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3–5 November 2010, Manchester, UK

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Abstract Book

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CONTENTS

38th Meeting of the British Society for Paediatric Endocrinology and Diabetes 2010

SPEAKER ABSTRACTS

ORAL COMMUNICATIONS

Speaker Abstracts

CME session

S1

Adrenal development, function and failure

John C Achermann
UCL Institute of Child Health, University College London, London, UK.

The human adrenal gland develops from around 4 weeks gestation and undergoes distinct changes throughout pre- and post-natal life. Defects in these processes can cause adrenal hypoplasia and result in adrenal insufficiency. Adrenal hypoplasia can be: i) secondary to abnormal pituitary function, ACTH synthesis or splicing; ii) the result of ACTH resistance (familial glucocorticoid deficiency; triple A syndrome); or iii) due to a primary defect in adrenal development itself (primary adrenal hypoplasia). Most causes of primary adrenal hypoplasia are X-linked and due to changes in the nuclear receptor DAX-1. Boys typically have salt-losing adrenal failure in early infancy or childhood and hypogonadotropic hypogonadism (HH) and impaired spermatogenesis in adolescence. Alternative presentations have now been reported including early puberty or adult-onset adrenal insufficiency. The molecular aetiology of X-linked AHC remains poorly understood as DAX-1 paradoxically represses transcription. However, transcriptional activation by DAX-1 may occur and adrenal stem cell development may be dysregulated. Other forms of primary adrenal hypoplasia may be due to defects in steroidogenic factor-1 (SF-1) or WNT4. In this session we will obtain insight into new aspects of adrenal development and function throughout the early lifespan; review some of the molecular causes of adrenal hypoplasia; and discuss the importance of these diagnoses for the paediatric endocrinologist.

S2

Congenital adrenal hyperplasia

Nils Krone
School of Clinical and Experimental Medicine, Institute of Biomedical Research (IBR), Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.

Congenital adrenal hyperplasia represents a group of autosomal recessive disorders in steroidogenesis causing deficient cortisol biosynthesis. The incidence of congenital adrenal hyperplasia in the general population of western countries is ~1 in 10 000 to 1 in 15 000 life births with about 95% of cases caused by 21-hydroxylase deficiency. Several novel forms have been discovered in recent years involving all steps in steroidogenesis. The existence of milder or non-classic sub-forms of CAH clinically presenting with atypical pattern and/ or late-onset of disease is now well established. Some forms affect only adrenal steroid hormone biosynthesis (21-hydroxylase deficiency, 11β-hydroxylase deficiency), whereas others lead to combined impairment of adrenal and gonadal steroidogenesis (deficiencies of steroidogenic acute regulatory protein, P450 side-chain cleavage enzyme, 3β-hydroxysteroid dehydrogenase type 2, 17α-hydroxylase, and P450 oxidoreductase). All conditions have a specific steroid hormone fingerprint with pathognomonic plasma hormone and urinary steroid hormone profiles. Establishing the differential diagnosis is essential, as different forms of CAH require different approaches to steroid hormone replacement. During different life spans type and dose of glucocorticoid can change. The relative mineralocorticoid dose per body surface area declines with increasing age. Replacement doses are monitored by clinical and biochemical parameters, with suppression of steroid hormones commonly indicating overtreatment. CAH has become an inborn condition affecting patients who are now well in their fifties. Comprehensive long-term data on mortality are not available. Pharmacotherapy with current approaches is challenging, with keeping the balance between glucocorticoid overexposure and androgen excess. The caring physician has to be aware on co-morbidities involving cardiovascular disease, metabolic complications, fertility problems, psychosexual and psychologic health. Patients are ideally looked after by a multi-disciplinary team. An important emerging task for paediatric health care provision in CAH is primary and secondary prevention of long-term health problems.

S3

Cushing's disease

H Storr
London, UK.

Abstract unavailable.

S4

Physiology and developmental biology

Ieuan Hughes
Cambridge, UK.

Abstract unavailable.

S5

Clinical evaluation of suspected cases of DSD

F Ahmed
Glasgow, UK.

Infants rarely present with truly ambiguous genitalia and such children should be evaluated by experts who work within a multidisciplinary team that is dedicated for evaluation and management of children and adults with suspected and confirmed disorders of sex development. The paediatric endocrinologist who is a vital, and often, the central member of this clinical team needs to lead the clinical evaluation of the infant systematically but also needs to be sensitive to the needs of the infant, the parents and the rest of the team. A thorough knowledge of the underlying pathophysiology and the strengths and weaknesses of the investigative tools that are available for reaching a diagnosis is crucial.

S6

What is going through the surgeon's mind when he is sitting in the DSD clinic?

S O'Toole
Glasgow, UK.

Abstract unavailable.

RCN CYP diabetes community session

S7

IT barriers and potential solutions

P Hindmarsh
University College Hospital, London, UK.

As medical science and technology have advanced health care delivery in diabetes has struggled to provide consistent high quality care. In the United Kingdom the National Service Framework (NSF) for Diabetes and guidelines from the National Institute for Clinical Excellence lay out the direction of care but do not performance manage care to achieve real improvements in health.

There remains a shortfall between knowledge acquisition and safe and appropriate translation into practice. Diabetes mellitus is a classic chronic disease that requires continuous monitoring/input, involves different specialities and a high level of patient/parent involvement. Although the complexity is acknowledged in practice there is little evidence that health care systems really understand these complexities and tend to go on providing the type of care that was delivered 10–20 years ago. Service provision is prone to widespread inconsistencies in care delivery and outcomes. The Health care offered for children and adolescents with diabetes has safety and quality problems because the system that is utilised is largely outmoded. If we wish to advance the course for Paediatric and adolescent diabetes then system redesign is essential.

This redesign will require practice of the principles of chronic care:

1. Use protocol or plan that says what has to be done, at what time intervals and by whom. Links multiple visits and contacts.
2. Redesign to incorporate regular patient contact, collect adequate data and look to how to provide education and training to manage their condition.
3. Focus on patient information and self management. Structured programmes.
4. Links with carers of chronic illness patient.
5. Registries for proactive management and outcome evaluation.

This presentation will evaluate how this might be achieved using examples from several of these areas.

S8

Regional networks and PBR

M Hannigan
NHS Diabetes Main Office, Newcastle upon Tyne, UK.

There are 23 000 children with diabetes in England and managing diabetes in a child or young person can be a complex process. Historically care has been variable and the experience of the child or young person is not always positive. This situation has been compounded by a lack of a paediatric diabetes tariff and networks to support best practice.

NHS Diabetes is supporting a number of new innovative projects to develop regional paediatric networks to support existing agencies and work, also to instigate changes to policy and direction. NHS Diabetes committed to a piece of work to identify better and more appropriate ways to fund services. The work in this area developing better understanding the financial constraints, challenges and flows within the NHS paediatric diabetes services and to answer the two key questions;

○ What does it cost to treat a young person with diabetes to the standards set out in Making Every Young Person with Diabetes Matter.

○ How do we ensure that we get finances to flow into the services whilst also ensuring that those providers deliver an appropriate quality of service to those standards for their local population.

The aim of the NHS Diabetes paediatric programme is therefore to drive up the quality of care for all children in England. This presentation today will describe the structure and remit of the paediatric programme, the networks and the status of the paediatric tariffs to be implemented and developed in 2011 and beyond.

The purpose of attending and speaking at regional events and national events such as this, is share the work and to seek the views, ideas from your everyday practice finding common issues and helping to inform discussions in all the above areas.

S9

Child protection and social service challenges

H Chamberlain
Manchester, UK.

Abstract unavailable.

S10

Cultural barriers to effective DM management

R Amin
London, UK.

Abstract unavailable.

S11

Accreditation in paediatric diabetes in the UK and England

J Allgrove
London, UK.

Abstract unavailable.

S12

A recipe for business success … and staff motivation

Steve Head
Headstart-uk, Newbury, UK.

Ingredients

- 1 Cupful of Self Belief
- 3 oz of Clarity
- 4 KG of Building on your Strengths
- A large portion of Understanding the impact you are having on your customers
- A dollop of Personalised service

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Method

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S13

Enabling sustained improvements on CSII: how to fine tune!

John Pemberton
Salford Community Diabetes Team.

This talk starts by focussing on how to set insulin to carbohydrate ratio and duration of insulin action and then how to test if they are set correctly. The talk then progresses into showing the mismatch between carbohydrate absorption and insulin action and how to use practical tips and pump tricks to reduce post-prandial glycaemia. The talk finishes with suggestions of when to use different bolus options such as dual wave (split) and extended (square).

S14

First hand experience of diabetes services: challenges and solutions

Lauren Kay & Jenna Kay
Manchester, UK.

Abstract unavailable.

Symposium 1 – Transition and Therapeutics

S15

GH replacement into adult life

H Gleeson
Manchester, UK.

GH deficiency (GHD) has implications throughout the lifespan. In childhood, reduced linear growth is the primary consequence of untreated GHD, while in adulthood, untreated GHD is associated with a number of abnormalities. The phenotype of GHD in adulthood differs depending on timing of onset. Childhood onset (CO) patients have reduced bone mineral content (BMC) and lean body mass (LBM) despite GH replacement therapy (GHRT) during childhood compared with adult onset. These differences suggest the CO GHD phenotype is developmental. It is these developmental deficits that have lead to a focus on GHRT in patients with CO GHD in the transition period, spanning from the completion of puberty into young adulthood. The aim of GHRT during this time is to normalise body composition and cardiovascular health with the long-term aim of reducing the morbidity and mortality observed in patients with hypopituitarism.

There is evidence that GHRT at this time aids to reduce this deficit in muscle and bone. This may have the effect of improving physical performance and reducing fractures later in life, however, the epidemiological evidence is currently lacking. There is also inconsistent evidence that cardiovascular risk is increased and QoL is reduced and that these improve with GHRT. It is possible, and there is some evidence to support this, that certain patient groups may demonstrate a worsening cardiovascular risk profile and QoL after a more sustained period of time off GHRT. More studies are required to provide the endocrinologist and the patient with adequate information to inform treatment decisions.

It is essential that paediatric and adult endocrinologists address a young person's wider healthcare needs, including actively encouraging independence and decision making. They should work together with young people and their families to ensure that transition between services is seamless so that they continue to engage with health care whether they opt for GHRT or not.

S16

Sex hormone replacement and fertility for adolescents and young adults: who needs it and how should it be done?

Margaret Zacharin
Department of Endocrinology, Royal Children's Hospital, Parkville, Victoria 3052, Australia.

Major changes in paediatric and adult medical practice have been seen over recent decades with increased prevalence of and longevity in chronic diseases, a marked increase in organ transplantation, rapid increases in recognition of new genetic disorders associated with altered gonadal function. Along with these changes has come recognition of the pivotal importance of adolescent bone mass accrual, to decrease the impact of adult bone loss for those who have a chronic medical condition.

These changes have brought new challenges for management strategies and planning of fertility options for affected young men and women. Novel treatments, such as bisphosphonate use have changed the face of some paediatric bone disorders, but may impact on possible future risks for pregnancies in affected individuals. Ethical issues surrounding harvesting of gonadal tissue from minors without proper informed consent, the possibility of removal of gonadal tissue rendering a functional gonad non-functional and confronting issues of donation and ownership of chromosomal material, all impinge on current practice management.

Normal timing of entry into puberty and progress of puberty is essential to optimize linear growth and appropriate feminization or virilization, as well as having a major effect on bone size and mass, with 40–50% of total bone mass for life accumulated during puberty.

Insults to the gonadal axis, either primary or secondary, may result in absent, delayed or arrested puberty but hypogonadism is often only one manifestation of a complex disorder. Holistic care will optimise outcome. This presentation will outline management strategies for different types of male and female hypogonadism, with particular attention to optimising timing and type of hormone replacement treatment in specific circumstances of chronic disease, after cranial radiation, organ transplantation, in disability and in specific disorders of hypogonadism such as Turner syndrome and hypogonadotrophic hypogonadism. New treatment options incur potential risks and raise new ethical issues. Risks for aortic dissection in Turner Syndrome during pregnancy and the use of cardiac MRI for evaluation is now mandatory. Use of ICSI provides new hope for fertility in Klinefelter syndrome. Adolescent use of gonadotrophins in hypothalamic hypogonadism improves adult fertility management in males.

Management outcomes should aim to strike a balance between the achievement of height and adult appearance, while recognizing limitations imposed by the nature of the underlying condition. Awareness of a window of opportunity for best possible outcome can only be achieved through regular surveillance together with a comprehensive knowledge of conditions affecting patients. We should have the capacity to pass our patients to adult care with adequate advice regarding future risks, fertility prospects together with an understanding of the complexity and evolution of their condition.

S17

Steroid replacement

R J M Ross
University of Sheffield, Sheffield, UK.

Cortisol secretion follows a distinct circadian rhythm, with circulating levels low at sleep onset, beginning to rise between 0200 and 0400 h, peaking within an hour of waking and then declining through the day. This circadian rhythm is determined by the central endogenous clock (pacemaker) of the hypothalamic–pituitary–adrenal (HPA) axis, located in the hypothalamic supra-chiasmatic nucleus. The HPA axis plays an important role in maintaining alertness and modulating sleep. Conditions associated with insomnia including depression, sleep apnoea and chronic fatigue disrupt the circadian rhythm of cortisol leading to metabolic abnormalities and increased cardiovascular risk. Patients with adrenal insufficiency have lost the normal circadian rhythm of cortisol and increased morbidity due to fatigue and excess mortality mainly from cardiovascular events and infections. Patients with congenital adrenal hyperplasia (CAH), have an even greater problem because of the challenge of both replacing glucocorticoid and controlling androgen excess. A recent large cohort study in the UK, CaHASE, has revealed evidence of greatly impaired health status in adult patients with CAH. Thus, there is a need for physiological circadian cortisol replacement to address some of these issues. Chronocort is a new approach to delivering hydrocortisone therapy. This modified release formulation replaces the overnight circadian rhythm of cortisol. Pilot formulations have demonstrated the ability to mimic the circadian cortisol rhythm in normal volunteers and studies in patients with CAH have confirmed the ability to control morning androgen levels.

In conclusion, there is a need to develop new formulations of glucocorticoid replacement and chronocort provides one option for addressing this challenge.

Symposium 2 – Metabolic Bone Disease

S18

Vitamin D in health and disease

Z Mughal
Manchester, UK.

Abstract unavailable.

S19

New developments in phosphate metabolism: understanding the mechanisms of hypophosphataemic rickets

Jeremy Allgrove
London, UK.

During the past ten years there has been an explosion of understanding of the metabolism of phosphate which centres around fibroblast growth factor 23 which is now thought to be the 'phosphotonin' that had long been suspected.

Discovery of this hormone, which is synthesised by osteocytes, is secreted and circulates in plasma, therefore qualifying it as a true hormone, has led to an understanding of the mechanisms of the various forms of hypophosphataemic rickets. Its principal action is to increase urinary phosphate excretion by counteracting the tubular reabsorptive actions of the sodium/phosphate cotransporter in renal tubules. It is under the control of several other factors including PHEX, DMP1 and ENPP1 all of which combine to deactivate it and of GALNT3, FGFR1 and Klotho, which either activate it or contribute to its action in renal tubules.

Inactivating mutations in PHEX, DMP1, ENPP1 or activating mutations in FGF23 itself lead to excess phosphate loss and hypophosphataemic rickets whilst inactivating mutations of GALNT3, Klotho or FGF23 cause hyperphosphataemic tumoral calcinosis.

The relationships and interactions between these different components of the phosphate metabolic pathway will be described.

Catherine Hall Memorial Lecture

S20

Catherine Hall Memorial Lecture: Congenital hyperinsulinism and DOPA-PET CT

M Skae
Manchester, UK.

Congenital hyperinsulinism of infancy (CHI) is a rare disorder of insulin dysregulation, resulting in persistent hypoglycaemia and its sequelae. More than half of patients have loss-of-function mutations in *ABCC8* or *KCNJ11* genes encoding subunits of ATP-sensitive potassium (K_{ATP}) channels. Histologically, disease pathology is subdivided into diffuse or focal disease; the latter associated with paternal mutations and somatic loss of maternal heterozygosity in these genes. The advent of ^{18}F-DOPA PET-CT imaging has permitted the reliable, non-invasive diagnostic differentiation between focal and diffuse forms of disease. Pancreatic β-cells, like other neuroendocrine cells, possess the unique ability for amine-precursor uptake decarboxylation (APUD), acting as highly specific targets for the ^{18}F-DOPA tracer, thus giving the investigation a sensitivity as high as 94%. This is particularly useful in cases unresponsive to medical treatment where pancreatic resection is undertaken. Over the last decade, with the introduction of rapid genetic analysis and ^{18}F-DOPA PET-CT imaging, clinicians have been able to effectively differentiate between focal and diffuse CHI processes, hence altering surgical practice and limiting surgical complications by allowing limited pancreatic resection in cases of focal disease. However, the short half-life (110 min) and difficulty in manufacturing Fluorine18 has prevented its regular production in the United Kingdom (UK). Scanning of UK CHI patients has therefore been conducted in other EU nations, requiring transfer of sick infants at substantial cost and risk of morbidity. Therefore, the need for the establishment a UK ^{18}F-DOPA PET-CT service remains paramount, and is currently being undertaken in Manchester.

Symposium 3 – The Beta cell

S21

Altered beta-cell signalling and congenital hyperinsulinism of infancy (CHI)

M Dunne
University of Manchester, Manchester, UK.

Ion channels play a key role in the regulation of insulin release. Conveying the signals associated with glucose metabolism, ATP-sensitive potassium (K_{ATP}) channels induce a depolarisation of the cell membrane which in turn regulates Ca^{2+} influx and Ca-dependent exocytosis of insulin-containing granules. Congenital hyperinsulinism is caused by channelopathies through *loss-of-function* mutations in the genes which encode K_{ATP} channels (*ABCC8*, *KCNJ11*) or by metabolopathies in which defects in glucose metabolism lead to altered channel activity. In both situations, β-cells no longer rest and are constitutively active with elevated levels of intracellular Ca^{2+} due to inappropriate closure of K_{ATP} channels. In contrast, *gain-of-function* defects in *ABCC8* or *KCNJ11* are a cause of type 2 diabetes, and neonatal diabetes. Through studies of the function of β-cells isolated from more than 140 patients following surgery, we have now documented the relationship between loss of K_{ATP} channel function and the histopathophysiology of CHI. This approach has allowed us to characterise a spectrum of defects related to impaired ion channel function, identify subsets of patients in which CHI is unrelated to defects in K_{ATP} channels and to critically examine the properties of β-cells isolated from the pancreas of focal CHI patients. Through a greater understanding of the ionic basis of CHI we have initiated studies related to the rescue of K_{ATP} channels in β-cells from patients and have begun to explore the rational basis of new therapeutic opportunities.

S22

The yin and yang of beta cell genetics

S Ellard
Institute of Biomedical and Clinical Science, Peninsula Medical School, Exeter, UK.

The opposite phenotypes of diabetes and hyperinsulinism can be caused by different types of mutations within the same genes. For example, rare activating *GCK* gene mutations cause hyperinsulinism whereas the more common loss-of function mutations result in mild fasting hyperglycaemia in the heterozygous state or recessively inherited permanent neonatal diabetes.

The knowledge that inactivating mutations in the *KCNJ11* and *ABCC8* genes encoding the beta-cell ATP sensitive potassium (K_{ATP}) channel subunits Kir6.2 and SUR1 are the most common cause of congenital hyperinsulinaemic hypoglycaemia led to the identification of gain-of-function mutations as a common cause of neonatal diabetes. Most patients with K_{ATP} neonatal diabetes achieve improved glycaemic control and quality of life with sulphonylurea tablets.

Some patients experience both hyperinsulinism and diabetes as a consequence of a single gene mutation, but at different stages of their life. Both dominant K_{ATP} channel missense mutations and mutations in the *HNF4A* transcription factor gene can cause increased birth weight, presumably due to increased insulin secretion *in utero*, neonatal hyperinsulinaemic hypoglycaemia but with an increased risk of diabetes in later life.

S23

Neonatal diabetes

J P H Shield
Manchester, UK.

Neonatal diabetes or monogenic diabetes of infancy can manifest as a transient or permanent condition. TNDM is most commonly caused by imprinting disorders on chromosome 6q24 (TNDM1.Uniparental Isodisomy Chromosome 6, Paternal Duplication of 6q24, loss of maternal methylation). Recently it has been identified that over half of those with maternal hypomethylation at 6q24 have relaxed maternal methylation at other imprinted loci and that the majority of these patients have mutations in transcription factor *ZFP57*. Transient neonatal diabetes has also been described with mutations in the genes encoding the ATP-sensitive potassium channel *ABCC8* (TNDM2) and *KCNJ11* (TNDM3). TNDM1 is characterised by third trimester IUGR, low birth weight and very early onset diabetes. Treatment is usually with insulin but remission occurs within 3 months with a liability to relapse in adolescence or early adulthood. PNDM is a more diverse condition with an unknown genetic cause in about 40% of cases. Diabetes may be caused by defects in pancreatic development (*IPF-1, GLIS3, PTFA1*, and most recently *NEUROD1* the latter two having severe cerebellar hypoplasia), defects in Beta cell function (*KCNJ11, ABCC8*, homozygous *GCK* inactivating mutations) or increased islet cell destruction (*INS* and *EIF2AK3* by apoptosis and *FOXP3* by the only autoimmune condition causing neonatal diabetes). Whilst the effectiveness and diversity of treatment is very dependent on associated organ damage accrued from the diverse mutations, *KCNJ11* and *ABCC8* mutations are remarkable as one of the first successful examples of pharmacogenetics: identification of patients with these mutations causing neonatal diabetes led to many being successfully transferred from a previous lifetime of insulin therapy with relatively poor glycaemic control to excellent control on oral sulphonylureas. With the rapid advances in molecular biology techniques more causes of permanent neonatal diabetes are likely to be identified soon.

Plenary guest lecture

S24

Practical use of continuous glucose monitoring

R Hanas
Sweden.

Abstract unavailable.

Symposium 4 – Diabetes Care

S25

Corneal confocal microscopy and diabetic neuropathy

R Malik
Manchester, UK.

Abstract unavailable.

S26

Living with diabetes: normal but different, different but normal

Marie Marshall
Royal Manchester Children's Hospital, Manchester, UK.

Background

The notion of 'normal' is dominant in the lives of children with type 1 diabetes and their parents, because living with diabetes not only makes families different but it also makes their pursuit of 'normal' more visible.

Aim

To develop a theoretical understanding of how children and their parents living with type 1 diabetes construct and perceive 'normal', and how they integrate 'normal' into their daily lives.

Method

Conversational interviews were undertaken (independently) with 14 children, aged 4–17 years and their parents, from different ethnic backgrounds, and at differing lengths of time since diagnosis.

Results

The children and their parent's everyday lives are shaped by the distinct and discrete and sometimes dissonant understandings of the concepts of 'normal' and 'different'. Tensions arise because, from diagnosis onwards, children perceive themselves to be '*normal but different*' whereas their parents perceive them to be '*different but normal*'.

Conclusion

This subtle misalignment in emphasis creates dissonance between children and parents, as their individual focus and experience of diabetes means different things to them. It is crucial that practitioners explore these individual insights as it is this dissonance that can influence the way in which children and their parents choose to live with and (self)-manage diabetes.

Endocrine Nurse session

S27

RCN CYP specialist care forum: endocrine community update

L Martin
Paediatric Endocrine Unit, Barts and the Royal London NHS Trust, London, UK.

Background
2003 saw the formation of a special interest group within the Royal College of Nursing (RCN) for the growing number of paediatric nurses working within the field of endocrinology. While this group has strong links with the British Society of Paediatric Endocrinology and Diabetes (BSPED) and the British Endocrine Society (BES), it was felt these societies were strongly medical and that a unified voice for paediatric endocrinology nurses would be a useful addition.
2009 saw some changes within the RCN – ultimately leading to the Children and Young People (CYP) Endocrine community becoming part of the larger CYP Specialist Care forum.
Purpose
The RCN CYP Endocrine community aims to offer support, advice and expertise to nurses and professionals working with children, young people and their families with an endocrine disorder.
Aims
To:
• raise the profile of paediatric endocrine nursing
• share best practice and develop national guidelines and protocols for nursing children with an endocrine disorder
• promote nursing research and development in order to uphold best practice
• encourage multidisciplinary team working by providing support, information and advice to any healthcare professional caring for a child or young person with an endocrine disorder
Discussion
The BSPED meeting is an excellent opportunity for members of the CYP Endocrine community to discuss the group's future objectives. As part of the RCN, we have the opportunity to put forward bid proposals in order to fund projects, as well as utilise the personalised webpage facility and online discussion rooms provided on the RCN website. Our community, as part of the larger RCN CYP Specialist Care forum, also has the potential to have substantial input into the forum's annual conference which is next scheduled for 15 March 2011.

