Endocrine Abstracts

November 2015 Volume 39
ISSN 1479-6848 (online)

43rd Annual Meeting of the British Society for Paediatric Endocrinology and Diabetes 2015

25–27 November 2015, Sheffield, UK

published by
bioscientifica

Online version available at
www.endocrine-abstracts.org

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Volume 39
November 2015

43rd Annual Meeting of the British Society for Paediatric Endocrinology and Diabetes 2015

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43rd Annual Meeting of the British Society for Paediatric Endocrinology and Diabetes 2015

CME Training day Abstracts

CME TRAINING DAY ABSTRACTS

CME1

Induction of puberty

Sabah Albi
Ledds, UK.

Abstract unavailable.

CME2

Consultant paediatric endocrinologist, Great North Children's Hospital, Newcastle Upon Tyne

Debbie Matthews
Newcastle-Upon-Tyne, UK.

Polycystic ovary syndrome (PCOS) may be diagnosed in adult women using the Rotterdam criteria and includes the presence of at least two of the following:- androgen excess, ovulatory dysfunction, or polycystic ovaries on ultrasound scan. The diagnosis of PCOS in adolescents is challenging since these criteria may define normal pubertal physiological features. PCOS is a diagnosis of exclusion and investigation for other possible underlying pathologies, such as non-classical congenital adrenal hyperplasia, is important. PCOS may be associated with other co-morbidities, such as obesity and insulin resistance and these should be actively sought. The use of a 'symptoms-based' approach for adolescents is discussed, focusing treatment on the primary presenting problems (frequently hirsutism or menstrual irregularity). The first line treatment of PCOS in adolescents is the use of hormonal contraceptives such as the oral combined contraceptive pill (OCP). The progestogen in the OCP suppresses LH and ovarian androgen production while the oestrogen increases SHBG, thus reducing circulating bioavailable androgen. The OCP seems to have more impact on distressing symptoms such as hirsutism, acne and menstrual irregularity than metformin. The role of metformin in treating PCOS in adolescents is also discussed, together with the difficulties in planning duration of treatment. Other approaches include lifestyle measures (exercise programmes and healthy diet) in those girls with PCOS who are also obese. Non-medical therapies, such as physical means of hair removal, are described, particularly for girls who decline or do not tolerate medical treatment.

DOI: 10.1530/endoabs.39.CME2

CME3

Approach to adrenal insufficiency

Nils Krone
Birmingham, UK.

Adrenal insufficiency represents a sign and symptom of an underlying specific condition. A key diagnostic question is the differentiation between primary and secondary/ tertiary adrenal insufficiency (AI) to define the aetiology and manage the patient appropriately. The most common cause for primary adrenal insufficiency is congenital adrenal hyperplasia (CAH) representing a group of autosomal recessive conditions leading to glucocorticoid deficiency and other steroid hormone imbalances. The most common cause for secondary/tertiary AI is the iatrogenic use of glucocorticoids suppressing the hypothalamic–pituitary–adrenal (HPA) axis. The majority of the other forms of primary and secondary adrenal insufficiency are rare conditions. It is critical to establish the underlying aetiology of each specific condition as a wide range of additional health problems specific to the underlying disorder can be found. In recent years, several novel conditions leading to AI caused by deficient pathways and mechanism other than classic endocrine pathways have been described. After establishing the correct differential diagnosis, adequate replacement with steroid hormones during normal life and stress is essential to avoid under- and over-treatment, which can cause significant future health problems. This presentation will provide an overview on the diagnostic approach to adrenal insufficiency, an update on the differential diagnosis and treatment of patients with adrenal insufficiency.

DOI: 10.1530/endoabs.39.CME3

CME4

DSD – what's new?

John Archermann
London, UK.

Abstract unavailable.

CME5

Interpretation of dynamic tests

Jeremy Kirk
Birmingham, UK.

Whilst some hormones are secreted constantly, others have diurnal (eg. cortisol and androgens) and pulsatile (eg. growth hormone) secretion. As a consequence they require dynamic function tests to stimulate their production. It is worthwhile remembering that background data is not only limited but also often historical, going back over many decades. Often different units have different tests, assays & also cut-offs, which make comparison difficult. In a previous national audit there were 14 different protocols for the short hCG test, involving doses of hCG ranging from 500 – 15,000 iU. Whilst many units use a historical cutoff for GH-deficiency of $\sim$ 6.7 μg/L, the most commonly used current GH assays have cutoffs ranging from 4.32 – 7.77 μg/L. Ideally each unit should set their own cutoffs, although in practice this rarely happens. There may also be considerable overlap between normal and abnormal eg. with pre-puberty and gonadotropin deficiency, and often the tests will need to be interpreted in the light of the clinical features and other supporting information. Each test can produce false negatives and also false positives, so the most important thing is proper selection of patient and also tests; you may not get the result you were expecting (or want!)

DOI: 10.1530/endoabs.39.CME5

CME6

Abstract unavailable.

CME7

Unusual cases of diabetes mellitus

Andrew Hattersley
Exeter, UK.

Abstract unavailable.

Main Symposia

Industry sponsored Satellite Symposium

Symp1.1

Complications for Growth Hormone Therapy

Gary Butler
London, UK.

Abstract unavailable.

Symp1.2

Novel insights into pituitary dysfunction - Congenital hypopituitarism: new genes, new phenotypes

Mehul Dattani
Genetics and Genomic Medicine Programme, UCL Institute of Child Health London, London, UK

Congenital hypopituitarism (CH) is a rare but life-threatening condition that is associated wth significant morbidity and mortality. It occurs in 1 in 4000 to 1 in 10000 live births, and may present variably. In the newborn period it is associated with conjugated hyperbilirubinaemia, micropenis with undescended testes in affected males, hypoglycaemia and possibly features of hypothyroidism including lethargy and feeding difficulties. Later on, it may present with early growth failure, or in milder cases even later. The condition includes GH, ACTH, TSH and gonadotrophin deficiencies; diabetes insipidus is usually rare unless midline abnormalities are present, as is the case with Septo-Optic Dysplasia (SOD). The diagnosis is based on a combination of auxology, biochemistry, and neuroimaging. Mutations in a number of genes have been identified in association with congenital hypopituitarism and SOD. These include a number of developmental genes such as *HESX1, SOX2, SOX3, OTX2, GLI2, ARNT2, IGSF1, TCF7L1, BRAF, LHX3, LHX4, PROP1* and *POU1F1*. Mutations have also been identified in genes that are implicated in Kallmann syndrome, such as *FGF8* and *FGFR1*. Phenotypes, inheritance and penetrance can be variable, and much remains to be learned about the molecular basis of these conditions. Management of congenital hypopituitarism includes hormone replacement including rhGH, hydrocortisone, thyroxine, sex steroid and DDAVP as necessary. Both CH and SOD can also be associated with autism, neurodevelopmental delay and obesity, the management of which is highly challenging. In this presentation, data will be presented that will compare the phenotypes of SOD with CPHD without midline defects, with relevant genotype-phenotype correlations.

DOI: 10.1530/endoabs.39.Symp1.2

Symposia 1 Translational Endocrinology

S1.1

New approaches to diagnosing short stature
Peter Clayton
Manchester, UK.

Abstract unavailable.

S1.2

Thyroid – from bench to beside
Krish Chatterjee
Cambridge, UK.

Abstract unavailable.

S1.3

Pitutiary gigantism
Márta Korbonits
London, UK.

Abstract unavailable.

Symposia 2 Bone

S2.1

New therapies in paediatric bone disease
Nick Bishop
Sheffield, UK.

Abstract unavailable.

S2.2

The diagnostic role of ALP – what the endocrinologist needs to know
Wolfgang Högler
Birmingham, UK.

Abstract unavailable.

Symposia 3 Obesity and Type 2 Diabetes

S3.1

What have we learnt from the GOOS study?
Sadaf Farooqi
Cambridge, UK.

Childhood obesity is a major and growing clinical concern strongly influenced by environmental factors such as changes in diet and levels of physical activity. However, within a given environment, some children develop severe obesity which is strongly influenced by inherited factors which modulate eating behaviour and energy expenditure. We have studied a cohort of individuals with severe, early onset severe obesity ($n=6000$) called the Genetics of Obesity Study (GOOS). Candidate gene studies in this cohort have previously led to the identification of patients with mutations in multiple genes involved in leptin–melanocortin signalling. Whole exome sequencing is proving to be an increasingly important tool in understanding the genetic heterogeneity associated with obesity leading to the discovery of multiple new genes. The discovery of how genetic variation at an individual and at a population level contributes to weight gain can drive further understanding of the molecular and physiological pathways involved in weight regulation and suggest targets for drug discovery and for therapeutic intervention.

DOI: 10.1530/endoabs.39.S3.1

S3.2

The complications of childhood obesity – TDM and beyond
Tim Barrett
Birmingham, UK.

Abstract unavailable.

S3.3

Bariatric surgery
Roger Ackryod
Sheffield, UK.

Abstract unavailable.

Symposia 4 Diabetes

S4.1

The NICE guidelines for diabetes in children and young people
Jerry Wales
Brisbane, Australia.

Published in August 2015, this was an update of the 2004 guidelines including for the first time guidance concerning Type 2 in Children. Monogenic diabetes fell outside the scope of the group and the update should be read alongside recent publications on Adult type 1 diabetes, diabetes in pregnancy, the diabetic foot, coeliac disease and the Technology Appraisal of insulin pumps. The Adult type 2 guidance will be published shortly.

Guidelines must meet standards of trustworthiness to be authoritative and the mechanisms for quality assurance and economic analysis of NICE guidance will be discussed.

Highlights of the update include lower targets for a team message – HbA $<6.5\%$; carbohydrate counting and intensive insulin from day 1; recommendations on a minimum of five tests per day; the use of CGMS for selected groups and a new treatment protocol for DKA.

The 2004 guidelines specified that there should be provision of psychological and educational support for all, but this has still not been universally implemented 11 years later and it is likely some of the new guidance may also be difficult to implement within current constraints.

Finally the group chose key areas for future research around DKA, Type 2 diabetes management, optimal psychological care, education programmes, glycaemic index and the use of CGMS with pumps in the young.

Future NICE updates may be piecemeal as new information becomes available rather than comprehensive reviews.

DOI: 10.1530/endoabs.39.S4.1

S4.2

What should pediatricians be telling adolescent diabetics?

Simon Heller
Sheffield, UK.

Abstract unavailable.

S4.3

A lifetime of diabetes – what have we learned?

Bill Lamb
Newcastle Upon Tyne, UK.

