIP compared with other groups of CHI patients.

Methods
Thirteen patients with CHI were recruited from a single referral centre. Fasting and post-prandial GLP-1 (7–36) and GIP were measured in patient plasma using ELISA. Data were compared between patients with ABCC8/KCNJ11 mutation-positive CHI (CHI-F and CHI-D, focal and diffuse, n=6), mutation-negative persistent CHI (CHI-UV, unclassified variant, n=2), and mutation-negative transient CHI (n=5) using ANOVA and post-hoc tests.

Results
Our data revealed no differences in plasma incretin concentrations between transient CHI and ABCC8/KCNJ11 mutation-positive patients, but demonstrated markedly different plasma incretin concentrations in CHI-UV patients compared with all other groups (P<0.05).

Conclusion
These data provide evidence that measurement of plasma GLP-1 (7–36) and GIP may aid the identification and diagnosis of a novel sub-group of CHI patients, and suggest that KATP channel genes do not play a significant role in nutrient sensing in enteroendocrine cells.

DOI: 10.1530/endoabs.33.P18

P19

6-Mercaptopurine linked with hyperinsulinemic hypoglycaemia in two children with acute lymphoblastic leukaemia
Christina Wei1, Andrea Simmons3, Oliver Tunstall1 & Christine P Barren3
3St Georges Hospital, London, UK; 2Royal London Hospital, London, UK; 1Bristol Royal Hospital for Children, Bristol, UK.

Introduction
Hyperinsulinaemia is a rare side-effect of 6-mercaptopurine (6MP) with unclear mechanism(s). The occurrence of hyperinsulinaemic hypoglycaemia (HIH) is reported here for the first time in children on 6MP for acute lymphoblastic leukaemia (ALL).

Case 1
Caucasian female, diagnosed with ALL aged 4 years, was treated under UKALL2003 regime A. During an admission for neutropaenic sepsis, asymptomatic hypoglycaemia was noted pre-breakfast for 3 days. Laboratory glucose was 2.1 mmol/l with raised insulin 33.5 mU/l on day 1. Full hyperglycaemic screen on day 3 showed glucose 2.3 mmol/l, insulin 36.7 mU/l and C-peptide 1087 pmol/l. Remainder of investigations (GH, cortisol, ammonia, lactate, acylcarnitine, free fatty acid, and 3-β-hydroxybutyrate) were normal. Synacthen stimulation test excluded primary adrenal disorders (peak cortisol 1124 mmol/l). Hypoglycaemia resolved after 6MP was discontinued. Two pre-breakfast hypoglycaemia (both 2.3 mmol/l), associated with reduced oral intake during illness, were recorded the following month while she was back on 6MP.

Case 2
Female of Bangladeshi origin, diagnosed with ALL, aged 4 years was treated under UKALL2003 regime A, modified to prednisolone due to dexamethasone toxicity. One year into treatment, she presented with symptomatic hypoglycaemia (dizziness, vomiting, and glucose 2.6 mmol/l) while fasted for a procedure under general anaesthesia. Continuous glucose monitoring revealed nocturnal hypoglycaemia (BM <2.6 mmol/l) which continued despite larger evening meals and slow release carbohydrate snacks pre-bed. Hypoglycaemic investigations showed glucose 2.6 mmol/l, insulin 11.5 mU/l, and C-peptide 520 pmol/l. Remainder of investigations (as per case 1) were normal. Blood glucose levels normalised after switching 6MP administration to the morning. Five months later, she represented with hypoglycaemia after 6MP dosage increase, which resolved after reduction. Discussion
Hyperinsulinaemia is a possible mechanism of 6MP associated hypoglycaemia. Paediatricians need to be aware of hypoglycaemic risk in young ALL patients on 6MP treatment. Glucose levels should be actively monitored during periods of fast or reduced oral intake.

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**P20**

**18F-DOPA PET and enhanced CT imaging for congenital hyperinsulinism: Our experience of using oral sedation**

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**Methods**

27 18F-DOPA PET/CT and contrast enhanced CT imaging scans were performed on 22 consecutive patients with CHI (median age 2.1 years). All medications including octreotide and glucagon were discontinued 48 h before the scan. Single bed position PET/CT images over the pancreas were acquired under light sedation with oral chloral hydrate (dose 50 mg/kg). Four PET dynamic data scans were acquired at 20, 40, 50, and 60 min post injection for duration of 10 min each. Results were assessed by visual interpretation and quantitative measurements of standardized uptake values (SUVs) in the head, body, and tail of the pancreas.

**Results**

Of the 22 patients, 16 showed diffuse and six showed focal 18F-DOPA PET pancreatic uptakes. Six patients had an accumulation of 18F-DOPA in the pancreas and a SUV ratio value of > 1.5, indicating focal disease. The remaining 16 patients had diffuse accumulation of 18F-DOPA in the pancreas (SUV ratio < 1.3). All the children tolerated oral sedation well. All patients diagnosed with focal lesions underwent surgery and were cured eventually.

**Conclusion**

18F-DOPA PET/CT offers excellent differentiation of focal from diffuse CHI and enhanced CT technique permits precise preoperative localisation of the lesion and anatomical landmarks. Also, excellent quality of images were obtained after giving oral sedation (chloral hydrate) in all children without need of general anaesthesia.

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**P21**

**Long-term endocrine and exocrine outcome of medically unresponsive diffuse congenital hyperinsulinism managed with near-total pancreatectomy: 18 years’ experience**

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**Introduction**

Diffuse congenital hyperinsulinism (CHI) is a major cause of severe hypoglycaemia. One treatment option is near-total pancreatectomy, which carries a risk of diabetes mellitus (DM) and pancreatic exocrine insufficiency.

**Objective**

We report our centre’s experience on 36 consecutive medically unresponsive diffuse CHI children managed with near-total pancreatectomy.

**Methods**

Following near-total pancreatectomy, these children underwent regular 24-h blood glucose profile, controlled fast and oral glucose tolerance tests to assess glucose homeostasis. Clinical and biochemical evidence (faecal elastase 1) of pancreatic exocrine insufficiency was also evaluated.

**Results**

From 1994 to 2012, 36 children (male/female, 16/20) underwent near-total pancreatectomy for medically unresponsive diffuse CHI. The mean (±s.d.) birth weight (g) and gestational age (weeks) was 4080 ± 730 and 38 ± 2 respectively. The patients presented with severe hyperinsulinaemic hypoglycaemia at a median age of 1 day. Molecular genetic analysis revealed ABCC8/KCNJ11 mutation in 31 patients. The median age at pancreatectomy was 0.17 years. The diagnosis of diffuse disease was reached either by pancreatic venous sampling or 18F-DOPA PET–CT. Histology confirmed diffuse disease in all patients. Hypoglycaemia persisted post-pancreatectomy in 16 patients (44%), necessitating either total-pancreatectomy, treatment with octreotide, diazoxide and/or frequent high carbohydrate feeds. Over a mean (±s.d.) follow-up period of 8 (±4.75) years, 18 children developed DM. The cumulative risk of DM after 5 and 10 years post-pancreatectomy was 74 and 86% respectively. Twenty-six patients (72%) showed biochemical evidence of pancreatic exocrine insufficiency, only seventeen (47%) of which developed clinical pancreatic exocrine insufficiency necessitating pancreatic enzyme replacement.

**Conclusions**

Near-total pancreatectomy for CHI is associated with high risk of DM, however not all patients with post-pancreatectomy go on to develop clinical or biochemical evidence of pancreatic exocrine insufficiency. There seems to be a poor correlation between biochemical and clinical pancreatic exocrine insufficiency.

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**P22**

**Evaluation of Postprandial Hyperinsulinaemic Hypoglycaemia in Children**

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**Introduction**

Hyperinsulinaemic hypoglycaemia (HH) is characterized by dysregulated insulin secretion and is typically associated with reduced fasting tolerance. We aimed to evaluate the clinical and biochemical characteristics of children presenting with postprandial hyperinsulinaemic hypoglycaemia.

**Methods**

Retrospective data collection on children who presented with symptomatic postprandial hypoglycaemia. Children with postprandial hypoglycaemia second-ary to gastrointestinal surgery (such as dumping syndrome) were excluded. Prolonged OGTT was performed as per standard protocol.

**Results**

We identified six children with a mean age of 6.08 (±2.01) years who presented with symptomatic hypoglycaemia occurring typically within 2-3 hours after a meal. The symptoms included lethargy, tiredness, hunger and shakiness. In one child seizures were noted during the hypoglycaemic episode. The family history included type two diabetes in two families, postprandial hypoglycaemia in one family and type one diabetes in another family. All children had a normal fast tolerance for age with a mean fast duration of 17.8 (±1.78) hours and appropriately suppressed insulin levels at the end of the fast (< 2 mU/L). All children were noted to mobilize fatty acids at the end of the fast and also demonstrated normal glucocorticoid response. Metabolic screening did not reveal any abnormality. Prolonged OGTT revealed HH (mean blood glucose 2.78 mmol/l and mean insulin concentration 6.95 mU/L) occurring at an average time length of 170 (±36.3) minutes after the glucose load. Treatment with acarbose was noted to be beneficial in three children, diazoxide improved the glycaemic control in one child and two children were managed with frequent feeds.

**Conclusion**

We describe a group of children with symptomatic postprandial hypoglycaemia who demonstrated HH between 2-3 hours post glucose load. Prolonged OGTT is necessary to identify these episodes. Acarbose is beneficial in children with postprandial HH who do not respond to dietary modification. Further research is required to understand the molecular basis of this postprandial HH.

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**P23**

**Can we prevent hypoglycaemic brain injuries in term babies with no risk factors of Hyperinsulinaemic Hypoglycaemia?**

Clare Gilbert, Kate Morgan, Louise Hinche, Pratik Shah, Anitha Kumaran & Khalid Hussain

Great Ormond Street Hospital NHS Foundation Trust, London, UK.

**Introduction**

Hyperinsulinaemic hypoglycaemia (HH) represents the most common cause of hyperinsulinism in neonates, often termed as congenital hyperinsulinism of infancy (CHI). CHI is characterised by inappropriate raised insulin secretion from the pancreatic β-cells in relation to blood glucose concentration. Insulin suppresses NEFA and BOHB production. Neurological damage is a known risk associated with hyperinsulinaemic hypoglycaemia (HH).

**Results**

We identified six children with a mean age of 6.08 (±2.01) years who presented with symptomatic hypoglycaemia occurring typically within 2-3 hours after a meal. The symptoms included lethargy, tiredness, hunger and shakiness. In one child seizures were noted during the hypoglycaemic episode. The family history included type two diabetes in two families, postprandial hypoglycaemia in one family and type one diabetes in another family. All children had a normal fast tolerance for age with a mean fast duration of 17.8 (±1.78) hours and appropriately suppressed insulin levels at the end of the fast (< 2 mU/L). All children were noted to mobilize fatty acids at the end of the fast and also demonstrated normal glucocorticoid response. Metabolic screening did not reveal any abnormality. Prolonged OGTT revealed HH (mean blood glucose 2.78 mmol/l and mean insulin concentration 6.95 mU/L) occurring at an average time length of 170 (±36.3) minutes after the glucose load. Treatment with acarbose was noted to be beneficial in three children, diazoxide improved the glycaemic control in one child and two children were managed with frequent feeds.

**Conclusion**

We describe a group of children with symptomatic postprandial hypoglycaemia who demonstrated HH between 2-3 hours post glucose load. Prolonged OGTT is necessary to identify these episodes. Acarbose is beneficial in children with postprandial HH who do not respond to dietary modification. Further research is required to understand the molecular basis of this postprandial HH.

**References**

Aim
To describe the clinical course and neurological outcome of three term neonates with severe hypoglycaemic brain injury who have had delayed diagnosis of hyperinsulinaemic hypoglycaemia.

Methodology
We recruited three patients who presented in the neonatal period with biochemically confirmed HH and referred to a tertiary endocrine hospital. Detailed clinical information was collected including MRI brain scan reports. Clinical presentation
All three patients were born by normal vaginal delivery and were discharged within 24–36 h of life.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gestation (weeks)</th>
<th>Birth weight (g)</th>
<th>Presentation</th>
<th>Blood glucose (mmol/l) on presentation</th>
<th>Medications</th>
<th>MR/CT brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>36 + 4</td>
<td>2750</td>
<td>On day 3 with history of poor feeding, lethargy, movements,</td>
<td>0.4</td>
<td>Diazoxide and Chlorothiazide</td>
<td>MRI – grossly abnormal with evidence of cortical necrosis</td>
</tr>
<tr>
<td>Case 2</td>
<td>39</td>
<td>3250</td>
<td>On day 4 with lethargy, poor responsiveness and seizures.</td>
<td>0.6</td>
<td>Diazoxide and Chlorothiazide</td>
<td>MRI and CT – subtle reduced attenuation within the cortex and white matter in keeping with generalised cerebral oedema related to hypoglycaemia</td>
</tr>
<tr>
<td>Case 3</td>
<td>38</td>
<td>3460</td>
<td>On day 3 with poor feeding, lethargy and seizures</td>
<td>&lt; 0.3</td>
<td>Diazoxide and Chlorothiazide</td>
<td>MRI – bilateral extensive periventricular white matter infarction with diffuse cerebral swelling and oedema, typical of hypoglycaemic brain injury</td>
</tr>
</tbody>
</table>

Conclusion
CHI leads to severe hypoglycaemia leading to severe brain injury and subsequent neurodevelopmental handicap. The identification, early diagnosis and prompt management of patients with hyperinsulinaemic hypoglycaemia are essential if brain damage is to be avoided. These infants are often difficult to identify due to the symptoms being non-specific. DOI: 10.1530/endoabs.33.P23

P25
Gene expression profiling reveals possible role of growth factors in beta cell hyperplasia in congenital hyperinsulinism
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Introduction
Congenital hyperinsulinism (CHI) is a clinically heterogeneous condition. Mutations in ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, UCP2 and HNF1A are known to cause CHI. There are two histological subtypes of CHI: diffuse and focal. Apart from the functional channel defect, β-cell hyperplasia has been observed in diffuse CHI. We aimed to understand the gene expression pattern in pancreatic tissue of patients with diffuse CHI when compared to normal controls and to compare the expression pattern in patients with known genetic aetiology of CHI with that of patients without a genetic aetiology.