S28

Endocrine Nursing: raising the profile

J Collin
Keele, UK.

I have been the module leader for the Paediatric Endocrinology: exploring practice module for several years. Amongst those nurses who access or contribute to the course it is clear to see the wealth of knowledge, clinical expertise, enthusiasm for the subject area and professional commitment to delivering high quality nursing care to children, young people (CYP) and their families. Excellent examples of nursing care for CYP are presented in the assignments and every year I applaud the interest and motivation demonstrated by the nurses I meet. However it appears that Paediatric endocrine nurses are modest and tend to hide their 'lights under bushels'. There is scant evidence in the published literature of the important contribution they make to the care of CYP. This paper shares some examples of the excellence demonstrated over the years and urges you all to develop systems and access existing awards to enable dissemination of your work.

S29

Survivorship, what it is and where it is going?

T Urquhart
Sheffield, UK.

Approximately 1 in 650 children will develop a childhood malignancy by the age of 15 years. Improvements in diagnosis, treatment and supportive care over the last 30 years mean that approximately 80% of children diagnosed with cancer can now expect to survive more than five years. Approximately 1 in 250 young adults in the UK is a survivor (more than five years from end of therapy and disease-free) of childhood cancer. In the adult field it is estimated that 2 million people in the UK are living with or beyond cancer (Macmillan 2004), and that annually this will increase by 3.5%.
Late effects are the physical and psychosocial problems that result from the cancer and its treatment. There are a number of well established Late Effects Services across the UK, including our service in Sheffield. The role of the Late Effects Service is to provide ongoing surveillance and management of late effects in survivors whilst providing appropriate information and support to both survivors and their families / carers.
The cancer reform strategy (DoH 2007) outlined the need for increased focus on survivors. NHS Improvement in collaboration with Macmillan and the Department of Health subsequently established the National Cancer Survivorship Initiative (NCSI) in 2008 to implement this area of the Cancer Reform Strategy. The Children's and Young Peoples Improving Outcomes Guidance (CYP IOG, NICE 2005) has looked at all areas of the care of children and young adults with cancer, including late effects. These initiatives have all led to an increased awareness of survivorship issues and focus on improving services.
The NCSI has established work streams in 7 areas of survivorship; i) Assessment, care planning and immediate post treatment approaches to care. ii) Managing active, progressive and recurrent disease, iii) Late effects of treatment, iv) Survivors of childhood cancers, v) Work and finance, vi) Self management and vii) Research. 17 test communities have been identified by the NCSI for the adult survivorship pathways and 10 for children and young people.
Undoubtedly there will be implications for nursing as these survivorship initiatives offer a new way of working. There are not only clinical or medical needs to be met, but psychosocial as well, highlighting the importance of effective communication skills. Nurses will be faced with new challenges and opportunities to demonstrate their clinical and interpersonal skills.
The burden of survivorship has enforced recognition of this new cohort of patients and government initiatives are in place to enhance the quality of care available to them.

S30

Psychological impact of chronic illness for children and families

S Rust
Manchester, UK.

Abstract unavailable.

Oral Communications

Oral Communications 1

OC1.1 Best Abstract Winner

Longitudinal FT_4 levels in the first 4 weeks of life are an independent factor affecting brain growth in extreme preterm babies born <28 weeks' gestation

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Background
Low thyroid hormone concentrations in the first few weeks of life in preterm infants may be linked with poor neurodevelopment. We conducted a multi-centred randomised controlled trial of thyroxine (T_4) supplementation in babies born under 28-weeks' gestation (TIPIT study). A post hoc subgroup analysis was undertaken to examine brain growth and development.
Methods
Seventy-eight infants received T_4 supplementation and 75 received placebo. There was no difference in outcome between these groups. Longitudinal free T_4 (FT_4) plasma levels were measured weekly during the initial 4 weeks after birth. Comparisons were made between the 2 subgroups with FT_4 values in the lowest and highest quartiles. A multivariate analysis of independent factors affecting width of subarachnoid space as a measure of brain volume at 36 weeks CGA was undertaken. In addition, 38 babies had MRI brain scans at term equivalent using diffusion tensor imaging (DTI). DTI enables quantitative assessment of white matter development, before myelination is visible on conventional MRI, by measurement of apparent diffusion coefficient (ADC).
Results
Among placebo infants, the lowest quartile of FT_4 was associated with lower gestational age, lower birth weight and larger subarachnoid space ($P=0.04$) at 36 weeks CGA. These infants also had a higher mortality compared with those infants in the highest quartile ($P=0.01$). These associations were not seen in infants given supplemental T_4. Among scanned infants ADC values in posterior corpus callosum and posterior limb of the internal capsule were lower among babies in the highest quartile of FT_4.
Conclusion
Our findings suggest that longitudinal FT_4 levels in the first 4 weeks of life are an independent factor affecting brain growth at 36 weeks CGA. A lower ADC suggests myelination was more advanced in the highest quartile of FT_4 compared to the lowest quartile.

OC1.2

Growth Hormone Deficiency in children is associated with selective cognitive deficits

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Aims
Recent evidence suggests that Growth Hormone Deficiency (GHD) may be associated with cognitive impairment in adults. These findings are supported by neurobiological studies documenting the presence of GH receptors in many regions of the brain, including the hippocampus and the prefrontal cortex. However to date no comprehensive investigation of the cognitive sequelae of growth hormone deficiency in children has been undertaken. We aimed to determine the effect of GHD on standardized measures of memory, executive function, IQ, motor abilities, language, behaviour and communication.
Method
Sixteen children (aged 9 ± 1.6 years) with isolated growth hormone defiency (peak GH level <6.7 μg/l on provocation with a low IGF1) and fourteen short stature [normal peak GH in response to stimulation (>10 μg/l), normal IGF1 measurements and normal growth rate] controls (aged 8.6 ± 1.3 yrs) underwent a comprehensive neuropsychological assessment.
Results
We observed significantly worse performance in GHD patients compared to short stature controls on the Verbal Comprehension Index of the Wechsler Intelligence Scales for Children-IV (WISC-IV, $P<0.05$), Pattern Recognition Memory ($P<0.05$) and the Movement-ABC ($P<0.05$) tasks. These findings remained significant after controlling for socioeconomic status (all P values <0.05) and the presence of autistic features (all P values <0.05) in covariate analyses. No significant group differences were found on the language, behaviour and communication measures (all P values >0.05).
Discussion
These preliminary findings show subtle deficits in measures of verbal intelligence, visual memory and neuromotor function in children with GHD compared to a control group, and suggest a role for GH in specific neurocognitive functions.

OC1.3

Semen cryopreservation in adolescent minors with cancer: a 10-year experience

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Background
Increased childhood cancer survival has resulted in an accruing adult cohort faced with potential infertility. Pre-treatment semen cryopreservation can protect reproductive capacity in adolescent minors, but continued unique legal, ethical and educational barriers prevent consistent service provision across the UK. The effect of pubertal maturation, disease and treatment on the ability to produce sperm also remains poorly defined in this cohort. We present our 10-year experience of providing such a service in a tertiary teenage oncology unit.
Aims
To ascertain the relationship between age, Tanner pubertal stage, endocrine biochemistry and gonadotoxicity risk with offer, uptake and success rates of semen cryopreservation in underaged males with cancer.
Methods
Retrospective audit of case notes and reproductive laboratory data of 204 males aged 12–18 years (median 15.0) with new or relapsed malignancy in our unit in three consecutive cycles (January 1999 to September 2009).
Results
Semen cryopreservation was offered to 152/204 (75%) patients, particularly those who were older (Audit 1, $P=0.002$; Audit 2, $P=0.069$; Audit 3, $P=0.000$) and more pubertally mature (Audit 3, $P=0.015$). Pubertal staging was poorly assessed across all audit cycles compared to baseline endocrine biochemistry despite repeated recommendations (59/204, 29% vs. 145/204, 71%; $P=$NS between cycles). Of those offered, 71% attempted to store semen, with 51% of these producing viable samples. Advanced pubertal stage (Tanner 3+) was the only significant determinant of success ($P=0.03$), but not age, gonadotoxicity risk or plasma testosterone concentration. Correlational analysis further revealed no association between plasma LH/FSH/testosterone concentrations with sperm count or semen volume.
Implications
Semen cryopreservation is a viable fertility preservation option for adolescent cancer patients, and should be offered to all before treatment, acknowledging the caveat of a ~50% chance of success. Pubertal staging is the only significant prognosticator of this and should be routinely assessed as part of the counselling process.

OC1.4

The Growth Hormone Receptor Exon 3 Deleted Polymorphism is Associated with Birth and Placental Weight

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In humans Growth Hormone Receptor (GHR) transcripts exist in two isoforms, the full-length (*GHRfl*) or exon 3 deletion isoform (*GHRd3*). Individuals with the *GHRd3* isoform are associated with an increased response to recombinant human GH. The *d3/fl-GHR* polymorphism does not influence adult height. However, an association with the *d3/fl-GHR* polymorphism has been found with antenatal growth especially in small for gestational age (SGA) infants. Here we

demonstrate that the *d3/fl-GHR* polymorphism influences both birth and placental weight in white Caucasians ($n=1048$) derived from the University College London Hospital Fetal Growth Study (UCL-FGS) and Moore-Well-being of Women Baby-Bio-Bank cohort.
Study Methods
Uncomplicated singleton white Caucasian pregnancies were recruited by the UCL-FGS ($n=1650$) and the Baby Bio Bank cohort ($n=310$). Genomic DNA was available for analysis from 774 infants from the UCL-FGS and 274 from the Baby Bio Bank cohort. The two isoforms GHR transcript variants were analysed using multiplex PCR.
Results
The frequency of *d3/fl-GHR* polymorphism was similar to previous reports and within the Hardy-Weinberg equilibrium. There were no demographic differences in birth weight and placental weight between the genotyped group and the total cohort mean. There was a significant underrepresentation of wild type *fl/fl* (29%) and overrepresentation of *d3/d3* (14%) genotype in the SGA infants within the cohort (Chi square 17.7, $P<0.001$). *Fl/fl* was overrepresented in LGA infants (Chi square 5.79, $P=0.05$). ANOVA with *post hoc* test demonstrated a significant association of GHR isoforms with placental weight ($P<0.001$) and birth weight SDS ($P=0.04$) with the *d3/d3* genotype associated with a smaller size. In stepwise regression analysis the *d3/fl-GHR* genotype, booking weight and parity influenced placental weight ($R=0.35$; $P<0.001$). This genotype was not related with antenatal anthropometric measurements, cord concentration of growth hormone or insulin like growth factor 1 & 2 or postnatal size.
Conclusion
These data suggest that the *d3/fl-GHR* genotype is associated with placental weight and birth weight.

OC1.5

Factors affecting changes in insulin sensitivity and insulin secretion during Growth Hormone treatment in children born small for gestational age

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Background
Individuals born Small for Gestational age (SGA) are at high risk of development of type 2 diabetes. Growth hormone (GH) therapy can also adversely affect glucose metabolism.
Aim
To explore the factors associated with changes in insulin sensitivity (IS) and insulin secretion during one year of GH treatment in children born SGA.
Methods
In the NESGAS clinical trial, we studied 82 (55♂) pre-pubertal children (age 3.9–9.9 years) born SGA who had failed to catch-up. Subjects underwent a short intravenous glucose tolerance test to measure acute insulin response (AIR), a marker of insulin secretion. HOMA was used to calculate IS and the disposition index gave an estimate of insulin secretion for the degree of IS. The measurements were repeated after 12 months of GH treatment (67 μg/kg/day).
Results
Following GH treatment, IS markedly decreased (209 ± 117 vs 118 ± 54 $P<0.001$). However, a compensatory rise in AIR (1455 ± 813 vs 2431 ± 1514, $P<0.001$) resulted in similar disposition index (3.07 ± 1.69 vs 2.82 ± 1.33, $P=0.29$). Fall in insulin sensitivity was related to increases in both IGF-I levels ($r=-0.31$, $P=0.013$) and height ($r=-0.28$, $P=0.03$). Rise in IGF-I levels predicted increases in AIR independent of height gains and changes in IS (($\beta=0.05$ (CI: 0.01–0.09)). Furthermore, increases in the IGFI levels, not the height gains predicted AIR at one year of GH treatment, independent of IS ($\beta=0.04$ (0.02–0.07)). Birth weight, gender, age, and IGF-I levels and height before GH treatment were not related to changes in insulin sensitivity and insulin secretion.
Conclusion
We found that while markers of GH action were related to fall in IS during GH therapy, increases in IGFI levels were associated with improvement in insulin secretion. IGFI is a determinant of beta- cell function in animal models. Our findings suggest a role of IGFI response to GH, in modifying beta- cell function and glucose metabolism.

OC1.6

Altered Metabolomic Profile in Children Born Small for Gestational Age without Post-Natal Catch-up Growth

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Background
Approximately 1000 children per annum born small for gestational age (SGA) will fail to catch-up and become eligible for GH treatment. The reason for this failed growth is often not defined. Understanding mechanisms that cause growth failure in SGA and finding potential biomarkers of poor growth is therefore important. We are using the new technique of Metabolomics as one avenue to address this. Metabolomics is the quantification of small molecule metabolites in a living system, including metabolic intermediates and signalling molecules.
Aim
To compare the metabolome in fibroblast cell lines derived from SGA without catch up growth versus normal controls.
Method: Skin biopsies were obtained from four SGA children without post-natal catch up growth and aged matched controls, and fibroblast cell lines were generated. Cells were incubated with media, which was removed after 24 h for analysis (***metabolomic footprint***). Cells were then lysed by three freeze thaw cycles (generating a ***metabolomic fingerprint***) and both sets of samples were analysed by gas chromatography mass spectroscopy.
Results
Twenty-one metabolites in the footprint and 18 in the fingerprint were significantly different between SGA and control samples. These included increased levels of amino acids such as alanine ($P<0.05$), lysine ($P<0.001$) and glutamine ($P<0.05$) in the fingerprint and secondary signalling molecules involved in the PI-3 kinase pathway were down regulated, including myoinsitol ($P<0.001$) and inositol-1-phosphate ($P<0.05$) in the footprint.
Conclusion
Samples from SGA children without post-natal catch up growth have a significantly different metabolomic profile to controls. This translates to alterations in energy producing pathways, an up-regulation of the urea cycle and potential aberrations in cell signalling. These studies are being extended into metabolomic profiling in both plasma and urine in SGA children with and without catch-up growth, in order to identify whether one or more of these metabolites may be a useful biomarker.

OC1.7 Best Abstract Winner

Enhancement of the canonical Wnt pathway in Rathke's pouch results in pituitary tumours reminiscent of human adamantinomatous craniopharyngioma

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Wnt/beta-catenin signalling pathway is required during embryonic development for normal cell proliferation, differentiation and for organ homeostasis in adulthood. Over-activation of this pathway has been implicated in human cancers such as colon or skin cancers. Here, we demonstrate that enhancement of the Wnt pathway in the embryonic Rathke's pouch causes over-proliferation of progenitor cells and severe differentiation defects in the *Pit1*-lineage, which results in extreme growth retardation and hypopituitarism. Mutant mice mostly die perinatally but those that survive weaning develop lethal pituitary tumors. Histopathological analysis revealed that these murine tumors most closely resemble human adamantinomatous craniopharyngioma rather than any other pituitary tumor, including pituitary adenomas, Rathke's cleft cysts, xanthogranulomas, posterior pituitary tumors (e.g. pituitocytomas) or even the adult (papillary) form of craniopharyngioma. This tumorogenic effect only occurs when Wnt pathway over-activation occurs in the early Rathke's pouch progenitors, but not when committed or differentiated cells are targeted. Together, our findings provide new insights into the roles of the Wnt pathway in the control of pituitary cell proliferation and demonstrate, for the first time, a causative role the Wnt pathway in an undifferentiated multipotent pituitary progenitor in the genesis of murine pituitary tumors that are reminiscent of human craniopharyngioma

OC1.8

Clinical and Molecular Characterisation of 300 patients with Congenital Hyperinsulinism

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Background
Congenital hyperinsulinism (CHI) is a clinically heterogeneous condition. Mutations in seven genes (*ABCC8, KCNJ11, GLUD1, GCK, HADH*, *SLC16A1* and *HNF4A*) are known to cause CHI.
Aim
To characterise the clinical and molecular aspects of a large cohort of patients with CHI.
Methodology
300 patients with biochemically confirmed CHI were recruited. Detailed clinical information was collected prior to genotyping. *ABCC8* and *KCNJ11* genes were sequenced in all patients with diazoxide unresponsive CHI. Mutations in the *GCK*, *GLUD1* and *HADH* genes were sought in patients with diazoxide responsive CHI with hyperammonaemia (*GLUD1*), raised 3-hydroxybutyryl-carnitine (*HADH*) or positive family history with delayed presentation (*GCK*). If no mutations were identified and in all other patients with diazoxide responsive CHI; *ABCC8*, *KCNJ11* and *HNF4A* genes were sequenced.
Results
Mutations were identified in 146/300 patients (48.6%). Mutations in *ABCC8/KCNJ11* were the commonest genetic cause identified ($n=117$, 39%). Among diazoxide unresponsive patients ($n=105$), mutations in *ABCC8/KCNJ11* were identified in 92(87.6%); of whom 63 patients had recessively inherited mutations while four patients had novel dominantly inherited mutations. A paternal mutation in the *ABCC8/KCNJ11* genes was identified in 23 diazoxide unresponsive patients; of whom 7 had diffuse disease. Among the diazoxide responsive patients ($n=183$), mutations were identified in 51 patients. These include mutations in the *ABCC8* ($n=25$), *KCNJ11* ($n=3$), *HNF4A* ($n=7$), *GLUD1* ($n=16$) and *HADH* ($n=3$).
Conclusions
A genetic diagnosis was possible in 48.6% of patients in this large series. Mutations in the *ABCC8* gene were the commonest identifiable cause. The vast majority of patients with diazoxide responsive CHI (72%) had no mutations identified. Understanding the genetic aetiology of CHI in this large cohort of patients will provide novel insights into pancreatic beta-cell physiology and have implications for hypoglycaemia and diabetes mellitus.

Oral Communications 2

OC2.1

Space-time clustering of elevated TSH levels on newborn screening

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Introduction
Studies have reported a rising incidence of congenital hypothyroidism (CHT) although the pathophysiology of most cases is unknown. A rising incidence is not simply a reflection of changing assay methodology and environmental factors may have an aetiological role. If so, then cases may exhibit space-time clustering, where cases occur at similar times and close proximities to other cases.
Methods
We investigated whether there is evidence of space-time clustering of elevated thyroid stimulating hormone (TSH) in newborns. Around 35,000 infants are screened every year in this single centre by measuring blood spot TSH levels. The study region represents a mixture of heavily populated areas and widespread rural communities and has a population of 3.1 million. Data on cases, including dates of birth and postal (zip) code, were available from 1st January 1994 and 31st March 2006. The data were analysed using space-time clustering statistical methods (geographical distance and nearest neighbour/NN approaches).
Results
Data on 207 cases of elevated TSH values, a proxy for CHT and the most robust single marker of abnormal gland development or function, were available from 1994 to 2006 inclusive. We established that more than 93% of infants had raised serum TSH values (>5 mU/l). Analysis showed statistically significant evidence of space-time clustering ($P=0.005$ and $P=0.02$, using geographical distance and NN threshold approaches respectively). Clustering was most marked for cases born within 0.1 – 0.5 year (1–6 months) of one another.
Conclusions
This is the first study to find significant space-time clustering of cases of elevated TSH levels in newborns, a surrogate for space-time clustering of CHT. Whilst the reasons for the clustering are unclear, it would appear from this analysis that environmental exposures are likely to be involved, although environmental determinants of genetic mutations and epigenetic factors cannot be ruled out.

OC2.2

An unbalanced maternal diet in pregnancy is associated with epigenetic effects in the offspring

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Epigenetic dysregulation may be one mechanism underpinning the link between early life conditions and later cardiometabolic risk. In animal models, environmental manipulations including modified maternal diet change DNA methylation and offspring phenotype. Manipulations altering the epigenetic state reverse the phenotype suggesting causality. We have previously reported higher blood pressure (BP) and cortisol in an adult cohort whose mothers were advised to eat a high-protein, low-carbohydrate diet during pregnancy. Here we investigated the hypothesis that this unbalanced maternal diet alters DNA methylation at genes important in growth (insulin-like growth factor, IGF2) and glucocorticoid signalling (glucocorticoid receptor, GR; 11β hydroxysteroid dehydrogenase type 2, HSD2).
Height, weight, waist circumference and BP were measured in 34 individuals (mean age 40y) for whom maternal diet and birth parameters were known. DNA was extracted from peripheral blood mononuclear cells and pyrosequencing used to measure DNA methylation at the differentially methylated regions of IGF2 and the promoters of GR and HSD2.
In univariate analyses, there was an inverse relationship between birth length and IGF2 methylation and a positive correlation between HSD2 methylation and birthweight. These findings remained significant in regression analyses. Methylation at IGF2 and HSD2 were also significantly positively associated with adult anthropometry including weight, waist circumference, BMI and BP. In exploratory analyses of maternal diet, methylation at GR and HSD2 was significantly higher in those whose mothers followed specific dietary advice to increase protein and reduce carbohydrateintake.
Thus, methylation at key genes regulating fetal growth, BP and glucocorticoid signalling is associated with early life parameters and adult cardiometabolic risk factors. Additionally, maternal diet impacts on DNA methylation at genes involved in BP and HPA axis regulation. These results suggest epigenetic modifications play an important role in the early life programming of adult disease risk and that this may be estimated in accessible leucocyte DNA.

OC2.3

The phenotype of late-presenting congenital hyperinsulinism

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Background
Children with hypoglycaemia due to Congenital Hyperinsulinism (CHI) usually present in the neonatal period but late presentations also occur. The phenotype of late-presenting CHI has not been well described.
Aim and methods
We have reviewed the clinical course of children ($n=22$) presenting with CHI after 1 month of age in relation to mode of presentation, rapid K_{ATP} genetic mutation analysis, neurodevelopment, clinical progress and treatment at last follow-up.
Results
In this cohort of 22 children (14 males), the median (range) age at presentation was 0.7 (0.3 – 8.1) years with serum insulin levels of 22.0 (2.7 – 56.0) mU/l at the

time of hypoglycaemia. Weight at presentation was variable at 0.8 (−2.8 – +4.0) SDS; 7 children (31%) had developmental delay and 15 (77%) had seizures. Age at presentation was significantly later in those with developmental delay than in those with normal development [1.7 (0.6 – 8.1) v 0.6 (0.3 – 1.1) years, $P=0.002$]. Neonatal transient hypoglycaemia was present in 2 children. Five children (23%) had K_{ATP} mutations (4 *ABCC8*, 1 *KCNJ11*); 3 children had mutations in other genes (*GLUD1*, *GCK* and *MEN1*) and in 14 children (64%), no mutations were identified. All children received Diazoxide to treat hypoglycaemia; 12 (54%) were responsive to Diazoxide, of whom 3 underwent spontaneous remission. Seven children, who had either paternal heterozygous K_{ATP} mutations or no mutations, underwent 18-fluorodopa PET-CT scanning; of them, 6 children (85%) had focal lesions, all of whom underwent pancreatic surgery. On histology, 2 children had insulinomas, one with an *MEN1* mutation and the other with a heterozygous *ABCC8* mutation.

Conclusions

Children with late-presenting CHI often have developmental delay and seizures at presentation. A significant proportion of them have surgically resectable focal lesions, either focal CHI or insulinomas. It is important to recognize that CHI may present with hypoglycaemia in mid-childhood.