Abstract unavailable.

S4.4

Abstract unavailable.

Diabetes Professionals Session

DP1

Latest developments in monogenic diabetes

Andrew Hattersley
Exeter, UK.

Abstract unavailable.

DP2

Novel method of teaching – Immunology in diabetes

Alison Green
Exeter, UK.

Abstract unavailable.

DP3

Structured education during transition: WICKED

Simon Heller
Sheffield, UK.

Abstract unavailable.

DP4

Emotional resilience and mindfulness for both health care professionals and CYP and families with diabetes

Paul Manning
Sheffield, UK.

Managing diabetes as a chronic health condition is never ending and many young people, especially teenagers, would like a 'day off'. Managing diabetes alongside the normal rigours of adolescence means that the struggle with independence and acceptance of responsibility can have a knock-on impact upon how well patients engage in clinic appointments and their overall diabetes care. This in turn impacts upon parents; who may over- or under-compensate to address this, but inadvertently reinforce the young person's fear of having too much or too little independence, and therefore contribute to them feeling overwhelmed and so avoidant of taking responsibility: a vicious cycle.

For diabetes health care professionals, the struggle to engage patients (and families) in taking responsibility to manage diabetes well, is a constant pressure. We feel responsible for ensuring the long-term health of the young people we work with, yet struggle despite our best efforts to achieve this for all. Our teams are subject to the need to evidence our success, and have the constant threat of financial sanctions if this isn't achieved. In the NHS climate, where 'more for less' is a mantra, teams can feel overwhelmed and often understaffed. It is no wonder that health care professionals can feel 'burnt-out' and question their skills and abilities to achieve the best for their patients.

Emotional resilience refers to the ability to cope and adapt to stressful situations. This is a skill that can be learnt: self-awareness via Mindfulness practice, tolerance of difficult emotions, setting realistic expectations, empowering responsibility taking through problem-solving skills development, and being focussed upon values-based actions are key to this. 'Practicing what we preach', we can instil these skills in the patients and families we work with towards a more optimistic future with diabetes.

DOI: 10.1530/endoabs.39.DP4

DP5

Specialist, advanced and consultant nurse roles: new RCN guidance

Judith Campbell
Manchester, UK.

Abstract unavailable.

DP6

Disordered eating

Frances Hanson
Leeds, UK.

Disordered eating is more common amongst people with type 1 diabetes than their peers without this condition. Anorexia nervosa, bulimia, eating disorder not otherwise specified (EDNOS) and deliberate insulin omission are more common in type 1 diabetes. Binge eating disorder is more prevalent in type 2 diabetes. These disorders present difficulties and dilemmas in personal diabetes management on a daily basis, and significantly increase risk of diabetes complications, particularly diabetic ketoacidosis (DKA) and retinopathy.

The necessary focus on food choices, counting carbs and monitoring their effects on blood glucose may precipitate disordered eating in vulnerable patients. Identifying those at high risk, use of screening tools and sensitive conversations about weight issues can facilitate early interventions. An interdisciplinary approach is most constructive to manage these complex patients and their relationships with food.

DOI: 10.1530/endoabs.39.DP6

DP7

Integrating advanced technologies into patient centred consultations

Fiona Campbell
Leeds, UK.

Abstract unavailable.

DP8

Abstract unavailable.

Endocrine Nurse Session

ENDOCRINE NURSE SESSION

EN1

Ipsen awards winner

Kate Davies
London, UK.

Abstract unavailable.

EN2

Bones at ground level

Elaine Walker
Sheffield, UK.

An overview of current understanding of bone biology. Including new innovations in therapy,bone growth and vitamin D metabolism. An update on bone health for the specialist nurse working in paediatric endocrinology.

DOI: 10.1530/endoabs.39.EN2

EN3

Replacement steroids where do we go from here?

Sally Carney
Sheffield, UK.

The aim of this presentation is to build on the discussion that developed at the BSPED Nurse Meeting in 2014.
Consensus grew around the importance of standardisation of the advice our adrenal insufficient patients receive, in order to maintain a healthy lifestyle and prevent the risk of adrenal crisis. The evidence suggests that there may be a diversity in the management of adrenal insufficiency within the UK. Despite appropriate education, adrenal crisis is a possibility but it may be under-managed.

DOI: 10.1530/endoabs.39.EN3

EN4

Abstract unavailable.

Oral Communications

Oral Communications 1

OC1.1

Gonadotropin-independent precocious puberty of uncertain aetiology

Ved Bhushan Arya & Justin H Davies
University Hospital Southampton, Southampton, UK.

A 5.65-year-old boy was referred with a 2-month history of accelerated growth and pubic hair development. Weight and height were >98th C. Pubertal assessment was G3 PH2 AH1 TV 5 ml/4 ml. There was no family history of precocious puberty. No birthmarks, or abdominal masses were present. Blood pressure was normal. Investigations revealed elevated testosterone (7.1 nmol/l), suppressed gonadotropins (LH <0.2 IU/l), normal 17-OHP, androstenedione and DHEAS, prepubertal LHRH test and advanced bone age, consistent with a diagnosis of gonadotropin-independent precocious puberty (GIPP). Further investigations revealed elevated serum HCG (11.1 (0–5)), normal AFP, normal ultrasound testes and abdomen, chest X-ray, MRI pituitary, and normal sequencing of LH receptor gene. Bone scan did not identify any abnormal uptake suggestive of fibrous dysplasia.

Treatment with cyproterone acetate was complicated by adrenal insufficiency that required hydrocortisone replacement. At 6.5 years, there was evidence of gonadotropin-dependent precocious puberty and decapeptyl was added. At 7 years of age, treatment was changed to anastrazole (aromatase inhibitor) and bicalutamide (androgen receptor antagonist) due to no clinical or biochemical improvement.

Serum HCG remained elevated on serial monitoring. CSF HCG was measured, which was elevated and CSF/blood HCG ratio was suggestive of local production. Repeat MRI brain and MRI mediastinum was normal.

At age 8.9 years, the HCG and testosterone levels spontaneously returned to normal. The height velocity slowed down. There was no bone age advancement after the initiation of anastrazole. Adrenal function recovered gradually after the discontinuation of cyproterone.

At last clinic review (12.02 years), there was no bone age advancement, serum HCG remained normal and treatment was discontinued. Given the initial persistently elevated HCG, we speculate that GIPP was secondary to an HCG producing tumour that spontaneously resolved.

DOI: 10.1530/endoabs.39.OC1.1

OC1.2

Delayed puberty due to a non-functioning pituitary adenoma

Dinesh Giri, Victoria Price, Ajay Sinha, Mohammed Didi & Senthil Senniappan
Alder Hey Children's Hospital, Liverpool, UK.

Background

Constitutional delay of growth and puberty (CDGP) is the commonest cause of delayed puberty in boys and differentiation of CDGP from other causes of delayed puberty can sometimes be challenging. We report a boy with delayed puberty due to a pituitary adenoma.

Case

A 15-year-old boy was referred for endocrinology consultation with concerns regarding short stature and delayed puberty. There was no history or laboratory evidence suggestive of chronic illness. The tanner pubertal staging showed A1P2G2 with testicular volumes of 4 ml on the right and 3 ml on the left side. The glucagon stimulation test that performed at the referring hospital showed a peak GH of 4.3 μg/l and the GnRH test showed a peak LH of 11.6 U/l. A repeat primed glucagon stimulation test showed a peak GH of 2.07 μg/l confirming GH deficiency. He was commenced on growth hormone therapy. An MRI scan revealed the presence of a pituitary lesion (2×1.5×1.7 cm), which was slightly displacing the optic chiasma. A formal ophthalmology examination did not show any visual abnormality. Further investigations showed a normal Synacthen test, normal thyroid function, and a slightly elevated prolactin at 475 pmol/l (0–350). The lesion was removed by transphenoidal surgery and the biopsy confirmed pituitary adenoma. There was no progression of puberty 6 months after the surgery suggesting hypogonadotropic hypogonadism and testosterone therapy was commenced.

Conclusion

Non-functioning pituitary adenomas are rare in adolescence. Although the most common cause of delayed puberty in boys is CDGP, this is a diagnosis of exclusion. Detailed history, physical examination, auxology, bone maturation, biochemistry, and MRI based on clinical findings may be necessary to exclude other causes of hypogonadism.

DOI: 10.1530/endoabs.39.OC1.2

Oral Communications 2

OC2.1

Severe hyponatremia with neurological involvement in a child with adrenal insufficiency

Carley Frerichs, Hussain Alsaffar, Renuka Ramakrisnan, Poonam Dharmaraj, Ram Kumar, Senthil Senniappan & Urmi Das
Alder Hey Children's NHS Foundation Trust, Liverpool, UK.

Case report

A 13-year-old male presented with a 10-day history of vomiting. He was haemodynamically stable. His biochemistry was evaluated revealing a sodium level of 96 mmol/l. He had been seen 2 years previously with short stature. Sodium was normal at this time. He had speech and language delay, learning difficulties and was under investigation for autism. He had reportedly salt craved for years. Potassium, urea, creatinine, and glucose were normal throughout the admission. Further investigations revealed a cortisol level of 222 nmol/l, ACTH 1438 ng/l (NR 7–63), urine Na 105 mmol/l, 17-OHP 40 nmol/l, renin >23.7 nmol/l per h (NR 0.3–2.2), aldosterone <100 pmol/l, normal VLCFA, androstendione 2.6 nmol/l (NR <2.2), FSH 0.2 IU/l, LH 0.1 IU/l, testosterone 0.4 nmol/l, and prolactin 319 mU/l (NR 56–278). Urine steroid profile showed low cortisol and high 17-OH pregnanolone, pregnatriol and 11-oxoP3, which would be consistent with 21-hydroxylase deficiency, however androgens were not elevated. A standard short Synacthen showed a flat cortisol response with normal stimulated 17-OHP.

He was treated with i.v. hydrocortisone, i.v. fluids, and sodium supplementation. His sodium levels rose slowly over 7 days to normal concentrations. He then began to exhibit slurred speech, immobile face, abnormal behaviour, aggression, ataxia, and tremor. MRI demonstrated extra pontine myelinosis and diffuse high signal in the globus pallidus, putamen, and caudate nuclei bilaterally with no diffusion restriction. The symptoms resolved over the next 8 weeks. Adrenal antibodies were positive suggestive of Addison's disease and the patient was discharged home on hydrocortisone, fludrocortisone and sodium supplements.