Methods
Fresh frozen pancreatic tissue samples were obtained from six children with diffuse CHI who underwent near total pancreatectomy. RNA was extracted by standard techniques (TRIZol reagent). RNA Integrity was assessed by Agilent-derived RNA integrity number (RIN) and the presence of intact 18 and 28 s bands on the Agilent Bioanalyzer trace. Gene expression microarray (standard Affymetrix techniques) was undertaken on the six diffuse CHI (four with ABCC8 mutation and two without any known mutation) and two normal RNA samples.

Results
We observed significant overexpression of growth factors and their regulatory proteins like IGF1, IGF2 and IGF2BP3 in diffuse CHI patients. Uncoupling proteins like UCP2 are up regulated in diffuse CHI patients. An anti-apoptotic factor OLFM4 is overexpressed in one of the diffuse CHI patients without any known mutation. Growth factor receptor-binding protein (Grb14) is significantly downregulated in the other diffuse patient without any known mutation possibly enhancing insulin-induced signalling. The markers of cellular proliferation Ki-67 and FOXM1 were significantly overexpressed in diffuse CHI.

Conclusions
The data, first of its kind in CHI, has suggested the potential role of growth factors and anti-apoptotic factors in the β-cell hyperplasia in diffuse CHI. Agents targeting IGF pathways can be a potential therapeutic option to ameliorate the β-cell proliferation in CHI.

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P26
Screening for Coeliac disease in children diagnosed with diabetes mellitus
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Background
Coeliac disease has higher prevalence in children with diabetes mellitus than in the general population, and can have significant impact on quality of life causing faltering growth, prolonged fatigue and recurrent abdominal pain.

Objective
To compare current practice in screening for coeliac disease in children with diabetes mellitus with recommended standards and to investigate the value of follow-up screening for coeliac disease in children previously diagnosed with diabetes mellitus.

Methods
One hundred and forty-six children under 19 years old who had been diagnosed with diabetes mellitus were retrospectively included. Results of coeliac screening at diagnosis (IgA Anti-TTG) and annual coeliac screening were analysed. Case notes of children who had positive results were analysed to see if symptoms were documented. Children with positive antibodies were referred to tertiary hospital and biopsy undertaken. Positive biopsy was taken as gold standard for diagnosis.

Results
In this retrospective study of 148 children diagnosed with diabetes mellitus, 7 were diagnosed with coeliac disease through screening, 6 of whom were on follow-up. 3 were symptomatic. We found the prevalence of coeliac disease to be 5%.

Conclusions
We recommend routine continued surveillance screening for coeliac disease after the diagnosis of type 1 diabetes in children.

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P27
Are paediatric patients attending their annual diabetic retinopathy screening?
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Background
Glycaemic control and duration of diabetes mellitus play an important role in delaying or preventing diabetic retinopathy. NICE guidelines state that for type 1 diabetes, those aged 12 years and over must be offered annual retinopathy screening. This audit aims to assess compliance with the guidelines and the prevalence of retinopathy.

Methods
This was a retrospective audit of paediatric diabetic patients registered to Good Hope Hospital attending diabetic retinopathy screening in 2011 and 2012. Data was obtained from the Retinal screening co-ordinators and the Optimize database.

Results
All children aged 12 at the start of the year of screening with type 1 or type 2 diabetes were included. Data collected included: demographic factors, screening attendance and results; HbA1c levels, and durations of diabetes.

Conclusions
There was no statistically significant difference in HbA1c at the time of LA diagnosis compared to 3 months prior.

P28
Resurgence of Lipoatrophy as a complication of treatment with insulin
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Background
Lipoatrophy (LA) was commonly associated with insulin use prior to the development of purified insulin in the 1970’s, and then has virtually disappeared. In the last few years, however reports of LA among patients using analogue insulin preparations have increased. We report a case series of 4 patients from a tertiary paediatric diabetes unit presenting with LA while on treatment with analogue insulin via a continuous s.c. insulin infusion pump (CSII).

Methods
Four patients have presented within the last 2 years with LA, from our clinic population of 328 patients.

Results
All four patients were on insulin aspart via CSII for the management of type 1 diabetes (T1DM) (Table 1).

Table 1 Demographic data (at time of diagnosis of LA unless otherwise specified).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Duration of diabetes (years)</th>
<th>HbA1c (months prior to diagnosis) (%)</th>
<th>LA at diagnosis (%)</th>
<th>Follow up (months)</th>
<th>LA resolved Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>12</td>
<td>3.3</td>
<td>8.3</td>
<td>7.8</td>
<td>3</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>3</td>
<td>1.5</td>
<td>7.1</td>
<td>6.9</td>
<td>1</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>10</td>
<td>1.6</td>
<td>6.8</td>
<td>7</td>
<td>5</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>8</td>
<td>2.4</td>
<td>8.9</td>
<td>9.7</td>
<td>19</td>
<td>Y</td>
</tr>
</tbody>
</table>

There was no statistically significant difference in HbA1c at the time of LA diagnosis compared to 3 months prior.

Conclusions
Lipoatrophy as a complication of insulin therapy in patients with T1DM is re-emerging. LA causes undesirable cosmetic appearances and may cause variable glycaemic control. We have not seen any cases with multiple injections, so it is possible that the continuous infusion of analogue insulin is an important factor. LA should be reported to drug companies and the Yellow Card system of adverse drug effects. This will facilitate observation of trend, and help monitor associations.

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P29
Prevalence and screening of thyroid and coeliac disease in type 1 diabetes mellitus
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Introduction
Children with type 1 diabetes mellitus are at increased risk of autoimmune thyroid and coeliac disease. Reported prevalence figures for thyroid and coeliac disease in this population has been reported in European studies as 3–8%1 and 1–10%2 respectively. Current NICE guidelines (June 2009) recommend screening for both conditions at diagnosis, and then screening annually for thyroid disease thereafter. We aimed to: i) estimate prevalence of these conditions in a British cohort; ii) determine whether NICE guidelines are being adhered to.

Methods
We ran a search on a web-based platform for paediatric patients with diabetes (Twinkle.Net) in a Greater London district general hospital trust for details of patients’ thyroid function and anti-transglutaminase antibody tests during the past

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year. Electronic clinical notes and correspondence were individually checked for diagnoses of autoimmune disease.

Results
Prevalence of coeliac disease was 4.29%, and 2.45% for thyroid disease (n = 163). 76.07% of all patients had thyroid function tests in the last year and 70.83% of newly diagnosed patients had an autoimmune screen at diagnosis, in accordance with NICE guidelines.

Conclusion
Despite international variation in diabetes epidemiology, our prevalence figures are consistent with the limited literature. Screening for asymptomatic disease was sub-optimal, with poor patient compliance in adolescents playing a role. Untreated thyroid and coeliac disease can adversely affect glycaemic control, and therefore clinicians' awareness of their prevalence and regular screening is paramount.

References

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P30
GAD and IA2 autoantibody positivity is associated with a requirement for insulin treatment: results of the UK national paediatric type 2 diabetes cohort

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1Birmingham Children’s Hospital, Birmingham, UK; 2University of Birmingham, Birmingham, UK.

Objectives
To establish the frequency of islet cell autoimmunity in children with a clinical diagnosis of type 2 diabetes (T2DM) and describe associated clinical and laboratory findings.

Methods
We recruited children with paediatrician diagnosis of T2DM and body mass index (BMI) above 85th centile for age and sex. Patients with other confirmed diagnoses such as monogenic and type 1 diabetes (T1DM) were excluded. Clinical data was collected into a national database. Blood was taken for diabetes auto-antibody status to exclude diagnoses of T1DM. Autoantibodies were measured using standardised radiobinding assays: GADA and IA-2A with 35-S labelled antigens and IAA with I-125 labelled Insulin in the reference laboratory in Bristol.

Results
Of the 130 recruited to the UK national cohort who have had antibody testing to date, 14 (11%) were positive for either GAD2 or IA2 antibodies (AAb positive). Of these, 8 (6%) were positive for a single antibody, and 6 (5%) positive for both antibodies. Children were not classified as AAB positive if they were only positive for insulin autoantibodies, as this is likely an indicator of previous insulin treatment. Diabetes autoantibody positivity was significantly associated with a reduced pooled C-peptide (median 530 vs 1270 P = 0.0016), and previous insulin treatment (86 vs 31% P < 0.001). There was a trend towards differences in sex, BMI-SDS and HbA1c between the groups, with more girls being antibody negative, the AAB positive group having a lower BMI-SDS, and higher HbA1c.

Conclusion
Approximately 11% of patients presenting with T2DM are in fact autoantibody positive, suggesting a masked diagnosis of T1DM. This is associated with insulin treatment and a reduced C-peptide. This suggests the need to do autoantibody testing on all children with a diagnosis of diabetes, even if it is suspected T2DM, and predicts the need for insulin treatment 2 years after diagnosis in AAB positive patients.

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P31
Growth and metabolic control in children and adolescents with type 1 diabetes mellitus associated with other autoimmune diseases

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Aim
To study the effect of type 1 diabetes mellitus (T1DM) and concurrent autoimmune condition (AI) on long term glycaemic control and growth in children.

Methods
Twenty-eight children with T1DM and associated autoimmune condition were matched by sex and age at onset with two controls each. HbA1C, height SDS, weight SDS and BMI SDS were measured between 6 months and 5 years after developing T1DM.

Results
We included 28 children with T1DM and AI (10 males) and 56 (20 males) age and sex matched controls with T1DM. Out of the 28 patients with AI conditions, 21 (75%) had coeliac disease (CD), 8 (28%) had autoimmune hypothyroidism (AH) and 1 (4%) patient had both CD and AH. Development of an AI condition occurred at 2.3±3.1 years after diagnosis of T1DM. There was no significant difference in growth parameters height SDS, weight SDS and BMI SDS between children in the AI group compared with controls from diagnosis to 5 years after diagnosis of T1DM. Children in the AI group had a significantly better HbA1c control 6 months after diagnosis, but no significance was noted at 1, 2, 3 and 5 years. Multiple logistic regression of factors showed no independent risk factors that affected the development of an AI.

Conclusion
Suboptimal therapeutic control of an autoimmune condition such as coeliac disease and T1DM is known to lead to impairment in growth and substantial morbidity. Our study shows children with T1DM developing a concurrent autoimmune disease were not at risk of worsening metabolic control or growth impairment long term.

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P32
Diabetes mellitus related to Williams syndrome: first report of childhood onset

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Introduction
Williams syndrome (WS) is a multi-systemic disorder caused by a deletion in the 7q11.23 region 7q11.23. Childhood endocrine follow-up is mainly aimed to monitor hypercalcaemia and thyroid function. A high prevalence (63–71%) of impaired glucose tolerance and DM in WS is reported. WS guidelines recommend Oral Glucose Tolerance Test (OGTT) starting from 30 years of age. We demonstrate evidence of IGT and DM in WS at a much earlier age.

Case report
A 15.6 years old WS female presented with history of polyuria and polydipsia. She was never overweight and initially presented with glycosuria, moderate ketonuria and hyperglycaemia without acidosis, during a gastroenteritis at the age of 4.2. Subsequently diabetic ketoacidosis appeared, insulin was started but shortly stopped for persistent hyperglycaemia. Subsequent glucose monitoring was normal and remained off insulin. At the age of 10 nocturnal polyuria became evident. Glycosuria, without ketosis or hyperglycaemia, was confirmed and classified as ‘renal glycosuria’ due to WS renal impairment. Recent investigations confirmed glycosuria without ketonuria, and raised HbA1c (51 mmol/mol). OGTT confirmed DM (T0=7.8 mmol/l; T120=15.3 mmol/l). Insulin assessment was not available, C-peptide secretion was impaired (T0 = 0.1 mmol/l; peak T0=0.32 mmol/l). Autoimmunity is still pending. Type 2 like DM with β-cells impairment was considered most probable and diet modifications and Metformin treatment were started, improving glucose metabolism.

Conclusions
We describe the youngest patient with DM associated with WS. Main hypothesis for the underlying etiopathogenesis suggest hyperinsulinism secondary to insulin sensitivity reduction linked to genes involved in deletion. Lack of studies in childhood raises the issue about the timing of onset of DM. It is possible that hyperinsulinism could be present for many years before IGT. Our finding demonstrates for the first time the need for studies aimed to assess the prevalence of glucose metabolism abnormalities in WS during childhood with appropriate intervention.

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P33

Transition of young people with diabetes: 3 years experience in a single centre

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Background

Transferring children with chronic illnesses into adult services is a major challenge. The diabetes transition process in our unit was being redesigned and this audit was performed to provide a historical benchmark relating to the previous setup. During the audit period, young people had a joint appointment in the paediatric service with an adult nurse specialist and then were referred by letter to the adult diabetes team.

Aim

We collected key data from the year before and after transition which included age, number of appointments offered and attended, average HbA1c, hospital admissions and whether patients had annual review before transition.

Methods

Data from patients transitioned over 3 years period (n=46) was collected retrospectively from case notes and laboratory database.

Results

The majority of patients were transitioned at the age of 17 years. Ninety-six percent were transitioned to adult services in the same trust. The number of appointments offered per year before transition was more than after. Attendance rates in the year before and after transition were 60 and 55%. Out of 46 patients, 7 did not attend any appointments in the year after transition, 6 of them were male and most had poor glycaemic control. Three were subsequently lost to follow up. Mean HbA1c before and after transition was 9.5 and 9.8% respectively. Hospital admissions were more in the year before transition.

Conclusions

This audit provided key information around the year of transition. Glycaemic control and clinic attendance is poor around transition. Following this audit, the transition process has been redesigned. We need to particularly target young boys with poor glycaemic control to engage with services to prevent them becoming lost to follow up.