OC2.4

Morbidity and Mortality of Infants with Salt Wasting Congenital Adrenal Hyperplasia in an Unscreened Population

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Due to the non-specificity of symptoms in male neonates affected by salt-wasting (SW) CAH, it is hypothesised that a proportion die prior to diagnosis in countries lacking a newborn screening (NBS) programme, such as the UK. The aim of this study was to analyse 17-hydroxyprogesterone (17-OHP) in stored NBS blood spot samples, to detect undiagnosed cases of CAH. Samples were retrieved from storage for neonates who were born between 1994 and 2006, who subsequently died before 7 months of age. They were analysed, following anonymisation, for 17-OHP using the AutoDELFIA®. The control group comprised patients with SW-CAH, attending clinic, who gave consent for analysis of their stored NBS sample ($n=37$, 18 males, 19 females).

Using data provided by the Office for National Statistics, 1798 babies met the study group criteria. Of these, 1198 samples (67%) were retrieved and analysed following identification on NBS databases. Grouped according to gestational age and corrected for storage time, the mean and maximum bloodspot 17-OHP was as follows. Deceased full-term $n=279$, mean = 6 nmol/L, max = 107 nmol/L; deceased pre-term $n=365$, mean = 28 nmol/L, max = 251 nmol/L; deceased unknown gestational age $n=553$, mean = 13 nmol/L, max = > 394 nmol/L.

In the control group, there was evidence of hyponatraemia at presentation in all 18 males but only 16% of females. Of 18 NBS samples taken prior to commencing hydrocortisone (2 females, 16 males), the lowest level of 17-OHP was 179 nmol/L and 14 had levels greater than the highest standard (> 268 to > 420 nmol/L). Mutation analysis (8 common mutations) was performed for all samples from the deceased group with 17-OHP results > 179 nmol/L ($n=6$, 3 males, 3 females) and no mutations were identified.

Therefore, despite evidence of increased morbidity (hyponatraemia) in affected males, we found no increase in mortality. In conclusion, this research does not support the hypothesis that, in our unscreened population, males affected by SW-CAH are dying prior to diagnosis.

OC2.5

Correlation of clinical and functional data to predict pubertal outcome in PAIS

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Introduction:

Advances in MDT working in Disorders of Sexual Development (DSD) are supported by activities which call for national and international collaborations. In the EuroDSD programme we are collecting clinical data and performing functional studies to assess the pubertal outcome of PAIS patients raised male.

Methods

Clinical information including birth phenotype, surgery, medication and pubertal outcome, from 16 post pubertal PAIS patients with known AR mutation have been collected from the UK. AR mutants were recreated and function defined by; promoter transactivation, ligand binding and N/C terminal interaction assays. Mutants R840C/H and L712F were chosen for further analysis on the basis of the functional data, poor genotype to phenotype correlation and their location at receptor surface BF3 or AF2, respectively.

Results

Clinical data suggest that EMS (external masculinisation score) at birth > 5 predicts better pubertal outcome. All of the mutations tested displayed some functional defect in at least one of the in vitro assays. Differences were observed in different cell systems, reflecting the difficulty in finding an in vitro model which reflects pubertal progression status.

Conclusion

We propose that predictions of pubertal outcome in PAIS with a known mutation can be guided by EMS at birth. More PAIS patients with the same mutation as our current cohort are needed from the UK and beyond to collect data on variability in pubertal outcome and the range of androgen doses required to complete puberty. More patients with different AR mutations are also required in order to establish correlations between functional and clinical data. The Euro DSD database which is the basis of current and future collaborative ventures currently holds 645 entries of anonymised data from 12 different countries. We gratefully acknowledge the support of BSPED members which has enabled us to contribute 179 sets of data to this valuable resource.

OC2.6

Novel *TSHR* mutations in a large cohort of consanguineous families with congenital non-goitrous hypothyroidism

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Introduction

Non-syndromic autosomal recessively inherited non-goitrous congenital hypothyroidism (CHNG) can be caused by mutations in *TSHR*, *PAX8, TSHB,* and *NKX2-5.* We aimed to investigate mutational frequencies of these genes and genotype/phenotype correlations in consanguineous families with CHNG.

Design

Since consanguinity in individuals with a presumptive genetic condition is often an indicator of an autosomal recessive inheritance and allows firmer correlations to be established between genotype and phenotype, we planned to execute our study in consanguineous families.

Methods

One hundred and thirty-nine children with CHNG phenotype born to consanguineous families were first investigated for evidence of linkage to the four known-CHNG genes by microsatellite marker analysis. Mutation analysis by direct sequencing was then performed in those cases in whom linkage to the relevant candidate gene could not be excluded. In addition *in silico* analysis of the predicted structural effects of *TSHR* mutations was performed and related to the mutation specific disease phenotype.

Results

Homozygous germline *TSHR* mutations were detected in 6 families (5%), but no mutations were detected in *PAX8, TSHB,* and *NKX2-5*. Four of *TSHR* mutations had not previously been described. Genotype-phenotype correlations were established and found to be related to the predicted structural effects of the mutations.

Conclusions

Known-causative genes account for the development of CHNG only in a minority of cases and our cohort should provide a powerful resource to identify novel causative genes and to delineate the extent of locus heterogeneity in autosomal recessively inherited CHNG.

OC2.7

Wide range of eye abnormalities in patients with hypopituitarism: is this showing a novel genetic aetiology?

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Background and Aim
The development of the pituitary gland is closely linked to this of the eyes and forebrain, as they all originate from the same embryonic origin, the anterior neural ridge. The constellation of symptoms leading to septo-optic dysplasia (SOD) is well established; other ophthalmic signs may be under-reported. The aim of the study was to define if patients with hypopituitarism present with eye abnormalities, which are distinct from optic nerve hypoplasia (ONH), and if this association could help the genetic diagnosis of the condition.
Methods
We studied case records of patients referred over the last ten years from national and international centres.
Results
We identified 96 patients with hypopituitarism (male:female1.2:1), who had eye abnormalities that were distinct from ONH. Hypopituitarism was familial in 14.5% ($n=14$) and in 5.2%, patients were of consanguineous pedigrees. The spectrum of eye abnormalities included: colobomas not associated with CHARGE syndrome ($n=11$, 1.5%), pigmented disorders of the retina ($n=4$, 4.2%), retinal dysplasia ($n=13$, 13.5%), congenital cataracts, ($n=3$, 3.5%), amaurosis ($n=3$, 3.5%), anophthalmia or microphthalmia ($n=32$, 33.3%). Other eye abnormalities ($n=30$, 31.2%), ranged from glaucoma to blepharophimosis, staphylomas and atypical appearance of the optic discs. In four cases with retinal pigment defects or retinal dysplasia there was a single pituitary hormone deficiency, isolated GHD ($n=2$) or ACTHD ($n=2$). In all other cases, retinal abnormalities were associated with multiple pituitary hormone deficiencies. SOX2 mutations were identified in 40% (13/32) of patients with anophthalmia or microphthalmia and they all had gonadotrophin deficiency. In two patients we identified mutations in *OTX2* and *BMP4*. We found no mutations in *HESX1, PROP1, GH1, SIX3, PAX6* or *SOX3* in this cohort.
Conclusions
Patients with hypopituitarism may present with variable eye abnormalities and monitoring for pituitary hormone deficiencies is recommended in children with congenital eye abnormalities.The systematic study of the association of eye and pituitary abnormalities may help to identify novel genes implicated in pituitary development.

OC2.8

Radio-iodine therapy for autoimmune hyperthyroidism. A two centre, retrospective evaluation of practice and outcomes

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Radio-iodine (I^{131}) (RI) is regarded as an effective therapy for patients with autoimmune hyperthyroidism (AH). Treatment protocols and outcomes are well defined in adult endocrinology practice but not for children and adolescents where RI is now considered a safe therapy option after relapse following anti-thyroid drugs (ATD). We retrospectively evaluated the use of RI in 36 patients (6M) with AH from 2 regional units located in the North and East of England. Data on indications for RI, age and timing of referral and outcome of therapy were collected. Remission defined as euthyroid / hypothyroid status and independence from ATD. Results: Mean (range) age AH diagnosis was 11.5y (3–17). Mean interval between diagnosis and RI and age at RI was 41.2 months (1–104) and 14.8y (3.3–19) respectively. Indications for RI therapy: patient choice at diagnosis ($n2$), post ATD relapse ($n16$), ATD side effects ($n13$), or poor concordance with ATD ($n5$). Median (range) RI dose was 400 MBq (113–550). At 6 months post-RI, 21 (4M, 17F) patients achieved remission, 11 (2M, 9F) remained thyrotoxic (4 condition unknown). Six patients received a 2nd dose of RI and 5 restarted ATD therapy for mean 6.8 (4–12) months before remission established. Remission failure 6 months post-RI tended to be associated with lower mean (range) RI dose (333.0 (113–550) vs 381.7 (391–417) MBq), longer course of ATD (34.0 (0.5–90) vs 25.6 (6–78) months), younger age (13.2y (3.3–19) vs 15.3y (10.2–19.2)), high FT4 at diagnosis (91.4 (65–130) vs 49.03 (26–67.6) pmol/L) and large goitre ($n8$).
Conclusion
RI therapy is an effective treatment option for young patients with relapsed AH after ATD. However, remission failure 6 months after RI was frequently observed (33%). Individual optimization of RI dose taking into account thyrotoxic characteristics at presentation and duration of ATD are required to improve AH remission outcomes.

Oral Communications 3

OC3.1

Altered Expression of HCN Channels in Patients with Congenital Hyperinsulinism of Infancy (CHI)

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Hyperpolarisation-activated cyclic nucleotide-gated channels (HCNCs). are selective for Na^+/Ca^{2+} under physiological conditions and are responsible for the rhythmical electrical behaviour of pacemakers in the heart and brain. Their role in human pancreas has not been reported previously. Congenital hyperinsulinism of infancy (CHI) is an inherited disorder of inappropriate insulin secretion often caused by gene defects in the subunits of K_{ATP} channels (*ABCC8, KCNJ11*). We aimed to investigate the expression and function of HCNCs in pancreatic tissue and assess their relationship to CHI. Tissue was isolated from adult control human pancreas and from six patients following pancreatectomy for CHI to examine HCNC gene and protein expression by RT-PCR and immuno-fluorescence, respectively. HCNC expression was also assessed in pancreatic tissue from *ABCC8*-knockout mice. The role of HCNCs in glucose-stimulated insulin secretion (GSIS) from control mouse islets was assessed by ELISA. *HCNC1-4* mRNA was detected in islets isolated from both adult control and CHI patient pancreatic tissue. Co-expression of HCNC isoforms with insulin confirmed that HCNC1, −2 and −4 were β-cell specific in control human and rodent islets. By contrast, in all patient tissues expression of HCNCs was altered, and in 5 out of 6 cases, HCNC was not expressed in β-cells. We found similar data in islets of *ABCC8*-knockout mice, but not their litter-mate controls ($n=3$). The HCNC agonist lamotrigine had no effect on GSIS ($n=3$), but GSIS was significantly inhibited by the HCNC blocker zatebradine ($n=3$) thereby confirming that HCNCs may play a role in glucose homeostasis. These studies provide the first data on expression of HCNCs in the human pancreas and we also found that HCNC expression in β-cells is altered in CHI patients and we speculate that this is as a consequence of physiological remodelling.

OC3.2

***In vitro* recovery of functional K_{ATP} channels in congenital hyperinsulinism of infancy (CHI)**

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Congenital hyperinsulinism (CHI) is characterised by unregulated insulin secretion from pancreatic β-cells. The most severe forms are associated with defects in SUR1 and Kir6.2 (encoded by *ABCC8* and *KCNJ11*), which form K_{ATP} channels in β-cells. Diazoxide therapy often fails in the treatment of CHI and may be due to reduced cell surface expression of K_{ATP} channels. We investigated methods to increase surface expression of K_{ATP} channels using conditions known to increase trafficking in recombinant expression systems. Tissue was isolated during pancreatectomy from 8 patients with CHI and from adult cadaver organ donors with permission. Isolated cells were maintained at 37°C or 25°C in the presence or absence of [1] PMA, forskolin and IBMX; [2] 4-phenylbutyrate; or [3] BPDZ154. Surface expression of functional K_{ATP} channels was assessed by patch-clamp electrophysiology. RT-PCR on RNA from CHI β-cells and mutation screening of DNA were used document the expression of K_{ATP} channel genes. In 5/8 patients, all of whom had *ABCC8* mutations, no changes in K_{ATP} channel

activity were observed under different cell culture conditions. However, in 3 patients, *in vitro* recovery of functional K_{ATP} channels occurred. Patient #1 demonstrated recovery of K_{ATP} channel function *in vitro* following incubation of cells at 25°C with/without 4-phenylbutyrate. K_{ATP} channels were recovered in Patient #2 β-cells following incubation with PMA, forskolin and IBMX, or BPDZ154. Patient #3 β-cells demonstrated K_{ATP} channel recovery following incubation with BPDZ154. All 3 patients had mutations in *ABCC8* detected by DNA screening or by RT-PCR on pancreatic RNA. This study demonstrates that modified cell culture conditions enhance cell surface expression of K_{ATP} channels in CHI β-cells and suggests that chemical modification of SUR1 by agents such as 4-phenylbutyrate may have some clinical benefit in the future treatment of CHI.

OC3.3

Are there practical alternatives to the inpatient mixed meal tolerance test for patients with Type 1 diabetes?

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Introduction
Stimulated serum C-peptide (sCP) during a mixed meal tolerance test (MMTT) is the gold standard measure of endogenous insulin secretion in Type 1 diabetes (T1D). However invasiveness of sampling, the need to discontinue insulin prior to testing and rapid processing of samples limits its widespread use, particularly in children. Practical alternatives would increase utility.
Aims
To assess if in a MMTT: 1.It is necessary to omit insulin. 2. Fasting C-peptide can replace stimulated C-peptide measurement. 3. Urinary C-peptide is an alternative to serum C-peptide.
Methods
We studied 51 T1D patients (age diagnosis median (IQR)18(13–24y), diabetes duration (0.2–65.9y). We performed a standard MMTT without insulin and a MMTT with the subject's normal morning insulin. We measured sCP at 0min and 90min, and urine C-peptide creatinine ratio (UCPCR) at 0 min (second morning void) and 120min, following a liquid mixed meal (Ensure High Protein).
Results
(1) 90minute sCP values were only slightly lower in the MMTT with insulin compared to the standard MMTT without insulin (mean sCP 0.28 v 0.35 nmol/l $P=0.01$) despite a much lower glucose increment (4.1 v 9.8 mmol/l, $P<0.0001$). 90min sCP was highly correlated between the two tests ($r=0.97$, 95%CI 0.95, 0.98). (2) Fasting sCP was well correlated with 90min sCP ($r=0.89$, 95% CI 0.81, 0.94). (3) Second void fasting UCPCR and 120min UCPCR were both well correlated with 90min sCP (fasting UCPCR: $r=0.83$, 95% CI 0.72, 0.90; 120min UCPCR: $r=0.87$, 95% CI: 0.78, 0.92).
Conclusion
Omitting insulin during a mixed meal tolerance test may not be necessary. Measurement of fasting serum C-peptide and fasting or meal stimulated urinary C-peptide are other practical alternatives that may be useful in routine practice, avoiding the need for inpatient investigation.

Oral Communications 4

OC4.1

Cyclical variation in the incidence of type 1 diabetes in children from northeast England

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Background
Environmental factors play a role in the aetiology of type 1 diabetes. A particular role for infectious exposures has been postulated. Temporal variation in incidence would be consistent with this hypothesis. We specifically aimed to test predictions of increasing incidence occurring among cases of type 1 diabetes in children (aged 0–14 years) that might arise as a result of an environmental mechanism.
Subjects and methods
The study analysed 526 cases of type 1 diabetes diagnosed in children who were resident in a geographically defined region of northeast England during the period 1990–2007. Age-specific and age-standardised incidence rates were calculated. Temporal trends and patterns were analysed using Poisson regression.
Results
Age-standardised incidence rates increased from 14.6 per 100 000 persons per year in 1900–1995 to 27.4 per 100 000 persons per year in 2002–2007: an overall increase of 5.3% per annum (95% confidence interval [CI] 3.4–7.1). Furthermore, there was a regular six-year cyclical pattern of plus or minus 25% in incidence rates (rate ratio $=1.25$; 95% CI 1.11–1.42).
Conclusions
The results are consistent with the involvement of one or more environmental exposures in aetiology. A possible role for a specific infectious agent should be considered.

OC4.2

Medium term impact of continuous subcutaneous insulin infusion (CSII) on HbA1c levels: A regional meta-analysis of 185 patients

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Background
The use of CSII in children with T1DM is increasing. Several meta-analyses have concluded that there is an improvement in glycaemic control with CSII but most of these investigations have included adults and have been of short duration (<6 months). Our aim was to assess the medium term impact of CSII on HbA1c levels in patients managed with CSII in one region of The UK.
Methods
Data was collected retrospectively from 7 centres within North-East England. These centres manage the majority of young people on CSII (>95%) in the locality. Only patients under the age of 18 who had been on insulin injections for 1 year prior and at least 1 year of CSII therapy were included. HbA1c data pre and post CSII initiation was collected and then analysed using meta-analysis software (Review Manager 5.0) and Minitab v15.0. Results are expressed as mean differences, calculated from end of treatment values, with 95% confidence intervals (CI) for continuous outcomes. Pooled results were meta-analysed using the generic inverse variance method with a fixed-effects model. Statistical significance was set at a P value ≤ 0.05.
Results
Data from 185 patients was included in the meta-analysis. There was a significant improvement in HbA1c favouring CSII therapy at 4 months post CSII initiation ($P=0.05$, weighted mean difference -0.23; 95% confidence intervals -0.47, 0.00) but this trend was not sustained at 1 year ($P=0.88$, weighted mean difference -0.02; 95% confidence intervals -0.30, 0.26) or 2 years ($P=0.27$, weighted mean difference 0.19; 95% confidence intervals -0.14, 0.51).
Conclusions
The impact of CSII in isolation is remarkably similar to many other initiatives involving new insulin regimens in T1DM with a short term improvement in HbA1c that wanes in the longer term.

OC4.3

Maintaining optimum glycaemic control in children with diabetes during Day Case Endoscopy

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Screening for coeliac disease is routine at annual review in the Oxfordshire Children's Diabetes Service and oro-gastro-duodenoscopy (OGD) is carried out following positive serology. Our protocol for Diabetes management during Day Case Endoscopy for confirming CD was revised in 2002 following audit. We re-audited our current practice to check adherence to the protocol and degree of blood glucose control.
Data was collected from case notes, nursing notes and drug charts for 16 children (10 girls),mean age 10.83(4.4 – 18y), who had OGD between June 2007 and July

2009. 9/16 were on multiple injections, 3 on thrice daily and 4 on twice daily regimens. All children had their usual insulin dose the night before and their last meal 6 hours before OGD. 2 had squash till 2 hours before the procedure. 8/16 followed the morning insulin protocol, 7 did not, and one had insufficient information.The protocol dictates commencing intravenous fluids with Dextrose saline on admission; all but one did so. A sliding scale of intravenous insulin should start, but 4 did not. Mean blood glucose(BG) was 14.4(3.2–19.4) mmol/L initially, 6.6(4–18) at OGD and 10.8(4.9–18.6) at discharge 3 hours after completion of the procedure.Mean BG was 11.05(8.4–12.5) for people adhering to the protocol and 8.74 (5.3–15.2) for those who did not.14/16 had BG above 12 mmol/l of whom 7 followed protocol. 4/16 had BG less than 4.0 mmol/l of whom 3 followed the protocol.

The previous protocol failed to achieve good glucose control. Hypoglycemia was commoner in children who strictly adhered to the guidelines in all respects, prompting more use of intravenous glucose and distress to patients and parents. We have since simplified our hospital protocol to one which is less interventional and achieved better control in the few who had OGD on the new protocol.

OC4.4

Support for insulin injections in schools – a survey

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Introduction

One in 700 children of school age have diabetes. Children spend on average a quarter of their waking lives in school. It is important that children receive adequate support and supervision in school for the effective management of diabetes.

Aim

To evaluate the support given by the schools for lunch time insulin injections, from the perspective of parents of children with diabetes.

Methods

Questionnaire completed by direct interview of the parents during routine outpatient appointments from September 2009 to July 2010. All children in nurseries and primary schools were included in the study.

Results

Fourty seven children from 32 schools were included in the study. The mean age is 7.4 years and the mean duration of diabetes is 3 years. The mean HbA1c is 8.3%. Only 15% of the schools are willing to learn to administer insulin. 75% of the schools are willing to supervise the injections, if given education and support but not willing to take up the responsibility of administering the injections. 18% of children are able to continue lunch time injections only by parents going into school to give the injections or by children travelling home during lunch time. Overall, 53% of children are not having lunch time injections for various reasons but 16% of these children do not have lunch time injections purely due to lack of support in the school. All 5 preschool children are on basal bolus regime but anticipate problems when starting school.

Conclusions

At least 30% more children will be able to commence or continue lunch time injections if more provision is arranged at school. This could potentially improve glycaemic control, thereby reducing the risk of long term complications. Combined national and local initiatives to achieve this may be the best way forward.

Oral Presentations

OP1.1

Insulin pump therapy in children with type 1 diabetes and its effect on growth and metabolism: 4 years experience

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Background
Pump has become increasingly more popular amongst clinicians in the management of children with type 1 diabetes (T1DM). It improves the metabolic control in most patients though it may have a negative effect on growth. Eighty children with T1DM at our institute are currently treated with continuous subcutaneous insulin infusion (CSII) to achieve optimum glycaemic control.
Aims
To identify the effect of CSII on hospital admissions, hypoglycaemic episodes, HbA1c, BMI and insulin daily requirement.
Methods
The data were collected retrospectively for 55 patients on CSII in the period 2004–2008. The means of pre and post HbA1c were calculated from three values for each, i.e. 1 year pre and 1 year post CSII. The weight, height, BMI scores and the insulin requirement pre CSII were statistically compared to the same parameters 1 year post CSII.
Results
55/325 children with T1DM were commenced on CSII based on NICE criteria. 52.7% ($n=29$) males and 47.3% ($n=26$) females. The mean age of diagnosis was 6.5 (1–15) years and the mean age of starting CSII was 9.8 (1.7–17) years. The CSII was initiated by a trained specialist team in all patients. 38.2% ($n=18$) patients $\geq$12 years were offered CSII because multiple dose injections (MDI) failed to achieve target HbA1c. In 61.8% ($n=37$) patients $<$12 years MDI therapy was considered to be impractical or inappropriate. There was a reduction in HbA1c and hypoglycaemic episodes post CSII but not in hospital admissions. There was a significant reduction in insulin requirement but an increase in BMI SDS post CSII. The CSII was not discontinued in any of our patients because of non sustained improvement in glycaemic control.
Conclusions
CSII has a significant reduction in hypoglycaemic episodes and insulin daily requirement but may worsen the BMI in children with T1DM.

OP1.2

An audit of education and knowledge surrounding social aspects of type 1 diabetes in adolescents

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Background
Adolescence is a time of change and is associated with a deterioration in glycaemic control. Education is an important part of diabetes care and enables patients to understand how to manage their condition. An audit was carried out to assess whether adolescents with type 1 diabetes were being educated about social aspects of diabetes.
Method
Fifteen adolescents between the ages of 13 and 17 were asked to subjectively score their knowledge of nine different social situations and the effect they could have on someone with diabetes. They were also asked to score the quality of information and the importance of each topic.
Standards
Hundred percent of adolescents reporting good knowledge and good quality information (a score of 7 or more out of 10).
Results
Knowledge of food and exercise was best (86.7%). Worst knowledge was surrounding pregnancy and smoking (13.3%). The quality of information provided was highest for food and diet (100%) and lowest for pregnancy (0%).
Conclusion
More needs to be done to increase knowledge of how pregnancy, alcohol, smoking and illegal drugs can affect someone with diabetes. This could be taught through group sessions or during clinic and with support from parents, siblings and close friends.