Conclusion

It is rare for Addison's disease to present with such profound hyponatraemia with normal potassium and no cardiovascular compromise. Central pontine myelinosis is typically associated with rapid corrections of sodium, although extra pontine myelinosis and basal ganglia changes have rarely been reported in adults with Addison's disease.

DOI: 10.1530/endoabs.39.OC2.1

OC2.2

Inguinal hernia repair in a girl, a missed opportunity to diagnose 17β-HSD

Syed Furrukh Jamil[1,2] & Tim Cheetham[1,2]
[1]Darlington Memorial Hospital, Darlington, UK; [2]Great North Children's Hospital, Newcastle-upon-Tyne, UK.

17β-hydroxysteroid dehydrogenase deficiency (17β-HSD) is a rare autosomal recessive disorder of sexual development affecting testosterone biosynthesis. Affected individual typically present with genital ambiguity at birth, inguinal gonads or excessive virilisation at puberty in a phenotypic female.

Case

We present a case of a 14-year-old girl who was referred by the GP because of concerns about upper lip hair growth and deepening of her voice. She was born at term with no complications. She had an inguinal hernia repaired at age 6 but her past medical history was otherwise unremarkable.

Examination revealed no breast development, adult pattern pubic hair and clitromegally (B1 P4).

A deep voice, acne, and male habitus was noted. No gonads could be palpated in the inguinal canal.

Karyotype was 46,XY confirming 46,XY DSD and inguinal gonads were visualised on US with no Müllerian structures. Biochemical investigations demonstrated a normal steroid profile, pubertal LH and FSH and raised androstenedione to testosterone ratio, suggestive of 17β-HSD.

Our patient met with key members of the team including clinical psychology and subsequently opted to undergo bilateral gonadectomy and pubertal induction with exogenous oestrogen. The diagnosis of 17β-HSD was subsequently confirmed at the molecular level.

Conclusion

A girl with inguinal hernia requires a careful assessment and the operation note confirmed that when our patient had undergone hernia repair at 6 years a gonad had been identified. There is an argument for rearing the child with 17β-HSD diagnosed in the neonatal period as a male which highlights the potentially powerful impact of the environment on gender identity.

DOI: 10.1530/endoabs.39.OC2.2

Oral Communications 3

OC3.1

Long standing autoimmune hypothyroidism with macro-orchidism and pituitary mass: Van Wyk-Grumbach syndrome

Hussain Alsaffar, Supriya Phanse, Carley Frerichs, Mohammed Didi & Senthil Senniappan
Alder Hey Children's Hospital, Liverpool, UK.

Introduction

Van Wyk-Grumbach syndrome was first described in 1960 in patients presenting with long standing juvenile hypothyroidism, delayed bone age and precocious puberty. Literature review indicates only few cases reported in males compared to females. We are reporting this case in a male patient who presented with short stature.

Case

A 7.25-year-old boy was referred for endocrine opinion due to short stature. He had not grown over the last 18 months. Further history revealed learning difficulties, constipation and tiredness for almost 3 years. Examination showed dry skin, dry hair, central adiposity, mildly hypertrophied calf muscles, and bilateral enlarged testicles (8 and 6 ml of right and left testicles respectively). Height was 107.3 cm (−3 SDS) and weight was 22.7 kg (−0.33 SDS). Bone age was 3.94 years. Biochemical evaluation revealed: TSH 1047 (0.3–3.8 mU/l) with undetectable free thyroxine (T_4), prolactin 1064 (0–350 mU/l), IGF 13.6 (12–62 nmol/l), cholesterol 9.26 (<4.40 mmol/l), ALT 118 (8–36 IU/l), creatinine kinase 495 (24–195 IU/l), and serum creatinine 70 (27–57 μmol/l). Synacthen test was normal and LHRH test revealed a pre-pubertal response. MRI pituitary showed a homogenously enlarged anterior pituitary with no interruption of the stalk or effect on the optic chiasm. Thyroid peroxidase antibodies were strongly positive. He was commenced on oral T_4 and his symptoms improved. Thyroid function and the abnormal biochemistry normalised in 6–8 weeks.

Discussion

High circulating TSH concentrations acting directly on FSH receptors has possibly led to proliferation of sertoli cells and testicular enlargement in our patient. Pseudo muscular hypertrophy could be associated with raised creatinine kinase. Enlarged pituitary gland is likely to be due to thyrotroph hyperplasia.

Conclusion

We present a rare case of long standing hypothyroidism with macro-orchidism and pituitary mass.

DOI: 10.1530/endoabs.39.OC3.1

OC3.2

Unmasking of diabetes insipidus in a newborn with hypocortisolaemia after commencing hydrocortisone.

Felvira Godinho, Rooha Ijaz Ghauri, Shrinivas Tambe & Ignatius Losa
Macclesfield District General Hospital, Macclesfield, UK.

Hypopituitarism is a condition of inadequate or absent production of the anterior pituitary hormones (http://emedicine.medscape.com/article/923789-overview). We report a case of newborn with hypocortisolaemia in whom starting hydrocortisone unveiled diabetes insipidus and panhypopituitarism.

Case presentation

A term baby girl born by normal delivery to Caucasian parents presented with poor feeding, hypothermia and hypoglycemia with blood glucose of 1.8 mmol/l. She was treated for suspected sepsis. On day 2, she was noted to be hyponatremic (129 mmol/l), hyperkalemic (6.6 mmol/l), and the 17-OH progesterone was normal. She had hypoglycemia screen that revealed low cortisol of 46 nmol/l. Hydrocortisone was started after failed short Synacthen test (cortisol of <30 nmol/l at 0 min and 90 nmol/l at 60 min). Hypoglycemia resolved but she was noticed to have developed hypernatremia (147 mmol/l) and polyuria (5.8 ml/kg per h). Paired plasma and urine osmolality revealed underlying diabetes insipidus that was possibly obscured by concomitant cortisol deficiency. She was also noted to be hypothyroid and an ophthalmic review showed optic atrophy.

Discussion

Hypopituitarism is common but congenital form is rare.[1] Congenital hypopituitarism may be the result of complications around delivery, or may be the result of insufficient development (hypoplasia) of the gland, sometimes in the context of specific genetic abnormalities like mutations in *HESX1* and *SOX2*.[2] Neonates with congenital hypopituitarism may present with nonspecific symptoms. As cortisol is necessary to excrete a free water load, cortisol deficiency may obscure diabetes insipidus.[3]

Conclusion

Hypopituatisrism can be an evolving condition with other hormone deficiencies becoming evident over a period of time. This case highlights the importance of looking for posterior pituitary dysfunction while managing hypocortisolaemia.

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DOI: 10.1530/endoabs.39.OC3.2

Oral Communications 4

OC4.1

An unusual case of non-type 1 diabetes mellitus, presumed mitochondrial in aetiology, presenting with hyperglycaemia, ketosis and lactic acidosis

Elspeth Ferguson & Neil Wright
Department of Diabetes and Endocrinology, Sheffield Children's NHS Foundation Trust, Sheffield, UK.

Background

Non-type 1 diabetes mellitus (T1DM) and T2DM accounts for up to 4% of cases of paediatric diabetes. The most common form is maturity-onset diabetes of the young, however rarer forms exist.

This case highlights a number of important points to be considered when investigating patients with ketoacidosis that is not typical of T1DM. An understanding of the ketogenic pathway and knowledge of differential diagnoses for ketoacidosis and their appropriate investigations is key.

Case

Our female patient initially presented at 2 years of age with acute gastroenteritis, and a significant metabolic acidosis (pH 7.17), associated with elevated ketones and lactate. Laboratory blood glucose was 10.6 mmol/l. A diagnosis of severe dehydration secondary to gastroenteritis, with a reactive hyperglycaemia was made. Six months later she represented with lactic acidosis and ketosis during another acute illness. She was hyperglycaemic (lab glucose 62.1 mmol/l). However, symptoms resolved after the acute episode and she remained well. A personalised emergency regimen was devised to reduce the risk of decompensation during acute illness.

Over a 2-year period, the patient underwent repeat oral glucose tolerance tests which demonstrated gradual progression from normal, to impaired glucose tolerance to overt diabetes mellitus. Continuous glucose monitoring demonstrated significantly raised blood glucose levels on a daily basis, predominantly post-meals. Insulin was therefore commenced.

A number of investigations have been performed to determine a cause of her diabetes and metabolic abnormalities. Autoantibodies were negative. Despite extensive metabolic investigations no definitive underlying diagnosis has been determined but urinary organic acid results suggest a possible mitochondrial disorder.

Conclusions

Thorough investigation and individualised management plans are key in patients presenting with non-typical forms of diabetes mellitus. Managing metabolic and diabetic causes of ketoacidosis can cause a treatment dilemma. Mitochondrial causes of diabetes should be considered in patients presenting in this way.

DOI: 10.1530/endoabs.39.OC4.1

OC4.2

Hereditary persistence of foetal haemoglobin in a type 1 diabetic patient impacting glycaemic control and influencing safeguarding issues

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We report a 9-year-old Caucasian boy with type 1 diabetes mellitus and elevated blood glucose measurements, which did not correlate with apparent normal range HbA1c values. Safeguarding concerns due to raised blood glucose levels were raised at school, but were not pursued due to normal range HbA1c. Haemoglobinopathy screen showed hereditary persistence of foetal haemoglobin (HPFH) giving the falsely reassuring HbA1c levels. Subsequent fructosamine measurement confirmed the true picture of poor glycaemic control.

Method

Case report: serial analysis of blood glucose measurements and HbA1c taken over a two-year period. Haemoglobinopathy screen and fructosamine measurement. Results: Serum fructosamine elevated at 689 μmol/l. Haemoglobinopathy screen showed 27.2% foetal haemoglobin (normal range 0.1–1.5 at this age). Genetic analysis; heterozygous non-deletional HPFH trait.

Discussion/conclusion

Haemoglobinopathies can affect the accuracy of HbA1c measurements. These cases have been reported more commonly in patients of South East Asian, Mediterranean, and African descent. This case reports a 9-year-old Caucasian child with type 1 diabetes and non-deletional HPFH trait. The diagnosis came to light after inconsistent HbA1c levels with respect to blood glucose measurements. Safeguarding concerns raised from school were revisited after high fructosamine levels confirmed poor glycaemic control. This case showed the importance of lateral thinking when standard HbA1c measurement does not reflect the blood glucose results: alternative measurements of glycaemic control should be considered.