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P34

Reduced acute complications, improved glycaemic control and reported quality of life in young diabetic patients on continuous s.c. insulin infusion (CSII)

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Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK.

Objectives

The use of CSII in very young diabetic children was initially limited. The criteria for continued use are better long term glycaemic control and reduced hypoglycaemic episodes. The objective of this study was to evaluate the benefit of CSII on glycaemic control, acute complications and quality of life of diabetic patients.

Methods

Retrospective analyses of data from patients with type 1 diabetes from our database that were started on CSII from 2007 to 2012 were done. Their glycosylated hemoglobin (HbA1c), hypoglycaemic episodes, diabetic ketoacidosis and reported quality of life were documented in the year before CSII and compared post-CSII.

Results

There were 17 patients, 9 males, 8 females with mean age at diagnosis of diabetes at 5.1 (range 1.5–10) years. Mean age at CSII initiation was 9.9 (range 3–15) years and mean time taken for transferring a patient from MDI to CSII was 4.8 years. Mean basal insulin dose before CSII was 0.45 units/kg, reduced to 0.3 units/kg at CSII initiation. At 1 and 3 years post-CSII, 0.33 units/kg and 0.38/kg respectively. Mean basal insulin was significantly higher in girls than boys (29.6 vs 16.8, P = 0.018) before CSII initiation and not significantly different at start and 3 years post-CSII.

Mean Hba1c was 66 mmol at CSII initiation, decreased to 64.5, a month later and continued to improve 3 years post-CSII except in 3 patients > 12 years with initial decrease but no significant difference 3 years post-CSII.

There was significantly less blood sugar excursions, diabetic ketoacidosis and hypoglycaemic episodes post-CSII with improved quality of life measured by flexibility, autonomy, socialization and sleep.

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P35

Tired, tachycardic, toxic, teenagers: fluids in severe DKA

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DKA guidelines aim to reduce risk of cerebral oedema. We present the outcomes of three young females with severe DKA with reduced conscious level at diagnosis that required deviation from these guidelines.

A. 12-year-old, pH 6.88 with DKA and sepsis. Received 20 ml/kg initial fluid bolus. CT head scan was normal. Hyponatraemia required further fluid boluses, inotropes and an increase in fluids to 65% above the rate on DKA protocol. Although slow to wake after stopping sedation (4 days), she sustained no obvious neurological deficit. MRI head was normal.

B. 13-year-old, pH 6.72 with DKA, acute renal failure and candida sepsis. Received 20 ml/kg initial fluid bolus. Initial CT head scan was normal. Peritoneal dialysis was required days 7–11 as she was anuric. She was slow to wake from sedation. MRI brain showed severe diffuse ischaemic changes. She was discharged neurologically normal aside from right foot drop.

C. 14-year-old, pH 6.6 with DKA, peri-arrest, profound shock, candida sepsis and renal failure. Received 120 ml/kg fluid boluses and inotropes to gain cardiovascular stability. Initial CT head scan was normal. Poor perfusion led to necrotic skin lesions and caecal perforation. Haemodialysis was required. MRI head scan showed multifocal acute haemorrhagic striatal and leukoencephalopathic lesions. She is now making good progress with apparently normal cognitive function.

These cases demonstrate the challenges involved in treating those with severe DKA. In two of the cases, patients received large fluid volumes to restore circulating volume however did not develop cerebral oedema. The cases of severe renal failure were challenging as fluid and glucose management from a renal point of view can differ from diabetes management plans.

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P36

Insulin pumps for adolescents and young people; main problems observed in Macclesfield: United Kingdom

Hussain Alsaaffar & Surendran Chandrasekaran
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Introduction

Continuous s.c. insulin infusion delivered via insulin pump has enabled patients with diabetes mellitus type 1 to improve metabolic control and lead healthier lives. However some patients are experiencing problems with their pumps.

Aim and methods

A service review was carried out to look at the incidence of pump related problems using an online questionnaire survey.

Results

The response rate was 85% for the survey. 42 out of 85 (49.4%) children and young people are currently using insulin pumps. Different brands of insulin pumps are being used (Roche Combo, Medtronic and Animas vibe). 20 patients (56%) experienced some sort of problem with their pumps at some point. 16 patients (44%) did not experience any problem. 17 patients (85%) who had experienced problems with pumps contacted the pump company help line and found it helpful. The main problem was insulin administration failure/error (29.6%). Others were complete pump failure, battery and screen issues, bubble in tube and operational errors. Pump problems led to no clinical problems in majority but did lead to diabetic ketoacidosis on 4 occasions, hyperglycaemia in 5 cases and hypoglycaemia once which needed hospitalisation.

Conclusion

Insulin administration failure/error was the main problem reported by majority of our patients/parents. Most of our patients/parents found insulin pump company advice helpline is very useful.
P37

Insulin pumps for adolescents and young people improve their quality of life
Hussain Alsaffar & Surendran Chandrasekaran
Macclesfield District General Hospital, Macclesfield, UK.

Introduction
The study aimed to review the service provided for children and young people with type 1 diabetes mellitus focusing on their quality of life (QoL) before and after commencing insulin pump therapy.

Methods
An online survey using survey monkey was carried out. Each questionnaire had 10 questions and it was filled by either patients or their parents based on the age group.

Results
Forty-two patients are currently on insulin pump therapy. The response rate was 85% (3642). The average length of insulin pump therapy was 33 months with a mode of 2 years. Fifty-three percent of our patients are using Roche Combo insulin pumps, 39% on Medtronic and 6% on Animas vibe.

All patients were on multiple daily injections (MDI) and carbohydrate counting before being commenced on insulin pump therapy. The QoL was classified into general, physical and moral states and each was ranked poor, medium or good. Significant improvement was noticed on all aspects of QoL after being started using the insulin pump. The general state improved dramatically in 75% of patients, moral state in 55% and better physical activity in 35% of them (Figure 1).

Conclusion
Continuous subcutaneous insulin infusion delivered via insulin pump has enabled children and young people with type 1 diabetes mellitus to have better quality of life in Macclesfield.

DOI: 10.1530/endoabs.33.P37

P38

Three Families with Diabetes Mellitus and Sensorineural Deafness
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Background
Diabetes mellitus (DM) is one of the commonest chronic disorders of children, and Type 1 DM is the most frequent form of diabetes in children. Rarely DM is associated with other systemic features. DM and sensorineural deafness (SD) are features of rare syndromes like Wolfram syndrome, Rogers syndrome and Mitochondrial DM. Wolfram syndrome (also known as DIDMOAD syndrome) is caused by loss of function mutations in the WFS1 gene and the clinical features include diabetes insipidus, DM, optic atrophy and SD. Rogers syndrome is caused by mutations in the SLC19A2 gene and is characterised by the occurrence of megaloblastic anaemia, DM, and SD. Mitochondrial DM is caused by mutations in MT-TL-1 and patients have DM with mitochondrial disease.

Patient/methods
We report three unrelated families (two consanguineous and one non consanguineous) with six affected children with DM and sensorineural hearing loss. These patients do not have any developmental or eye abnormalities; nor do they have any mental or neurological disorders, nor any learning disabilities. Genomic DNA was extracted and amplified using polymerase chain reaction and the exons and the exon–intron boundaries were sequenced for possible mutations in WFS1, SLC19A2, and MT-TL1.

Results
No mutations were identified in the coding regions of the genes WFS1, SLC19A2, MT-TL1 to explain the clinical phenotype of these patients. This suggests that there might be another unidentified genetic aetiology in these patients to account for the phenotype.

Conclusion
In the three families, mutations in the known genes (WFS1, SLC19A2, and MT-TL1) which cause DM syndromes associated with SD have been excluded. This suggests that these patients may have other novel genetic causes for DM and SD. Further work including homozygosity mapping and whole exome sequencing are in progress to find the genetic mechanism of DM and SD in these patients.

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P39

Extreme hyperlipidaemia with poor glycaemic control in type 1 diabetes
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Background
Poorly controlled diabetes is associated with dyslipidaemia including high cholesterol and LDL concentrations. This increases the long term risk of atherosclerosis and cardiovascular complications. In children and young people with type 1 diabetes, management with lipid lowering agents is controversial and to date long term evidence of benefit is limited. We report a case of severe dyslipidaemia and the impact of improvement in glycaemic control.

Case
A 15-year-old female with type 1 diabetes was referred to a tertiary metabolic unit for advice on management of extreme hyperlipidaemia. At annual review, 8 years after diagnosis, she was found to have a triglyceride concentration of 43.9 mmol/l and cholesterol that was unmeasurable as the sample was too lipaemic. There was a family history of obesity and her father had been prescribed lipid lowering medication from his GP. The patients’ weight was 55.8 kg with a BMI of 24.33. She was post pubertal and her HbA1c was 14.2%. The referring team commenced a bezafibrate, but this was not tolerated.

Initial management included intensive diabetes education with an improvement in HbA1c to 10.3% and a measurable cholesterol of 16 mmol/l. Insulin pump therapy resulted in further improvement (HbA1c 7.8%; cholesterol 6.7 mmol/l; triglycerides 1.96 mmol/l). 1 year following the start of insulin pump therapy, this improvement was sustained (Cholesterol 5.1 mmol/l; triglycerides 1.25 mmol/l).

Discussion
This case of extreme dyslipidaemia in an adolescent with type 1 diabetes illustrates the close relationship between glycaemic control and lipid metabolism. Optimising the HbA1c will help identify individuals with dyslipidaemia who require further metabolic and molecular genetic assessment.

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P40
Sensor augmented insulin pump therapy in children with steroid induced diabetes (SID)
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Steroids are commonly used to treat many chronic illnesses and as part of chemotherapy regimen in children. The hyperglycaemia caused by steroids is poorly recognised and can lead to adverse outcomes. Early recognition and appropriate management of hyperglycaemia is therefore crucial. Fasting blood glucose (BG) levels can be normal and the most sensitive time to test BG is 2 h after lunch. Steroids may also result in secondary adrenocortical insufficiency. In practice this means that steroids with shorter duration of action e.g. prednisolone given at breakfast may cause early morning hyperglycaemia the following day. This would have implications for the choice of insulin preparations and the timing of administration.

The increment of insulin dose is needed daily for several days until BG within the target range is achieved. With this approach in some patients BG levels remain outside the target range for many days. In others, severe insulin resistance secondary to steroids may demand more rapid increase in the insulin dose. We report a child who was at high risk of developing SID and in whom tight BG control was desirable was commenced on sensor augmented insulin pump therapy (SAIPT). His BG levels were highest at lunch time. He was initially treated with prandial insulin but when commenced on longer duration of basal insulin analogue at breakfast, led to early morning hyperglycaemia the following day. SAIPT was useful in adjusting the dose of prandial and basal insulin and BG targets were achieved within 72 h with out subsequent hyperglycaemia. This is the first case report of SAIPT in SID. We conclude that SAIPT can be used in patients at higher risk of developing SID, hyperglycaemia requiring rapid increase in insulin and who remain at higher risk of hyperglycaemia secondary to insulin treatment or adrenal suppression.

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P41
How to manage steroid induced diabetes in children
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There are no established guidelines on the management of steroid induced diabetes (SID) in children. Steroids are commonly used to treat many chronic illnesses and as part of chemotherapy regimen in children. The hyperglycaemia caused by steroids is poorly recognised and can lead to adverse outcomes. Early recognition and appropriate management of hyperglycaemia is therefore crucial. Fasting blood glucose (BG) levels can be normal and the most sensitive time to test BG is 2 h after lunch. Insulin remains the main stay of treatment and has three components; basal, prandial and supplemental insulin requirements. As hyperglycaemia mainly occurs after meals; the prandial insulin is the primary need. Careful adjustment of insulin doses would then be required alongside calculation of carbohydrate-to-insulin ratios.

Administration of steroids may result in secondary adrenocortical insufficiency. The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration and duration of therapy. This would have implications for the choice of insulin preparations and the timing of administration and the weaning schedule. If the BG remains persistently uncontrolled i.e. > 10 mmol/l, i.v. insulin can be used. The use of i.v. insulin can also provide an estimate of the patient’s 24-h insulin requirements. I.v. insulin should only be used on a temporary basis and need for continued use should be reviewed on a daily basis. Patients will need to be monitored carefully if discharged on steroids. The discharge plan needs to include strategies to interpret BG trends and how to adjust the insulin dose with weaning schedule of steroids. East of England Paediatric Diabetes Network has established guidelines on how to manage SID in the East Anglian region. Clinicians and health care professions should be aware of timely and appropriate management of SID.

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P42
A retrospective audit to observe the effect of the use of bolus calculators and carbohydrate counting have on blood glucose control in children and young people with type 1 diabetes
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Automated Bolus Calculators (ABC) were introduced into two inner city hospitals with a high deprivation index in August 2010. Objective To observe the change in HbA1c for 3–6 months after the introduction of ABC and carbohydrate counting. Also to explore the effects of age, gender, psycho-social circumstances on HbA1c as well as the uptake of insulin pump therapy after implementation.

Method
ABC were offered to all families who were carbohydrate counting or required a method of calculating a correction bolus. Two ABC were used: Accuchek Expert, Roche and Insulins, Abbott. They were trained to use devices to give insulin bolus advice for meals and corrections as required. HbA1c was recorded at time of obtaining the meter and on average 167 days after implementation. Data was collected retrospectively. Patients using the meter within the year of diagnosis were excluded. Results were statistically analyzed using a paired t-test.

Results
Sample size 105. Mean HbA1c decreased by a small but statistically significant amount (0.41%) (2.54 mmol/l) P<0.001. 80% of the sample size carbohydrate counted all their meals whereas 15% counted only evening meals. Those reported to have no known psycho-social problems had an improved mean difference in the HbA1c compared to those who did.

Conclusion
ABC, whether used for a corrective dose, or with carbohydrate counting shows a statistically significant change in HbA1c over time. There were reductions in HbA1c when stratified by age, gender, difficulties, or carbohydrate counting. These were not statistically significant however the sample size was under-powered to detect significance in the different subgroups. This evidence supports the belief that regular usage of this meter alongside carbohydrate counting has a positive effect on HbA1c. Accurate advice is best obtained when using ABC alongside carbohydrate counting.