OP1.3

Intensive insulin therapy in adolescent type 2 diabetes

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Background
Glucolipotoxicity contributes to declining B-cell function and acceleration of type 2 diabetes (T2DM). Intensive insulin therapy has been shown to rapidly reverse glucolipotoxicity and improve B-cell function, particularly if given soon after diagnosis. Recent trials in adults have shown promise, with 50% in remission at 1 year after intensive insulin therapy.
Methods
We report 4 cases of young people with T2DM treated with intravenous insulin for 2 weeks (blood glucose clamped between 4–7 mmol/L using insulin sliding scale). Three were recently diagnosed ($<$6 months) and were insulin and metformin-naïve. One recently diagnosed adolescent was lean (BMI 17.3 kg/m^2), the remainder were obese (BMI 35.2–44.6 kg/m^2).
Results
Remission (defined as normoglycaemia without insulin or metformin treatment) was achieved in all 3 patients with recent onset T2DM. Of these, one obese subject continues to have good diabetes control (A1c 6.5%) without treatment after 9 months follow-up, while a second obese subject required metformin 6 months after treatment (current A1c 6.4% on metformin 1 g/day, 27 months after treatment). The lean subject required metformin within 6 weeks of treatment (current A1c 7.9%, on metformin 1 g and rosiglitazone 4 mg/day). The patient with pre-existing T2DM on insulin achieved remission 2 weeks after treatment and developed difficult to control hypoglycaemic episodes reflective of B-cell dysregulation (3 months off treatment, now on insulin pump, A1c 11.1%).
Conclusions
We report a disappointing experience with intensive insulin therapy in young people with type 2 diabetes. However, prolonged remission and good glycaemic control was achieved in the both obese subjects with recent onset diabetes, suggesting further work is required to identify whether intensive insulin therapy at diagnosis may benefit selected patients.

OP1.4

Differences in metabolic effects of twice daily versus multiple daily insulin injections in children with type 1 diabetes

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Introduction
Two insulin regimes are commonly used in type 1 diabetes (T1D): twice daily (BD) premixed insulin (short and intermediate acting), and multiple daily injections (MDI) of short acting insulin with once daily bolus of long acting insulin. MDI is associated with better glucose control in adults, but the evidence base is weaker for children.
Objectives
We aimed to compare children started on MDI to BD from diagnosis, on HbA1c as a measure of glucose control, and weight gain.
Methods
In our unit newly diagnosed children were started on BD insulin till 2005 when we changed over to MDI. Those on BD were offered a changeover to MDI. We collected data on all children with T1D between 2003 and 2009: HbA1c and body mass index standard deviation score (BMI SDS) at diagnosis of T1D or changing over to MDI and after 12 months.
Results
There were 88 (45f) children started on BD insulin (group 1), 29 (10f) on MDI (group 2), and 36 (20 f) children started on BD then changed to MDI (group 3). Mean HbA1c at baseline and 12 months: Group 1 (11.4%, 9.1% ($P<0.001$)); Group 2 (11.5%, 7.9%, ($P<0.001$)); Group 3 (8.9%, 9.2% ($P=$ns)). The improvement in HbA1c in group 2 versus group 1 at 12 months was 1.1% ($P<0.001$). The results for mean BMI SDS at baseline and 12 months were: Group 1 (0.41, 0.90 ($P<0.001$)); Group 2 (0.28, 0.56 ($P=0.04$)); Group 3 (0.8, 0.8 ($P=$ns)). The difference in BMI SDS at 12 months between groups 1 vs 2 (0.34) was not significant ($P=0.1$).
Conclusion
MDI from diagnosis results in better glycaemic control and a trend to less weight gain at 12 months than BD. Children who start on BD then switch to MDI after 12 months do not show the same benefit.

OP1.5

Lack of 'Hawthorn Effect' in a diabetes pump clinic

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Clinical trials of multiple dose insulin (MDI) or pump therapy (CSII) suggest a short term effect with a waning of effect over time – the 'Hawthorn Effect'. This may relate to interest in the patient during the trial or to lack of reinforcement of the education and training programme. We reviewed our experience in this area where we have used a structured education programme for CSII and MDI over the last 6–8 years and used Quality Control Theory to explore changes in glycosylated haemoglobin (HbA1c) with time in our Diabetes Clinic (293 Children and Young People with Diabetes, <19 years, 129 on CSII therapy).
All clinic mean HbA1c for 2009–2010 was 8.2% with 36.4% attaining a HbA1c below 7.5 and 50.4% under 8.0%. Overall CSII achieved a lower HbA1c compared to MDI in both the paediatric (CSII 7.8%; MDI 8.4%) and adolescent age groups (CSII 8.4%; MDI 8.8%). Over the last 26 quarters Control Theory analysis revealed a stable system in both CSII and MDI groups with an average HbA1c of 7.8% (s.d. 1.0) in the CSII group and 9.0% (s.d. 1.5) in the MDI group. During the time period no value fell outwith the 3 sigma boundary. There was a significant decline in the s.d. of values in the CSII over this time period ($P=0.005$).
These data demonstrate that over a 6 years period both CSII and MDI groups demonstrate a stable system in term of HbA1c. This would imply that the structured education programme coupled with reinforcement maintains diabetes control, appearing to avoid waning of effect over time. The declining s.d. also suggests reduced variability in control in the clinic. Using Quality Control Theory may allow for better definition of the types of intervention that may be of value in the management of children and young people with diabetes.

Brief Communications

BC1.1

Investigation of premature adrenarche reveals a high incidence of congenital adrenal hyperplasia (CAH)

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Background
Premature pubic hair development, with or without manifestations of androgen production, is a common clinical presentation. Premature adrenarche (PA) needs to be differentially diagnosed from congenital adrenal hyperplasia (CAH) and may be associated with early development of puberty.
Aim
To study the characteristics at presentation, endocrine profile and outcome of patients who presented with premature pubic hair development. We studied retrospectively case notes of 64 patients [49 female (76.6%), 15 male (23.4%)] who have been referred for investigation over the last five years.
Results
Patients presented at a mean age of 7.2 ± 2.09 years with a mean height SDS of 1.57 ± 1.35 (range -1.62–5.22). Apart from premature development of pubic hair, other symptoms included increased body odour (50.0%), acneiform changes (25.0%), accelerated growth (18.8%) and mood changes (10.9%). PA was confirmed in 79.7% ($n=51$), virilising CAH due to *CYP21* mutations was diagnosed in 14.1% ($n=9$) and CAH due to *CYP11B1* mutations in 6.2% ($n=4$). Children with CAH were taller at presentation compared to those with PA (height SDS 2.5 ± 1.4 vs 1.3 ± 1.2, $P<0.05$) but there was no significant difference in the age, weight or BMI SDS at presentation. Compared to children diagnosed with PA, those with CAH had significantly higher DHEAS (4.5 ± 2.5 vs 2.6 ± 1.6 μmol/l), A4 (11.8 ± 10.9 vs 2.9 ± 1.9 nmol/l) and testosterone (2.27 ± 2.3 vs 0.79 ± 0.24 nmol/l). ROC curve analysis showed that a basal 17OHP greater than 4.9 nmol/l has a 77% sensitivity and 95.8% specificity in diagnosing CAH. Although long term data are not complete, 9.8% of patients with PA developed early puberty and in 3.9% there was evidence of PCOS on ultrasound.
Conclusion
The increased percentage of CAH may result from selection bias. Although rare, CAH due to *CYP11B1* mutations should be suspected. Long term follow up will elucidate the natural history of PA.

BC1.2

Knowledge, perceptions and actions of obese paediatric patients

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Introduction
The UK has seen a steady rise in childhood obesity over the last 30 years, with nearly a third of children aged 2–15 now overweight or obese. Childhood obesity represents a significant health burden, costing the NHS many millions of pounds.
Aim
The aim of this study was to investigate the knowledge, perception and actions of obese patients at the Royal Manchester Children's Hospital (RMCH), to guide recommendations for improving the weight management service.
Methods
Questionnaires were sent to 118 patients involved in the 'Metformin in Obese Children and Adolescents' (MOCA) trial and patients on the metabolic clinic. Fifty-five multiple-choice questions were asked on 5 subject areas: personal details, diet, exercise, home life and health. Questions asked about the participants' current behaviour, knowledge and perceptions in each area.
Results
Forty-nine questionnaires were returned. The mean age of respondents was 16 years and 80% were female. A third of participants were confused about how to eat healthily, and nearly a quarter admitted not understanding food labels. Despite 94% knowing that 5 portions of fruit or vegetables a day was recommended, 89% were not meeting this target. 63% said they were not very/not at all active. Seventy-three percent wanted to be more active but only 36% found exercise at school enjoyable. Most participants wanted to learn about cooking healthy foods. Worrying about being overweight was prevalent (80%) and may be a good indicator of motivation to change.
Conclusions
This survey identified a number of areas in which knowledge could be improved, including healthy eating and understanding food labels. Cooking could be used as a basis for educating young people about healthy food. Exercise sessions outside of the school environment could provide an opportunity for enjoyable activity leading to weight loss. Motivational techniques combined with education would be most beneficial.

BC1.3

Experience of management of children and adolescents with thyrotoxicosis in the West of Scotland 1987–2009

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Background
Hyperthyroidism is a significant medical condition in paediatric patients with serious health consequences. Optimal treatment remains debatable.
Objective
To review 23 years' experience of paediatric hyperthyroidism in the West of Scotland.
Methods
Case notes of patients treated for thyrotoxicosis in Glasgow, Paisley, Ayrshire and Lanarkshire from 1987 until 2009 inclusive were retrospectively reviewed. Patients with Down's (3) and Di George (1) syndrome, neonatal Graves' disease (3), toxic nodular goitre (2), and Hashimoto's encephalopathy were excluded.
Results
Fifty-six patients were identified of whom 45 (40 F:5 M) were eligible for analysis. Median (range) age at diagnosis was 9.8 (1.5–14.7) years, 37 had Graves' disease (GD) and 8 Hashimoto's. Antithyroid drugs (ATDs) [Carbimazole 44, PTU 1] were used initially in all patients (28 dose titration, 17 block and replace), with 3 changing to PTU because of Carbimazole intolerance. Thirteen patients remain on ATDs, 7 for <3 years, 6 for 3–12 years. Sixteen (36%) patients entered remission after stopping medical treatment, 7 within 3 years and 9 after 3.3–11.5 years. Of these, 6 subsequently relapsed and were given ATD $\pm$ radioiodine treatment. Four patients were treated electively; 3 with surgery (2 relapsed) and one with radioiodine (also relapsed). Twelve patients did not remit after 3.7 (1.3–8) years and were given second line treatment because of unsatisfactory control/compliance problems/side effects – 6 radioiodine (2 euthyroid, 4 hypothyroid with subsequent compliance problems in 2); 6 sub-total thyroidectomy (4 euthyroid, 1 hypothyroid, 1 relapsed).
Conclusion
Only 10/45 (22%) patients experienced sustained remission after stopping ATDs (7/10 requiring >3 years medical treatment) while second line treatment was not always optimal. A care plan for each patient should be devised in consultation with the family, and should consider age, social situation and educational stage.

BC1.4

Lessons from Klinefelter syndrome (47,XXY): a common DSD but with significant variation in presentation

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Background
Klinefelter syndrome (KS) is the commonest sex chromosomal disorder. Characteristic features include male phenotype with hypogonadism and progressive testicular failure, gynaecomastia and learning difficulties. The association between mediastinal germ cell tumours (GCT-M) and KS is well established, with KS occurring in 20% of GCT-M patients and the reported incidence of GCT-M in KS being 1.5 per 1000 (Nichols, 1991). Genital anomalies are also known to be rarely observed in KS (Lee *et al.*, 2007).
We report two unusual presentations of KS.
Case 1
A baby, with an antenatal diagnosis of KS (47, XXY), was born to non-consanguineous parents with normal female genitalia showing no evidence of clitoromegaly, labial fusion or palpable gonads, with separate urethral and vaginal openings. Antenatal counselling had prepared parents for a male infant. A poor testosterone response to HCG stimulation, low anti-mullerian hormone and markedly elevated gonadotrophins were consistent with gonadal dysgenesis. Postnatal karyotyping confirmed 47, XXY with preservation of the SRY gene.
Case 2
An 8-year-old boy presented with precocious puberty and severe virilisation. Investigations included a suppressed GnRH (peak LH & FSH 0.6 IU/L), raised serum testosterone (9.2 nmol/L), β-HCG levels (24 U/L) and alpha fetoprotein

(90 IU/L). A GCT-M was detected on CT-imaging. The tumour was successfully surgically resected and treated with chemotherapy. Significant behavioural outbursts 22 months after treatment prompted karyotype screening confirming a diagnosis of KS in the patient retrospectively.

Conclusions

These cases demonstrate the diversity of the KS phenotype. In antenatally diagnosed KS, clinicians must be mindful that abnormal genitalia should be included in the possible phenotypic features described in the condition. Screening for β-HCG secreting tumours is also essential in KS children presenting with early/precocious puberty. We also recommend early karyotype screening in children with a diagnosis of GCT-M to exclude associated KS.

BC1.5

Exploration of the perceived information needs of girls with Turner Syndrome and their parents

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Introduction

The age range at diagnosis, complexity of the syndrome and the sensitive and emotional nature of the issues involved in a diagnosis of Turner Syndrome (TS) present specific challenges for health professionals in sharing information with girls and their families. However little is known about the perceived information needs of parents and there has been no study of the views of girls with TS.

Methods

A qualitative design was employed to explore the experiences of girls with TS and their parents. A purposive sample of 15 families with daughters aged 9–16 years were recruited from a Growth Clinic in a Tertiary Paediatric Endocrinology Clinic. Girls and parents participated in a total of 27 semi-structured interviews. Participants were encouraged to identify issues of most importance to them and interviews were conducted informally in the participant's home. Interviews were recorded with permission and transcribed. Data were analysed using the Framework Approach of the National Centre for Social Research.

Findings and conclusion

The need for and understanding of information varied across families and between individual family members. Three dimensions described by families in their quest for information included gathering and receiving information, making sense of information and using and sharing information. Across these domains parents described the difficulty of distinguishing between their daughters' 'normal' personalities and presenting features of TS, whether social, cognitive or physical. Parents' key tension was between viewing their daughters as 'normal' and recognising and adapting to problems associated with TS. This tension influenced with whom, when, what and how information was shared between health professionals, parents and girls. These findings provide a basis for developing evidence based approaches to information sharing.

Poster Presentations

P1

Adverse drug reactions and corticosteroids in acute paediatric admissions

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Introduction
Adverse drug reactions (ADRs) are a significant cause of morbidity in childhood. We undertook a prospective study to investigate ADRs causing admission to a UK paediatric hospital: this report focuses on corticosteroids (CS).
Methods
Three investigators assessed all acute admissions over a 1 year period and identified ADRs by cross-referencing clinical presentations to known ADR profiles using a standardised causality tool.
Results
Of 240/8345 (2.9%) acute admissions had an ADR. CS contributed to causality in 102/240 (42.5%) ADR admissions. 57/102 (55.9%) were oncology admissions with febrile neutropenia who had received CS alongside chemotherapy. 45/102 (44.1%) of the CS-related ADR admissions occurred in paediatric non-oncology patients. 23/45 (51.1%) of these occurred in children re-admitted with post-operative bleeding (22/23 post-tonsillectomy) after elective surgical procedures, the majority of whom had received intra-operative CS and pre/post-operative NSAIDs. Children receiving Immunosuppression (IS) that included CS with culture-positive bacterial infections or known adverse events such as shingles, accounted for 17/45 (37.8%) of these non-oncology ADR admissions. In addition, two children (4.4%) were admitted with hyperglycaemia, one (2.2%) with hypertension and one with impaired healing of a surgical wound. One child was admitted with adrenal suppression following long-term administration of intra-nasal steroids.
Conclusion
Children receiving CS contributed almost half of the ADR admissions to a UK paediatric hospital. Some of the CS ADRs observed in this study were serious and caused by steroids. In other cases, CS were concomitant medication and the contribution of CS to ADRs among oncology, IS and tonsillectomy patients should be assessed. Strategies to reduce the burden of ADRs attributable to CS in children should be developed.

P2

Optimization of treatment in children with 21-hydroxylase deficiency using cortisol profiling

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Introduction
A number of different parameters are used to assess adequacy of treatment in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Hydrocortisone day curves are established practice in our unit. To determine the value of this procedure, outcomes were monitored using the European Society for Paediatric Endocrinology 2002 guidelines for the management of 21-hydroxylase deficiency.
Methods
Two hourly cortisol profiles were undertaken in 26 children with 21-hydroxylase deficiency (age range: 0.13–16.02 years) between August 2009 and January 2010.
Results
Conforming to the ESPE guidelines we have shown:

- Comparable or reduced dosage of hydrocortisone (mg/m^2 per day) compared to reported European averages in infants and children; age 0–1 years ($n=3$): mean hydrocortisone 17.3 vs 17.5 mg/m^2 per day; age 1–16 years ($n=23$): mean hydrocortisone 12.9 vs 15 mg/m^2 per day.
- Adequate replacement of glucocorticoid in 92.3% (mean 24 h cortisol >150 nmol/l; range 125–468, mean 207 nmol/l).
- Hydrocortisone dose alterations following profiling in 38.5% of children (increase in 60%, reduction in 40%).
- Favourable growth and avoidance of steroid-related side effects demonstrated by:
  Of 77.0% BMI between ± 2 SDS (range -2.25 to 3.2, mean $+0.60$) and 80% height SDS between ± 2 SDS of mid-parental height SDS (range -2.23 to 2.95, mean 0.22).
- Control without complete suppression of adrenal androgens in the majority (androstenedione <8 nmol/l in 81.8%).

In addition profiling enabled:

- Tailoring of hydrocortisone timing and frequency to improve emulation of physiological secretion in 30.8% (with or without dose adjustment).
- Exclusion of nocturnal hypoglycaemia by concurrent glucose profiling.

Conclusion
Cortisol profiling in children with 21-hydroxylase deficiency is an effective method of fine-tuning dosage and timing of hydrocortisone treatment.

P3

Pseudohypoaldosteronism Type 1 in Infants: A UK Experience

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Background
Type 1 pseudohypoaldosteronism (PHA) is characterised by resistance to aldosterone action, resulting in salt wasting, hyperkalaemia and metabolic acidosis in the neonatal period. Type 1 PHA can be classified as Renal PHA (autosomal dominant (AD)), and the more severe Multiple target organ defect / systemic PHA (autosomal recessive (AR)). The aim of this study was to ascertain the incidence of PHA, and characterise mode of presentation, management and clinical outcomes of such patients presenting to a UK tertiary centre.
Methods
Case notes of newly diagnosed infants presenting with PHA were retrospectively reviewed from January 2006 to December 2009.
Results
Six patients were diagnosed with PHA. Initial presentation ranged from 4 to 28 days of age. At presentation all subjects had significant hyperkalaemia and hyponatraemia. Initial management consisted of fluids and use of glucocorticoids and mineralocorticoids until the diagnosis was elucidated. Subsequent results revealed a plasma aldosterone range of 12 580–83 390 pmol/l and plasma renin activity range of 41.3–$>$250 nmol/l per h. Following therapy, these returned to normal values. Four of the patients are likely to have AD PHA and were managed with sodium supplements and initially required low potassium milk. Two patients have AR PHA and required intensive and prolonged electrolyte and feeding support with low potassium feeds and significant sodium supplementation. One of the patients with AR PHA has a confirmed mutation on the SCNN1A gene. The birth rate in the area studied is approximately 42 000/year, giving a PHA incidence of 1 in 21 000.
Conclusion
All infants presenting with hyperkalaemia, hyponatraemia and weight loss should have an assessment for adrenal function including mineralocorticoid status. The AD form responds well to salt supplementation whereas infants with AR PHA are prone to frequent episodes of electrolyte imbalance.

P4

Neonatal adrenal suppression from maternal steroid use: A retrospective case note study

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Introduction
Infants born to mothers on antenatal steroid medication may develop adrenal suppression postnatally which can be potentially life-threatening. However, the incidence is unknown and screening for at risk infants is not universal.
Aim
The aim of our study was to review the outcome of infants born to mothers on antenatal steroids.
Method
We retrospectively reviewed our neonatal "paediatric alerts" for mothers on antenatal steroids between 2000 and 2009. Mothers on continuous oral steroid for >6 months before delivery were included in the study. Three cortisol levels were obtained at 8 hourly intervals on postnatal day 3. Adrenal suppression was defined as ≥ 2 levels of cortisol <100 nmol/l. All results are presented as mean $\pm$standard error of mean.

Results
Data were available for analysis in 50 appropriate patients. Nine (18%) patients had results consistent with adrenal insufficiency (mean cortisol 86±8.5 nmol/l). All 9 mothers were on prednisolone (mean daily dose 14±4 mg). Eight patients were started on replacement steroids. One (2%) patient on replacement steroids was admitted to hospital with adrenal crisis at 2 months old. All 8 patients on replacement steroids had normal synacthen test at 4 months old and steroids were stopped. Comparing patients with normal versus suppressed cortisol levels, mean maternal steroid dose (converted to prednisolone dose) was 16±2 and 14±4 mg respectively ($P=0.70$) and mean duration of maternal steroid therapy was 130 ±24 and 108±50 weeks respectively ($P=0.70$).
Conclusion
Adrenal suppression occurs in a significant proportion of infants born to mothers on antenatal steroids, independent of the duration or dose of maternal steroid therapy. Although this appears to be temporary, there is still a small risk of developing adrenal crisis. Screening for adrenal suppression postnatally is therefore recommended in infants at risk.

P5

A 30 years review of congenital adrenal hyperplasia in Northern Ireland
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Background
Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition with significant consequences if not correctly diagnosed and treated. We have reviewed the patients with CAH presenting in Northern Ireland between 1976 and 2010.
Aims
To determine the age, sex and clinical features at presentation; treatment modalities including perineal surgery in childhood; and long-term outcomes including final height and surgery in adulthood.
Methods
The medical notes of patients diagnosed with CAH in this time period were reviewed. A literature review was performed and our data compared with that previously published.
Results
Thirty-seven patients (22 female, 15male) from 30 families presented with CAH over this time period giving an incidence of 1:23,092 live births. Eighteen (49%) were diagnosed shortly after birth (83% virilised females); 13 (35%) presented in the first few weeks of life with adrenal crises (85% male); and 6 (16%) presented with virilisation in later childhood. Six (16%) children had diagnosis confirmed on genetic testing. All children required glucocorticoid replacement. Of 35 (95%) required mineralocorticoid replacement; three children were treated with human growth hormone and two children required suppression of early puberty. Mean final height was −1.5 SD below mean adult height in boys and girls. In the first 16 years reviewed, 8 (80%) girls had perineal surgery in childhood, compared with 2 (16%) in the second 18 years. Two (9%) women had adrenalectomy. Eleven (58%) of those transferred to adult services have been lost to follow-up.
Conclusions
The incidence of CAH is less here than in the rest of the UK with more females affected than males. The majority present in the first few weeks of life. Mean final height is often impaired. The trend towards later surgery heightens the need for close adolescent follow-up.

P6

Adrenal responses to a simplified low dose short synacthen test (LDSST) in children with asthma
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Introduction
Impairment of the hypothalamic–pituitary–adrenal (HPA) axis has been reported widely in children treated with inhaled corticosteroids (ICS). The integrity of HPA axis has been assessed using low (500 ng/1.73 m^2 body surface area) and standard (250 mg) dose short synacthen tests (SST). Serum cortisol is measured at 0, 15, 20, 25, 30 and 35 min intervals in the low dose SST (LDSST) and at 0, 30 and 60 min in the standard dose SST (SDSST). The LDSST may be more sensitive: however, the frequency of sampling makes it technically difficult.
Objective
To study cortisol responses to a simplified LDSST.
Methods
Patients with asthma treated with ICS for >3 months underwent a simplified LDSST with sampling at 0, 15, 25 and 35 min. Responses to the LDSST were categorised as normal (peak cortisol ≥500) or impaired (peak cortisol <500).
Results
One hundred and thirty-six patients (79 male) median age 10.7 years (range 5.1–16.7) were studied. Treatment characteristics (drug, median dose and range) were as follows: (1) fluticasone 500 μg (100–2000), $N=108$ (2) budesonide 800 μg (200–1600), $N=20$ (3) beclomethasone 400 μg (200–800), $N=8$. Basal cortisol correlated strongly with peak cortisol ($P=0.005$). Forty-seven (34.6%) patients (31 male) age 10.5 years (5.1–16.2) had an impaired response including 25/63 (39.7%) of patients treated with fluticasone ≥500 μg/day. Peak cortisol occurred earlier in patients with an impaired response and patients with a normal response were twice as likely to peak at 35 min (15 vs 34%, $P=0.019$). There was no difference in age, gender or ICS dose between normal and impaired groups.
Conclusion
The frequency of impaired responses to the simplified LDSST is comparable to that reported in similar cohorts of children studied with more intensive sampling. These preliminary data suggest that simplification of the LDSST does not result in significant loss of specificity.