DOI: 10.1530/endoabs.39.OC4.2

Oral Communications 5

OC5.1

Mutations in *IGSF10* cause self-limited delayed puberty

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Background

Abnormal pubertal timing affects over 4% of adolescents and is associated with adverse health and psychosocial outcomes. Previous studies estimate that 60–80% of variation in the timing of pubertal onset is genetically determined. However, despite this strong heritability, little is known about the genetic control of human puberty. Self-limited delayed puberty (DP) segregates in an autosomal dominant pattern, but in the majority of patients the neuroendocrine pathophysiology and its genetic regulation remain unclear.

Methods

We performed whole exome sequencing in 52 members of seven families from our patient cohort with DP, with follow-up targeted re-sequencing of candidate genes in a further 42 families. The functional consequences of the identified mutations in one candidate gene were interrogated via expression of WT and mutant proteins in mammalian cells. For this gene we defined tissue expression in human and mouse embryos by *in situ* hybridization and immunohistochemistry. The effects of gene knockdown were investigated via *in vitro* neuronal migration assays, and *in vivo* using a transgenic zebrafish model with fluorescently labeled GnRH neurons.

Results

We identified four rare mutations in *IGSF10* in ten unrelated families, which are tightly associated with the DP trait within our cohort ($P = 3.47 \times 10^{-4}$). The identified mutations are in evolutionarily conserved positions, and two mutations result in intracellular retention with failure in secretion of the N-terminal fragment of the protein. *IGSF10* mRNA is strongly expressed in the nasal mesenchyme in mouse and human embryos, during the time-period when GnRH neurons migrate from their nasal origin towards the hypothalamus. *IGSF10* knockdown caused reduced migration of immature GnRH neurons in the *in vitro* analysis, and perturbed migration and extension of GnRH neurons in the zebrafish model.

Conclusions

We present our novel finding that mutations in *IGSF10* cause delayed puberty in humans, through misregulation of GnRH neuronal migration during embryonic development.

DOI: 10.1530/endoabs.39.OC5.1

OC5.2

Genetic characterisation of children with short stature and GH or IGF1 insensitivity by single gene and whole exome sequencing

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Background

GH insensitivity (GHI) encompasses growth failure, low serum IGF1 and normal/elevated serum GH. IGF1 insensitivity results in pre- and postnatal growth failure with normal/relatively high IGF1 levels.

Objective

To undertake candidate gene (CGS) and whole exome (WES) sequencing to obtain a genetic diagnosis in children with short stature and GHI or IGF1 insensitivity.

Methods

As a referral centre for GHI genetics, since 2008, we have received DNA samples from 106 children (58M) with short stature (mean height −4.04 SDS, range −9.37 to −0.6 SDS) and normal/high GH. 100 patients had GHI (mean IGF1 −2.53 SDS; range −8.2 to −0.25) and six had IGF1 insensitivity (mean IGF1 2.36 SDS; range 0.6 to 4.4 SDS). CGS was undertaken followed by WES in unsolved cases. WES has been completed in 39 patients and five relatives.

Results

CGS identified homozygous mutations in the following genes in 27 patients: *GHR* (21), *IGFALS* (3), *OBSL1* (2), *CUL7* (1), and heterozygous mutations in three patients: *STAT5B* (1) and *IGF1R* (2). Carrier status was confirmed in eight relatives (seven in *IGFALS* and one in *GHR*). WES identified mutations in genes known to cause short stature in 11 patients: compound heterozygous *IGFALS* (1), homozygous *GHR* (5), heterozygous *PTPN11* (2), homozygous *CCDC8* (2), and heterozygous *SOS1* (1). WES also identified changes in 22 novel, putative candidate genes in 16 patients.

Conclusions

A genetic diagnosis was obtained in 39% (41/106) of patients, whose DNA was sent for investigation. 73% were determined by CGS and 27% by WES. As well as identifying mutations in other candidate genes, WES also identified mutations in the *GHR* and *IGFALS* genes, which had not been detected on CGS. Diagnoses with similar phenotypes included SRS, Noonan and 3M syndrome. 22 novel genes with potential impact on growth have been identified and are currently under further investigation.

DOI: 10.1530/endoabs.39.OC5.2

OC5.3

Dominant negative STAT5B variants in two families with mild GH insensitivity and eczema

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Background
Homozygous mutations in *STAT5B* result in GH insensitivity and immune dysfunction. Heterozygous dominant negative mutations have not been described.
Aims and objectives
To assess *STAT5B* sequence in children selected for a phenotype suggestive of Stat5b deficiency. To further characterize genomic *STAT5B* variants in two families.
Methods
Selection of children from a tertiary Paediatric Endocrine Centre with short stature and biochemical features of GH insensitivity, with additional features of Stat5b deficiency (raised prolactin, frequent infections, lung pathology, or arthritis). Sanger sequencing of *STAT5B* from genomic DNA. Functional analysis of mutant *STAT5B* in HEK293 cells.
Results
Five children were selected that fulfilled selection criteria. A mutation in *STAT5B* was found in one child, whose brother subsequently presented with a similar phenotype. Another family was identified in a separate cohort of short children with features of GH insensitivity. Family 1: the index case grew at −2.9 s.d. from the age of 2 years. Investigations revealed IGF1 <25 ng/ml, IGFBP3 1.29 ng/ml (NR 0.8–3.9), prolactin 265–653 mU/l (NR 59–271), provoked GH-peak 17.3 μg/l, and normal GH-peaks on overnight sampling. A standard and extended three-step IGF1-generation test (2 weeks GH s.c. at 0.7, 1.4, and 2.4 mg/m^2 per day) showed a poor response. His brother had short stature (−2.9 s.d.), mild speech delay, eczema, undetectable IGF1, a GH peak of 13.9 μg/l and poor response in the IGF1-generation test. Both brothers had elevated IgE concentrations. Family histories were positive for short stature, eczema and transient hyperprolactinaemia. A heterozygous missense variant c.1433C>T (p.Ala478Val) was identified within the conserved STAT5B DNA-binding domain, and segregated with the phenotype. Family 2: male monozygotic twins presented at age 14 yrs with short stature (−5.3 SDS), eczema and a history of mild respiratory infections. Investigations revealed a provoked GH peak of 16.2 μg/l, low IGF1 (56 μg/l) and elevated IgE concentrations. rhIGF1 therapy led to modest catch-up growth. A *de novo* heterozygous variant (c.530A>C; p.Gln177Pro) was identified. Neither of the *STAT5B* variants are listed in control databases. Functional evaluation of the FLAG–STAT5B mutants indicated normal protein expression and phosphorylation but severely compromised nuclear translocation or transcriptional function compared to WT. The variants inhibited either translocation and/or transcriptional activity of WT FLAG–STAT5B, suggesting a dominant-negative mode of action.
Conclusion
This is the first description of dominant-negative *STAT5B* mutations in subjects with short stature and mild GH insensitivity. Eczema may also be related to impaired STAT5B function.

DOI: 10.1530/endoabs.39.OC5.3

OC5.4

White matter integrity and neurocognitive deficits in children with hyperinsulinemic hypoglycaemia and ketotic hypoglycaemia: a comparison study

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Background
Children with hyperinsulinaemic hypoglycaemia (HH) are at a high risk of brain injury, while children with ketotic hypoglycaemia (KH) are believed to be neurologically normal, due to the absence and presence respectively of ketone bodies that act as an alternate fuel during hypoglycaemia. Our objective was to ascertain if children with HH sustain greater white matter (WM) injury in comparison to children with KH.
Methods
Neurologically normal children between 5 and 16 years of age with HH and KH were recruited from the endocrine and metabolic outpatient clinic database from 2009 to 2012. Wechsler Intelligence Scale for Children Fourth edition (HH, $n=21$ and KH, $n=14$), conventional neuroradiological assessments (HH, $n=21$ and KH, $n=14$), and diffusion tensor imaging (HH, $n=15$ and KH, $n=12$) were performed. Fractional anisotropy (FA) images that reflects white matter integrity were aligned and voxelwise statistical analysis was performed using Tract-Based Spatial Statistics.
Results
On conventional neuroimaging reduced white matter was seen in 7/21 (33%) with HH and 4/14 (28.5%) with KH. Perceptual reasoning (HH 91.9 vs KH 105.8, $P=0.006$) and Full scale IQ (HH 89.3 vs KH 100.5, $P=0.026$) was significantly lower in HH group. Significantly low FA values were seen in global white matter ($P=0.018$) especially in the genu ($P=0.021$), splenium ($P=0.043$), and body of corpus callosum ($P=0.022$) in HH group. In children with HH mean WM FA correlated significantly with full scale IQ ($r=0.586$, $P=0.035$) and perceptual reasoning index ($r=0.691$, $P=0.009$). FA values of body of corpus callosum correlated positively to full scale IQ ($r=0.675$, $P=0.011$).
Conclusion
Children with HH manifest abnormalities in global white matter and corpus callosum that correlates with cognitive deficits. Future longitudinal studies are required to confirm this and delineate the pattern of deficits at key developmental stages.

DOI: 10.1530/endoabs.39.OC5.4

OC5.5

A novel, missense, mutation (P81R) in the TRH receptor gene in congenital central hypothyroidism

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Background
Congenital, isolated, central, hypothyroidism (CCH), is rare and evades diagnosis on TSH-based congenital hypothyroidism screening programmes in the UK. Genetic ascertainment is therefore paramount in enabling prompt diagnosis and treatment of familial cases. Recognised causes include *TSHB* and *IGSF1* gene defects, with only two previous reports of biallelic, highly disruptive (nonsense; R17X, in-frame deletion and missense; p.S115-T117del+T118), mutations in the TRHR gene. Here, we describe the first homozygous missense mutation in *TRHR*, associated with a typical phenotype.
Case
A female infant from a consanguineous Pakistani family, presented with prolonged neonatal jaundice and was found to have central hypothyroidism (TSH 2.2 mU/l (NR 0.4–3.5) and free T_4 7.9 pmol/l (NR 10.7–21.8)), with otherwise normal pituitary function. With *TSHB* or *IGSF1* mutations being usually associated with profound or X-linked CCH, a *TRHR* mutation was sought.
Results
Sequencing identified a homozygous mutation (P81R) in *TRHR*, substituting arginine for a proline residue in transmembrane helix 2 (TM2) which is highly conserved amongst G-protein coupled receptors (GPCRs). Functional studies showed that although the mutant receptor was expressed and localised to the cell membrane normally, its ability to bind radiolabelled TRH and signal via Gqalpha was markedly impaired, likely due to disruption of structure of TM2.
Conclusion
We describe the first deleterious, missense *TRHR* defect associated with moderate CCH. Importantly, the location of the mutated amino acid (proline 81) highlights a previously unanticipated functional importance of the second TM in mediating hormone binding and receptor activation. Future identification of other, naturally-occuring, *TRHR* mutations may map the molecular basis of ligand binding and activation of TRHR which are poorly understood.