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P43
Challenges in Meeting Best Practice Guidelines at a District General Hospital in Yorkshire: a review of the changes that need to be made and the financial implications
Sarah Martin
Sheffield Children’s Hospital, Sheffield, South Yorkshire, UK.

Introduction
It was recognised there was a need to improve the current diabetes service provision at a District General Hospital in Yorkshire to meet the payment by results (PBR) best practice tariff. This tariff is based on recommendations by NICE, the Department for Health and the regional tertiary centre.

Objective
The main change to be implemented by this district general hospital was the creation of a 24 h diabetes service staffed by trained professionals. This would allow the trust to meet the best practice tariff and aim to reduce the number and length of hospital admissions for young people with diabetes.

Method
The strengths and weaknesses of the current service provision were examined. The case for change looked at 7 specific aspects: risk management; productivity and cost effectiveness; recruitment and retention of staff; modernisation of service provision; patient choice and implementation of national guidance.

Three options for implementation of proposed change and their consequences were then examined: no change to current practice (option 1); a 24 h on call service staffed by specialist nursing staff (option 2) and a 24 h on call service staffed by a combination of trained medical staff and nurses (option 3).

Results
The additional cost to the trust of implementing option 2 was £30 560 versus a cost of £56 020 to implement option 3. The financial incentive for meeting the PBR best practice tariff would be £30 340. The additional savings that could be made by reducing admission rates and length of admissions was calculated to be between £21 846 and £159 552.

Conclusions
The most cost effective option would be option 2 which involved setting up a 24 h on call service staffed by specialist nursing staff. This service would meet current
government recommendations and the PBR best practice tariff. These options were presented to the trust and are currently under review.

DOI: 10.1530/endoabs.33.P43

P44
Mealtime insulin carbohydrate ratios and intensive insulin therapy
Melanie Kershaw1, Simon Jones2, Ruth E Krone3, Nils Krone4, Nicholas Shaw5, Jeremy Kirk6, Lesley Drummond7 & Timothy Barrett8
1Birmingham Children’s Hospital, Birmingham, UK; 2University of Birmingham, Birmingham, UK.

Background
Our practice is to commence newly diagnosed children and young people (CYP) with diabetes, over 5 years old, on multiple daily insulin (MDI), using fixed insulin to carbohydrate ratios (ICRs) with meals across the day. ICRs are subsequently adjusted according to blood glucose response, individualising insulin treatment. We know intensified insulin therapy includes use of varied ICRs, reflecting varying insulin sensitivity at different times of day. We do not know whether glycaemic outcomes are better if varying ICRs are introduced from diagnosis, or subsequently.

Aims
To retrospectively audit ICRs in children with newly diagnosed diabetes at diagnosis, 6 weeks and 3 months to identify evidence for individualised treatment.

Methods
Case note review of consecutive CYP presenting with diabetes, commenced on MDI between August 2010 and 2012, recording ICRs for each mealtime at diagnosis, 6 weeks and 3 months.

Results
MDI was commenced in 55 of 93 CYP presenting with diabetes, of which 48 records were retrieved for analysis (87%). Median age was 11.2 years (range 1.86–16.9 years). Carbohydrate counting and fixed ICRs were commenced in 45 CYP from diagnosis. Of three commenced on fixed mealtime doses, two were carbohydrate counting before 6 weeks. Two children had mealtime insulin temporarily discontinued by 6 weeks. One third of CYP were on the same ratios at 6 weeks and 3 months as they were at diagnosis, and the same ICR across the entire day.

Conclusion
Up to one third of our CYP had evidence of inadequately intensified or individualised insulin therapy at 6 weeks and 3 months. We are concerned this limits our ability to improve outcomes. We have adjusted our approach, utilising variable ICRs from diagnosis to avoid losing this important educational element, placing a greater focus on post-prandial glucose testing, frequent clinical reviews and greater emphasis on patient education.

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P45
Local factors influencing service improvements in median HbA1c in children and young people with diabetes between 2003 and 2012
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1Birmingham Children’s Hospital, Birmingham, UK; 2University of Birmingham, Birmingham, UK.

Background
HbA1c is a marker for the risk of long-term complications of Diabetes. Our unit cares for 349 children and young people (CYP) with diabetes, over 5 years old, on multiple daily insulin (MDI), using fixed insulin to carbohydrate ratios (ICRs) with meals across the day. ICRs are subsequently adjusted according to blood glucose response, individualising insulin treatment. We know intensified insulin therapy includes use of varied ICRs, reflecting varying insulin sensitivity at different times of day. We do not know whether glycaemic outcomes are better if varying ICRs are introduced from diagnosis, or subsequently.

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Conclusion
Up to one third of our CYP had evidence of inadequately intensified or individualised insulin therapy at 6 weeks and 3 months. We are concerned this limits our ability to improve outcomes. We have adjusted our approach, utilising variable ICRs from diagnosis to avoid losing this important educational element, placing a greater focus on post-prandial glucose testing, frequent clinical reviews and greater emphasis on patient education.

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P46
Jennifer Fichierri & Peter Hindmarsh
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Children and adolescents with type 1 diabetes treated at University College Hospital London (UCLH) from an African background have poorer glycaemic control compared to the British population (British mean HbA1c 7.8 (0.1), African mean HbA1c 9.4 (0.5) P<0.001). Haemoglobin A1c is an element of the haemoglobin to which glucose is bound. The ideal range is between 6.5 and 7.5% and is considered to represent good glycaemic control. Patients who persistently have an HbA1c over 8.0% are at increased risk of the long-term complications of diabetes, retinopathy, neuropathy and nephropathy. The purpose of the study is to find appropriate educational methods to improve HbA1c.

We undertook an observational study over a 1 year period with patients self-allocated by attending the support group or not. The intervention was support groups involving translated education sessions, meeting with other children and families with good glycaemic control, culturally specific dietary advice and translated advice leaflets.

Data was available in full for 15 participants. One patient was lost to follow up. Four support groups were run with participants attending on average 2-3 of the sessions (intervention). In the intervention group the average HbA1c was 8.8% (2.3) before and 7.8% (1.5) after 3 months (P=0.03) after attending at least three support group sessions. In the control group the average HbA1c before was 9.0% (1.0) and after 8.8% (1.2) P>0.5.

This preliminary data suggests there may be an improvement in HbA1c due to a support group intervention. The sample size is small and due to the self-selection bias may have been introduced. Nonetheless the data suggest larger randomised trials of group intervention are warranted.

DOI: 10.1530/endoabs.33.P46

P47
Factitious hypoglycaemia due to exogenous insulin ‘Don’t forget the skin’
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Introduction
Serum C Peptide is traditionally used to diagnose factitious Hypoglycaemia due to exogenous Insulin. However in our case we were able to initiate child protection work up on the basis of skin marks which were noted during child’s admission in hospital.

Case report
2-year-old male presented with 3 days history of diarrhoea and vomiting. Past history and examination were unremarkable. Mother had gestational diabetes and was on insulin during pregnancy whilst Grandmother who died 1 month previously had type 2 diabetes managed with Insulin. He was admitted and commenced on ORS. His blood glucose (BG) dropped to 2.8 mmol/l. He had Hypoglycaemia screen and BG improved with sugary fluids. He continued good oral intake and was discharged the following day. He had 2 further repeat admissions with history of poor oral intake, floppy episodes, none of which were witnessed on the wards. On 3rd readmission he was kept in for prolonged observation during which he was noted to have low BG (2.6 mmol/l) with low
blood ketones of 0.3 mmol/l. He required > 8mg/kg per minute of i.v. glucose to maintain euglycaemia. This was consistent with hyperinsulinism. Hypoglycaemia screen was repeated. Marks which matched imprints made by an insulin pen, were noted on the legs and arm of the child the next day. We instituted strict 1:1 nursing to ensure mother and other family members had only supervised access to child and his BG improved. Police Protection Order was put in place. Results showed insulin > 100 mU/l, C Peptide < 50 pmol/l, confirming exogenous insulin administration. Mother was arrested by the police. Child remained well and now is fostered. Presence of insulin pen imprints enabled us to suspect exogenous insulin administration prior to receiving hypoglycaemia screen results. We recommend thorough skin examination in any child with persistent hypoglycaemia.

DOI: 10.1530/endoabs.33.P47

P48

Development of a next generation sequencing panel for disorders of sex development (DSDs)
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1West Midlands Regional Genetics Laboratory, Birmingham Women’s NHS Foundation Trust, Birmingham, UK; 2West Midlands Clinical Genetics Service, Birmingham Women’s NHS Foundation Trust, Birmingham, UK; 3School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK.

Disorders of sex development (DSDs) refer to a range of congenital disorders where the chromosomal, gonadal or anatomical sex is atypical. Patients typically present in the newborn period where ambiguous genitalia often prevents immediate gender assignment or during the adolescent period where atypical sexual development becomes apparent. Genetic testing is key in establishing the diagnosis allowing for personalised management of these patients, and can significantly reduce the period of uncertainty for families regarding the sex of rearing of their child. Cytogenetics may provide guidance on possible causes and if further investigations are indicated. However a definitive molecular diagnosis is only made in around 20% of cases. Current molecular testing strategies for DSDs are not ideal, as tests for only a few of the many associated genes are currently available and are tested sequentially. The development of next generation sequencing allows for multiple genes to be investigated in a single test at a reduced cost compared to current sequencing strategies. Such a test for DSDs would eliminate the long waiting times currently being experienced by patients due to sequential testing. A TruSeq custom amplicon panel has been designed encompassing 32 genes associated with DSDs including WT1, SOX9, AR, ARX, ATRX, SRD5A2, CTP11R1 and STAR. Initial validation of the assay has been carried out with 30 patients carrying known mutations. Details of the panel and results obtained to date will be presented.

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P49

Precious puberty in an infant is not normal
Harshan Lamabadusuriya, Helen Wolfenden, Taffy Makaya, Kate Wheeler & Fiona Ryan
Oxford Children’s Hospital, Oxford, UK.

Background
A 5-month-old girl presented with a history of acute abdominal distension over several weeks. Three weeks previously she had developed pubic hair, and some early breast development. The GP had reassured parents on two occasions that this was normal. On examination she had Tanner breast stage 3 bilaterally, pubic hair stage 3, mild cliteromegaly, and gross abdominal distension.

Investigations
An ultrasound scan revealed a massively enlarged right ovary measuring 10 cm × 6.7 cm × 7.7 cm. The left ovary appeared normal. The uterus was adult in configuration with a thickened endometrium of 8 mm. There was ascites throughout.

Table 1 Baseline blood investigations.

<table>
<thead>
<tr>
<th>Test (units)</th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>2598</td>
<td>0–55</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>3.3</td>
<td>1.0–2.5</td>
</tr>
<tr>
<td>Leutinising hormone (LH) (IU/l)</td>
<td>&lt;0.1</td>
<td>0–1.0</td>
</tr>
<tr>
<td>Follicle stimulating hormone (FSH) (IU/l)</td>
<td>0.3</td>
<td>0–2</td>
</tr>
<tr>
<td>Human chorionic gonadotropin (HCG) (IU/l)</td>
<td>&lt;2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Inhibin A (pg/ml)</td>
<td>284.2</td>
<td>&lt;19</td>
</tr>
<tr>
<td>Inhibin B (pg/ml)</td>
<td>8856.2</td>
<td>&lt;111</td>
</tr>
<tr>
<td>Alpha feto protein (AFP) (IU/ml)</td>
<td>74.3</td>
<td>Within normal range for age</td>
</tr>
<tr>
<td>Cancer antigen-125 (CA-125) (IU/l)</td>
<td>994</td>
<td>0–30</td>
</tr>
</tbody>
</table>

Bone age on TW3 scoring was not advanced.

Progress
Right salpingo-oophorectomy was performed (right ovary weighing 260 g). At operation the ovarian capsule was noted to be breached. Histology confirmed a Juvenile Granulosa Cell tumour. No tumour cells were reported in the peritoneal fluid. The tumour was staged as Stage 1c on account of there being a capsular breach and a mitotic rate of up to 23 mitoses per high power field but no evidence of distant metastases. Her baseline and post-op blood investigations are presented in Tables 1 and 2. In view of this she received postoperative chemotherapy. Within 3 weeks tumour markers had normalised, and pubertal staging had regressed to Tanner stage 1.

Table 2 Day-3 post-op bloods.

<table>
<thead>
<tr>
<th>Test (units)</th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (nmol/l)</td>
<td>&lt;0.4</td>
<td>1.0–2.5</td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>&lt;43</td>
<td>0–55</td>
</tr>
</tbody>
</table>

Conclusion
Precocious puberty in infancy must always be investigated promptly.

DOI: 10.1530/endoabs.33.P49

P50

Early puberty in two girls with Prader–Willi syndrome
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Introduction
Prader–Willi syndrome (PWS) is characterised by hypotonia, obesity, short stature, and hypogonadism probably due to hypothalamic dysfunction (hypogonadotropic hypogonadism (HH)). Exaggerated adipogenesis is however commonly noted in these patients. Early puberty is rarely described: we report two girls with PWS diagnosed with premature sexual maturation.

Case reports
Case 1: this 8-year-old girl was neonatally diagnosed with PWS (maternal uniparental disomy (MUPD)) of chromosome 15. At 2 years of age she started GH treatment to improve final height and muscle tone. At 6.5 years she was growing rapidly (height velocity 8.8 cm/year) and was B2 and PH3. On LH/FSH testing FSH increased from 6 to 39.3 U/I and LH from <0.2 to 7.6 U/I. On LH/FSH testing FSH increased from 6 to 39.3 U/I and LH from <0.2 to 7.6 U/I. On LH/FSH testing FSH increased from 6 to 39.3 U/I and LH from <0.2 to 7.6 U/I. On LH/FSH testing FSH increased from 6 to 39.3 U/I and LH from <0.2 to 7.6 U/I. On LH/FSH testing FSH increased from 6 to 39.3 U/I and LH from <0.2 to 7.6 U/I. On LH/FSH testing FSH increased from 6 to 39.3 U/I and LH from <0.2 to 7.6 U/I. On LH/FSH testing FSH increased from 6 to 39.3 U/I and LH from <0.2 to 7.6 U/I.