P7

Glucocorticoid hypofunction in Myotonic Dystrophy
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Myotonic Dystrophy is an autosomal dominant multi-system disorder characterised by muscle weakness and myotonia, with associated cardiac, ophthalmic, gastrointestinal and endocrine abnormalities
A 16-year-old boy was referred with a 2 months history of difficulty releasing his hand-grip and problems with swallowing. The clinical diagnosis of myotonic dystrophy 1 was confirmed with genetic testing with the detection of a DMPK expansion mutation. During investigations he was found to have asymptomatic hypoglycaemia, with a random blood glucose value of 2.5 mmol/l and this was confirmed on repeat testing. Further investigations showed a raised random ACTH of 246 ng/ml with a cortisol level of 400 nmol/l. A low dose Synacthen test showed a maximum cortisol response of 441 nmol/l (basal level −399) confirming adrenal insufficiency.
It has been well documented in adults that myotonic dystrophy is associated with multiple metabolic and endocrine abnormalities. There is a four-fold increased prevalence of diabetes associated with hyperinsulinaemia in patients with myotonic dystrophy. Dysregulation of the hypothalamic–pituitary–adrenal axis has also occasionally been described. One previous study of 25 adults with myotonic dystrophy found lower levels of basal cortisol, higher average values of ACTH and a lower cortisol response following stimulation with CRH. This was the pattern of glucocorticoid hypofunction that was seen in our patient. We recommend considering glucocorticoid hypofunction in children with myotonic dystrophy, especially if symptoms of lethargy or hypoglycaemia are noted.

P8

Comparison of the low dose synacthen and glucagon stimulation tests in the assessment of adrenal function in children with short stature
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Introduction
The 1 μg low dose short Synacthen tests (LDSST) and the glucagon stimulation tests (GST) have been suggested to be safer alternatives to the insulin induced hypoglycaemia stress test. The aim of this study was to compare the peak plasma cortisol concentration in response to a LDSST followed 60 min later by a GST in children undergoing investigation for short stature.
Methods
We retrospectively studied 38 patients (19 female, 19 male) who underwent evaluation for short stature between May 2006 and January 2010. Their mean age was 11.08 years and median age was 11.1 (range 1.99–18.10 years).

An intravenous LDSST was followed by an intramuscular GST. Blood samples were drawn at 0, 20 and 30 min for the LDSST and 0, 30, 60, 90, 120, 150 and 180 min for the GST.
Results
From the 38 tests, four children in the LDSST and 17 in the GST group had a peak cortisol <500 nmol/l. Three children had a peak cortisol <500 nmol/l with both the LDSST and the GST. There was a biased relationship between the two tests with LDSST giving higher results at lower and GST at higher concentrations. Passing & Bablock shows that $GST=(1.91\times SST)-607$.
Discussion
The difference in peak cortisol concentrations may be due to the different pharmacological mechanisms that Synacthen and glucagon employ. The skewed distribution of responses would suggest that the difference is not due to the order in which the tests were performed. Our study would suggest that common cut-off values cannot be used for different secretagogues.

P9

Classical CAH due to a rare compound heterozygote mutation masquerading as pubarche in a 3 years old girl

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Background
Congenital adrenal hyperplasia, (CAH) is a common autosomal recessive condition, 95% of which is attributable to mutations in the 21-hydroxylase (CYP21) gene. There is a wide range of clinical features and genotype phenotype correlations for common mutations are well described.
Case
EG presented to the endocrine clinic at the age of 3.5 years with pubarche of 6 months duration and Tanner staging of PH3, B1and clitoromegaly (Prader stage 1) Urinary steroid profile, high 17OHP (undiluted>500 nmol/l) and testosterone (8.4 nmol/l) levels were all consistent with classical 21 hydroxylase deficiency. Blood pressure was 75 to 90th centile for height on several occasions and her plasma renin activity (elevated at 9.5 pmol/ml per h) normalised almost immediately on hydrocortisone treatment. There was no evidence of salt losing even during documented past admissions with gastroenteritis and urinary tract infections. TW3 bone age was advanced by 3.5 years.
Genetics
Compound heterozygote for two missense mutations (c.515T$>$A;p.lle172Asn-associated with simple virilising forms and the rarer c.1277G$>$A;p.Arg426His associated with salt wasting/simple virilising CAH).
Discussion
Unusually late presentation of a classical CAH with the genotype suggestive of more severe disease. Few previously described patients with this genetic combination had a varied clinical presentation ranging from virilisation requiring surgery to precocious puberty and advanced bone age. EG has also been difficult to manage requiring a higher glucocorticoid (17 mg/m^2) dose to suppress her ACTH drive and her accelerated bone age has persisted despite treatment. Should fludrocortisone be used in the setting of a normal renin and no salt wasting as mentioned in the literature?
Conclusion
This case highlights the fact that though genotype is useful, therapeutic decisions need to be made in conjunction with the clinical picture and the role of the clinician in performing appropriate hormonal studies at diagnosis as well as on treatment is essential to optimize therapy for each individual patient.

P10

Transient hypocortisolemia in post-operative cardiac patients: is it a cause for concern?

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Introduction
Cortisol insufficiency has been reported following cardiac surgery in infants but has not been associated with postoperative complications. In our hospital serum cortisol is measured following cardiac surgery when hypotension is refractory to two inotropes at maximal dose.
Methods
Retrospective case note study to describe features of adrenal insufficiency in post-operative cardiac patients with low serum cortisol.
Results
In the period 01/09/2009–28/02/2010, 188 patients, median age 180 days (range 4 days to 19 years) underwent cardiac surgery. Serum cortisol was measured in 12 patients and was <500 nmol/l (median 102 nmol/l, range <50–169 nmol/l) in 7 patients of whom one had biochemical features of adrenal crisis (Na 119 mmol/l, K 7.3 mmol/l) and seizures. Serum cortisol was ≥ 500 nmol/l (1134 nmol/l, 662–4525 nmol/l) in five patients. Patients with low cortisol levels were significantly younger than those in whom cortisol levels were ≥ 500 nmol/l (age 7 days, 3–30 vs 30 days, 17–910 $P=0.007$). All patients responded to treatment with hydrocortisone. 3/7 patients with a low serum cortisol underwent a short synacthen test 8–40 days following initial assessment (baseline cortisol 68, 192, 455, peak cortisol median 590, 836, 1335 nmol/l) including the infant with adrenal crisis (baseline cortisol 192 nmol/l, peak 836 nmol/l) and in 2 patients 09.00 cortisol and ACTH were measured (ACTH 3.0 pmol/l, cortisol 103 nmol/l and ACTH 5.5 pmol/l, cortisol 213 nmol/l). One patient died 5 days following surgery and 1 patient is currently being studied.
Conclusion
Our preliminary data reveal post-operative cortisol insufficiency can be associated with features of adrenal crisis. This study is retrospective hence we cannot comment on the relative contribution of cortisol insufficiency to postoperative hypotension. Further research is required to elucidate the cause of transient cortisol insufficiency, prevalence of associated symptoms and to define when hydrocortisone replacement therapy is beneficial.

P11

Investigating children of glucocorticoid remediable aldosteronism patients' – early testing is beneficial

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We present two cases of glucocorticoid remediable aldosteronism (GRA) diagnosed through screening the children of an affected mother.
GRA is a rare inherited cause of hypertension in children. A monogenic defect produces a chimeric gene, which codes for two enzymes involved in the production of aldosterone and cortisol. This leads to adrenocorticotropin stimulated aldosterone production. GRA is thought to account for 1% of primary aldosteronism with around 150 documented cases in the literature. Increasing numbers of cases are being confirmed through the availability of a relatively new highly sensitive and specific genetic test. This is superseding biochemical and suppression testing. Patients usually present with severe hypertension and are at risk of hypokalaemia and cerebrovascular aneurysms. Treatment is with corticosteroids or aldosterone antagonists.
The cases were referred from the local genetics team after organising testing at mother's request. Of three children, two were found to be positive for the genetic defect.
DH was a 7-year-old boy and RH a 3 years old girl who were both asymptomatic. Mother and maternal grandmother were positive for the GRA mutation. An 11 years old cousin was under treatment for the disease. History and examination was unremarkable for both. DH was noted to have systolic blood pressure above 99th centile (129/80) with RH at the 90th centile (102/54). Biochemical investigations were unremarkable. Echocardiography and brain magnetic resonance angiography were normal.
DH was commenced on a low dose of Spironolactone initially, which was increased to control blood pressure. RH was managed conservatively and then required Spironolactone following persistent hypertension 1 year from diagnosis. Both children are currently well with blood pressures within the normal range.
This case highlights the importance of screening relatives of those known to have GRA in order to instigate appropriate treatment and prevent complications.

P12

A family kindred with persistent Müllerian duct syndrome secondary to AMH deficiency

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Background
Persistent Müllerian Duct syndrome (PMDS) is characterised by the presence of Müllerian structures in a 46XY male. PMDS can result from either a defect in Anti-Müllerian hormone (AMH) production or in the AMH receptor. AMH causes the Müllerian ducts to atrophy, enabling the testes to move

transabdominally to the deep inguinal rings and into the scrotum. In the absence of AMH action, PMDS can cause problems with testicular descent. We present a family kindred with PMDS highlighting some important aspects of this condition.
Case presentations
Index case
An 18-month-old boy was referred with bilateral undescended testicles. Laparoscopy and orchidopexy revealed PMDS. He had a 46XY karyotype and AMH was undetectable, confirming AMH deficiency.
Case 2
His 9-year-old brother had previously undergone open orchidopexy for bilateral undescended testicles at 12 months. His testes became impalpable post-operatively and he was known to the endocrine service with a diagnosis of 'vanishing testes syndrome'. He was re-evaluated subsequent to the index case's diagnosis and PMDS was found on laparoscopy. His left testis was found at the inguinal ring, tethered to the Müllerian ducts, necessitating repeat orchidopexy.
Case 3
The father's brother also had bilateral undescended testes which were never operated on in childhood. He went through puberty appropriately but was not able to father children. He was diagnosed as having a Müllerian remnant when operated on for a seminoma of his intra-abdominal testis aged 40.
Conclusions
The Müllerian remnants were not observed originally in Case 2 as an open orchidopexy was performed through bilateral incisions, hence midline structures were not seen. Embryological knowledge of the genital tract is essential for understanding PMDS and associated pathologies. The Müllerian remnants are generally left *in situ*, however there are reports of uterine cancer in the literature, hence ongoing surveillance should be ensured.

P13

The European DSD register – the start of an international DSD network

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To improve the clinical management of children with disorders of sex development (DSD), there is a need for multi-centre collaborative research as well as clinical interaction. The European DSD Register that became operational in 2008 is a cornerstone of the EuroDSD programme and allows clinicians and researchers to interact in a secure, internet-based, virtual research environment (VRE).
Currently, 23 centres in 16 countries from four continents have expressed an interest in using the Register and 12 centres in nine countries from two continents are actively using the Register. Amongst the 702 cases in the Register, there are 429 cases that are female (61%) and 273 are male (39%). The median year of birth is 1993 (range 1927–2010) and the age of presentation ranges from <1 month to 53 years. There are 11 males who have 46XX karyotype and 292 females who have a 46XY karyotype and 200 out of these 292 cases are women over the age of 16 years. Disorders of androgen action are the commonest disorder type with 220 cases (31%). Of these cases 154 (70%) have complete androgen insensitivity syndrome and 63 (29%) have partial androgen insensitivity syndrome. Disorders of gonadal development are the next commonest disorder type with 153 cases (22%), and over half (52%) of these cases have partial gonadal dysgenesis. One hundred and eighty-seven (27%) of the total cases on the register have associated malformations present. Five hundred and fifty-four (79%) of cases on the register have a DNA sample available, and in 238 (43%) of these the genetic diagnosis remains uncertain.
There is a need to sustain this unique and successful resource for research and extend its use beyond the original partners of the EuroDSD programme. There is also a need to maintain and extend the clinical and research network and translate its efforts into improving standards of clinical care.

P14

Evaluation of terminology used to describe disorders of sex development

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Objective
The terminology used to describe abnormalities of sex determination and sex differentiation was revised in 2006. It was anticipated that new terms, such as "disorder of sex development" (DSD), would improve communication between health professionals, aid parental understanding and be acceptable to affected individuals. The purpose of this study was to evaluate whether the new terminology has been an improvement compared to previous nomenclature.
Subjects and methods
Using a questionnaire, we evaluated the acceptance of these new terms by parents of children with a DSD ($n=19$), health professionals ($n=15$) and parents of unaffected children ($n=25$).
Results
Comparing the term "DSD" to "intersex", overall 86.4% of participants preferred the term "DSD", and parents of a child with a DSD had an even higher preference (94.7%). Parents of a child affected by a DSD considered the new term "DSD" to improve their understanding of their child's condition (83.3% agree), aided explanation from a parent to an affected child (82.4% agree) and to wider family and friends (84.2% agree). Health professionals preferred the genotype-based terms, whereas parents considered these terms confusing. Overall 59.3% of participants agreed DSD was an acceptable new term.
Conclusions
There was broad support for the new terminology by parents and health professionals. The label "disorder of sex development" may be helpful to parents at the time when it is not possible to assign gender, after which aetiological-based diagnoses should be used where possible.

P15

Clitoral and penile sizes in healthy newborn babies in Ibadan, Nigeria

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Background
Standards of penile and clitoral lengths are useful for diagnosis of genital abnormalities. Micropenis could be the only sign in pituitary/hypothalamic dysfunction while clitoromegaly may reflect abnormalities of neonatal and maternal origin. Ambiguous genitalia if missed at birth could be fatal especially in cases of congenital adrenal hyperplasia. There are no African reports on normal reference ranges of both penile and clitoral sizes. This study aimed to generate key information that did not exist on the size of external genitalia of newborn babies in Nigeria.
Objective
To establish the normal reference values for penile and clitoral sizes in Nigerian infants and to compare with standards from other ethnic populations.
Methods
A total number of 515 healthy newborn babies delivered at gestational ages 28 weeks or more were enrolled in the study. Clitoral or penile lengths and widths were taken less than 72 h after birth in all of them.
Results
The mean penile length in the 264 Nigerian males studied was 3.4 ± 0.49 cm while the mean width was 1.2 ± 0.17 cm. Nigerian newborn had similar penile sizes as the Caucasians (3.4 ± 0.3 cm); larger than the Chinese (3.1 ± 0.4 cm) but significantly smaller than those of Indian (3.6 ± 0.4 cm), Turkish and Malaysian origin. The mean clitoral length in the 251 Nigerian females studied was 7.5 ± 1.8 mm while the mean clitoral width was 4.4 ± 0.89 mm. The clitoral sizes were significantly larger than those in the Caucasian (4 ± 1.24 mm), Korean and Japanese babies.
Conclusion
The overall figures in Nigerian newborns deferred from values obtained from other countries. There were significant variations in clitoral and penile sizes between different ethnic populations. The measurement of genital sizes should be part of routine newborn physical examination.

P16

IGF-2 deficiency in the growth disorder 3-M syndrome

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Introduction
3-M syndrome is an autosomal recessive disorder characterised by pre- and postnatal growth restriction, characteristic facial dysmorphism, normal intelligence and radiological features (slender long bones and tall vertebral bodies). It is known to be caused by mutations in the genes encoding Cullin 7 (a component of

the ubiquitination system) and Obscurin like-1 (a cytoskeletal protein). The mechanisms through which mutations in these genes impair growth are unclear.
Aims
The aim of this study was to identify novel pathways involved in the growth impairment in 3-M syndrome.
Methods
RNA was extracted from fibroblast cell lines derived from four 3-M syndrome patients and 3 control subjects, hybridised to Affymetrix HU 133 plus 2.0 arrays with quantitative real time PCR used to confirm changes found on microarray. IGF2 protein levels in serum and conditioned cell culture medium were measured by ELISA.
Results
1926 probesets differentially regulated between control and 3-M syndrome fibroblasts (defined as fold difference >2 and expression level >50 in one or more cell lines) were identified. 779 of these probesets were upregulated and 1147 downregulated. Of the top 10 downregulated probesets 3 represented *IGF2* while *H19* was identified as the 25 and 65th most upregulated probesets. qRT-PCR confirmed upregulation of *H19* ($P<0.001$) and downregualtion of *IGF2* ($P<0.001$).
Levels of IGF-2 secreted into conditioned cell culture medium were higher for control fibroblasts than for 3-M fibroblasts (10.2 ± 8 vs 2.6 ± 4.7 ng/ml, $P<0.01$). Serum IGF-2 levels did not appear reduced in 3-M syndrome ($n=6$ 1390 ±212 ng/ml).
Conclusions
3-M syndrome is associated with a gene expression profile of reduced *IGF2* expression and increased *H19* expression similar to that found in Silver Russell syndrome. Loss of autocrine IGF-2 in the growth plate may result in the short stature seen in children with 3-M syndrome.

P17

Feasibility of follow-up in short, small for gestational age (SGA) infants at 2 years – interim report

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Most SGA infants show rapid catch-up growth in the first year of life such that height is in the normal range by 2 years. However, around 10% fail to catch-up and remain short. This latter group generally presents to specialist growth clinics at school age. Earlier identification would facilitate monitoring of growth and timely intervention.
A 3-year, prospective population-based study was undertaken to determine the feasibility of identifying SGA babies who are short at birth, then re-measuring them at 2 years. All babies born at the Ayrshire Maternity Unit with BW $<$9th centile throughout 1 year (July 2008-June 2009) were identified. Length was measured and each infant categorised as follows: SGA (BW ≤ -2 SD); Short (BL ≤ -2 SD); SGA+Short (BW&BL ≤ -2 SD). Parents' heights were also measured. Babies who were short were invited for review at 2 years.
During the study period 3797 babies were born, of whom 256 (6.7%) were low BW ($<$2500 g) and 278 (7.3%) preterm ($<$37 weeks), similar to current Scottish population statistics (7.0% LBW; 7.6% preterm). Of 481 (12.7%) infants with BW $<$9th centile, 131 (27%) were not measured, of whom 21 had BW $<$2nd centile (-2 SD). Parental heights were not recorded in 205 (42.6%). Of the 350 babies who were measured, 159 infants were identified as either SGA (53), Short (50) or SGA+Short (56). The incidences of SGA (2.9%) and short stature (2.8%) are slightly greater than expected.
Despite the constraints of a busy maternity unit it has proved feasible to measure birth length in most babies with BW $<$9th centile. A significant proportion of short babies were between the 2nd and 9th centiles for weight indicating that the upper level is a more appropriate cut-off for short stature screening. The second phase of the study – re-measurement at 2 years – has just begun.

P18

The effect of pubertal timing on later adult obesity

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Introduction
Obesity has become an international epidemic, with complex multifactorial aetiology. Both modifiable and unchangeable risk factors must be identified, to target public health interventions. Some studies have suggested that earlier pubertal maturation increases risk of adult obesity, although others have found no relationship. We aimed to meta-analyse existing data and hypothesised that any association is likely to be confounded by childhood adiposity.
Methods
We conducted a systematic review, carrying out a computerized search of the literature using the following databases: MEDLINE, EMBASE, Web of Knowledge and the TRIP database. Forty-one papers described the effect of pubertal timing on adult adiposity after the age of 25 years; 37 reported adult Body Mass Index (BMI). Both authors independently reviewed and extracted pre-defined data from all selected papers. Meta-analyses were conducted in RevMan 5.
Results
Only six studies reported no significant relationship between pubertal timing and adult BMI. Meta-analyses showed that early menarche (menarche <12 years vs ≥12 years) increased adult BMI: standardised mean difference (SMD) 0.34 kg/m^2 (95% CI: 0.33–0.34) while late menarche (menarche ≥15 years vs <15 years) decreased adult BMI (SMD -0.26 (-0.36, -0.21). Early menarche increased the risk of adult obesity: pooled odds ratio of 2.00 (95% CI: 1.79–2.24). Data in males was insufficient to report. Only eight papers included data on childhood BMI, the majority reporting that childhood BMI only partially attenuated the association between early menarche and later obesity.
Conclusions
Earlier pubertal maturation is predictive of higher adult BMI and greater risk of obesity. This effect appears to be partially independent of childhood BMI. Further work is needed to examine potential mechanisms and the level at which interventions may be targeted.

P19

Outcome of rhGH treatment in patients with achondroplasia and skeletal dysplasias

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Background and aim
Achondroplasia (ACH) is one of the commonest skeletal dysplasias affecting 1:15 000–1:40 000 live births. The average attained adult height is 131 ± 5.6 cm for men and 124 ± 5.9 cm for women. Previous studies have shown that the use of rhGH may result in transient increase in the growth rate, but there have been no long-term data regarding adult height. We aimed to study a cohort of patients with ACH and other skeletal dysplasias who have been treated with rhGH and evaluate their response and attainment of adult height.
Methods
We studied 42 patients with skeletal dysplasia who have been treated with rhGH (mean dose 30 U/m^2 week) over the last 15 years: ACH ($n=24$), hypochondroplasia ($n=3$), short limb dysplasias ($n=6$), SED ($n=5$) and unclassified dysplasias ($n=4$).
Results
Patients with ACH (71% male, 29% female) started treatment at a mean age of 3.4 ± 2.5 years (1.2–9.0), with a HtSDS of -1.14 ± 1.5 (-3.30 to 1.86). Mean duration of treatment was 10.2 ± 3.2 years (4–15) for ACH and 9.5 ± 3.8 years (2–14) for other skeletal dysplasias. Growth velocity (GV) during the 1st year (7.8 ± 1.2 cm/year) was significantly higher than the GV observed in the 2nd and 3rd years (5.5 ± 1.5 cm/year and 4.8 ± 0.9 cm/year respectively, $P<0.05$). 80% of ACH patients have reached final height and 30% had a limb lengthening procedure. Taking into account the height gained by limb lengthening, children with ACH had variable height gain in puberty (8.8 ± 5.5 cm, range 0.2–21.8 cm). At end of growth, they had a change in Ht SDS from -0.89 ± 1.36 to 1.55 ± 0.84 ($P<0.05$).This difference became non significant once limb lengthening procedures were considered (-0.89 ± 1.36–1.07 ± 0.78, $P>0.05$).
Conclusions
Patients with ACH treated with rhGH have a more pronounced increase in GV during the 1st year. Final Ht SDS is not significantly different from pre-treatment Ht SDS. The evaluation of patients with other forms of dysplasias is difficult due to small numbers and the lack of disease specific charts.

P20

Retrospective analysis of patients with paediatric diagnosis of isolated growth hormone deficiency in a single centre from 1970–2000

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Introduction
Confirmation of permanent isolated growth hormone deficiency (IGHD) during childhood with subsequent adult transfer is important since such patients may benefit from adult GH replacement.
Methods
A chance encounter with a former patient experiencing symptoms of adult GHD but untreated prompted us to review the final diagnosis and follow-up status of our GH-treated patients with IGHD between 1970 and 2000. Case records were examined for initial/repeat GH stimulation levels (mU/l), pituitary imaging and clinical/auxological data.
Results
Ninety-five patients were originally diagnosed with IGHD, of whom 30 received human GH (hGH) and 65 received recombinant GH (rGH) treatment.
In the hGH group, IGHD was confirmed in four [repeat GH peak <10 (3), autosomal dominant IGHD (1)] and unconfirmed in 26 [initial GH peak <10 (18), 10–15 (6) and >15 (2)]; IGHD was considered unlikely in 4/26 – initial GH peak >10 & auxology compatible with constitutional delay in growth and adolescence (CDGA), familial short stature (SS), and idiopathic SS with peak GH >15 in 2.
31/65 in the rGH group had their original IGHD diagnosis re-evaluated. Repeat peak GH was ≤ 10 (6), >10–20 (4) and >20 (21). On the basis of clinical assessment, GH peak (initial <10, repeat <20) and imaging evidence, a final diagnosis of IGHD was considered secure in 7, excluded in 28 and changed in 28 (CDGA (14), familial SS (5), idiopathic SS (5), psychosocial (2), chronic disease (2)). IGHD was unconfirmed in a further 30, in whom initial peak GH was <10 (6), 10–15 (10) and >15 (14). Five of 11 patients with confirmed IGHD have documented adult endocrine follow-up.
Conclusions
Most patients treated with rGH for IGHD had normal variant short stature, with inadequate confirmation of the diagnosis. The rGH group pose a particular challenge in terms of tracing and re-evaluating for adult GHD.