DOI: 10.1530/endoabs.39.OC5.5

OC5.6

Bone histomorphometry in patients with *TMEM38B* mutations suggests a novel patho-mechanism leading to increased bone fragility

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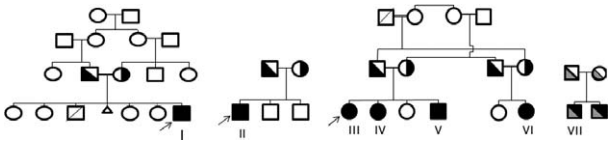
Background
TMEM38B is a ubiquitously expressed monovalent cation-specific channel protein hypothesized to play a role in intracellular calcium homeostasis. To date, only two unique recessively inherited exon deletions in *TMEM38B* have been reported in 17 individuals with osteogenesis imperfecta (OI). Data on bone histomorphometry and bone material property have not previously been presented.
Cases
Targeted next generation sequencing was performed using a custom designed gene panel in seven children who presented with increased bone fragility and fractures. Pre-bisphosphonate bone biopsies were performed in three affected individuals. Patient 2 had an unusual skeletal phenotype with postnatal radiographs at 2 months of age identifying excessive periosteal reaction (cloaking) in all long bones, which later consolidated to form rather wide bones and significant coxa vara. Patient 4 presented with an extensive anterior myocardial infarct aged 16 years.
Results
Individuals 1–4 were homozygous for the same c.507G>A mutation in exon 4 of TMEM38B. Patient 7 was compound heterozygous for an exons 1 and 2 deletion and c.63dupT, which introduces a premature termination codon. In contrast to classical OI, iliac crest bone histomorphometry identified markedly reduced bone resorption with normal or slightly increased bone matrix mineralization density.
Discussion
Our studies suggest that *TMEM38B* mutations create a unique bone material phenotype of increased bone fragility. Histomorphometrically, this condition not typical of OI caused by collagen-gene being instead characterized by, low bone turnover and formation and relatively normal bone matrix mineralization. We describe the first cardiac abnormalities in a patient with a mutation in *TMEM38B*. TRIC channels encoded by TMEM38B contribute to calcium flux across the endoplasmic reticulum. Abnormalities in the function of this channel may predispose affected individuals to stress-induced heart failure. This report indicates the need for careful cardiovascular risk assessment in OI caused by *TMEM38B* mutations, at least until the risk profile becomes clearer.



DOI: 10.1530/endoabs.39.OC5.6

OC5.7

Prevalence, management, and long-term outcomes of osteonecrosis in young people with acute lymphoblastic leukaemia

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Introduction
Osteonecrosis is an increasingly common complication in young people treated for acute lymphoblastic leukaemia (ALL). This is likely to be due to the now universal use of high dose steroids.
Aim
The aim of this study was to obtain information on prevalence, current UK management and long-term outcomes of patients.
Methods
We retrospectively collated data on patients with osteonecrosis for the most recently completed trial for children and young adults with ALL, UKALL2003, which recruited 3126 patients aged between 1 and 24 years. A questionnaire was sent to all participating centres. Patients with reported bone toxicity were previously identified by the central trial unit, and patients details were sent to each centre. Information regarding previously unreported patients with osteonecrosis was also requested.
Results
Data regarding 144 patients with osteonecrosis were received. The overall prevalence of osteonecrosis was 5% in children and young people with ALL, with the majority (75%) aged between 10 and 16 years. 86% had multifocal osteonecrosis, with a total of 415 areas affected. The most commonly affected joints were hips (144), followed by knees (126) and shoulders (57). Osteonecrosis was diagnosed by MRI in 71% of cases. Steroids were stopped in 61% of patients. Bisphosphonates were used in 32 patients, of whom nine had a history of fractures. 57 patients required surgery, with 27 patients requiring one or both hips replaced. After a median follow up of 70 months, 53 patients were reported to have no long-term effects, 56 had minimal disability, 15 had significant disability and five required a wheelchair. Nine patients died, and outcome data was not available for 8 patients.
Conclusion
Osteonecrosis is a significant problem for patients with ALL, with a large percentage of those affected requiring surgery. A uniform management strategy is required, including guidelines for use of bisphosphonates and continuation of steroid therapy.

DOI: 10.1530/endoabs.39.OC5.7

OC5.8

Neonatal TSH: is it useful and appropriate as an indicator of iodine insufficiency in the UK?

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Introduction
The World Health Organisation (WHO) states that in an iodine sufficient population <3% of neonatal TSH values will exceed 5 mU/l. In Belgium and Wales 2.6 and 1.5% of values were above 5 mU/l respectively.
Methods
Neonatal TSH (neoTSH) levels (AutoDELFIA fluoroimmunoassay, 2006–2013, Scotland) were analysed for prevalence of high value according to cut-off, season and feeding mode (IBM SPSS 22).
Results
Out of 413 296 measurements (after exclusion of preterm infants), only 0.7% of neoTSH was above 5 mU/l, from 0.6% (2006) to 1% (2012). Most (87.8%) neoTSH values were below 2 mU/l, the analytical sensitivity of the assay, therefore it is not possible to quote a median TSH value. Only 3.6% neoTSH values were above 3 mU/l and 0.2% above 8 mU/l. The mean neoTSH concentration increased ($P<0.021$) as collection age decreased a mean 5.07 mU/l at day 1 of life to a mean below sensitivity (<2 mU/l) at day 5 (81.1% of measurements between days 4 and 5). There was no significant seasonal interaction between the prevalence of neoTSH values >2 or >3 mU/l, but prevalence of neoTSH values >2 mU/l was significantly higher in mixed-fed (13.6%) and breast-fed babies (12.5%) compared to bottle fed babies (11.3%) (χ^2 $P<0.001$).
Discussion/conclusion
Our analysis indicates that, based on neoTSH values, Scotland is iodine sufficient. This is contradicted by reports of insufficient iodine intake/status in girls and women in the UK including Scottish centres. While neoTSH is useful at detecting moderate or severe iodine deficiency, there is concern that it is ineffective at identifying mild iodine insufficiency. The low analytical sensitivity (2 mU/l) of AutoDELFIA, used across the UK, makes robust analysis of TSH data below this level problematic. The discrepancy between our neonatal TSH data, the WHO cutoff and reports of mild iodine insufficient in the UK by urinary analysis indicates that a reassessment of best biomarkers of mild iodine insufficiency is required for this population. This must take in consideration the analytical sensitivity of the AutoDELFIA method. Observing the frequency of TSH values above 2 mU/l rather than using a cut-off point may be a more robust methodology.

DOI: 10.1530/endoabs.39.OC5.8

OC5.9

Assessing aortic dilatation using aortic sized index is inappropriate in children and adolescents with Turner syndrome

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Background
Aortic sized index (ASI) defined as aortic dimensions/body surface area (BSA), has been proposed as a method of identifying aortic dilatation in Turner syndrome. A recent paper reported centile charts of aortic dimensions across for BSA using echocardiogram in 451 children and adults with TS allowing for calculation of *Z* scores.[1]
Methods
We report *Z* scores for aortic root adjusted for BSA from clinical echocardiogram (ECHO) from a group of children and adults with TS. Results reported as median (range).
Results
Sixty-four individuals with TS (27, 45X) median age of 17.8 years (1.1, 58.2). 7/64 had a history of coarctation of aorta. Median ASI root for the whole cohort was 1.7 cm/m^2 (1.0, 3.7). Median root *Z* score for the whole cohort was −0.21 (−3.81, 3.96). 4/64 (6.3%) had ASI >2.5 cm/m^2, currently defined as significant aortic dilatation and very high risk of aortic dissection. Median ASI of these four individuals was 3.55 cm/m^2 (2.7, 3.6) whereas median aortic root *Z* score was +0.27 (−1.77, +3.44) with median age at ECHO 1.75 years (1.1, 36.8). ¾ of these individuals had root *Z* score within ±2 SD., all of whom were young growing children. Linear regression showed a significant association between age and ASI (β co-efficient = −0.37, P=0.002, 95% CI −0.03 to −0.006). This relationship was significant in individuals ≤18 years (β co-efficient = −0.86, $P \leq 0.0001$, 95% CI −0.14 to −0.09) but not in those >18 years (β co-efficient = −0.08, P=0.67, 95% CI −0.02 to +0.01).
Conclusion
Using current cut-offs of ASI >2.5 cm/m^2, 75% of TS individuals especially younger growing children were misclassified as having aortic dilatation when aortic dimensions were expressed as *Z* scores for BSA. The negative association between age and ASI especially in growing children suggests that ASI is not appropriate as a method of identifying aortic dilatation in young girls with TS. Recommendations for consideration of cardiothoracic surgery in children with TS and ASI >2.5 cm/m^2 may be unnecessary.[2]
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DOI: 10.1530/endoabs.39.OC5.9

OC5.10

Pegvisomant treatment for X-linked acrogigantism syndrome
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Introduction
Chromosome Xq26.3 microduplications have recently been identified, and explained this 11-year-old girl's marked tall stature. Her severe phenotype illustrates X-linked acrogigantism (X-LAG) and demonstrates therapeutic benefit from growth hormone receptor blockade.
Case
A 5.6-year-old girl presented with growth acceleration from 3 years and appearance of secondary dentition, greasy skin and blackheads from age 4. Past medical and family histories were unremarkable. Examination revealed height SDS +4.25 and mild coarsening of facial features. IGF1 was elevated (79 nmol/l (4–20)) with normal prolactin, TFTs and gonadotrophins. GH was elevated at baseline (38 μg/l) and failed to suppress on OGTT (nadir 16 μg/l). Serial contrast-enhanced MRIs over 6 years showed mild pituitary hyperplasia although no tumour. Genetic screening for *MEN1*, *AIP*, and leucocyte *GNAS* mutations was negative.
Treatment with somatostatin analogue, lanreotide (Somatuline Autogel), 2008–2012 achieved partial IGF1 reduction, although not normalisation with no reduction in height velocity. Concomitant cabergoline achieved no further IGF1 reduction. Aged 9 years, medication was stopped due to side effects and insufficient therapeutic benefit. Aged 11, there was increased height velocity (10.8 cm/year), predicted final height 6 ft 4 inch and increased IGF1 (106.4 nmol/l (9.8–57.2)). An alternative somatostatin analogue, octreotide (Sandostatin Lar), was trialled. After initial IGF1 reduction (61.1 nmol/l), IGF1 elevation continued as did increased growth.
Pegvisomant, a GH receptor antagonist, was trialled May 2015. In 2 months, there was IGF1 normalisation (24.3 nmol/l), ring size reduction, improved general well-being and no height gain.
Testing for chromosome Xq26.3 microduplication confirmed a genetic diagnosis of X-LAG and testing of her parents indicated a *de novo* mutation.
Summary
The case illustrates how discoveries in pituitary genetics have given a recent diagnosis to a child with severe growth hormone excess and pituitary hyperplasia. The initial response to pegvisomant therapy is encouraging and supports consideration of its use in similar somatostatin analogue resistant cases.
DOI: 10.1530/endoabs.39.OC5.10