Conclusion
Early puberty is uncommon in PWS, as patients characteristically have hypogonadotropic hypogonadism. Clinicians need to be aware that early puberty may also occur, although due to obesity initial signs of breast development may be masked.

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Endocrine Abstracts (2013) Vol 33
Case Report
A 14-year-old girl presented with facial and axillary hair, absent breast development and amenorrhea. There was no history of ambiguous genitalia, but genital examination was refused. Her karyotype was found to be 46XY, with a high testosterone level (22.6 nmol/l) and raised testosterone:dihydrotestosterone ratio (14:1). A urine steroid profile was normal. Pelvic imaging showed inguinal gonads but no uterus. Examination under anaesthesia revealed extensive virilisation, with 6 cm clitoromegaly.

Genetic sequencing found no mutation in the androgen receptor gene, 17 HSD3 or SRD5A2 genes. Subsequent analysis of the NR5A1 gene revealed a heterozygous mutation within exon 5, resulting in a ‘stop’ codon, which was determined to be the pathogenic mutation.

After intensive psychological counselling the presenting patient stated her desire for a female gender identity, and proceeded to laparoscopic gonadectomy, clitoral reduction, and oestrogen therapy.

Conclusion
This case highlights a rare presentation of NR5A1 gene mutations, in a patient with no genital ambiguity prior to puberty. The human SF1 protein, encoded by the NR5A1 gene, is one of the main regulators of enzymes involved in adrenal and gonadal steroidogenesis. It is expressed in undifferentiated gonads and there is wide phenotypic variation in XY patients with NR5A1 gene mutations. This case is a previously unreported presentation of this mutation, and highlights the variable presentation of SF1 protein mutations.

DO: 10.1530/endoobs.33.P51

P52
46,XX pure gonadal dysgenesis with tall stature due to an Xq21.2 deletion
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Introduction
46,XX gonadal dysgenesis without the phenotype of Turner’s syndrome is described as ‘pure’ and is not usually associated with other anomalies with the exception of the rare Perraault syndrome (46,XX-GD with sensori-neural deafness). We describe a girl in whom tall stature was a dominant feature.

Case Report
A girl was referred aged 15.6 years with primary amenorrhoea and slim build. Examination showed height 172.5 cm (+3.17 S.D.), weight 66.2 kg (+1.56 S.D.) (midparental height K0.13 S.D.), Tanner stage B1P4A1, LH 33.7 U/l, AMH <4 pmol/l, pre-pubertal cylindrical uterus on ultrasound measuring 3.75 cm with small areas of mixed echogenicity in both adnexae measuring 3.5 cm with small areas of mixed echogenicity in both adnexae consistent with ovarian dysgenesis. Puberty was induced with low dose ethinylestradiol and compliance was variable. At the time of adult transfer aged 19.5 years the girl measured 182.8 cm (+3.17 S.D.), weight 66.2 kg (+0.9 S.D.), Tanner stage B1P4A1. Genetic study showed a Xq21.2 microdeletion in one X chromosome in the girl but in neither parent.

Conclusion
The tall stature in our patient is not in keeping with parental heights and out of proportion to the compliance difficulties with estrogen treatment. We speculate that the Xq2.2 deletion has affected genes influencing not only ovarian genesis but also growth suppression.

DO: 10.1530/endoobs.33.P52

P53
Rapid molecular genetic diagnosis aiding personalised treatment of 5-α reductase type 2 deficiency
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Introduction
Steroid 5-α reductase type 2 deficiency causes 46,XY disorder of sex development (DSD) and is an autosomal recessive disorder resulting from mutations in the SRD5A2 gene. SRD5A2 facilitates the conversion of testosterone to dihydrotestosterone (DHT), crucially required for masculinisation of external genitalia. Thus 46,XY individuals with SRD5A2 mutations present with varying severity of undermasculinisation.

We describe the clinical presentation, investigations and management of two infants with novel SRD5A2 mutations.

Cases
Two children presented in the neonatal period with ambiguous genitalia. Patient 1, born to non-consanguineous Indian parents presented with microgenitosomia, bulbocavernosus hypoplasia and genital ambiguity at birth. Patient 2, born to consanguineous Pakistani parents presented with microgenitosomia. In both patients, scrotal testes were palpated, karyotype was 46XY and pelvic ultrasound did not reveal Mullerian structures.

Following three injections of chorionic gonadotrophin, plasma testosterone:DHT ratio was equivocal in both patients (15 and 14 respectively). Rapid molecular genetic analysis, performed within 3 days by direct DNA sequencing of the SRD5A2 gene revealed novel mutations in both patients: patient 1 was compound heterozygous for the g.237_250dup and g.264C>G genetic variants in the SRD5A2 gene that results in a premature stop codon 150 bp downstream and predicted to result in an aberrant protein. Patient 2 had a homoyzgous mutation, c.598G>A in exon 4 of the SRD5A2 gene that is also predicted to result in an abnormal protein, p.(Glu200Lys).

Topical Androgel cream (DHT 2.5%) applied once daily resulted in good phallic growth in both boys and surgical correction was planned at an older age.

Conclusion
Establishing the diagnosis of SRD5A2 deficiency is vital for personalised treatment and counselling. Rapid genetic analysis of the SRD5A2 gene is recommended in suspected patients. Development of comprehensive rapid DSD assays will support such a diagnostic strategy, enabling timely diagnosis and institution of appropriate personalised treatment.

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P54
Causes of precocious puberty in children referred to an Endocrine Unit in the Northwest of Turkey
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Introduction
Although data from developed countries about precocious puberty (PP) are abundant, data from developing countries are scarce. The aim of our study was to analyze the frequency of the variants of PP in children who had applied to our department.

Patients and methods
Retropective analysis of 367 children (349 girls and 18 boys) with features of PP referred for evaluation to our clinic between the years 2006–2012 was performed.

Results
Premature telarche (PT) was diagnosed in 117 (30.5%) girls with the mean age of 3.9 ± 2.8 years. Their mean height SDS was 0.3 ± 1.1 s.d. Premature adrenarche (PA) was diagnosed in 102 (30.5%) children (140 girls and eight boys), having the mean age of 7.1 ± 1.2 years. Their mean height SDS was 0.9 ± 1.0 s.d. Central precocious puberty (CPP) was diagnosed in 127 (34.6%) children (121 girls and six boys) with the mean age of 8.3 ± 1.4 years. Of the patients with CPP, 95.3% (121 patients; 115 girls and six boys) were diagnosed as idiopathic. Organic causes for CPP were detected in only 6 (4.7%) girls. Of these six girls, two had hypothalamic hamartoma, one had astrocyctoma, one had tuberous sclerosis, one had meningomyelocele and one had traumatic brain injury. Peripheral precocious
puberty (PPP) was diagnosed in 11 children (seven girls and four boys), having the mean age of 7.3 ± 2.2 years. Congenital adrenal hyperplasia (CAH) was diagnosed in four girls and two boys, and McCune–Albright syndrome in three girls.

Conclusion
The results of this study indicated that most of cases with PP are affected with CPP especially with idiopathic form of it, followed by PT. CAH might be the most frequent cause of PPP in our population as expected.

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P55
Diagnostic spectrum of female pubertal delay
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Introduction
Delayed onset of puberty is quite a common presentation in adolescent endocrine clinics, and the most common cause, particularly in boys is considered to be constitutional delay of growth and maturation. In girls, however, it is more likely that there is a significant underlying problem.

Aim
To review the aetiology of pubertal delay in female patients referred to a single tertiary centre.

Methodology
All female patients referred to the endocrinology clinic with delayed puberty, arrested puberty and primary amenorrhea between January 2007 and December 2012 were identified using our clinic patient database. A review of medical case notes was carried out to identify the aetiology of pubertal delay, and information was also obtained on investigations, treatment and outcome. Patients with known conditions associated with pubertal delay, pituitary/gonadotoxic therapy or secondary amenorrhea were excluded.

Results
Thirty-three patients were identified with a median age of presentation of 15.5 years. A total of 15 different reasons for pubertal delay were found in our population. The three most common causes were low BMI, constitutional delay of puberty (no abnormality found and no therapeutic intervention required for onset of menses) and idiopathic primary ovarian failure, but intracranial lesions (craniopharyngioma, prolactinoma), structural abnormalities of the genital tract (Mayer–Rokitansky syndrome) and genetic/chromosomal anomalies (androgen insensitivity syndrome, Turner mosaic) were all identified.

Conclusion
Although simple maturational delay can be a common cause of delayed puberty, in our study we found that a large number (88%) of our patients had a significant underlying aetiology. Seven girls (21%) had a marked eating disorder or other reason for a very low BMI. These results confirm the importance of thorough evaluation of all girls presenting with delayed puberty.

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P56
Review of the service for Turner syndrome patients at University Hospital of North Staffordshire
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Management of children with Turner’s syndrome in the Paediatric Endocrine Service in the last 15 years were reviewed retrospectively. There were 19 children with age range from 2 to 16 years. The age distribution at diagnosis showed 12/19 (63%) diagnosed below 1-year-old of those 5/12 (42%) were diagnosed by amniocentesis. 4/19 were diagnosed between 1 and 5 years old, only 3/19 came to medical attention after 10 years of age. Two were mosaic karyotype

In terms of route of referral: the majority has been referred by neonatal consultant 11/19, seven patients has been seen by primary health care professionals for concern regarding short stature or failure to thrive. Only one girl who delayed puberty has been referred by school nurse.

Looking at Turner’s syndrome features: only one girl had most of the clinical features of the syndrome. 2/19 suffer from cardiac problems. 7/19 had failure to thrive and short stature. 1/19 didn’t had any clinical features and diagnosed by amniocentesis. Coeliac disease has been diagnosed in one of the patients, one child with dysplastic kidney and another one with hypothyroidism.

In the initial assessment in the endocrine service all the children had hearing test, echo cardiomgram and renal ultrasound. The entire patients were seen 2-3 times/year and had annual blood tests. 1/19 patients (58%) on GH and most of the girls has been started on pubertal induction (5/7) before 13 birthdays.

Conclusion
Even though adolescent gynaecology service was mentioned to the child and family, only one patient was seen in that clinic.

Summary
Health care professional need to suspect and diagnose this condition early to provide appropriate support and treatment. There is a need to develop turner syndrome clinic and care pathway to improve transitional care service.

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P57
Middle ear disease in Turner syndrome: prevalence and risk factors
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Introduction
Middle ear disease in Turner syndrome (TS) is common, often resulting in troublesome temporary hearing loss, and more rarely to serious suppurative disease with cholesteatoma formation. We have examined the prevalence and pattern of middle ear disease in our TS clinic in relation to age and karyotype.

Methods
Case note review of all girls with TS attending clinic 1989–2012, scoring the most serious middle ear problem for each as: none (0), otitis media (OM) ± effusion (OME) only (1), OME requiring intervention (e.g. grommets) (2), supplicative OM/perforation/retraction pocket (3) and cholesteatoma (4).

Results
Of 173 subjects with TS, current median (range) age 25.6 (1.8–45.3) years, data were available in 155 as shown.

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>OM (n=70)</th>
<th>OME (n=35)</th>
<th>OME (n=10)</th>
<th>OME (n=9)</th>
<th>OME (n=11)</th>
<th>OME (n=14)</th>
<th>Other (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45,X</td>
<td>0</td>
<td>23</td>
<td>13</td>
<td>9</td>
<td>6</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>45,X/46,XY</td>
<td>1</td>
<td>13</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>45,X/46,XY</td>
<td>2</td>
<td>17</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>46,XY/47,XXX</td>
<td>3</td>
<td>17</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>45,XY</td>
<td>4</td>
<td>12</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median age for girls with category 3 and 4 involvement was 9.25 (1.7–15.90) and 12.05 (7.1–15.2) years respectively, significantly older than the usual age of grommet insertion for OME (4-6 years).

Conclusion
The prevalence of middle ear disease in our TS population is at least 54%. Girls with 45,X monosomy and isochromosome of Xq and those who experience effusion are more at risk.

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P58
Exploring the culture of listening amongst children’s nurses in an outpatient department: A mini-ethnographic study
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Background
In the human communication process listening is often reduced to a passive, innate activity and often considered as ‘just listening’ (Wolvin 2010). Kilkelly & Donnelly (2011) advocates the promotion of a listening culture whereby children are able to voice and have their views listened to, not only to satisfy legal requirements. Much of paediatric services today are provided in the out-patient setting.

Objective
The study aimed to explore and describe the current listening culture and gain understanding of the challenges and difficulties that children’s nurses face when listening to patients in an outpatient environment. The purpose of the study was to
P59

Screening log data can be used to inform protocol modifications, increasing patient recruitment to a challenging clinical trial

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Background

Delivery of clinical trials to time and target is critical for studies to be financially viable and relevant. Feasibility studies are informative. However, protocol acceptability and recruitment rates can only be accurately ascertained once a study is open.

The SCIP study (SubCutaneous Insulin: Pumps or Injections?), randomises patients to treatment with multiple daily insulin injections (MDI) or pumps at diagnosis of type 1 diabetes (T1D). A consent rate of 50% of eligible patients is required to achieve target recruitment (316 patients from 14 centres). We report how screening logs informed protocol changes to optimise recruitment.

Methods

The following data were recorded: time from diagnosis to i) screening, ii) information giving, iii) consent, iv) randomisation and v) start of randomised treatment. Reasons given for declining to participate, or not inviting a patient to participate were recorded. These data were used to inform changes to study protocol.