P21

Endocrine, hypothalamic and neuro-developmental outcomes following treatment for craniopharyngiomas

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Introduction
The management of Craniopharyngioma is associated with significant long-term morbidity. We retrospectively assessed the endocrine, hypothalamic and neuro-developmental morbidity (at most recent clinic review) in survivors of Craniopharyngioma diagnosed between 1/01/98 and 31/12/09, and currently being managed at our centre.
Methods
We identified 63 patients in our cohort of which 25 were randomly selected for analysis (11 males, 14 females). Eight-four percentage ($n=21$) underwent definitive debulking surgery (complete resection (CR) in 33% {$n=7$}, and partial resection (PR) in 66.6% {$n=14$}), and 68% ($n=17$) received adjuvant radiotherapy (DXT) at initial presentation. Disease recurrence was seen in 11 (44%) patients: CR: $n=4$; PR: $n=6$; DXT: $n=7$.
Results
Ninety-two percentage ($n=23/25$) had more than two pituitary hormone deficiencies with GH and TSH deficiencies being the most prevalent (88%; $n=22$). Twenty patients had ACTH deficiency, whilst 16 had DI. BMI data was available in 16 patients; 50% had BMI >30.0 kg/m^2, and the mean BMI was 30.49 kg/m^2. Neuro-developmental data was available in 23 patients; 69.6% ($n=16$) were either in employment, higher education, or attended mainstream schools, 26.1% ($n=6$) attended mainstream schools, but had educational needs (4 of which required assistance at school), and 1 patient attended a special needs school. Behavioural issues (mainly related to anger about their condition, excessive weight gain, and subsequent isolation at school) requiring psychology input was observed in 6 patients. Of the 25 patients, 4 were registered blind, 5 had a history of sleep disorder, and 1 had temperature dysregulation.
Conclusion
The majority of our Craniopharyngioma patients diagnosed in the last decade have had partial debulking surgery followed by adjuvant radiotherapy at initial presentation. Endocrine morbidity remains highly prevalent and 50% of our patients were obese at their last clinic review. Neuro-developmental outcomes are however encouraging as 70% presently (current mean age: 13.03 years) do not require cognitive assistance.

P22

GHT does not improve QOL in all conditions

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Growth hormone treatment (GHT) is used to improve height, and potentially quality of life (QOL), in children with abnormal growth patterns. Previous QOL research suggests children with acquired growth hormone deficiency (AGHD) benefit more from GHT than those treated for other conditions.
The aim was to determine child and parent reported QOL change over 1 year depending on GHT and diagnosis.
One hundred and twenty-two children (mean age $=11.3$ years) were recruited from 16 UK endocrinology clinics. Inclusion criteria were diagnoses of idiopathic growth hormone deficiency (IGHD; $n=36$), AGHD ($n=27$), Turner syndrome ($n=18$), and a control group of short stature children referred to endocrinology units who were not prescribed GHT ($n=41$); aged 5–17 years, with no other chronic condition and not treated with sex hormones. Parents, and children over 10 years, completed measures of the child's quality of life (PedsQL^{TM}) on beginning GHT (T1), after 6 months (T2) and 12 months (T3).
To date, 62 children and parents of 112 children have completed questionnaires. There were no age differences between diagnostic groups. Increase in stature from T1 to T3 in GHT groups was equivalent to controls (all *t*-tests n.s.; IGHD:7.8 cm; AGHD:7.2 cm; Turner:7.4 cm; controls:6.8 cm). A diagnosis by time repeated-measures ANOVA on child PedsQL^{TM} scores revealed improvements over time (T1 $=75.0$, T2 $=77.5$, T3 $=81.4$) $P=0.001$, that were not related to diagnosis. Repeating the analysis with parent ratings of child QOL revealed similar increments over time (T1 $=69.1$, T2 $=73.9$, T3 $=75.0$) $P<.001$, also not related to diagnosis. However, *post hoc* tests showed parents of AGHD children reported lower QOL overall $P=.001$ and at T1 for AGHD (mean $=58.1$) compared to all other groups (means: IGHD $=68.1$, Turner $=66.0$, Control $=74.7$); $P=.007$.
Current data do not suggest GHT is associated with improved QOL over a 1 year period. However, a lower overall QOL in children with AGHD suggests GHT should be particularly considered for this group.

P23

The impact of inflammatory bowel disease on pubertal growth is most marked in boys with Crohn's disease

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Background
Puberty is understood to be commonly effected in adolescents with Crohn's Disease (CD) and ulcerative colitis (UC). However, the extent of this effect and related problems with growth, have rarely been quantified.
Objective
To determine the impact of CD and UC on pubertal growth.
Methods
Retrospective study of 148 children with IBD (casenotes available, 135) who fulfilled the criteria for describing growth spurt parameters (91): CD-M(30); CD-F(11); UC-M(14) and UC-F(12) had median age at diagnosis of 12.8, 11.6, 11.6 and 10.8 years.
Height at diagnosis (HAD) and height at peak height velocity (HPHV), converted to SDS, defined Size; age at PHV (APHV) defined Tempo; and PHV, converted to SDS adjusted for pubertal stage, defined Velocity of the growth spurt. The median interval between height measurements was 0.4 years. Results were expressed as median (range).
C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, alkaline phosphatase levels, haematocrit and platelet counts were compared using 1 year cumulative data prior to timing of population mean APHV, with delay in APHV.

Results

Group	HAD SDS	HPHV SDS	APHV (years)	PHV SDS
CD male	−0.56 (−2.15;1.8)	−0.48 (−2.35;1.34)	14.3 (12.4;16.3)	1.2 (−4.18;4.73)
CD female	−1.17 (−1.95;0.40)	−1.17 (−1.70;0.66)	12.8 (10.3;13.8)	1.1 (−1.4;6.8)
UC male	−0.12 (−1.18;1.37)	−0.11 (−1.31;1.53)	13.7 (12.8;15.7)	1.75 (−1.45;9.6)
UC female	−0.57 (−1.32;1.51)	−0.02 (−1.83;1.58)	12.2 (10.1;14.0)	0.75 (−1.6;10.2)

A statistically significant negative impact on 2 parameters, HAD ($P=0.001$) and APHV ($P=0.001$), was seen in the CD-M group as compared to the normal population. Individually, 8/30 CD-M cases had one or more parameter affected: 2 subjects had HADSDS <-2, 3 subjects had HPHVSDS <-2, 3 subjects had an APHV >2 years above population mean, and 2 subjects had a PHVSDS <-2. Median ESR showed a significant association with delay in APHV in the whole group ($r=0.329$; $P=0.018$).

Conclusion

As a group, disorders of the pubertal growth spurt are more likely to occur in CDM. Achieving disease control may be important in timely progression through puberty.

P24

Short stature with deletion of chromosome 15q and duplication of 16q (q26.3:q23.1)

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Introduction

The IGF1-receptor (IGF1R) gene is located on the distal long arm of chromosome 15 (bands q26.3). Short stature due to mutation or deletion of IGF1R gene is rare. Mutation of this gene is better known compared to deletion as a cause of growth hormone resistance. We report a girl with pre and postnatal growth failure with chromosome 15q deletion and 16q duplication.

Case report

Our patient was born at term weighing 2.7 kg (2nd centile). She was ventilated for 2 days for respiratory distress syndrome. She had multiple VSD, dysmorphic features of flat mid-face, small mouth, thin upper lip and limb deformities of prominent interphalangeal joints and bilateral metatarsus varus. At 6 weeks old she required tracheostomy for congenital subglottic stenosis. Chromosomal analysis showed 15q deletion and unbalanced duplication of 16q [46xx, del(15) t(15;16) (q26.1:q22.3)]. The father was a balanced translocation carrier of chromosome 15 and 16. She had moderate learning difficulties and developmental delay. At age 5, both weight and height were <2 SDS. Bone age was delayed by 2.7 years. IGF1 was 2.5 nmol/l (4–20) and IGFBP3 was normal. GH stimulation test to glucagon was normal. By age 10, her height was -2.6 SDS. Repeat IGF1 was 11.8 nmol/l (12–50). Comparative genomic hybridisation (CGH) studies refined breakpoints to (q26.3:q23.1) and interestingly, the IGF1R gene was not deleted as it was proximal to the deletion. She is awaiting commencement of growth hormone therapy.

Conclusion

Pre and postnatal growth failure due to IGF1-receptor gene deletion on chromosome 15 is rare. These children have dysmorphic features and limb deformities. Although her IGF1R gene was not deleted, she fits the described features and we hypothesise that epigenic effects have lead to functional IGF1-receptor dysfunction. Alternately her low IGF1 represents partial IGF1 deficiency. Previous case report has reported benefit from growth hormone therapy.

P25

Leucine sensitive hyperinsulinaemic hypoglycaemia in patients with 3-hydroxyacyl- coenzyme A dehydrogenase deficiency (HADH)

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Background

HADH encodes for the enzyme 3-hydroxyacyl-coenzyme A dehydrogenase (HADH) and catalyses the penultimate reaction in the beta-oxidation of fatty acids. Mutations in the *HADH* gene have recently been described to cause protein sensitive hyperinsulinaemic hypoglycaemia (HH). Protein sensitive HH (specifically leucine sensitivity), is also associated with the hyperinsulinism-hyperammonaemia syndrome (HI/HA syndrome) caused by activating mutations of *GLUD1* that encodes the enzyme glutamate dehydrogenase (GDH).

Aims

(i) To investigate whether the patients with protein sensitive HH due to *HADH* mutations are leucine sensitive. (ii) To evaluate whether patients with *HADH* mutations have increased basal GDH activity and loss of GTP inhibition, as seen in patients with HI/HA syndrome.

Research design and methods

An oral leucine tolerance test was conducted in three patients with HH due to *HADH* mutations (P258L, IVS6-2a$>$g, M188V). The serum ammonia level was measured in all 3 patients. The activity of GDH and the effect of added GTP were determined in lymphoblast homogenates from all three patients.

Results

In response to the oral leucine load, all three patients demonstrated severe hypoglycaemia with simultaneous increase in the serum insulin concentrations, demonstrating leucine sensitivity. None of the controls showed leucine sensitivity. The basal GDH activity and the half-maximal inhibitory concentration of GTP expressed in nmol/l (IC50) were similar to that of controls. The serum ammonia level was normal in all patients.

Conclusions

Mutations in the *HADH* gene are associated with severe leucine induced HH. The mechanism of leucine hypersensitivity does not involve excessive activity of GDH, as observed in patients with HI/HA syndrome and is currently not known. Understanding this mechanism of leucine induced HH in patients with HADH mutations will provide further novel insights into fatty acid and protein interactions in the pancreatic beta-cell. These observations also have important implications for patient management.

P26

Stem cell lines derived from patients with congenital hyperinsulinism

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Congenital Hyperinsulinism (CHI) is primarily a β-cell disorder with an incomplete pathogenesis. The purpose of this study was to generate *in vitro* models of the disease for the purposes of investigating the relationship between gene defect and β-cell development and function. We obtained post-operative resections of pancreatic tissue from four patients with hyperinsulinism. The tissue was collagenase treated and maintained in cell culture conditions. Cell lines developed spontaneously from each patient and were expanded and cryopreserved for subsequent studies. PCR, immunohistochemistry and intracellular Ca^{2+} microfluorimetry techniques were used to examine the molecular and physiological properties of these cell lines. Genotyping reveled that all of the patients carried mutations in the SUR1 gene, *ABCC8*. In each of the cell lines – designated Nes139 (V1430fs), Nes140 (A4V/IVS38-1G$>$T), Nes143 (R620C/N), Nes144 (T172fs/ c.1818-?_1923+?del) islet and pancreatic endocrine progenitor cell selective markers have been identified and their expression stable over several passages and continuous cell culture. These include; Nkx2.2, NeuroD1, Gata6, Maf B, Pax6, Sox4, FoxA2, Arx, Hlbx9, Pbx1, Gata4, Hnf1B, Hnf1A, Hnf4A, Pdx1 and Sox9. Each of the cell lines failed to express Ngn3, Brn4, Pax4, Islet1, IAPP and insulin. Functional studies were undertaken with a number of agonists to raise cytosolic Ca^{2+} level and assess cell viability in the undifferentiated state, $n=6$ experiments in each case. Whilst ATP (0.1 mM) and histamine (0.1 mM) readily raised intracellular Ca^{2+}, each of the cell lines failed to consistently respond Acetylcholine (0.1 mM), depolarising concentrations of KCl (40 mM) and glucose (15 mM). Collectively, the data show that the CHI-derived cell lines display an appropriate molecular and physiological phenotype for populations of proliferating pancreatic progenitor cells. Our results suggest they represent cells of the secondary transition phase of pancreatic development. Future studies will look towards the inductive potential of these cells to produce mature insulin-secreting β-cells.

P27

Feeding problems and their associated predictive factors in congenital hyperinsulinism of infancy (CHI)

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Congenital Hyperinsulinism (CHI), a common cause of persistent hypoglycaemia in infancy can be associated with feeding problems (FP). The extent of FP in CHI is not known. The commonest genetic cause of CHI is mutations in ATP-sensitive potassium (K^+_{ATP}) channel genes (*ABCC8* and *KCNJ11*).

Aims

To define FP in CHI patients presenting to a regional centre, in relation to medication and K^+_{ATP} mutations.

Patients and methods

We retrospectively analysed data in 35 genotyped patients with persistent CHI, with National Research Ethics Service (NRES) approval and consent. Children with FP were formally assessed by a Speech and Language Therapy (SALT) service (recurrent vomiting or inability to tolerate prescribed feed volumes) and classified into 4 categories (poor suck, swallowing in-coordination, vomiting and food refusal). Children with FP were compared with children without FP with regard to mutation analysis, medication, presence of diffuse CHI and birth weight.

Results

Seventeen (48%) CHI patients were identified with FP. Positive K^+_{ATP} mutations (*ABCC8* = 17, *KCNJ11* = 4) were identified in 21 cases. When compared to those without FP, patients with FP had significantly higher K^+_{ATP} channel mutations (Chi-square test; $P < 0.001$), genetically proven diffuse disease (Chi-square test; $P < 0.001$) and birthweights (Chi-square test; $P < 0.05$). Severe FP (FP ≥ 2 categories) were associated with homozygous/compound heterozygous mutations in the *ABCC8* gene (Chi-square test; $P < 0.001$), diffuse disease (Chi-square test; $P < 0.002$) and Diazoxide unresponsiveness (Chi-square test; $P < 0.001$). Fourteen (82%) patients required gastrostomy feeding and at 6 months follow-up, 12 (71%) continued to have 1 or more FP.

Conclusions

Feeding problems occur in approximately half of CHI patients. Patients who are K^+_{ATP} channel mutation positive, Diazoxide unresponsive or have diffuse disease are more likely to have severe FP. We recommend early feeding assessment and intervention in children with CHI as these problems persist in the first year of life.

P28

Properties of a pancreatic side-population stem cell lines from a patient with congenital hyperinsulinism

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NES2Y cells were derived several years ago from a patient following surgery for Congenital Hyperinsulinism (CHI). These cells have the inductive capacity to form insulin-secreting cells, but they are largely uncharacterized. The purpose of this study was to examine the expression and function of the ATP-binding cassette protein ABCG2 and to characterize the cells for their expression of markers of Side Population (SP) progenitor cells and Stellate Cells (SC). Cells were maintained under standard conditions with or without the addition of mitoxantrone (MTX, 20-50 nM for 1, 3 or 6 days) to the cell culture medium. PCR, immunohistochemistry, high content analysis and flow cytometry techniques were used to examine the molecular and functional properties of these cells. Based upon the exclusion of fluorescent dyes such Hoechst 33342 and DCV by ABCG2, we estimated that approximately 30% of native cells expressed a defined SP phenotype which was increased to approximately 60% following exposure to MTX. MTX-induction led to enhanced ABCG2 detection at the plasma membrane and the nucleus, and to a marked decrease in the rate of cell proliferation. Pancreatic endocrine progenitor cell selective markers were found (by RT-PCR) to be expressed over several passages including NKX2.2, PAX6, Nestin, PDX1, NKX6.1 and SOX9, but the cells did not express NEUROD1 and Neurogenin3. NES2Y cells were also found to express a number of SC markers including vinculin, vimentin, synaptophysin, α-smooth muscle actin, glial fibrillary acidic protein, neural cell adhesion molecule, desmin and CRP2. Immunofluorescence confirmed the presence of vimentin protein. Collectively these data suggest that NES2Y cells share common features of SC and SP stem cells and that they express progenitor cell markers consistent with their inductive capacity to form insulin-secreting cells.

P29

Cardiac abnormalities in children with congenital hyperinsulinism (CHI)

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Congenital hyperinsulinism of Infancy (CHI) can be associated with cardiac problems such as septal hypertrophy and reversible hypertrophic cardiomyopathy (Breitweser et al. 1980, Harris et al. 1992); however, the prevalence and range of cardiac abnormalities in CHI has not been well investigated.

Aims and methods

With National Research Ethics Service approval and consent, we retrospectively reviewed the prevalence of cardiac abnormalities in 48 children with CHI. Forty-three patients were genotyped for potassium channel (K_{ATP}) mutations. Echocardiography was used to detect structural abnormalities and parameters for left/right/biventricular hypertrophy (LVH/RVH/BVH) and interventricular septal thickness in diastole (IVSd) were used to quantify myocardial dysfunction, with serial echocardiography to assess cardiac improvement. Electrocardiograms (ECG) were used to corroborate muscle hypertrophy.

Results

In our cohort of 48 children, 94% (45/48) required diazoxide therapy for CHI management and 48.8% (21/43) had positive K_{ATP} mutations. Median age at echocardiography was 23 days (5 days to 10.8 years). Cardiac structural abnormalities were present in 15 (31%) (5 patent ductus arteriosus, 4 atrial septal defect, 2 ventricular septal defect, 2 branch pulmonary artery stenosis, 1 atrial stenosis and 1 aberrant subclavian artery). Myocardial hypertrophy was present in 26(54%) (20 LVH, 1 RVH, 5 BVH) with increased IVSd in 8(17%) children with LVH. ECG abnormalities consistent with myocardial hypertrophy were present in only 24% (5/21). Cardiac medications (diuretics, digoxin, beta blockers) were required in 7 (15%), with improved function and discontinuation of therapy in 6 (75%). No significant associations were found between birthweights, genotypes and cardiac defects using Chi-squared analysis.

Conclusion

Our results show that a third of CHI patients have cardiac defects. Almost a fifth had symptomatology severe enough to require treatment, with reversible pathology in 75%. We advocate early cardiac assessment in infants with CHI, with baseline echocardiography as the investigation of choice.

P30

Pigmentary hypertrichosis and non autoimmune insulin dependent diabetes mellitus (PHID) syndrome is associated with chronic inflammation and elevated serum amyloid A protein

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Background

PHID is a novel syndrome caused by mutations in *SLC29A3*, which encodes for the nucleoside transporter protein hENT3. It is associated with multiple endocrine manifestations including severe short stature, pubertal delay and pancreatic exocrine insufficiency. Mutations in *SLC29A3* have also been linked to H syndrome and familial Rosai Dorfman Disease (RDD). A key feature of these syndromes is persistent inflammation. Currently there is no treatment for these patients.

Aims

To study the mechanism of the inflammatory response in patients with PHID.

Methods

Serum amyloid A protein (SAA) is a marker of the inflammatory response and was measured at the National Amyloidosis Centre at the Royal Free Hospital in London in 2 patients with mutations in *SLC29A3*. Immunohistochemistry determined the subcellular localisation of hENT3. As the inflammatory response activates the interleukin-1 beta (IL-1b) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, the effect of *SLC29A3* knockdown was investigated on inflammation by observing the activation of the downstream transcription factor NF-κB.

Results

In both patients SAA was significantly elevated (99.1 and 30 mg/dl respectively, control <10 mg/dl). hENT3 was localised to the mitochondrion in cultured placental cell lines (TC1) while in fibroblasts it was observed in the endosome. NF-κB was activated when *SLC29A3* was silenced.

Conclusions
PHID syndrome is associated with significant elevation of SAA which reflects the underlying inflammatory response. The persistent inflammation might explain the multiple endocrine manifestations observed in patients with PHID syndrome. Our preliminary data suggests that the inflammatory response involves activation of NF-κB. These observations might allow patients with PHID syndrome to be treated with drugs which block the IL-1b and NF-κB pathways (such as anakinra).

P31

An unusual case of diabetes complicated by massive insulin oedema following onset of insulin therapy

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Insulin oedema is uncommon and poorly understood. It has been reported mainly in the adult literature. We present one of the youngest cases reported in the literature.
A previously obese 9-year-old boy gradually lost weight over 18-month period and experienced polyuria and polydipsia for several months. He presented in diabetic ketoacidosis (blood glucose 24 mmol/l, pH 7.13, bicarbonate 6.6 mmol/l, potassium 3.13 mmol/l, urinary ketones 3+) which responded well to treatment. Admission weight was 37.4 kg, height 149.8 cm and BMI 16.7. He developed significant hypokalaemia and required increased concentrations of KCl in the intravenous fluids (35 mmol/500 ml) to maintain normal levels. Recovery was otherwise uneventful and was discharged on basal bolus insulin regime. From 5 days post initiation of insulin therapy, he developed increasing generalised oedema. By the 8th day, he gained a significant amount of weight of 11.8 kg and had periorbital, leg, thigh and scrotal oedema. He was extremely well. No renal, hepatic or cardiac cause for oedema was found. Abdominal ultrasound was normal including inferior vena cava and iliac veins. He was treated conservatively and the oedema resolved over 4 weeks. Over next 19 months, he gained weight dramatically despite ever decreasing insulin requirements. Currently aged 11.5 years, his height is 163.8 cm, weight 95 kg and BMI 35.4. Insulin requirement is only 13 units/day and is also on Metformin. HbA1c is 5.7%. There is no family history of diabetes. Further investigations showed GAD antibody negative, MELAS m.3243 A>G & 3271 T>C mutation negative.
This case highlights the importance of recognizing insulin oedema, a worrying but benign complication of insulin therapy. This case also presented a diagnostic quandary making it difficult to classify the type of diabetes he had.

P32

Is point-of-care glucose testing sufficiently accurate to be reliably used for clinical decision-making?

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Background
Point-of-care tests (POCT) for glucose promote timely clinical management. We assessed the precision and accuracy of POCT compared with laboratory measurements in children undergoing dynamic function tests.
Methods
Split samples of venous blood were tested on POCT meters (Precision PCx Plus and Precision Xceed Pro) and in the laboratory (ADVIA 2400). Clinical reliability was assessed against the ISO 15197 standard: In at least 95% of cases, discrepancy between reference and point-of-care glucose should be <0.83 mmol/L for glucose <4.2 mmol/L or $<20\%$ for glucose ≥ 4.2 mmol/L. The data were reanalysed after applying a correction factor for glycolysis in sample tubes of $+0.39$ mmol/L, derived from a large prospective trial.
Results
A total of 1688 pairs of samples were analysed from 206 patients. The data were highly correlated ($R=0.958$). Linear regression results, expressed in a Passing-Bablok equation as $Y=0.856X+1.048$ ($P<0.001$), and Bland-Altman difference plots (intercept $+0.941$, slope -0.115) both demonstrated higher POCT results at low glucose values and lower results for high glucose values as compared with laboratory results. Only 84.7% (linear regression) and 87.9% (Bland-Altman) of values fell within the tolerated error margins. This increased to 95.5% and 97.8% after adjusting laboratory values for glycolysis.
Conclusion
The Precision meters overestimate plasma glucose for hypoglycaemic states and underestimate them for hyperglycaemic states. When values are adjusted for glycolysis prior to laboratory measurement, this discrepancy remains significant but the meters meet the ISO 15197 requirements.