Oral Communications 6

OC6.1

Somatostatin-expressing cells contribute to the pathobiology of atypical congenital hyperinsulinism in infancy
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Background
Atypical congenital hyperinsulinism in infancy (CHI-A) represent patients who generally present symptoms of hypoglycaemia later in the neonatal period, are poorly responsive to medical intervention and have no known genetic cause of disease. Our objective was to compare the expression profiles of insulin and somatostatin in islets from patients with CHI-A, diffuse CHI (CHI-D) and age-matched control tissue.
Methods and materials
CHI tissues were obtained following pancreatectomy, and age-matched control tissue following autopsy. CHI-D patients were positive for defects in *ABCC8*; CHI-A was not associated with defects in CHI-associated genes. Insulin- (INS$^+$) and somatostatin-expressing cells (SOM$^+$) were identified by immunohistochemistry and quantified following digitization of paraffin-embedded tissue samples; Ki67 was used as a marker of cell proliferation and NKX2.2 as a transcription factor which maintains β-cell phenotype in islets with limited expression profile in δ-cells following birth.
Results
We examined islets from CHI-A (n=47) and compared to control (n=50) and CHI-D (n=26) islets. In CHI-A, 49.5% of the islets (n=23) had a quiescent profile associated with condensed cytoplasm, nuclear crowding and reduced numbers of centrally-located INS$^+$ cells. In control and CHI-D, >90% of islets were composed of >70% INS$^+$ cells and <20% SOM$^+$ cells (n=61). In contrast, >70% of quiescent CHI-A islets had <30% INS$^+$ cells and >65% had more than 20% SOM$^+$ cells; with 30% of islets composed of >50% δ-cells (n=20). Surprisingly, 'quiescent islets' had twofold higher rates of proliferation than unaffected islets from the same tissue, and >60% δ-cells were positive for NKX2.2; a transcription factor that was only present in a limited number of δ-cells in control islets.
Summary/conclusion
Marked increases in NKX2.2 expression in CHI-A δ-cells combined with increased numbers of SOM$^+$ cells and rates of proliferation imply that an immature δ-cell profile contributes to the pathobiology of CHI.
DOI: 10.1530/endoabs.39.OC6.1

OC6.2

Mutations in *BRAF* are associated with septo-optic dysplasia and cardiofaciocutaneous syndrome
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Background
Mutations in *BRAF* are a rare cause of cardiofaciocutaneous syndrome (CFC). Recently, *BRAF* mutations have been reported in papillary craniopharyngiomas,

Table 1

Case/gender (M/F)	**Case 1** (M)	**Case 2** (F)	**Case 3** (F)
BRAF mutation	c.770 A>G (p.Q257R)	c.1403T>C (p.F468S)	c.721 A>C (p.T241P)
GH peak (μg/l) (age/year)	5.9 (2.5 years)[a]	5.1 (9.7 years)[b]	11 (6.2 years)[b]
IGF1 (μg/l), NR	61, 20–180	69, 111–551	74, 88–474
fT_4 (pmol/l) (age/year) NR	16.6 (3.4 years), 10.3 (3.8 years) 7.3–21.1	9.4 (9.8 years) 10.8–19.0	Normal
TSH (mU/l) (age/year) NR	0.7 (3.4 years), 0.58 (3.8 years) 0.34–0.56	3.0 (9.8 years) 0.4–4.6	
LH and FSH (IU/l) (age/year)	Stimulated: 4.1, 8.0 (14.1 years) Testosterone 0.5 nmol/l	Basal: 44.5, 53.5 (13 years) Oestradiol: <44 pmol/l	-
Tanner stage	1	1	
Cortisol peak (nmol/l)	-	-	433[c]
MRI features	Small anterior pituitary Absent corpus callosum Hypoplastic optic nerves	Reduction in white matter Enlarged lateral ventricles Hypoplastic corpus callosum Hypoplastic optic nerves Normal anterior and posterior pituitary and stalk	Pending

NR, normal range; a, clonidine; b, glucagon stimulation; c, modified Synacthen.

but have not been described in patients with other hypothalamo-pituitary abnormalities. We describe three patients with CFC and septo-optic dysplasia (SOD) associated with heterozygous *BRAF* mutations.

Cases

Patients presented in childhood with clinical features of genetically proven CFC, short stature (height <0.4th centile) and MRI features of SOD. In cases 1 and 2, GH deficiency was initially observed (see Table 1), with case 1 subsequently developing gonadotrophin deficiency and a low-normal T_4 and TSH, requiring levothyroxine replacement. Case 2 developed TSH deficiency and case 3 partial ACTH deficiency.

In situ hybridisation performed on human embryonic brain and hypothalamo-pituitary sections showed strong *BRAF* mRNA transcript expression at Carnegie stages (CS) 19, 20, 23, and 8 post-conception weeks, in the hypothalamus/ventral diencephalon, Rathke's pouch, trigeminal ganglia, retina, spinal cord, and ganglia.

Conclusion

We report the first novel association of SOD and CFC secondary to *BRAF* mutations. Endocrine features include GH deficiency, with evolution of other pituitary abnormalities. Patients with CFC should be screened for pituitary defects as these may be associated with morbidity. BRAF therefore appears to be implicated in normal hypothalamo-pituitary function.

DOI: 10.1530/endoabs.39.OC6.2

OC6.3

Skeletal changes in pre-pubertal children with loss of function mutations in the melanocortin-4 receptor

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Background

Obese children are at greater risk of fracture. However, previous evidence suggests that obese children with a mutation in the melanocortin-4 receptor (MC4R) have a high age-adjusted bone mass. MC4R deficiency is associated with increased linear growth, so bone mass may be over-estimated due to patients being taller. We therefore aimed to compare body size-adjusted bone mass of lean and obese pre-pubertal children with those who have a mutation in MC4R.

Methods

We retrospectively reviewed the DXA derived total body bone area (BA (cm^2)), bone mineral content (BMC (g)), and bone mineral density (BMD (g/cm^2)) in pre-pubertal Caucasian children (<12.0 years) with known loss of function variants in MC4R ($n=49$) from the Cambridge Genetics of Obesity Study (GOOS) cohort. Skeletal parameters were adjusted for height and weight and compared with those derived from Caucasian pre-pubertal obese ($n=22$) and lean ($n=110$) children.

Results

Mean age of the lean, obese and MC4R cohorts was 8.2 ± 2.0, 8.3 ± 1.8, and 7.4 ± 2.5 respectively ($P=0.06$). Mean height SDS was lower in lean children compared with obese and MC4R cohorts (ANOVA, $P<0.001$). BMI SDS of MC4R patients was significantly greater than obese (mean difference = 0.78 (0.22, 1.33), $P=0.003$) and lean (mean difference = 3.83 (3.46, 4.21), $P<0.001$). Body-size adjusted total BMC and bone area were greater in MC4R ($P=0.03$ and $P=0.004$ respectively) and obese ($P=0.003$ and $P<0.001$) when compared to lean subjects. In contrast body-size adjusted total BMD and BMC corrected for bone area was not different between the cohorts.

Conclusions

Pre-pubertal children with loss of function mutations in the MC4R and obese children have a higher body-size adjusted BMC compared to lean children. This is due to a larger bone size. Despite this, bone density does not increase. Mutations in MC4R do not appear to alter the bone phenotype when compared to obese children despite an increase in body size.

DOI: 10.1530/endoabs.39.OC6.3

OC6.4

Associated renal anomalies in children with Turner syndrome: 43-year experience from a single-centre

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Objective

To assess prevalence, clinical features, and follow-up of renal/urological malformations in patients with Turner syndrome (TS).

Methods

The medical records of 182 patients with TS born between 1970 and 2013 were retrospectively reviewed.

Results

Twenty-one girls (11.5%) were identified with renal/urological anomalies: 15 (71%) horseshoe kidney (HSK), 1 (4.7%) malrotation, 2 (9.5%) single kidney, and 1 (4.7%) duplex collecting system (DCS) associated with renal arteries abnormalities and vescico-ureteral reflux (VUR), 1 (4.7%) pelvic kidney and 1 (4.7%) crossed fused ectopia associated with DCS. In addition 5 (33%) patients with HSKs had associated urological anomalies: vesicoureteric reflux (1), DCS and VUR (1), pelvic–ureteric junction obstruction (1), calyceal and pelvic dilatation (2). In 12 patients (57%) urological anomalies were identified incidentally, in 7 (33.3%) diagnosis followed recurrent urinary tract infections (UTI) and the last 2 (4.7%) were diagnosed antenatally. Karyotype was 45,X0 in 9 (43%), mosaicism in the rest. Each patient had a renal ultrasound and DMSA to confirm the diagnosis, while three underwent micturating cystogram. On long-term follow 43% developed nephro-urological complaints: 3 (14%) were found to have renal parenchymal damage on DMSA scan, 2 (9.5%) recurrent UTI, 2 (9.5%) hypertension, 1 (4.7%) recurrent haematuria, and 1 (4.7%) progressed to chronic kidney disease stage 1. Only 1 (4.7%) patient required surgical intervention (pyeloplasty).

Conclusion

Urological anomalies were detected in 11.5% of our large series of patients with TS. Long-term follow-up of these patients shows that 43% of our study population developed a nephro-urological complaints, highlighting that once a urological anomaly is detected a close follow-up is warranted.