Results

Patients who consented were approached earlier than those who declined (median 3.0 vs 6.5 days). Most patients who declined stated a strong preference for MDI. The commonest reasons for ineligibility were i) first degree relative with T1D and ii) inability to complete study questionnaires. Eligible patients were not invited to participate when centres were unable to initiate pump therapy within protocol timelines. In response to these data research staff were encouraged to approach patients early. Eligibility criteria were refined so that patients with a parent, but not a sibling with T1D could participate and families who were not fluent in written English could be supported to complete questionnaires. Protocol timelines were also revised. These interventions resulted in an improvement in recruitment rate from 44.7 to 56.6%.

Conclusion

Screening log data can be utilised to address the needs of research staff and families, invited to participate in a study at a time of great uncertainty.

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P60

Dumping syndrome an often unrecognised problem following post nissen fundoplication, gastrostomy in infants

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Background

Dumping syndrome in infants who have undergone gastrostomy or Nissen fundoplication is a recognised phenomenon. The pathogenesis is possibly due to a bolus feed causing an incretin effect and leading to hyperinsulinaemic hypoglycaemia. Continuous glucose monitoring (CGM) systems have not been used in the past to study this phenomenon. We report CGM findings which are almost identical on three such post surgical infants.

Case series 1: a 36-week infant with VACTERL association underwent a gastrostomy and was noted to have hyperglycaemic episodes, once established on bolus enteral feeds. CGM revealed a typical sinuosoidal pattern of hyperglycaemia and hypoglycaemia related to feed timings (18% of the time <3 mmol/l over a 3-day period).

2: a term infant with complex congenital heart disease and 22q11 deletion underwent Nissen’s fundoplication and gastrostomy followed by post feed hypoglycaemia. CGM revealed hypoglycaemia (25% of the time) 2h after the feeds. Continuous feeds resulted in the reduction of this pattern (9%) on repeat CGM.

3: an 8-week infant with tracheal osseoplastic fistula and gastrostomy was noted to have swings in blood glucose levels after commencement of bolus feeds. CGM revealed significant hypoglycaemia (45%) while on bolus feeds.

Continuous feeds corrected the hypoglycaemias and all infants were gradually established on full bolus feeds. Bolus feeds administered using a pump was better than gravity dependant feeding.

Conclusion

Dumping syndrome should be actively sought for, in post-surgical neonates presenting with spontaneous hypoglycaemia. CGM findings seem to be unique and we recommend it as a useful tool to demonstrate the relationship between bolus feeds and hypoglycaemia. Further simple manipulation of feed delivery will result in resolution of abnormalities.

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Audit of obesity management in a tertiary endocrine centre
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Approximately 30% of children aged 2–15 years old in the UK are now either overweight or obese. There is some guidance on appropriate management within the UK for paediatricians, including a consensus statement by the Obesity Services for Children and Adolescents (OSCA) network. Obese patients referred to a tertiary paediatric endocrine clinic between January 2010 and December 2011 were audited retrospectively, with follow-up until the end of December 2012 included. Children with recognised syndromes, diabetes, underlying endocrine and oncology diagnoses were excluded. We looked specifically at investigations performed, medical interventions, follow-up and response to metformin. Twenty-nine new patients (55% females) were identified and followed up, with a median age at first clinic attendance of 13.5 (2.8–17.1) years. Median BMI was 35.0 kg/m². Ninety-seven per cent had BMI SDS ≥ 2 at presentation; 36% BMI SDS > 3.5 (very severely obese). Ninety-three per cent (n = 27) of patients had at least one blood investigation. All (n = 25) thyroid function tests taken were normal. Seventy-nine per cent (n = 23) of patients had either a fasting insulin level (16 patients) or an oral glucose tolerance test (seven patients): 74% had insulin resistance; 4% (one patient) had impaired glucose tolerance. Fourteen per cent were concurrently diagnosed with polycystic ovarian syndrome. Forty-one per cent (n = 12) were commenced on metformin. Six patients (20.7%) were discharged after the first visit. Eight patients (27.6%) were still under follow-up at the end of the study period; all of these were on metformin. The age and BMI Z-score of the obese participants were 12.9 ± 3.6 years and 42.3 ± 7.2 kg/m².

Outcome measures included weight, height, body fat percentage and blood pressure. Thirty-six children (81%) were referred for further management at a tertiary endocrine clinic and the variations in response to treatment. Management requires standardised guidelines advocating appropriate assessment and intervention in clinical management.

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Serial ‘body composition’ measurements will help resolve the continued weight gain dilemma in children with PWS
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Introduction
PWS children have higher body fat content and lower lean muscle mass as compared to normal population. Bioelectrical impedance analysis (BIA) estimates lean muscle mass and total fat content separately and thus is more useful than BMI. Continued weight gain despite treatment, can be distressing to patients and parents. We hoped to resolve this dilemma through serial body composition measurements.

Materials and methods
Patients and families are given pro-active advice on calorie intake and consistent dietary practices to prevent unnecessary weight gain. Three-day food diaries are used to assess macro and micro nutrient intake. GH therapy is used in eligible children. Height, weight and BMI are recorded at each visit and body composition measurements by BIA annually after 4 years of age.

Results
Retrospective case note review identified 6 children who had at least 1 BIA measurement; mean age was 9 years; mean body fat was 42.3% and mean lean muscle mass was 19.6 kg (reference ~ 28% and 25.9 kg respectively).

Three children had four serial measurements and two were on GH. Patient 1 had 6.1 kg weight gain over 36 months, but body fat percentage decreased by 0.5% (34.9 to 34.4%). Patient 2 had 29.1 kg weight gain over 40 months, but body fat percentage decreased by 5.5% (48.7 to 43.2%). Patient 3 had 10 kg weight gain over 24 months but body fat percentage decreased by 1.8% (44.7 to 42.9%).

Conclusions
PWS children have much higher body fat percentage and considerably lower lean muscle mass as compared to normal children. Unnecessary fat weight gain can be minimised or even reduced with pro-active management. When inevitable weight gain occurs in PWS children, serial measurements help distinguish clearly between unnecessary fat weight gain and healthy lean muscle mass gain. No increment in percentage body fat can be reassuring to patients and their parents.

DOI: 10.1530/endoabs.33.P63

Immune cell dysregulation – contributing to the risk of development of metabolic disease in childhood obesity
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Background
Although the association between obesity, chronic low-grade inflammation and immune dysregulation is well described in adults, there is a paucity of literature regarding this in children. We hypothesised that childhood obesity is associated with significant immune dysregulation.

Methods
Expression of cytokines and microRNAs (miR) involved in the pathogenesis of metabolic disease were assessed in 49 participants aged 6–18 years. Invariant NKT cells, NK cells, T cells and B cells were enumerated by staining with relevant antibodies and flow cytometry.

Results
The age and BMI Z-score of the obese participants were 12.9 ± 3.1 years and 3.4 ± 0.4 respectively and the non-obese participants were 12.2 ± 3.2 years and 0.2 ± 1.1. None had type 2 diabetes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Obese (n = 29)</th>
<th>Non-obese (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>149 ± 104</td>
<td>27.2 ± 20.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Invariant natural killer T cell (% CD3+ T cells) iNKT</td>
<td>0.32 ± 0.03</td>
<td>0.54 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Soluble CD163 (ng/ml)</td>
<td>135.7 ± 9.32</td>
<td>109.1 ± 7.55</td>
<td>0.03</td>
</tr>
<tr>
<td>IL1β (pg/ml)</td>
<td>2108 ± 708.2</td>
<td>1518 ± 479.6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data expressed as mean ± s.o. P values calculated using independent-samples t-test.

CD163 is a macrophage surface receptor that is shed into the circulation and is measured in its soluble form in serum. Serum concentrations of sCD163 were associated with an increased risk of development of T2DM in a prospective adult study.

NK and iNKT cells regulate the innate and adaptive immune system and are dysfunctional in obesity.

MicroRNAs (miRs) are post transcriptional regulators of gene expression. MiR-33a and MiR-33b play an important role in cholesterol homeostasis and insulin signalling, with expression of both greater than three-fold higher in the obese children (P < 0.05 for both).

Conclusion
Immune cell distribution, tissue inflammation and metabolic gene expression are abnormal in obese children. This demonstrates the imperative to tackle obesity from an early age.

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Modulation of mesenchymal stem cell differentiation by alterations in GH action and cell-matrix interaction
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Introduction
Mesenchymal stem cells (MSCs) are a type of multipotent cells readily found within the bone marrow, capable of undergoing self-renewal and giving rise to cells with different characteristics, such as, osteoblasts, adipocytes and chondrocytes. MSC differentiation requires optimal cell–matrix interaction and is also dependent on a number of growth factors.
Aim
To investigate the effect of GH, Rho-associated kinase (ROCK) and extracellular signal-regulated kinase (ERK) signaling on human MSC differentiation on nanoscale topography (NQ450) which represents a physiological in vitro model for cell–matrix interaction.

Methods
MSC were cultured on NQ450 and flat surfaces for variable durations and markers of adipogenesis, chondrogenesis and osteogenesis, were studied by immunofluorescence and qPCR. The model was then used to study the effect of GH, and JAK, ROCK and ERK inhibitor.

Results
An increase in bone formation markers, osteopontin (OPN) and osteocalcin (OCN) on NQ450 was observed in both 28- and 14-day cultures on immunofluorescence. qPCR showed significantly higher expression of BMPR2 and SOX9 genes on NQ450 than standard flat topography. The presence of GHR antibody did not affect BMPFR2 expression on NQ450, but was associated with increased SOX9 levels, a marker of chondrogenesis. Although PPARG expression was not significantly higher on NQ450, an increase in PPARG expression was observed in the cells cultured on standard flat topography after GHR antibody exposure. The expression of OCN and OPN was stimulated with GH, reduced after inhibition of ROCK or ERK, and no cells were detected in the presence of JAK inhibitor.

Conclusion
ERK and ROCK signaling are important for topographically driven osteogenesis. Inhibition of GHR signaling shifted MSCs towards chondrogenic mode on NQ450 and adipogenic mode on standard topography. The interactive effect of GH and the ERK pathway on adhesion driven intracellular tension needs further study.

DOI: 10.1530/endoabs.33.P65

P66
Chronic kidney disease: an uncommon cause of galactorrhoea in an adolescent
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Introduction
Hyperprolactinaemia may occur in 30% of adults with chronic kidney disease (CKD), although rare in paediatrics. The pathophysiology might be further complicated by pre-existing pituitary abnormalities.

Case
Symptomatic hyperprolactinaemia developed in this adolescent girl with CKD and hypopituitarism. History involved neonatal hypoxic ischaemic encephalopathy (HIE) and renal cortical necrosis. CKD Stage 3 ensued. Growth declined by 2.3 years (height −4.78 SDS) and GH therapy for CKD commenced aged 4.3 years. By 8 years, without dose increase, she maintained height velocity >97th centile. GH deficiency seemed a possible alternative (due to pituitary vascular compromise during HIE). We identified additional anterior pituitary hormone deficiencies requiring replacement: TSH, ACTH, gonadotrophins, (TSH <600 mIU/l). Over preceding months, renal failure had progressed to CKD5 (GFR 15 ml/min per 1.73 m²) with peritoneal dialysis initiation, alongside ethinylestradiol dose increase from 10 to 20 mg monthly for 3 months) were commenced with good response. He required suboptimal (403 nmol/l). Hydrocortisone, thyroxine and testosterone (25 mg daily) were started on GH and hydrocortisone supplementation, the former was stopped after 1 year due to worsening of kyphoscoliosis requiring spinal surgery and instrumentation. Septum pellucidum was absent on MRI. Thyroxine was commenced at 2.1 years and growth hormone was commenced at 3.1 years. He required full-length stature and GH peak, r-hGH dose and birth weight.

Results
GH patients from high latitudes had a better Y1 HV than from intermediate and low latitudes (median (Q1, Q3): 9.8 (8.5, 11.4) vs 8.0 (7.0, 9.7) and 8.0 (7.0, 10.5) cm/year, respectively; P = 0.015). HV significantly correlated with SDE (r = 0.256, P = 0.006), but not with latitude (P > 0.05). For seven growth-related SNPs within GBR10, IGFBP3, TGF-α, CYP19A1, SOS1, TP53 and INPP4L, the effect of SDE and SNP was assessed using a generalised linear model corrected for multiple variables: gender, baseline age, BMI, distance to target height, GH peak, r-hGH dose and birth weight.

Conclusions
Growth response to r-hGH in GHD is influenced by both the carriage of specific growth-related SNPs and geographical location, which may be explained by daylight exposure.

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P67
Effect of latitude, summer daylight exposure and genetic background on growth response to recombinant human GH in GH deficient patients
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Introduction
Growth rate tends to be greater in children living at higher latitudes although the underlying mechanisms are unclear. The aim of this study was to compare height velocity (HV) in response to recombinant human GH (r-hGH) therapy in children with GH deficiency (GHD) living at different latitudes.

Design
Pre-pubertal children with GHD (n = 118) were enrolled from the PREDICT long-term follow-up prospective study (NCT00699855). Data were submitted from 28 centres in 14 countries. Ethnicity background was consistent with country of origin. Absolute latitude was that of the study site.

Methods
Patients were categorized into three groups based on latitude site: high (>75th percentile: ≥45°), intermediate (25th–75th percentiles: 34–45°) and low (<25th percentile: ≤34°). To look at mechanisms related to latitude effect, the average number of daylight hours during summer at each centre was recorded. First year treatment (Y1) HV (cm/year) was assessed. The effect on HV of summer daylight exposure (SDE) and carriage/non-carriage of nine single nucleotide polymorphisms (SNPs) previously associated with high growth response was analyzed, within GBR10, IGFBP3, TGF-α, CYP19A1, SOS1, TP53 and INPP4L. The effect of SDE and SNP was assessed using a generalised linear model corrected for multiple variables: gender, baseline age, BMI, distance to target height, GH peak, r-hGH dose and birth weight.

Results
GHD patients from high latitudes had a better Y1 HV than from intermediate and low latitudes (median (Q1, Q3): 9.8 (8.5, 11.4) vs 8.0 (7.0, 9.7) and 8.0 (7.0, 10.5) cm/year, respectively; P = 0.015). HV significantly correlated with SDE (r = 0.256, P = 0.006), but not with latitude (P > 0.05). For seven growth-related SNPs within GBR10, IGFBP3, TGF-α, CYP19A1 and TP53, HV was significantly affected by an interaction between the carriage of the SNP and SDE (P < 0.05).