P33

Audit comparing the body-mass index (BMI) of children, with type 1 diabetes, in Nottingham, with current and historical background populations in the UK

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Obesity is a growing epidemic and a major cause of morbidity and mortality. Maintaining a healthy weight is of even greater importance for diabetics, due to the increased risk of micro-vascular and macro-vascular complications.
There is suggestion that type 1 diabetic children are more likely to be obese than their peers (e.g. 'Type 1 diabetes children often overweight', www.diabetes.co.uk/news). In our study the BMIs of 262 children (aged 2–15 years), with type 1 diabetes, were compared with the background population (using UK90, National Child Measurement Programme and Health Survey for England data 2008).
Our population was found to have a mean BMI 1.0 standard deviation above the mean for age (85th centile, UK90 data). 26.3% (95% CI 21.4–32.4%) were obese (BMI>95th centile).
These results are consistent with the trend of increasing obesity over the last 30 years. However, when compared with the current national prevalence of 16% (HSE, 2008), our population of type 1 diabetics were significantly more likely to be obese. Obesity rates in younger patients (25.3% in 2–10-year-old) were not statistically different from older patients (27.0% in 11–15-year-old), in contrast to the background population (2–10 years 13.9%, 11–15 19.5%).
We now need to look at possible reasons for the difference in obesity rates so that therapeutic options can be devised. We plan to do further subset analysis to look at demographic factors and sex differences. We will also look at the effect on BMI of different insulin regimes and on ways of treating hypoglycaemia. With this increased awareness of the problem we will look at methods of continuing to promote healthy diets but with an increased emphasis on maintaining a normal BMI from diagnosis without inducing disordered eating behaviour and manipulation of insulin to achieve this.

P34

Undefined diabetes unfolds

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Introduction
Although type 1 diabetes is the most common type of diabetes in children, with the steady increase in type 2 and rare forms of diabetes, it may be sometimes difficult to ascertain the type of diabetes at the time of presentation. Some children present with a combination of features and do not fit into one of the classical types of diabetes. The rapid progress in the molecular genetics has helped to identify the specific diagnosis for these rare forms of diabetes. With the advent of newer techniques, the term 'undefined' diabetes is becoming obsolete as a definitive diagnosis may be possible in majority of the cases.
Case series
We report a cohort of children in our clinic, who were initially classified as 'undefined' type of diabetes. However over the years, majority of these children have received a definitive diagnosis which has helped appropriate treatment and counselling. In the cohort of 17 children (11% of clinic), we have confirmed 3 congenital generalised lipodystrophy (AGPAT-2 mutation), 2 Rogers syndrome, 2 DIDMOAD syndrome, 2 siblings – one with Cohen's syndrome and the other with insulin resistance, 1 Werner's syndrome, 1 MODY and 1 Prader Willi syndrome with diabetes. The mean duration for reaching a definite diagnosis is 3 years. We still have 5 children with 'undefined' type of diabetes who are being evaluated for a definitive diagnosis.
Conclusion
A detailed family history along with the evaluation of other associated features will aid the diagnosis. 35% of our cohort has severe visual involvement and it may be useful to consider routine visual screening in children with diabetes who are from a consanguineous background. It is essential to reach a definitive diagnosis, as this has implication for the siblings and the other family members. It also helps to estimate prognosis and plan for appropriate management.

P35

NAFLD in type 1 DM: a report of 2 cases

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Introduction
Non-alcoholic steatohepatitis (NASH) is part of the spectrum of non-alcoholic fatty liver disease (NAFLD). NASH commonly occurs in patients with type 2 DM and is less recognised in type 1 DM. The natural history of NASH in adult patients suggests potential development of progressive fibrosis and cirrhosis. However, secondary glycogenosis, commonly occurs in type 1 DM, is *reversible* when good glycaemic control is achieved, but may be misidentified as NASH because of similar clinical features but are differentiated histologically.
Case 1
Fifteen-year-old girl with type 1 DM for 8 years. Her weight was 44 kg with BMI 20 kg m^{-2}. She had numerous admissions with DKA. She presented with abdominal pain and distension. Her abdominal ultrasound showed diffuse hepatomegaly but was otherwise normal. Liver autoimmune and viral serology were unremarkable. Her HBA1C was 14%, ALT 579 IU/l (NR 1–40), AST 212 IU/l (NR 1–37), Alkaline Phosphatase (AlkP) 932 IU/l (NR 203–1151). Her liver biopsy showed generalised moderate macrovesicular and microvesicular steatosis suggestive of Insulin induced steatosis. Four months later, her HBA1C was 13.4%, ALT 15 IU/l, AST 12 IU/l, AlkP 744 IU/l.
Case 2
Fifteen-year-old girl with type 1 DM for 4 years. Weight 54 kg, BMI 24 kg m^{-2}. Frequent admissions with DKA. Presented with mild abdominal tenderness. Examination revealed 4 cm hepatomegaly. Results; Liver biopsy: microvacuolar steatosis, intracellular cholestasis, increased glycogen deposition and focal pericellular fibrosis. HbA1C 11.7%. ALT 132 IU/l, AST 204 IU/l, AlkP 458 IU/l. Six months later, ALT 17 IU/l, AST 25 IU/l, AlkP 254 IU/l.
Conclusion
We present 2 cases of NAFLD in adolescent girls with type 1 DM, both whose liver transaminases improved after intensified glycaemic control. Further studies are necessary to establish the prevalence of NAFLD in children with *type 1 DM* and to identify whether a period of intensification of insulin therapy is beneficial prior to invasive procedures.

P36

MCADD and IDDM-A rare combination

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Introduction
We describe an 11-year-old boy (N) with Medium-Chain Acyl Dehydrogenase Deficiency (MCADD) diagnosed at one year of life and type 1 IDDM diagnosed at 10 years.
History and discussion
N was diagnosed with MCADD when he was found hypoglycaemic. He was treated with the standard Emergency Regimen (a special feeding plan used if the child is unwell or not feeding well, wherein glucose polymer feeds are given frequently) and has had no further problems. When 10 years old, he presented in DKA, was diagnosed with diabetes mellitus and started on insulin therapy. The combination of MCADD and type 1 DM is extremely rare. The two conditions have major common themes: avoiding catabolism and hypoglycaemia. Avoiding catabolism is achieved in MCADD patients by giving glucose to stimulate endogenous insulin production, while in type 1 DM this is achieved by giving insulin as well. Thus at times of illness it has been advised that N should follow the Emergency Regimen but will also need closer monitoring of his insulin requirement. As N may not make as many ketones as one would expect during the times of diabetic crisis, ketonuria should be addressed urgently. Ketones may be produced as the block in fat oxidation is incomplete and also occasionally from protein breakdown. During catabolism instead of making ketones N will make a number fat metabolites some of which are neurotoxic.
Conclusions and recommendations
MCADD and type 1 Insulin dependent diabetes mellitus occurring together in the same individual is extremely rare. Management of both together revolves around good glycaemic control, while preventing catabolism.

P37

Type 2 diabetes in childhood: building a platform for interventions to prevent the progression to cardiovascular disease

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Type 2 diabetes (T2DM) is increasing in children in the UK and worldwide, most likely related to the rising prevalence of obesity. We are developing a UK national cohort of children (under 18 completed years) with diabetes defined by WHO criteria, suspected type 2, BMI above 85th centile; but who do not have genetically confirmed monogenic diabetes, secondary diabetes, or any evidence of pancreatic autoimmunity. The aim of this study is to describe the characteristics of the first 30 children recruited.
After writing to all consultants with an interest in paediatric diabetes, we were notified of 234 children fulfilling the inclusion criteria. Clinical data was collected by a standardized case report form and checked for consistency before loading onto a database. So far, we have details on 30 children. The median age at diagnosis of T2DM was 11.4 years (range 7.9–16.9 years), and the duration of diabetes is 2.8 years. The M:F ratio is 1:3, and 50% are from non-white UK ethnic origin. Only 2 children are prepubertal. Five children (20%) were identified coincidentally or with no symptoms; one child presented in diabetic ketoacidosis. No child is recorded with retinopathy, but out of 10 children screened for nephropathy, 4 have microalbuminuria. While almost all children (90%) are taking metformin, there are 14 (50%) of children managed with insulin in addition. All 18 children with data on family history, had one or more first degree relatives affected with type 2 diabetes.
The data confirm that most children are pubertal or post pubertal at diagnosis, probably reflecting increased insulin resistance. Ethnic minorities are disproportionately represented. The proportion of children managed with insulin in addition to metformin is higher than in previous surveys. A positive family history for type 2 diabetes is very common and could represent a useful predictive marker for T2DM.

P38

Insulin oedema in children with type 1 diabetes mellitus

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Generalised oedema as a rare complication of insulin treatment in the absence of renal, hepatic or cardiovascular disease was first described by Leifer in 1928. The true incidence of insulin oedema in children with type 1 diabetes mellitus is unknown and since it was first reported in 1979, there have been only 12 reported cases worldwide. Insulin oedema has been described both in patients with newly diagnosed diabetes receiving insulin therapy for the first time and also in those with established diabetes with a history of poor control. Insulin oedema is reported to have a higher incidence within the African population and in paediatrics is more common in females.
We report on the case of a 15-year-old girl of Caucasian origin with insulin dependent diabetes mellitus of 5 years duration with poor compliance and elevated HbA1c ($>14\%$) who presented with diabetic ketoacidosis. Following appropriate management she was discharged home after 48 h on subcutaneous insulin but subsequently developed bilateral periorbital, pedal and sacral oedema. In the absence of cardiac, hepatic or renal disease a diagnosis of insulin oedema was made. She was given advice on a salt restriction diet and the oedema resolved spontaneously after a week.
Insulin oedema is a rare condition which should be considered in children who present with oedema following insulin therapy in the absence of any other cause. Insulin oedema is more likely to occur in patients with a low BMI and those receiving >1 unit/kg/day of insulin. Its identification is important since it generally follows a benign course and usually requires no treatment. The severity of insulin oedema can vary greatly from mild pedal oedema to severe generalised oedema. In most cases the oedema resolves spontaneously within a few weeks. Other patients have been treated with diuretics.

P39

Case series: is thiamine responsive megaloblastic anaemia and diabetes associated with cardiac anomalies

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We describe four cases of Thiamine Responsive Megaloblastic Anaemia (TRMA), Rogers Syndrome. Three cases are siblings, the fourth from another family. They are all of Pakistani origin and born to consanguineous parents. All have the clinical triad of megaloblastic anaemia, non-type 1 diabetes mellitus, and sensorineural deafness.

The SLC19A2 gene mutation affects the transport of thiamine, which is required for normal tissue growth and development in humans. Thiamine supplementation has the following effects: anaemia resolves but the erythrocytes tend to stay macrocytic; hearing loss seems to be irreversible although may be delayed; Diabetes initially responds but most patients become fully insulin dependent after puberty.

All four cases have been on thiamine supplementation since diagnosis and insulin. Intracellular thiamine levels have been checked and are within the normal range. One case presented acutely in her 20 s with atrial fibrillation and was found to have a grossly dilated heart. Transoesophageal echo revealed a tricuspid valve anomaly. There were no previous cardiac symptoms and therefore a cardiac examination had not been performed when attending diabetes clinic. The other three, although asymptomatic were screened for cardiac complications. Two had normal hearts but one was found to have a large atrial septal defect requiring surgical intervention.

Cardiac anomalies are not one of the cardinal features of Rogers but have been infrequently described. It seems unusual that 2 of the 4 young people with TRMA in Sheffield have been found to have cardiac problems and we suspect an association. Neither of our cases had been suspected previously and had delayed diagnosis with potentially serious consequences. We would recommend cardiac screening of all cases, to detect anomalies early. We would be interested in hearing from paediatricians about other children with Rogers Syndrome.

P40

An audit on the process of transition from the paediatric diabetes service to the adult service at the University Hospital of Wales

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Introduction

The period of adolescence is a difficult time for most people and is the time when transition from the paediatric diabetic service to the adult occurs; therefore a smooth transition is essential. The National Service Framework for Diabetes identified transition from paediatric care to adult as an area where protocols could support better care. Placing emphasis on the transition services may help in ensuring effective long-term control and health improvement.

Methodology

The patients were identified from clinic lists; either due to transfer in the next year or transferred in the last three years and had attended the transition clinic. Out of 56 eligible pre-transition patients 13 responded and out of 48 post-transition 12 responded. Everyone available when contacted was happy to participate. A telephone survey regarding the transition process at the University Hospital of Wales was undertaken, addressing patient satisfaction and correlation with government guidelines. In addition we looked at the participating patients HbA1c values from the last 3 years to illustrate long-term control.

Results

Ten out of 13 pre-transition patients were not aware of transition. Those aware of transition felt the organisation of transition to the adult clinic was 'adequate'.

Changes/benefit to clinical practice

NSF guidance states that 'sufficient time should be given for young people to familiarise themselves with….transition', in the majority of cases this was not the situation. Many of the adults surveyed recommended earlier transition.

Conclusion

Overall the respondents were satisfied with the current transition process implemented at UHW, however improvements could be made regarding communication. The time span between the discussion with the patient, regarding the idea of transition and the process occurring was also highlighted as an area in need of improvement. To quote a respondent, 'I knew I was going (to the adult service) but not what would happen'.

P41

It's not just Coeliac disease: gastroenterology referrals from a paediatric diabetes clinic

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There is a well-recognised association between Coeliac disease and type 1 diabetes (T1DM). Four of our 68 patients have both conditions (5.9%). We present three other patients with T1DM and GI disease – two inflammatory bowel disease (IBD = 2.9%) and one primary sclerosing cholangitis (PSC) and IBD (= 1.5%).

Case 1

Sixteen years old male, with T1DM from 13-year-old, developed diarrhoea and abdominal pain with no weight loss or blood pr. Investigation showed microcytic anaemia, raised inflammatory markers and negative Coeliac screen. Colonoscopy revealed eosinophils, but repeat showed a pan-colitis. Diagnosis = Indeterminate colitis.

Case 2

Nine years old male, with T1DM from 2-year-old, developed lower abdominal pain and fluctuating bowel habit but with no blood pr. Negative Coeliac screen, normal FBC and LFTs but has iron deficiency and raised inflammatory markers. During surgery, for appendicitis, he was found to have mesenteric lymphadenopathy and a thickened ileum. Small bowel series was suggestive of terminal Crohn's disease. Terminal ileal biopsies showed lymphoid nodularity (non-specific). Commenced on Pentasa, which controls his symptoms. Diagnosis = Possible terminal Crohn's.

Case 3

Fifteen years old male, T1DM from 10-year-old, with abnormal LFTs on routine bloods. He is asymptomatic and anicteric. Liver biopsy was inconclusive but results of MRCP and MRI resulted in diagnosis of PSC. Despite being asymptomatic his colonoscopy showed a pan-colitis. Diagnosis = PSC and indeterminate colitis.

Conclusion

Coeliac disease is not the only GI condition seen in patients with T1DM. Previous reports have shown upto 10% of those with PSC have T1DM with about half being diagnosed prior to their liver disease. Patients with IBD have rates of T1DM upto 2.9% and there are recognised shared susceptibility loci. Remember when assessing new symptoms that autoimmune diseases often occur multiply. In our clinic 10.3% of patients have a GI co-morbidity of which 43% was IBD.

P42

Molecular genetic testing for hypophosphatemic rickets

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Hypophosphatemic rickets is a genetically heterogeneous disorder of defective renal phosphate transport and vitamin D metabolism with an X-linked dominant (XLHR), autosomal-dominant (ADHR) or autosomal-recessive (ARHR) pattern of inheritance. Germline mutations in the *PHEX* gene are associated with the X-linked form which affects both males and females. The autosomal dominant form is characterised by mutations in the *FGF23* gene and the autosomal recessive form by mutations in the *DMP1* (ARHR type 1) or *ENPP1* (ARHR type 2) genes. Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is an autosomal recessive disorder associated with mutations in the *SLC34A3* gene. Our laboratory has offered testing for *PHEX* gene mutations since 2002 and has recently extended this service to include all the genes listed above. Test methodology involves direct sequencing for all genes and dosage analysis by MLPA for the *PHEX* gene. A total of 181 index cases have been referred for testing. The mutation detection rate is 61% for the *PHEX* gene, increasing to 88% for cases with a family history and 13% for FGF23. Three patients with *SLC34A3* or *ENPP1* mutations have been identified. Inactivating mutations in *ENPP1* can cause arterial calcifications and it is therefore important to distinguish these patients to ensure an appropriate treatment regime. In total a genetic diagnosis has been obtained for 76% of probands referred for testing. Identifying the genetic aetiology confirms the clinical subtype, provides prognostic information and accurate estimation of the recurrence risk. Genetic testing early in life for at-risk individuals enables early diagnosis and prompt treatment to avoid irreversible bone deformities.

P43

Vitamin D status in paediatric oncology patients compared to control subjects: grounds for targeted supplementation

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Objective
Children with malignant disease are at increased risk of bone disorders, cardiovascular disease and further neoplasia. Vitamin D status may influence this risk and so we assessed Vitamin D levels in children with malignant disease undergoing active treatment or surveillance post-therapy.
Study design
This was an outpatient-based cross-sectional study of 60 children with a history of malignancy (cases: median age 11.1 years; range 1.5–24.4 years) and 61 control subjects (median age 8.4 years; range 0.2–18.0 years) who were attending hospital for the management of non-malignant disorders. Serum vitamin D (25OHD), PTH levels and bone biochemistry were determined. Vitamin D status (defined here by 25OHD levels) and its relationship to age, sex, ethnicity, time of sampling and presence of malignant disease was assessed using multiple regression.
Results
Vitamin D status was suboptimal in 62% of cases (25OHD $<$ 50 nmol/l). Vitamin D deficiency (defined here as 25OHD $<$ 25 nmol/l) was more common in children with malignant disease than controls (21.3% vs 3.3%; $P=0.013$). Month of sampling ($P<0.001$), ethnicity ($P<0.001$), older age ($P=0.011$) and history of malignancy ($P=0.012$) were associated with a poorer vitamin D status. Higher PTH levels were associated with significantly lower vitamin D status in controls ($r=-0.42$; $P=<0.01$) but not in cases ($r=-0.07$; $P=0.65$). The median Body Mass Index in the cases (18.7) was comparable to the controls (18.2).
Conclusions
Vitamin D levels are lower in survivors of childhood cancer in comparison to control children with the majority either insufficient or deficient. This may reflect poor diet, an increased amount of time spent indoors compared to their peers as well as the toxic effects of chemotherapy/radiotherapy. An assessment of Vitamin D status and, where necessary, appropriate supplementation may be of particular value in this group of children.

P44

A lifetime of aches, pains and hypocalcaemia

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A 13-year-old girl with a history of developmental dyspraxia, enamel hypoplasia and a raised creatinine kinase (CK) presented to her GP with fatigue on any physical exertion including walking. On questioning she has always complained of muscle pain and tiring easily since she was a young child. On blood testing it was identified that she was profoundly hypocalcaemic with a calcium adjusted for albumin of 1.52 mmol/l, phosphate of 3.20 mmol/l, parathyroid hormone (PTH) of 1.5 pmol/L and a of CK of 363 U/l. From these results she was diagnosed with autoimmune hypoparathyroidism and referred to a paediatric endocrinologist. She was prescribed 1-alpha-hydroxycholecalciferol, but despite treatment, and compliance there was no significant increase in the calcium or decrease in the CK. As the hypoparathyroidism was not the cause of the low calcium a number of other tests were conducted, until a calcium sensing mutation was suggested. DNA analysed showed that there was a T to C nucleotide substitution in exon 7 of the *CASR* gene (c.2495T$>$C), which is predicted to result in the replacement of the amino acid phenylalanine with serine at residue 832. This substitution is a change from an aromatic hydrophobic amino acid to an uncharged polar amino acid and is believed to be highly pathogenic. The resulting autosomal dominant hypocalcaemia causes inappropriate inhibition of PTH secretion and renal calcium absorption, due to the increased sensitivity of the calcium receptor expressed in both the parathyroids and the kidneys, resulting in hypocalcaemia. To treat this condition PTH injections have been offered, but have been rejected. The present treatment is with vitamin D, calcium and diuretics with frequent ultrasounds to monitor nephrocalcinosis. Both parents have had their calcium levels checked and both siblings are also unaffected therefore this is considered to be a *de novo* mutation.

P45

Metabolic bone disease of prematurity

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Premature infants are at significant risk of reduced bone mineral content and osteopenia. Inadequate phosphate and calcium uptake in-utero followed by poor postnatal intake in the presence of high growth velocity leads to metabolic bone disease in premature babies. It is not due to vitamin D or parathyroid hormone deficiency.
There is no national or international consensus on how to prevent or manage this condition leading to varied practice across the different units in the UK.
We conducted an audit at local neonatal unit to see if current available guidance was helpful for clinicians in making right decisions in preventing this common neonatal condition. Local neonatal guideline was used as a standard as there was no national standard.
We recruited 29 babies with birth weight $<$1.5 kg, admitted to neonatal unit between July 2007 and July 2009. Data was collected on a structured proforma by retrospective review of case notes and was analysed without using statistical tests. Of the 29 babies, 13 were excluded because of death or incomplete data. In 6/16 babies, oral phosphate treatment was indicated, however in only 4 babies treatment was started (66%). In 10 babies treatment was not indicated but 1 baby still was started on treatment. Five babies in whom oral phosphate treatment was started, the starting dose was appropriate however in 2/5 the dose of oral phosphate was not increased appropriately when indicated. One baby had possible Rickets but X-ray wrist was not taken and Rickets was not investigated or treated. This audit highlighted two main issues; one, lack of uniformity in managing metabolic bone disease in premature babies and two, inadequate details in the guideline leading to difficult interpretations and decision making.
There is a need for standardisation of the guidance at national level so as to avoid confusion and help clinicians making uniform decisions.

P46

Trends in clinical activity of a paediatric bone densitometry service

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Background
Bone densitometry by DXA is now considered routine part of clinical management of children at risk of osteoporosis. Data on activity of a paediatric DXA service would be helpful for service planning but are currently lacking.
Aim
A survey of referrals to the service and size-adjusted total body (TB) and lumbar spine (LS) bone mineral content for bone-area standard deviation scores (BMC for BA SDS) were obtained from the local database.
Results
From 2002–2009, 2089 DXA scans (57% male) were performed (median/yr$=$ 261, range 239–286), most were from gastroenterology (24.4%) and metabolic bone (19%) clinics. Total referral was 251 for 2009, with a decline in renal referrals, and increase in haematology and respiratory referrals. By clinical condition, 21% had IBD, 12% osteogenesis imperferta, 10% chronic kidney disease, 11% cancer-related, 5% poor mobility, 5% glucocorticoids, 5% arthritis, 4% cystic fibrosis, 3% hypogonadal, and 25% other miscellaneous concerns. Low BMC was more prevalent at LS than TB (1.7%, 0.2% respectively in ≤ -2.0SDS category, and 15.4%, 1.8% respectively in -1.0 to -1.9SDS category). Boys were 5.4 times more likely than girls to have LS ≤ -2.0SDS. By indication, lowest BMC values are summarised below

BMC SDS	Entero-pathy (%)	OI (%)	Meta-bolic disorder (%)	Hypogon (%)	Liver disease (%)	Poor mobility (%)	Renal (%)
<-2.0	15.5	7	3.2	3.4	3.1	5	1
-1.0 to -1.9	15.4	27.6	5.7	16.9	6.3	21	13.6

Conclusion
DXA scans are performed for many conditions associated with osteoporosis. Referrals for secondary osteoporosis may depend on clinical awareness about bone health as well as variations in clinical practice and need careful monitoring.