DOI: 10.1530/endoabs.39.OC6.4

OC6.5

The measurement of urinary gonadotrophins for assessment and management of pubertal disorders

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Objective
Prospective evaluation of the relationship between first morning urinary gonadotrophins (uGn) measured by immunoassay and corrected for creatinine (uLH:uCr and uFSH:uCr), and basal serum gonadotropins (sLH and sFSH) and in response to LHRH stimulation test. Prospective evaluation of uGn trend in patients receiving GnRH analogue (GnRH-a; decapeptyl SR, 11.25 mg, every 10–12 weeks).
Methods
Enrolled 15 (12M) patients evaluated for delayed puberty, 14 (F) for suspected precocious puberty and 16 (3M) on GnRH-a. Three first morning urine samples of three mornings before the stimulation test or before the GnRH-a injection were collected. For patients on treatment, three samples 5/6 weeks after injections were also collected. Data were expressed as median (range), and analyzed by SPSS v10.0 ($P<0.05$).
Results
Coefficient of variation (CV) of samples collected before the stimulation test was 0.28 (0–1.4) for uLH:uCr and 0.26 (0.05–0.99) for uFSH:uCr. Significant correlations between sLH and uLH:uCr ($r=0.7$; $P<0.001$) and between sFSH and uFSH:uCr ($r=0.9$; $P<0.001$) were identified.
Based on receiver operator characteristics analysis, a uLH:uCr value of 0.032 IU/mmol as a cut-off would detect a sLH peak >5 UI/l (sensitivity: 87%; specificity: 86%; and area under the curve: 0.89).
For patients on treatment, uLH:UCr CV of samples collected before the injection was 0.29 (0.14–0.85) and after 5/6 weeks 0.33 (0.04–0.63), while for uFSH:UCr, respectively, 0.24 (0.13–0.52) and 0.4 (0.08–1.3).
Median uLH:UCr and uFSH:UCr values before injections (0.01 and 0.34 IU/mmol) were significantly higher than after 5/6 weeks (0.008 and 0.09 IU/mmol) (P: 0.000 and P: 0.000 respectively).
Conclusion
UGn is a useful, non-invasive instrument for diagnosis and management of pubertal disorders.

DOI: 10.1530/endoabs.39.OC6.5

OC6.6

An assessment of auditory function in infants with congenital hypothyroidism

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Introduction
Thyroxine plays a key role in the development of the structures of the ear, the auditory pathway and in myelination of the central nervous system. The association between congenital hypothyroidism (CH) and neurodevelopmental outcome is clearly established. However, there is a lack of data about the prevalence and severity of hearing loss in the CH population.
Methods
Between 1/1/12 and 31/12/13, 187 children were diagnosed with CH and treated with levothyroxine after referral through the North Thames Newborn Screening programme at Great Ormond Street Hospital. Biochemical, sociodemographic, and technetium scan data were collected. All infants were referred for audiological assessment at 2 and 8 months. Auditory brainstem response (ABR) testing at 2 months and visual reinforcement audiometry (VRA) at 8 months, along with otoaucoustic emissions (OAE) testing was used to ascertain hearing outcomes.
Results
121/187 (64.7%) patients attended the 2-month hearing assessment, and 87/187 (46.5%) completed the 8-month assessment. Of those tested, results revealed a prevalence of mild hypothyroid-related hearing loss of 30% at 2 months and 18% at 8 months in this CH cohort. These are both statistically significant at the 5% level, when compared with the prevalence of 0.24% in the general paediatric population. Both TSH and T_4 levels were shown to have a strong positive relationship with hearing outcomes, $P=0.036$ and $P=0.001$ respectively. Gender ($P=0.639$), ethnicity ($P=0.675$), and thyroxine requirements ($P=0.806$) were not shown to have a statistically significant effect on hearing outcomes. ABR latencies at 2 months were shown to be slightly delayed at all intensities in agenesis patients, suggesting that there is delayed myelination in this group. 3/187 infants in this study failed the newborn hearing screening test.
Discussion/conclusion
Infants with congenital hypothyroidism experience greater hearing loss than the general paediatric population. Only 3/187 infants in this study failed the newborn hearing screening test, therefore it was concluded that the programme is not sufficient at identifying hearing loss in infants with congenital hypothyroidism. We recommend that auditory referral should be considered for all infants diagnosed with congenital hypothyroidism.

DOI: 10.1530/endoabs.39.OC6.6

OC6.7

Standard and modified release hydrocortisone formulations: cortisol levels and patient preference

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Background
Cortisol profiles during treatment with standard hydrocortisone (StdHC) formulations are unphysiological. Some patients, with low cortisol levels between doses, experience symptomatic hypocortisolaemia and may benefit from modified release hydrocortisone (MRHC). Plenadren is a MRHC licensed for once daily dosing in adults.
We offered Plenadren to patients with symptomatic hypocortisolaemia, documented to occur at times of low cortisol levels, and persisting despite manipulations in size and frequency of StdHC doses.
Aims and objectives
To describe: i) peak cortisol and time to cortisol <100 nmol/l after a dose of StdHC and Plenadren and ii) patient preference for StdHC and Plenadren.
Methods
Plenadren doses were calculated from total daily dose (TDD) of StdHC, rounded up to nearest 5 mg: 2/3 on waking, 1/3 at 1530–1630 h. Plasma cortisol was measured 2-h during StdHC treatment, and the following day after the morning dose of Plenadren. Plenadren doses were adjusted and treatment continued for 3 months when patients were offered continuing treatment with Plenadren or StdHC.
Results
Since 2012, eight patients (5M) age 11 years (8.8–13.3) with Addison's disease ($n=3$), pituitary irradiation/surgery ($n=2$), adrenal suppression ($n=2$), and pituitary compression ($n=1$), receiving StdHC 12.6 mg/m^2 per day (10.5–17.8), have been treated.
Following StdHC 6.1 mg/m^2 (3.3–7.1) and Plenadren 10 mg/m^2 (8.3–16.7), peak cortisol was 360.7 nmol/l (154–654) and 346 nmol/l (150–466) ($P=0.82$), and plasma cortisol <100 nmol/l at 4 h: $n=7$ and $n=1$, 6 h: $n=7$ and $n=4$, and 8 h: N/A, $n=7$ respectively.
Plenadren was given twice ($n=4$) or three times daily ($n=4$). After 3 months, six patients reported fewer headaches, improved energy, and school attendance. Two patients complained of nausea and resorted to StdHC.
Conclusions
In this small, highly selected cohort, two to three daily doses of Plenadren were required to maintain cortisol >100 nmol/l. Self-reported measures suggest some benefit from MRHC. Rigorous clinical trials are required to examine the place of MRHC in paediatric practice.

DOI: 10.1530/endoabs.39.OC6.7

OC6.8

An interstitial deletion within *GATA3* in association with abnormal pituitary structure and function

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Background
Haploinsufficiency of the *GATA3* gene located on chromosome 10p15, is well-recognised as the cause of hypoparathyroidism, sensorineural deafness and renal dysgenesis; the HDR syndrome. A number of abnormalities within the *GATA3* gene have been identified, with varying phenotypic characteristics. *GATA3* is associated with other abnormalities including, abnormalities of Mullerian structures, hypomagnesia, hemimegalenencephaly and diabetes mellitus.
GATA3 is expressed in the embryonic CNS, and has a role to play in the development of hypothalamic 5HT neurons. Knock-down of *GATA3 in-vitro* is associated with a decrease in expression of genes linked to IGF-signaling, including IGF1, IGF2 and several IGF-binding proteins. Within the anterior pituitary gland, *GATA* factors have been shown to increase glycoprotein α-subunit gene promoter activity (relating to thyrotroph and gondotroph function) and *GATA2*-deficient mice exhibit elevated levels of *GATA3* transcripts in the pituitary gland, suggesting that *GATA3* can compensate for *GATA2*. However, to date *GATA3* mutations in humans have not been reported in conjunction with pituitary dysfunction.
Report
We report the case of a female child who initially presented in the neonatal period with bilateral sensory neural deafness. At eight months of age she was diagnosed with hydrocephalus secondary to a Chiari 1 malformation, which required management with a third ventriculostomy. Subsequently she developed persistent proteinuria and haematuria, partial diabetes insipidus and growth hormone deficiency. Cranial MRI demonstrated a small anterior pituitary, an ectopic posterior pituitary and abnormalities of the cochlea.
CGH array demonstrated interstitial deletion on the short arm of chromosome 10 with breakpoints within p14. The deletion was approximately 7 Kb in size and contained part of the *GATA3* gene.
Conclusion
This case demonstrates a previously unreported clinical association between *GATA3* and structural abnormalities of the pituitary presenting as diabetes insipidus and growth hormone deficiency. Further work is required to investigate this association.

DOI: 10.1530/endoabs.39.OC6.8

OC6.9

The impact of intragastric balloon placement suppported by a lifestyle intervention programme on cortical and trabecular microstructure and strength in severely obese adolescents

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Background
The effect of profound weight loss following obesity surgery on skeletal microarchitecture and strength in adolescents has not been studied. Obese children are at an increased risk of fracture and childhood obesity leads to reconfiguration of trabecular bone without augmenting bone strength.
Objectives
To examine the impact of weight loss following 6 months treatment with an intragastric balloon supported by a lifestyle intervention programme on cortical and trabecular bone microstructure and bone strength in obese adolescents.
Methodology
We recruited 11 adolescents aged 13.8–16.8 years, BMI >3.5 SD., Tanner stage 4/5) to undergo intragastric bariatric balloon placement. Serial distal radial and tibial high resolution pQCT (peripheral quantitative computed tomography) imaging, subtotal body and lumbar spine (LS:L1 to L4) DXA was performed at baseline and 6 months. HRpQCT measures of microstructural properties included trabecular number (Tb.N, 1/mm), trabecular thickness (Tb.Th, mm), trabecular separation (Tb.Sp, mm), and cortical thickness (Ct.Th, mm). Biomechanical parameters were defined by miocrofinite element analysis. Results are expressed as (mean difference, 95%CI, significance(P)).
Results
Weight SDS and BMI SDS decreased significantly (-0.38 (-0.62, -0.13) and -0.27 (-0.44, -0.10) respectively, $P=0.005$). Total body bone mineral content (BMC), LS BMC and LS bone area all demonstrated age appropriate increases following the balloon. Cortical BMD (14.0 mg/cm^3 (8.2, 19.7), $P<0.001$) and cortical perimeter size (4.0 mm (0.5, 7.5), $P=0.029$) increased at the radius. Cortical area (2.4 mm^2 (0.1, 4.7), $P=0.042$), cortical BMD (11.1 mg/cm^3 (4.1, 18.0), $P=0.006$) and cortical thickness (0.02 mm (0.001, 0.04), $P=0.042$) increased at the tibia. Paradoxically, total bone area at the radius diminished (-6.1 mm^2 (-8.9, -3.2), $P=0.001$). Bone stiffness and estimated ultimate failure load did not significantly change following surgery.
Conclusions
There was no evidence of skeletal deterioration following intragastric balloon insertion despite a reduction in BMI SDS. Total body and regional bone accretion continued with the greatest gains in cortical bone. In the short term, balloon bariatric surgery does not cause bone loss in adolescence.