Conclusions
Growth response to r-hGH in GHD is influenced by both the carriage of specific growth-related SNPs and geographical location, which may be explained by daylight exposure.

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P68
Multiple pituitary hormone deficiencies in two patients with arthrogryposis multiplex congenita
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Introduction
Arthrogryposis multiplex congenita is a rare congenital disorder characterised by multiple joint contractures. The association with hypopituitarism has only been reported once before. We report two further children with multiple pituitary hormone deficiencies (MPHD) and arthrogryposis.

Case reports
Case 1: this 12-year-old girl was born to consanguineous parents; a previously affected sibling had died. She was dysmorphic with multiple joint ankylosis, dislocated hips and right knee, multicystic dysplastic kidney, sensorineural deafness, optic nerve hypoplasia and hydrocephalus requiring ventriculostomy. Septum pellucidum was absent on MRI. Thyroxine was commenced at 2.1 years (free T4 of 8.8 pmol/l (10.2–24.5) and TSH 15.4 mIU/l (0.4–5)). IGF1 (2.4 nmol/l (4–20)) and IGFBP3 (3.06 mg/l (0.5–2.9)) were both low. Glucagon stimulation test at 5 years showed low peak GH (3.4 mU/l) and cortisol (232 mU/l). She was started on GH and hydrocortisone supplementation, the former was stopped after 1 year due to worsening of kyphoscoliosis requiring spinal surgery and instrumentation. Case 2: this 3-year old boy with arthrogryposis had dysmorphism, contractures of hips, knees, shoulder, elbows, club feet, windswep deformity of hands, joint dimpling and finger webbing. He also had microgenisis, undescended testes and hypoplastic scrotum. LH/FSH testing was normal but the synacthen response suboptimal (403 mU/l). Hydrocortisone, thyroxine and testosterone (25 mg monthly for 3 months) were commenced with good response. He required herniometry, bilateral orchiopexy, triceps release and Achilles tenotomy.

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Microarrays and MRI scan performed at 16 months were normal. Glucagon stimulation test at 2.8 years for poor growth and low IGF1 (<3.3 nmol/l) demonstrated a peak GH response of 2.8 μg/l and GH therapy was commenced.

Conclusion
These cases illustrate an association between MPH and arthrogryposis. The mechanism is yet to be elucidated. We plan to undertake further genetic studies to evaluate the causality of this association.

DOO: 10.1530/endoabs.33.P69

Table 1 Reason for change

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<tr>
<td>Bruising</td>
<td>4</td>
</tr>
<tr>
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</tr>
<tr>
<td>Unhappy with device</td>
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<tr>
<td>Non-adherence</td>
<td>18</td>
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<td>Wanted simpler device</td>
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<tr>
<td>Needle-free</td>
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<td>Trial</td>
<td>9</td>
</tr>
<tr>
<td>Non-fridge</td>
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<tr>
<td>Other</td>
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Conclusions
Patients change GH device for a variety of reasons. GH adherence following changeover is variably altered, as are biological responses (HVSDS and IGF1).

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P71
GH neurosecretory dysfunction may be associated with structural abnormalities of the hypothalamic–pituitary axis
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Introduction
GH neurosecretory dysfunction (NSD) refers to children with abnormal auxology, normal GH responses to provocative testing, but with impaired spontaneous GH secretion over 24 h, leading to low IGF1 concentrations. It is thought to be due to abnormal hypothalamic function with aberrant GHRH and somatostatin secretion leading to impaired GH secretion and subsequently suboptimal growth.

Methods
We reviewed children admitted for spontaneous GH secretory profiles over the last 4 years. We aimed to identify children with growth failure who achieved adequate GH concentrations following stimulation but showed evidence of NSD on an overnight GH profile. We evaluated growth velocity and IGF1 before and after commencing GH treatment. All children diagnosed with NSD were further investigated using neuroimaging (MRI brain/pituitary).

Results
We identified four children with short stature (height < −2.5 SDS) and sub-optimal growth velocity who demonstrated inadequate endogenous GH secretion. These children had no or only one GH peak > 7 μg/l over 12 h. All children had previously passed a standard GH stimulation test with stimulated GH concentrations ranging from 10.2 to 21.1 μg/l. However IGF1 concentrations were below −2 SDS in all children. All four children had structural abnormalities of the hypothalamic–pituitary axis including septo-optic dysplasia, anterior pituitary hypoplasia, ectopic posterior pituitary and abnormalities of the infundibulum. Two children subsequently developed multiple pituitary hormone deficiency. All children were commenced on GH treatment and showed normalisation of growth velocity and IGF1 concentrations.

Conclusions
Structural abnormalities of the hypothalamic–pituitary axis may be associated with NSD of GH secretion. Children with significantly abnormal auxology may therefore warrant further investigation in the form of neuroimaging and overnight GH profiling even if they achieve a normal GH peak following provocation. Children with GH deficiency secondary to NSD clearly benefit from treatment despite not being NICE approved; this may soon require discussion with commissioning groups.

DOO: 10.1530/endoabs.33.P71
**P72**

Assessment of cortisol and thyroid hormone levels in neonates with myelomeningocele

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**Background**

GH deficiency has been reported widely in association with myelomeningocele and other pituitary hormone deficiencies occur less frequently. Following an episode of adrenal crisis in a newborn infant with myelomeningocele and multiple pituitary hormone deficiencies we introduced a policy of screening affected, newborn infants for pituitary insufficiency, focusing on thyroid function and cortisol levels.

**Patients and methods**

Data from 26 infants (13 males) were reviewed retrospectively. TSH sufficiency was assessed from an unstimulated measure of TSH and IT, ACTH sufficiency as assessed by the cortisol response to the low dose short Synacthen test (LDSST: Synacthen 150 ng). A peak cortisol ≥500 nmol/l was considered to be normal.

**Results**

Thyroid hormone levels were normal in all infants.

- Median (range) basal cortisol was 313 (<50–618) nmol/l and peak cortisol 693 (375–1617) nmol/l.
- 4/26 infants (16%) had a suboptimal cortisol response and were treated with hydrocortisone during periods of stress.
- Peak cortisol was >500 nmol/l in 3/4 patients with an impaired response during the neonatal period at reassessment 6 months later.

**Conclusion**

Infants with myelomeningocele undergo a number of medical and surgical interventions in the first year of life. In this group of patients it is particularly important to identify infants who may have an impaired cortisol response to stress. Our data suggest that routine assessment of the pituitary, possibly limited to assessment of ACTH, should continue.

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**P73**

Stopping desmopressin treatment in a child with hypopituitarism and epilepsy

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**Case**

A 10-year-old girl with panhypopituitarism and cerebral palsy secondary to Group B streptococcal meningitis as a neonate had full hormonal replacement therapy (hydrocortisone, thyroxine, DDAVP) since infancy. GH was started at 3 years of age. Sodium levels were always stable in the high normal range. She became epileptic aged seven and was started on sodium valproate. Recurrent chest infections occurred from age eight and she became colonised with Pseudomonas and required home oxygen. In the same year, she stopped feeding orally and became totally gastrostomy fed on a fixed volume of 1000 ml a day. Hydrocortisone was changed to prednisolone at aged seven to facilitate the effects of DDAVP through the day.

GH was stopped at aged nine when it appeared that she was not growing very well. She had been quite ill that year with recurrent chest infections. Her weight escalated despite a calorie reduction in feeds. Prior to stopping GH, her plasma sodium was 138 mmol/l. This fell to 129 mmol/l despite sodium supplements of 3 mmol/kg per day. Urine output was <3 ml/kg per h despite reduction of DDAVP dose. Urinary sodium peaked at 133 mmol/l.

**Management**

She was admitted for fluid assessment and a cortisol profile whilst hydrocortisone was reintroduced 6 hourly and DDAVP and sodium supplements stopped. Hyponatraemia and natriuresis persisted till GH was reintroduced at 0.026 mg/kg per day. Urinary sodium fell to <10 mmol/l in the first week of treatment. Urine output was <3 ml/kg per h on no DDAVP. She is still off DDAVP 15 months later.

**Conclusions**

There are a number of reasons for this complex child to stop DDAVP. Hyponatraemia and reduced urine output implies that there is some endogenous ADH secretion, although vasopressin levels were never confirmed. GH has potent renal tubular antinatriuretic effects. This, coupled with the antidiuretic effect of valproic acid must not be underestimated. Six-hourly dosing of hydrocortisone ensures residual DDAVP works effectively.

**DOp**: 10.1530/endobubs.33.P73

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**P74**

Comparison of Glucagon vs Clonidine stimulation test to diagnose growth hormone deficiency

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NICE guidelines (2010) recommend two different GH provocation tests demonstrating subnormal peak GH levels to diagnose isolated GH deficiency (IGHD). Choice of stimulation test varies in different units. In our centre, glucagon (GST) and clonidine (CST) stimulation tests are used to make a diagnosis of IGHD. IGF1 is done as part of the initial screening tests.

Purpose of this study was to compare the GST vs CST and to establish if IGF1 level provided any extra information. GH assay at our centre sets a peak GH level of ≥7 μg/l as normal.

44 children who underwent two GH stimulation tests were included. IGF1 levels measured in 42 children prior to GH tests. Whilst 33/44 (75%) had GST as first test, 11/44 CST as first test. Of the 33 children with subnormal GST (peak <7 μg/l), 21 (64%) had normal response to CST. Of the 11 children with subnormal CST, 1 (9%) subsequently had normal response to GST but 91% diagnosed to have GH deficiency after GST. No difference in age group of the children in both groups (median age 8.3 years GST first test vs 10.7 years GST first test) was identified. Results of IGF1 did not provide any additional information. 74% (17/23) of those diagnosed GH had low IGF1 levels (8/10 with GHD in CST group vs 9/13 in GST group).

Significant proportion who failed GST (first test) showed normal response in subsequent CST compared to those who had CST as first test. There were no predictors to choose either test as a first choice and hence avoid a second test if possible. Until a ‘gold standard biomarker’ of GHD becomes available, current NICE guideline recommendation of two GH tests to diagnose GHD stands with no evidence of choice of GST or CST as first test.

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**P75**

How late is too late to treat with Growth Hormone? A case study

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**Introduction**

13.1-year-old boy referred for growth hormone (GH) treatment with extreme short stature.

**Baseline investigations.**

- **Insulin tolerance test**
  - Peak GH — 29.3 mU/l
  - Cortisol 480 nmol/l (245–725)
  - 24 h GH profile 4 peaks >20 mU/l
  - IGF-1 13.9 nmol/l (23–90)
  - IGF-BP3 1.6 mg/l (2.1–5.3)
  - Bone age 11 years
  - Skeletal survey No evidence of dysplasia
  - Dual-energy X-ray absorptiometry (DXA) L1–L4 'Z' score: −3.2

- **Total body 'Z' score:** −3.1
- **Total body (%fat):** 9.0
- **Android fat (%):** 7.1
- **Gynoid fat (%):** 19.2

**Re-evaluation following 5 years of GH therapy at 19.3 years.**

- **Height** 159.3 cm (SDS: −2.51)
- **Tanner stage** G5
- **Height velocity** 2.5 cm/years
- **Parental adjusted height SDS** −1.82 SDS
- **IGF-1** 56.6 nmol/l (nmol/l)
- **IGF-BP3** 6.77 mg/l (mg/l)
- **Bone age** 17 years
- **DXA** L1–L4 'Z' score: −2.4
  - **Total body 'Z' score:** −3.0
  - **Total body (%fat):** 6.7
  - **Android fat (%):** 9.5
  - **Gynoid fat (%):** 11.4

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**Background**

Born premature at 28 weeks gestation, fraternal twin, birth weight: 1.06 kg (−0.58 SDS). Neonatal course complicated by respiratory distress syndrome, grade 2 Intraventricular haemorrhage, grade 2 Retinopathy and failure to thrive. Although not born small for gestational age, he was small at term (1.67 kg (−4.18 SDS)).

**Objective**

The aim of the study was to identify optimal GH sampling time points to avoid over diagnosis of GHD.

**Methods**

Results of 502 paediatric ITTs using two different sampling protocols (P1 [n = 459] and P2 [n = 43]).

**Conclusion**

There was no significant difference in the proportion of cases with GHD from P1 compared to P2.

**Results**

In both pubertal males and females, UG were significantly higher than during GnRH-a treatment.

**Conclusion**

These preliminary data suggest that UG reflect serum gonadotrophin concentrations and the finding of low UG in patients on GnRH-a therapy suggest that this test may represent a useful non-invasive method of assessing and monitoring responsiveness to GnRH-a therapy.
Conclusions
GH peaks that preclude GHD can be seen in samples even before the administration of insulin in 3% of children. 45 and 75 min samples precluded GHD deficiency in an additional 5–10% of children, avoiding potentially inappropriate and costly GH treatment or repeat tests. 120 min sampling did not contribute to GHD diagnosis.
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P79
Use of prolactin concentrations in disorders of pituitary function and optic nerve hypoplasia
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Introduction
Measurement of the anterior pituitary hormone prolactin is often performed in patients with pituitary pathology. Mild hyperprolactinemia occurs in subjects with hypothalamic disorders and/or pituitary stalk dysfunction, and is also described in patients with isolated optic nerve hypoplasia (ONH), this is proposed to be due to decreased dopaminergic tone.

Objective
To assess prolactin levels in patients with septo-optic dysplasia (SOD) (with/without hypopituitarism), multiple pituitary hormone deficiency (MHPD), isolated GH deficiency (IGHD) and isolated optic nerve hypoplasia (ONH).

Methods
Prolactin data were retrospectively analysed from our database of children with SOD, MHPD, IGHD and ONH. Prolactin was measured using the Immulite assay. 238 prolactin results were included: patients with SOD and hypopituitarism (n = 56), SOD with normal endocrine function (19), MHPD (73), IGHD (76) and ONH (uni- and bi-lateral) (14). Prolactin concentrations were compared using analysis of covariance using SPSS.