P47

Prevalence of congenital hypothyroidism (CHT) in infants presenting with prolonged jaundice

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Background
Among infants presenting with prolonged hyperbilirubinaemia there is anecdotal evidence that some babies who were Newborn Screening-negative for congenital hypothyroidism (CHT) have CHT diagnosed at the time of presentation with jaundice.
Aims
To determine the prevalence of CHT in babies presenting with prolonged jaundice and to assess the predictive value of lowering the TSH cut-off for a screen-positive result on the ability to identify babies at the time of newborn screening (NBS) who might subsequently present with hyperbilirubinaemia and abnormal thyroid function tests (TFTs).
Methods
We investigated infants presenting with prolonged neonatal jaundice (serum bilirubin >100 μmol/l at >2 weeks of age) to assess the prevalence of CHT among cases referred to a regional paediatric hospital over a 2-year period (Apr 07–Mar 09). The NBS record and serum TFTs were checked to identify those who were either screen positive (bloodspot TSH level >20 mU/l), 'persistent borderline' (2 bloodspot TSH 8–20 mU/l) or were found to have serum TFTs within the hypothyroid range.
Results
A total of 257 infants presented with prolonged jaundice, of whom 179 (70%) had serum TFTs. Five infants had a serum TSH >10 mU/l (range 11–422 mU/l, fT4 <4–22 pmol/l), bloodspot TSH in this group was 0.5–227 mU/l and two of these were identified as CHT screen positive A further 39 had serum TSH 5–10 mU/l (fT4 14–28 pmol/l), all had NBS TSH results <8 mU/l (0.4–4 mU/l). All children other than those identified as screen positive had normal follow up TSH levels and none were found to have CHT at 3 months of age.
Conclusions
Among our cohort of infants presenting with prolonged jaundice, there were only 2 children with confirmed CHT (prevalence of 0.79%). We conclude that the current NBS blood spot TSH cut-off >8 mU/l is a robust screening tool for CHT that prevents the occurrence of false negatives.

P48

A rare complication of Hashimoto's thyroiditis

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Primary thyroid gland lymphomas account for less than 5% of all thyroid malignancies. They mainly occur in the setting of lymphocytic thyroiditis or Hashimoto's disease. The majority are mucosa-associated lymphoid tissue lymphomas and diffuse large B-cell lymphomas. There have not been any cases of thyroid lymphoma reported in children in the last 20 years.
Our patient is a 9-year-old boy who was noted to have a lump on the right side of his neck in November 2009. He was initially treated with oral antibiotics for a coexisting upper respiratory tract infection. As there was no improvement, he had thyroid function tests performed. TSH was 55.17 mIU/l and FT4 was 10.1 pmol/l. Thyroid Peroxidase antibodies were 74 IU/ml. He was commenced on Thyroxine. An USS showed an irregular and inhomogeneous mass in the right lobe of the thyroid gland measuring 4 cm$\times$4 cm. Fine needle aspiration showed a thyroid lymphoma arising on a background of chronic lymphocytic thyroiditis.
As the mass rapidly increased in size, he was commenced on Prednisolone, which led to a reduction in the size of the mass. Bilateral bone marrow aspirates, trephine and CSF were negative. He had a CT scan of the neck and chest and a further biopsy which confirmed a B cell lymphoma showing a high proliferation index. He underwent hemithyroidectomy in April 2010. Histopathology revealed a residual necrotic nodule and Hashimoto's thyroiditis. He has since completed treatment on the B-Non Hodgkin's lymphoma protocol. In June 2010, he developed type 1 diabetes mellitus. He was positive for Islet cell antibodies but had normal GAD antibodies. He is currently on a basal bolus regimen.
We present a case of a thyroid lymphoma in a patient with Hashimoto's thyroiditis. It is important to be aware of this rare complication and its association with other autoimmune disorders.

P49

Timing of the first Guthrie test in preterm infants (32 weeks gestation or less) in Scotland and the efficiency of rescreening

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Background
Premature infants are at risk of delayed screening for congenital hypothyroidism (CH), which may markedly affect initial treatment time and neurodevelopmental outcome. Rescreening preterm infants at four weeks (30 days) of life has been recommended to detect cases with delayed TSH elevation.
Aim
To examine the performance of the CH screening programme in preterm infants aged ≤ 32 weeks in terms of timing of the initial Guthrie tests, and to evaluate the efficacy of rescreening in preterm infants.
Design
This retrospective study covers the period 2006–2009 inclusive. Age at initial blood spot sampling, age at repeat sampling and the prevalence of late testing in infants born ≤ 32 weeks' gestation were compared with matched, randomly-selected full-term newborns. In addition, preterm infants with abnormal capillary TSH concentration (>8 mU/l) on screening who were referred to a paediatrician for evaluation were further examined. Comparing preterm infants ($n=3511$) with term infants ($n=4000$) from 2006 to 2009 showed that median (range) age for Guthrie sampling was 6 (0–223) *vs* 5 (4–37) days respectively ($P=0.0001$). Late sampling (10 days) occurred in 362 of 3511 (10.31%) preterm cases versus 12 of 4000 full term infants (0.3%). However, the overall performance was one day improved during 2008 and 2009. Twenty-six preterm infants from the whole cohort had an abnormal TSH level and seven were referred by the laboratory for further evaluation. Five of the seven infants detected on repeat screening had recorded a normal initial capillary TSH concentration.
Conclusions
Delayed capillary TSH sampling in newborns continues to pose a problem, particularly for premature infants in the Scottish screening programme despite a recent slight overall improvement in performance measure. Our finding support the rescreening of preterm infants of ≤ 32 weeks gestational age for detecting delayed TSH elevation.

P50

Why the confusion in Hashimoto's encephalopathy?

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Neurological complications of thyroid disease are well recognised; however the distinct clinical entity of encephalopathy associated with autoimmune thyroid disease has been only occasionally reported in the paediatric population. We describe a case of Hashimoto's encephalopathy (HE) in a teenage girl.
A 13-year-old girl presented with seizures and prolonged confusion. Baseline blood tests, CSF analysis and CT Brain were essentially normal. She was discharged with the diagnosis of possibly an epileptic seizure. Over the next 3 weeks she re-presented with 2 further episodes of prolonged periods of confusion and visual hallucination. Extended investigation examining infective, metabolic and auto-immune causes of encephalopathy were negative except for much raised thyroid peroxidise antibodies (anti-TPO levels of 2767 IU/ml; Normal range 0–60 IU/l). Her thyroid function tests showed hypothyroidism: TSH – 12.51 mU/l (0.35–5.5), T_4 – 9.4 pmol/l (11–19.5) and T_3 – 4.8 pmol/l (3.5–6.5). She was commenced on thyroxine and a tapering course of prednisolone as treatment for presumed HE.
She has remained symptom free for over 8 months now.
HE is a disorder with persisting or fluctuating neurological symptoms in a patient with high anti-TPO antibody levels. Diagnosis is based on the triad of neuropsychiatric symptoms, detection of anti-TPO antibodies in blood and the elimination of other causes. Clinical response to corticosteroid therapy also supports the diagnosis. There is no correlation between antibody levels and clinical severity of illness. HE is unrelated to thyroid function status and affected individuals are usually euthyroid or mildly hypothyroid. Long-term prognosis is good, with 90% of patients in remission after 10 years. HE is likely to be under-diagnosed in children due to a low level of suspicion. Awareness of this disease is important as most patients respond to steroid therapy.

P51

Birth weight, thyroid function, calcitonin levels and growth in children with congenital hypothyroidism

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Children with congenital hypothyroidism (CH) due to anatomical defects (AD) have different thyroid hormone levels at presentation from those with dyshormonogenesis (DH). We set out to explore these differences at initial presentation and at follow up. We also compared calcitonin levels and growth in these subjects with healthy controls. Data for the CH children were collected from hospital notes for birth weight, gestation, sex, initial laboratory thyroid function, starting dose of thyroxine and imaging results. CH children were categorized as AD (agenesis, ectopia) or DH. All data are mean (sem) unless otherwise stated. We studied 38 children with CH (13 boys), median age (range), 9.7 (1.1–17.2) years, 11 with DH and 27 with AD and compared them with 71 age and sex-matched controls (40 boys), 10.1 (0.6–17.8) years. DH babies had lower birth weight SDS's corrected for gestation than those with AD, mean (S.D.): $-0.78(1.0)$ vs $+0.23(0.9)$, $P=0.01$ and subsequent weight and height SDS's were lower in CH than controls. Initial TSH values were higher in AD 129 (8.6) versus DH 8.8 (22.2) mU/l, total T_4 levels were lower in AD 81 (12.3) versus DH 16.6 (20.3) pmol/l. At 8.3 years, the only significant difference was in the thyroxine dose: AD 86 (5.3) versus DH 59 (6.5) μg, $P=0.004$. CH children had higher FT_4 levels than controls: 17.9 (0.58) vs 13.8 (0.22) pmol/l, $P<0.0005$; and higher TSH levels 4.6 (0.74) vs 1.96 (0.14) mU/l, $P=0.003$. Calcitonin levels were significantly lower in CH than controls $P<0.001$ with a trend towards lower levels in AD versus DH. CH children are small and remain small in childhood even after treatment. Calcitonin levels are significantly lower in CH children compared to controls. Differences exist amongst subgroups of CH children in thyroid hormone levels; AD have higher initial TSH and lower T_4 levels and require higher doses of L-Thyroxine. Differences persist during childhood in thyroid hormone levels in treated CH children compared to healthy controls.

P52

UK trends in the treatment of young patients with thyrotoxicosis using radioiodine

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Background
Radioiodine (RI) treatment of benign thyroid disease in young people has received a lot of attention recently with authorities in the US highlighting an encouraging short and medium term safety record. In this audit we surveyed treatment centres in the UK to assess the trend in RI administration in patients aged 21 years and under.
Methods
Over sixty Medical Physics Departments, dispersed to represent a suitable geographical coverage pattern for the UK, were contacted and asked to provide details of their use of RI in patients 21 and under during the period from 1990 to 2008. This represents more than half of the units likely to be administering RI to the young in the UK Information was collected on the age and number of young patients treated each year along with the respective total number of RI treatments carried out.
Results
Over half the units contacted (34) provided data on a total of over 42 000 treatments administered to people of all ages though information was more sparse over the early years due to lack of computerised records. The number of treatments recorded on patients under 22 during this period was 386 (0.899%) and the frequency of treatments in this group as a percentage of the total increased significantly throughout the study period from 0.23% in 1990 to 0.88% in 2000 and 1.48% in 2008.
Conclusions
RI administration to young people with benign thyroid disease in the UK has shown a steady increase in numbers over the last 2 decades. Most of these patients are likely to have Graves' disease and the trend suggests that paediatricians and families are becoming more comfortable with RI administration in the young. A means of tagging these patients so that there long-term health can be monitored is a logical next step.

P53

A novel disorder of increased energy expenditure with severe failure to gain weight and increased brown fat

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Introduction
Obesity is one of the biggest health challenges we currently face. Obesity results from imbalance of energy consumption and expenditure. Genetic studies on monogenic forms of obesity and Genome Wide Association studies have revealed neuronal mechanisms of genesis of obesity and/or leanness. We report a novel disorder of increased energy expenditure with severe failure to gain weight and increased brown fat.
Case report
The proband is a white Caucasian 3-year-old female, who currently weights only 2.7 kg. Despite receiving a high calorie intake of 180–200 kcal/kg/day she has failed to gain weight. All the investigations for failure to thrive are negative. Biochemically she has hypoglycaemia, continuous fatty acid oxidation, undetectable IGF-1 and IGFBP-3, secondary hypothyroidism and increased resting energy expenditure as repeatedly measured by indirect calorimetry. This increased energy expenditure is associated with depletion of fat from adipose tissue and the appearance of increased brown fat as demonstrated by immunohistochemistry.
Discussion
So far no human disorder has been described with this constellation of clinical features. This patient's biochemical investigations suggest that rather than storing fat and carbohydrates this patient is continuously burning these fuels simultaneously. There are several different rodent models of increased energy expenditure associated with depleted triglycerides in adipose tissue with increased fat oxidation (due either to loss of function or gain of function of the following genes ACC2, SIRT1, SRC2/3, Foxc2, PTP1B, DGAT, Eif4BC, NFAT). Recently several new genes have been identified which control brown fat formation (such as PRDM16 and BMP7). Using a candidate gene approach we have sequenced the ACC2, RIP140 and FTO genes and found no genetic defects. Along with metabolic studies to indentify the abnormalities of metabolic pathways whole genome exome sequencing is being performed to identify the underlying genetic basis. Understanding the mechanisms of the increased energy expenditure will provide new knowledge about energy expenditure and will have important potential implications for treating common forms of obesity.

P54

Association of malaria in pregnancy with maternal metabolic biomarkers, cord blood IGF-I and birth size in Nigerian infants: 'The Ibadan Growth and Vascular Health Study'

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Malaria is commoner amongst pregnant than non-pregnant women in Nigeria and is associated with a significant risk of having a low birth weight (LBW) baby which increases later risk of disease, in particular hypertensive heart disease in this population.
We have established a birth cohort in Nigeria and in this study; we aimed to identify possible biomarkers in maternal and/or cord blood related to birth size on the background of malarial status in pregnancy.
During pregnancy, anthropometric measurements, blood film for malaria parasites and assays for lipids, glucose, insulin and TNFα were obtained from 410 mothers and these analytes and IGF-I were obtained from 187 babies at birth. Data were analysed by non-parametric tests.
Prevalence of malaria parasitaemia in pregnancy was 48% associated with younger age, anaemia and thinner, shorter babies with smaller occipitofrontal circumference (OFC) and mid upper arm circumference (MUAC). There was no effect of maternal malaria on cord blood lipids, glucose, insulin and TNFα but median (range) cord IGF-I was significantly lower in babies whose mothers had malaria compared with those without malaria [60.4 (24,145) vs 76.5 (24, 150) ng/ml] ($P=0.03$).
Maternal glucose ($r^2=0.17$, $P=0.03$), insulin ($r^2=0.19$, $P=0.012$), cord blood insulin ($r^2=0.18$, $P=0.017$) and IGF-I ($r^2=0.17$, $P=0.025$) were all positively associated with birth weight. MUAC correlated positively with maternal cholesterol, LDL and cord IGF-I while OFC correlated with maternal glucose. On regression analysis, cord glucose ($\beta=0.04$, $P=0.025$) but more significantly IGF-I ($\beta=0.003$, $P=0.005$) were independently associated with birth weight.

Malaria in pregnancy was common and associated with LBW and lower IGF-I levels. Cord blood glucose and IGF-I but not maternal metabolic markers were significant determinants of birthweight. Follow up through infancy will determine whether poor growth and low IGF-I in those with maternal malaria is a persistent feature.

P55

A review of the endocrine transition service over the last 10 years

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Transitional care has become a high priority for the Department of Health (1). The paediatric and adult endocrinology teams have been running a joint transition service since October 2000. A review of this service was undertaken in order to examine its effectiveness and aid service improvement.

The details of all 81 patients, who had been through transitional care since October 2000, were acquired. Both their electronic records and adult endocrinology notes were reviewed for relevant information. A questionnaire and covering letter were designed and sent to all these patients to survey patient satisfaction and ensure the service was working as expected. The demographics of the transition population including diagnosis, sex and age at transition were recorded. The mean age of transition was 18.6 years. Currently 28 out of 77 (36%) patients have replied to the questionnaire (4 had died). In general patient satisfaction was high. Of the patients, 82% felt that the timing of transition was appropriate, 100% felt it was helpful to meet the adult endocrinologist prior to transfer and 81% felt that they were given enough information about their condition and the transition process. Certain outcomes measures have been associated with successful transition. In the cohort studied; the mortality rate was 4.9%, 3.7% of the patients had been admitted acutely within 2 years of transition and 11.1% had issues with adherance to treatment. The DNA rate at the second adult follow up appointment for our cohort was 15.7% which is significantly higher than that of general adult endocrine clinics (6–10%).

We therefore propose to improve the service by providing written information about the transition process and the conditions affecting our patients, addressing compliance issues and producing a written transition policy.

(1) Transition: getting it right for young people. Department of Health, March 2006.

P56

Hyperandrogensim secondary to topical testosterone exposure

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Topical testosterone gels are now a widely used method of testosterone replacement therapy and have been shown to be convenient and effective. The unintentional transfer of testosterone gel to children or partners by skin contact with the application site causing hyperandrogenism has been described.

A 3-year-old well girl was referred for assessment of precocious puberty. Pubic hair had been first noted by her mother 9 months earlier. There was no history of acne, body odour or vaginal discharge. Examination revealed a tall girl (>99.9th centile; MPH 75th centile) with no breast development but Tanner stage III pubic hair and clitoromegaly. Full physical examination was otherwise normal. She was normotensive. Testosterone levels were elevated at 2.5 nmol/l, as was her Androstenedione level at 1.1 nmol/l. 17-OH progesterone was normal and tumour markers were negative. Urine steroid profile was quantitatively normal but there was a modest increase in androgen metabolites. Bone age was advanced by 16 months. Ultrasound and MRI imaging of her ovaries and adrenals did not reveal a source of androgen production. Upon further direct questioning, her father revealed he was using topical testosterone replacement therapy, applied nightly to his shoulders. The patient was a poor sleeper and often came into the parent's bed to sleep. Her father was advised to switch application of the gel to the mornings. Her repeat testosterone level fell to <0.7 nmol/l upon retesting 4 months later and the clitoromegaly resolved. At follow up a further 6 months later, testosterone level had risen to 2.5 nmol/l. Measures to minimize secondary exposure were discussed again including showering prior to any contact with his daughter. Follow-up testing after these measures were adopted revealed normal undetectable testosterone levels (<0.7 nmol/l). Measures to minimize the risk of secondary exposure should be explained to patients using topical testosterone therapy.

P57

Retrospective audit of endocrine late effects in survivors of childhood cancer

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Introduction

The Paediatric Oncology Late Effects Clinic in Leicester was established in 1999, in order to monitor cancer survivors for the development of secondary co-morbidity, including that relating to endocrinopathy from treatment for the underlying oncological diseases.

Aim

As a retrospective audit of our clinical service against the current existing guidelines (UKCSSG, SIGN), specifically to monitor the endocrine standards with respect to axiology, pubertal staging and exclusion of thyroid disease as well as fertility counselling.

Methodology

Retrospective case notes audit was performed in all patients who completed cancer treatment between 1995–2000. A total of 142 patients were identified: 86 case notes were analysed, 43 patients were excluded from the analysis as they were deceased and 13 sets of notes were unidentified.

Results

Results revealed 52% Leukaemias, 23% lymphomas, 16% solid tumours and others 9%. Vertical height was measured in 71 (83%) of patients, Sitting height in 0% of the at risk patients with craniospinal irradiation. Impaired growth was found in 4 (4.6%) and 1 (1.1%) diagnosed with growth hormone deficiency. Pubertal staging was assessed in 87% of girls and 62% of boys. Received contraception and fertility counselling were documented by 46% of post pubertal girls and 33% of boys. In high risk patients 14% had palpation of the neck with 57% having thyroid function assessed.

Conclusion

The audit demonstrated a lack of compliance with existing guidelines. It identified urgent changes required for the clinical service as well as a benchmark to re audit the service in the light of service developments.

P58

Persistent hypernatremia in infants…think diabetes insipidus

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Introduction

Central diabetes insipidus (CDI) in infants is rare and is often associated with intra-ventricular haemorrhage, congenital toxoplasmosis, intracranial tumours and anatomical abnormalities of the brain. We describe two cases of CDI associated with brain malformations, diagnosed at very young age with good response to oral DDAVP.

Case 1

A 34-week IUGR girl born to consanguineous parents (first cousins) developed hypernatraemia on day three of life. By day nine, inspite of an intake of 200 mls/kg/day serum sodium increased to159 mmol/L with urine output of 5–8 mls/kg/hr. She had lost 12.5% of birth weight. Paired serum and urine osmolality were 328 and 75 mOsm/kg respectively. A trial of intranasal DDAVP increased urine osmolality (306 mOsm/kg), decreased serum osmolality (297 mOsm/kg) and serum sodium (145 mmol/L) confirming CDI. Intranasal DDAVP was continued. Investigations revealed normal anterior pituitary functions. MRI brain showed absent rostrum and genu of corpus callosum, normal pituitary gland and optic nerves. Treatment is ongoing with oral DDAVP.

Case 2

A seven-week-old boy presented with one-day history of temperature, irritability and poor feeding. Clinical examination was unremarkable. Investigations revealed persistent hypernatraemia with sodium in the range of 151–160 mmol/L. Urine output was 4 mls/kg/hr. Urine and serum osmolality were 168 and 321 mOsm/kg respectively. Administration of intranasal DDAVP (200 ng) resulted in normalising of serum sodium (146 mmol/l) and urine osmolality (304 mOsm/kg) confirming the diagnosis of CDI. Anterior pituitary functions were normal. Ophthalmology examination confirmed bilateral marked optic nerve hypoplasia. MRI brain was consistent with septo-optic dysplasia. Treatment is ongoing with oral DDAVP.

Conclusion

CDI must always be considered as a differential diagnosis of unexplained persistent hypernatraemia. Intranasal DDAVP is useful in diagnosis while oral DDAVP is an effective treatment modality.

P59

An unusual spectrum of phenotype in autoimmune polyendocrinopathy syndrome type 1: a case series of 5 patients within a single centre

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Introduction

The Autoimmune Polyendocrinopathy Syndromes (APS) comprise 4 clinical subtypes (1–4), APS type 1 is an autosomal recessive disorder caused by mutations in the AIRE (Autoimmune Regulator) gene. It should include at least 2 of the following 3 major criteria: chronic mucocutaneous candidiasis (CMC), hypoparathyroidism (HPT) and adrenal insufficiency (AI) although 50% of patients develop all 3 features, usually before the age of 20 years. In addition, there are several minor features that have been associated in a variable proportion of patients which can present at any stage. The aim of this case series is to highlight unusual clinical phenotypes seen in a paediatric population with APS type 1.

Methods

Retrospective review of case notes of patients with clinical APS type 1.

Results

Four patients were identified with clinical APS type 1. All the patients were Caucasian. Patients 1–3 have a known homozygous AIRE mutation.

Patient	Sex	Major criteria	Other features
1	M	AI; CMC	Polyarticular JIA; autoimmune colitis; exocrine pancreatic insufficiency; vitiligo; hypothyroidism
2	M	AI; HPT	Hypothyroidism; persistent transaminitis (chronic active hepatitis – CAH)
3	F	HPT	Hypothyroidism; primary ovarian failure; renal failure (secondary to nephrocalcinosis)
4	M	AI; CMC; HPT	Ectodermal dysplasia; alopecia totalis; interstitial nephritis
5	F	AI; CMC; HPT	CAH; dental hypoplasia; primary ovarian failure

Discussion

The five patients described demonstrate the range of conditions seen in APS type 1. Thus far, there has been limited genotype: phenotype correlation. Chronic active hepatitis and hypergonadotrophic hypogonadism can present in up to 50% of patients. Malabsorption including pancreatic insufficiency present in up to 20%. Of note autoimmune colitis and interstitial nephritis have not been described before in this condition.

Author Index

39th Meeting of the British Society for Paediatric Endocrinology and Diabetes

Save the Date

9-11 November 2011 | Mary Ward House, London, UK

Welcome to the capital city in 2011! London is hosting the BSPED and promises to make this a meeting to remember. The focus of the meeting will be translational research - from bench to bedside. Highlights of the meeting will include symposia on management of disorders of puberty, an update on adrenal disorders and on SGA, obesity and current/future therapies for the management of diabetes mellitus. There will be opportunities to present oral communications and posters during the meeting, and to interact informally with colleagues.

The 39th meeting will commence with a CME day on 9 November 2011. On 10 and 11 November 2011, the main conference will run in parallel with the Diabetes and Endocrine nurse specialist meetings, with oral communications presented in all 3 sessions.

www.bsped.org.uk

The Annual Dinner will be held on Thursday 10 November at an exciting off site venue.Tickets will include a three course Indian banquet with plenty of opportunity to circulate and meet with colleagues, and with lively post dinner entertainment which will include both Eastern and Western themes. All delegates are encouraged to attend for what promises to be a party to remember. Tickets can be purchased at the time of registration.

London will be preparing for the 2012 Olympics and the city will be livelier than ever. The meeting will be held at the historic Mary Ward House in the centre of the city. This is a beautiful Grade 1 listed property situated within walking distance of Euston and Kings Cross/ St. Pancras stations. It is also within striking distance of a number of hotels, shopping areas, Covent Garden and the Theatre district. We hope you will attend the meeting and take advantage of some of the many attractions the capital city has to offer.