Results
The mean prolactin levels in patients with SOD with hypopituitarism was 448.9 mU/l and in those with SOD and normal pituitary function was 339.1 mU/l. MHPD, IGHD and ONH patients had mean prolactin concentrations of 295.4, 185.2 and 284.6 mU/l respectively. Children with SOD and hypopituitarism had higher levels than those with MHPD (P = 0.008) and IGHD (P < 0.001). Four SOD patients (three with hypopituitarism) and two with MHPD had prolactin levels > 1000 mU/l. Five children with MHPD had prolactin levels below the lower limit of the assay, one is known to have a POU1F1 mutation. Mean prolactin concentrations in children with ONH and SOD without hypopituitarism were similar to the other groups, although a greater sample size is required to report this with confidence.

Conclusion
Prolactin is often measured in patients with suspected pituitary dysfunction. Higher prolactin levels are found in SOD patients with hypopituitarism. Undetectable prolactin levels in MHPD patients should instigate investigation of genetic causes.
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P80
Endocrine manifestations of CHARGE syndrome
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Introduction
CHARGE syndrome is a multi-organ disorder; 67% have mutations in the chromdomain gene CHD7. Endocrine abnormalities are increasingly recognized and we report our experience in a tertiary endocrine unit.

Methods/Study design
Children with CHARGE syndrome attending endocrine clinic were identified and data collected retrospectively from medical notes.

Results
31 patients (13 females) were identified. Mean age was 10.5 years (range 0.67–21 years). Whilst all children presented neonatally with congenital malformations and dysmorphic features, CHARGE diagnosis based on clinical criteria was made up to 4 years of age. CHD7 mutations were identified in 22 (71%). Mean age of endocrine referral was 10 years (range 0.1–17 years). Endocrine causes for referral were: three with short stature only, seven with short stature and hypogonadotropic hypogonadism (HH: delayed puberty, hypoplastic genitalia and/or undescended testes), 12 with HH and one with osteopenia. Mean height SDS was −2.2 (range −0.43 to −5.8). GH provocation testing (n = 5) showed a mean GH peak of 29.8 mU/l (range 21.9–45). Two patients received GH therapy. 19 patients (16/17 males, 6/13 females) had HH clinically; 17 (55%) were prepubertal. Of 14 (eight female) children in the pubertal age range, spontaneous puberty occurred in only three (all female). Puberty induction occurred in the remaining four (range 1.3–5.7 years). Three patients had low bone mineral density on DEXA scan. BMAD SDS −2.2 to −2.4. In one child low bone mineral density was associated with fractures and required treatment with bisphosphonates.

Conclusion
HH is the predominant endocrine problem in children with CHARGE syndrome, being more common in boys than girls (94 vs 46%), who consequently are more likely to require pubertal induction. These children may be at an increased risk of osteoporosis. Other endocrinopathies appear to be rare.
DOI: 10.1530/endoabs.33.P80

P81
The role of GH in early postnatal life in mice
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Introduction
GH concentrations are high at birth but it is unclear whether and where GH signaling takes place at this time. We assessed the response to GH in young normal and GH-deficient (GHD) pups.

Methods
Transgenic M2-GRF mice were significantly GHD from birth. Weight and plasma IGFI concentrations were normal, but reduced at 6–8 day of age (P < 0.001). 3 and 10-day-old GHD and normal (WT) mice were treated with bovine GH (bGH, 10 μg/g bw s.c. bd) or vehicle for 5 day (n = 5–8/group). Ten day old GH mice, but not WT mice, responded by increasing weight gain (P = 0.01), tibial length (P = 0.02) and plasma IGFI (P < 0.05). In contrast, these parameters were unaffected in response to bGH in 3-day-old GHD mice (P > 0.05). A single mouse GH (mGH) injection (1 μg/g bw i.p.) in GHD mice induced Stat5 signaling in liver and growth plate 25 min later, at both 0 and 7 day of age. When 7-day-old GHD and WT mice were killed at various times, GHD mice (n = 12) had undetectable plasma GH-concentration and no detectable pY-Stat5 in the liver. In 21 WT mice, GH-concentrations ranged from 4.1–55.2 ng/ml. Hepatic pY-Stat5 was detected in eight mice, and these mice had significantly higher plasma GH concentrations (24.4 ± 5.0 vs 9.1 ± 1.0 ng/ml, P = 0.001), and pY-Stat5 staining was most intense in the mice with the highest GH-concentration.

Results
In conclusion, 10-day-old but not 3-day-old GHD mice grow in response to 5-day bGH. In contrast, both 0 day and 7-day-old mice are able to respond to a single GH pulse by phosphorylating hepatic Stat5. This suggests that hepatic GHR signaling takes place from birth, but that this GHR activation does not result in growth acceleration or increased IGFI production. The presence of hepatic pY-Stat5 in mice that have high GH-concentrations suggests that hepatic Stat5 phosphorylation follows an endogenous GH pulse as in older mice.
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P82
The use of Radioactive Iodine in the treatment of childhood and adolescent hyperthyroidism
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Introduction
Treatment options for Graves’ disease (GD) and multinodular goitre include antithyroid medication, near total thyroidectomy and radioactive iodine (RAI). RAI is an established treatment for GD in the adult population but is used less commonly in children and the adolescent population due to concerns with regards to safety.

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Methods
A review of a series of 14 adolescent patients receiving RAI between 2007 and 2013 in our department was performed retrospectively. This was done via review of case notes, GP follow up details and direct patient interview.

Results
81 patients have been recruited (41BR, 40 DT). 77% were female, median age at presentation was 13 years (range 3–16 years) and 83% were aged 10–15 years. The median BMI SDS was 0.08 with a range from −1.92 to 2.4. The median baseline FT4 was 48 (range 13.5–150 pmol/l). The percentage of FT4 values in the range <25, 25–50, 51–75, 76–100 and >100 pmol/l was 6, 47, 15, 23 and 6% respectively. In 98% cases TSH was suppressed at diagnosis. The average starting time taken for FT4 and TSH to normalise according to local reference values. Results showed that TSH, 250 mIU/ml; fT4, 0.13 ng/dl; antiTPO Ab, 0.32. She had coarse facial feature, athletic build and creatinine phosphokinase (CPK) level, 621 U/l (33–211).

Conclusions
UK patients with thyrotoxicosis are not thin at presentation. Parents can be informed that FT4 will be within the normal range or close to normal range within 4 weeks if a dose of Carbimazole between 0.5 and 0.75 mg/kg is administered. TSH levels cannot be used to guide therapy in this early phase of treatment.

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P85
Kocher-Debre-Semelaigne syndrome: a report of three cases
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Introduction
Kocher-Debre-Semelaigne syndrome (KDSS) is a rare association of muscular pseudohypertrophy and long standing moderate-to-severe hypothyroidism in pediatric age group. This report describes three cases with KDSS.

Case 1
A 4-year-old girl was admitted to our department with growth failure and mental-motor retardation. She was diagnosed as primary hypothyroidism at the age of 15 days and was started on ·throxine but at the age of 6 months the therapy was discontinued by parents. Physical examination showed that her height SIDS was −5.01, weight SIDS −4.7. She had dry skin, pyocmotor retardation, strabismus of the right eye and hypertrophy of both calf muscles. Laboratory findings revealed that TSH, >100 mIU/ml; fT4, <0.3 ng/ml (normal range, 0.80–1.58) and creatine phosphokinase (CPK) level, 621 U/l (33–211).

Case 2
A 11 years 6 months old girl was admitted to our clinic with history of growth failure and weight gain in the last 1 year. On examination her height SIDS was −2.03 while weight SIDS was +0.32. She had coarse facial feature, athletic build and hypertrophy of both calf muscles. Laboratory findings revealed that TSH, 250 mIU/ml; fT4, 0.13 ng/dl: antiTPO Ab, 383 IU/ml (0–35) and CPK level, 2502 U/l.

Case 3
A 10 years 9 months old girl was referred to our outpatient clinic with history of growth failure for 2 years. On physical examination her height SIDS was −2.8, while weight SIDS was +1.19. She had coarse facies and bilateral hypertrophied calf muscles. Laboratory values were TSH, 615 mIU/ml; fT4, 0.3 ng/dl: antiTPO Ab, 1000 IU/ml and CPK level, 2096 U/l.

Conclusion
We emphasize that because KDSS may be develop due to untreated hypothyroidism, musculoskeletal system should be carefully assessed in hypothyroid children and adolescence.

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PTEN hamartoma syndrome: unravelling the complexities of childhood screening
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Background
PTEN hamartoma tumour syndromes (PHTS) are rare autosomal dominant inherited disorders characterised by macrocephaly, multiple hamartomas and an increased risk of several cancers, including breast, thyroid and endometrium. PTEN encodes a tumour suppressor phosphatase that regulates cell survival and migration. Published guidelines are available for adult patients but screening in children is currently not standardised. Moreover, there is poor genotype-phenotype correlation and age-related penetrance in PTEN mutations, making decisions around appropriate paediatric surveillance highly complex.

Aim
To examine the literature for existing guidelines and epidemiological data to produce a comprehensive screening plan for our paediatric PHTS patients.

Patients and methods
We manage two siblings with a confirmed germline truncating mutation in PTEN (R233X) inherited from their mother, who developed Hashimoto’s thyroiditis and a compressing thyroid goitre requiring near-total thyroidectomy aged 28 years. Both children have macrocephaly and developmental delay with autistic-spectrum features but are otherwise asymptomatic (aged 7 and 6 years). A primary search of Medline via PubMed and secondary searches via national guideline databases were carried out.

Results
12 relevant papers and two published guidelines (NICE guidelines, National Comprehensive Cancer Network guidelines) were identified. The risk for tumour development in patients with PTEN mutations is considered low in childhood, and no screening guidelines were found for paediatric patients. Surveillance is recommended from 18 years unless there is a family history of cancer <23 years. However, a recent case series reported the development of thyroid nodules and cancer from early childhood.

Conclusions
Available guidance for the management of childhood of PHTS patients is limited. The lack of paediatric reports of PHTS-associated cancer may be explained by previous diagnostic limitations. We recommend yearly physical examination (particularly of skin and thyroid) and yearly thyroid ultrasound upon diagnosis. In view of the high lifetime risk of malignancy it is important to keep patients under close surveillance.

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An unexpected diagnosis of follicular–variant papillary thyroid carcinoma in an 11-year-old male
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Introduction
Thyroid carcinoma in childhood is rare, but may present with distant metastases. We present an unexpected diagnosis of follicular–variant papillary thyroid carcinoma (FVPTC) presenting to acute services with cyanosis.

Case report
An 11-year old boy presented to A&E with a two month history of cyanosis, worse with exertion, but not associated with respiratory distress or limitation of exercise tolerance. He had peripheral cyanosis, clubbing and oxygen saturations 78% (air). CT chest showed bilateral, extensive miliary nodules, in keeping with interstitial lung disease. Differential diagnoses included sarcoidosis, tuberculosis and pulmonary alveolar microlithiasis. Following lung biopsy, histology showed FVPTC; subsequent neck examination then revealed a thyroid mass with bilateral cervical lymphadenopathy, confirmed on thyroid ultrasound and MRI neck. Thyroid function test (TFT) was normal (TSH, 4.4 mU/l and FT4 13.1 pmol/l). After radical thyroidectomy and neck dissection, histology confirmed FVPTC. Full lymph-node resection was not possible. MRI brain showed four distinct lesions; abdominal CT showed bilateral renal metastases. TFT remained normal post-operatively, but after one cycle of radio-iodine therapy, levothyroxine supplementation was introduced (75 µg once daily). Papillary thyroid cancer is the commonest differentiated thyroid cancer; FVPTC is a common subtype. Regional lymph-node involvement is common in young patients (60–80%), 10–20% have distant metastases. Females predominate; 12% have history of local irradiation; 10% have family history. Adult series have shown younger age and lung-metastases only are associated with good prognosis. A paediatric series of 83 patients aged under 21 at diagnosis of differentiated thyroid carcinoma with distant metastases showed 100% 10-year survival.

Conclusion
This case highlights the importance of considering unlikely causes of common presentations. FVPTC in young patients with widely metastatic disease tends to be extremely radio-iodine responsive, with high cure rate, however this case has more wide-spread metastases than previously reported and the reversibility of the lung disease is unknown.

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Low remission rates and high failure rate for medical treatment of thyrotoxicosis in childhood and adolescence: strategic implications for stopping antithyroid drugs
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Background
Paediatric thyrotoxicosis due Graves’ disease (GD) and Hashimoto’s thyroiditis (HT) disease is both more rare yet more severe than in adulthood. Antithyroid drug treatment (ATD) is with carbimazole or PTU either alone (dose titration (DT)) or with l-thyroxine (l-T4) – block and replace (BR).

Methods
We have examined outcome of medical treatment in a cohort of patients treated from 1989 to 2012 according to whether medical treatment was given for <3 or >3 years.

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Results
62 patients (8 M) with either GD (50) or HT (12), median (range) age 10.8 (1.8–15.8) years at diagnosis, received initial DT (42) or BR (20) treatment with ATD. Outcome was available in 36 patients receiving ATD for median (range) 5 (3–16.2) years and in 12 patients for 2 (0.3–2.8) years. In the <3 years group, seven patients had surgery and three radioiodine (RI) for poor control, while two (one GD and one HT) remitted when ATD was stopped. In the >3 years group 20 stopped ATD for possible remission of whom ten relapsed (all GD) and ten remitted (5HT), one had surgery and 12 had RI for failed therapy while three remain on ATD after 5.5–8.3 years.

Conclusion
Paediatric thyrotoxicosis may follow a protracted course with variable age of remission and high relapse rate as well as high rate of failure with ATD. We therefore recommend that patients on BR therapy do not discontinue their medication abruptly, but instead are weaned slowly off ATD according to thyroid function tests after stopping L-T4 therapy, in the hope of anticipating incipient relapse.

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