DOI: 10.1530/endoabs.39.OC6.9

OC6.10

Neuroradiological features in a cohort of 53 children with Thickened Pituitary Stalk (TPS) and/or idiopathic central diabetes insipidus

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Introduction
Children with TPS and/or ICDI represent a diagnostic and management conundrum. Agreed radiological criteria for TPS are lacking.
Aims
To longitudinally characterize the neuroradiological features of children presenting with TPS and/or ICDI due to different aetiologies (oncological, inflammatory, idiopathic).
Methods
We searched the terms 'thickened pituitary stalk' or 'idiopathic diabetes insipidus' in electronic radiology at our centre over the last 30 years. 53 patients presenting with ICDI (38) TPS (10) or TPS+ICDI (5) were identified and their MRI scans reviewed.
Results
Median age at diagnosis was 9.02 (6.47) for TPS, 8.29 (8.13) for CDI, 3.84 (6.98) TPS+ICDI. During the follow-up (TPS 2.45 (3.14), ICDI 5.12 (5.31), ICDI+TPS 3.11 (3.89) years) 18 ICDI patients (47%) evolved to include TPS (3 with germinoma, 8 with LCH, 7 Idiopathic), whereas only 1 patient with TPS (LCH) developed CDI. All patients with a final diagnosis of LCH had TPS at presentation. Top and middle stalk sizes were bigger in LCH patients compared to germinomas and idiopathic groups. Idiopathic patients presented with any pattern of thickening, whereas germinomas presented with upper and middle thickening only and LCH with uniform, upper and middle thickening. 73.3% of LCH patients presented with small anterior pituitary, despite similar prevalence of anterior pituitary deficits at presentation compared with germinomas and idiopathic cases. 85.7% of germinomas and 69.6% of idiopathic cases had absent posterior pituitary at presentation.
Conclusions
Half of the patients with ICDI will develop TPS during a median 5 years follow-up. LCH patients present with bigger stalk sizes and higher prevalence of pituitary hypoplasia, whereas germinomas and idiopathic patients have more frequently absent posterior pituitary. Pattern of thickening differs across the groups with germinomas presenting more frequently with upper stalk thickening, LCH with upper and middle thickening and idiopathic with any pattern of thickening.

DOI: 10.1530/endoabs.39.OC6.10

Oral Communications 7

OC7.1

Wolfram syndrome: natural history and genotype-phenotype correlation based on EURO-WABB registry show gender differences in disease severity

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Background
Wolfram syndrome (WS) is a rare autosomal recessive disorder, characterised by early-onset diabetes and optic atrophy. It is caused by mutations in *WFS1*.
Objective and hypotheses
This study aimed to comprehensively review the natural history of WS in a large cohort of patients from the EURO-WABB registry.
Method
Data from EURO-WABB patients with WS was analysed in conjunction with the Leiden Open Variation Database (LOVD) for genotype-phenotype correlation.
Results
174 WS patients (90M:84F) had standardised data available. Mean age of diagnosis was 8.39 yrs (s.d. 4.39). Most patients followed a classical sequence of clinical manifestations (deafness – median age of onset 1 (range 0–9 yrs); insulin-dependent diabetes – 5 (1–32 yrs); optic atrophy – 8 (0–32 yrs); diabetes insipidus – median age – 13 (3–34 yrs); urological abnormalities – median age 16 (12-20 yrs) and neurological abnormalities – median age 25.5 (7–40 yrs)). 11 patients (6.3%) had hypergonadotrophic hypogonadism. A proportion of patients had abnormalities not usually associated with WS: retinal dystrophy (4.6%, n = 8), chronic renal failure (5.7%; n = 10) and cardiomyopathy (2.8%, n = 5). 91 patients had mutations found in both alleles. 16 patients had only one mutation identified. 56 patients had no mutation in either allele identified. 80.8% of all mutations were located within exon 8. Most mutations were nonsense with predicted effects of reduced or truncated WFS1 protein. There was no significant genotype–phenotype correlation for age of onset of diabetes or optic atrophy (nonsense vs missense mutations). There was a gender difference in disease severity with earlier age of onset of insulin dependent diabetes (M = 4 yrs; F = 5 yrs; P = 0.04) and incidence of mental health disorders with males being more frequently affected (26M:15F) although this was not significant.
Conclusion
Analysis of the core data from EURO-WABB, the largest standardised patient cohort to date, shows a sequence of clinical manifestations similar to published literature. The phenotypic spectrum of WS is much wider than previously reported. Of note, is the male preponderance with mental health problems including depression and psychosis.

DOI: 10.1530/endoabs.39.OC7.1

OC7.2

Insulin and glucose profiles following an oral glucose tolerance test in patients with cystic fibrosis and classification tree modelling of insulin:glucose profiles as a tool to predict changes in lung function

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Introduction
Individuals with cystic fibrosis (CF) frequently exhibit altered insulin and glucose metabolism and many develop cystic fibrosis related diabetes (CFRD). Lung function is influenced by glucose metabolism with changes in glucose metabolism resulting in deterioration in lung function. Recommendations suggest CF patients should have an OGTT annually to screen for the development of CFRD. We examined the OGTT profiles to ascertain whether simpler fasting measures of insulin resistance and beta cell function derived from the OGTT could predict future lung function.
Methods
Data on insulin, glucose and C-peptide were collated over a period of 3 consecutive years for 81 patients with CF (aged 9–17) during their annual OGTT. This was correlated with lung function (FEV1 and FVC). A number of surrogates of insulin resistance and beta cell function such as HOMA score, QUICKI and fasting insulin:glucose ratios were examined together with markers of lung function using classification tree modelling to establish whether these surrogates could predicted future changes in lung function.
Results
Patients with CFRD and impaired glucose tolerance (IGT) showed significantly later peaks of both insulin and glucose following an oral glucose load compared to CF patients with normal glucose metabolism and the general population. Insulin and glucose both peaked late at 90 min in those with CFRD and IGT compared to a peak glucose at 30–60 min and peak insulin level at 60 min in those with CF and normal insulin:glucose handling.
A classification tree model incorporating data of fasting C-peptide, fasting insulin and glucose and 30 min insulin and glucose was 78.4% accurate in predicting a 10% change in FEV1 a year later.
Conclusion
CF patients whose insulin reserve and glucose handling is declining surprisingly show very delayed peaks in absorption of glucose and in production of insulin. This delay predicts declining lung function. Classification tree models offer a potentially useful tool by which to identify patients most at risk of future declines in lung function though they are not as yet refined enough to replace screening by OGTT.

DOI: 10.1530/endoabs.39.OC7.2

OC7.3

Safety and efficacy of atorvastatin treatment in children with familial hypercholesterolaemia

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Introduction
Familial hypercholesterolaemia (FH) has a gene frequency of at least 1/500 with >80% those affected remaining unidentified. Affected individuals have elevated LDL levels from birth which is a major cause of treatable premature coronary artery disease. NICE guidance recommends statin treatment from the age of 10 yrs for children with a confirmed diagnosis of FH. We were the first centre in England to have commissioned contact tracing and cascade testing to confirm the diagnosis of FH. Previously the genetic test for the common mutations (FH20) was only 50% sensitive. New next generation sequencing techniques are >90% sensitive. We describe biochemical and genetic characteristics of 36 children with confirmed FH, and the safety and efficacy of early atorvastatin treatment.
Methods
All children with a clinical or genetic diagnosis of were offered lifestyle advice, dietetic review, consultation with specialist genetic counsellors, specialist paediatric follow-up and fasted lipid profiles. Genetic investigations included FH20, NGS and cascade testing (direct gene sequencing for known mutation in relative).
Results
20/36 had previously had FH20 testing (13 mutations identified). A further 11 mutations were identified using NGS and ten using cascade testing. 25 mutations were LDL-R, 9:ApoB, 1: mutation negative, 1: unknown variant. 28/36 were on Atorvastatin at doses of 10 mg ($n = 14$), 20 mg ($n = 13$) and 40 mg ($n = 1$). Mean (range) age at onset of treatment was 10.1 (0.1–16.0). Mean (s.d.) BMISDS was 0.48 (1.27). Mean (s.d.) LDL pre-treatment vs post-treatment was 5.3 (1.3) vs 3.0 (0.6) mmol/l, ($P < 0.001$). The 50th percentile LDL for the normal population at this age is 2.25 mmol/l. There were no side effects, CK or LFT abnormalities related to statin treatment.
Conclusions
Contact tracing and cascade testing with NGS is highly effective in identifying children with FH. Early data suggests atorvastatin treatment is safe and effective from the age of 10 yrs but further data is required to establish long term safety and improved cardiovascular outcomes children.

DOI: 10.1530/endoabs.39.OC7.3

OC7.4

The cost-effectiveness of the KIds in control of food structured education programme for adolescents with type 1 diabetes

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Objectives
Kids in control of food (KICK-OFF) is a 5-day structured education programme for 11–16 year olds with type 1 diabetes who use multiple daily insulin injections. This study evaluates whether KICk-OFF would be considered a cost effective use of NHS resources by decision makers in the UK.
Methods
A cost effectiveness analysis comparing KICk-OFF to usual care was conducted. Data from the KICk-OFF trial were extrapolated to simulate lifetime outcomes using the Sheffield type 1 diabetes policy model. Baseline patient characteristics and effectiveness on HbA1c, severe hypoglycaemia and diabetic ketoacidosis came from the trial data. In the model HbA1c is the key predictor of future events (retinopathy, neuropathy, nephropathy, myocardial infarction, stroke, revascularisation and angina). KICk-OFF implementation costs were calculated using data from participating trial centres. Analysis was conducted in the full cohort and a high baseline HbA1c (>9.5%; 80 mmol/mol) subgroup. Treatment effect durations of 2 years, 4 years and lifetime were tested. Uncertainty was examined using probabilistic sensitivity analysis.
Results
Using the full cohort and 4 year treatment effect duration, KICk-OFF provided more quality adjusted life years (+0.0394 QALYs) at a higher cost (£1135) per person than usual care. The incremental cost per QALY gained was £28 813 per QALY gained, just within the range of £20–30 000 which NICE would consider cost effective (42.6% chance of being below £20 000). In the full cohort the value changed considerably with the treatment effect duration. For the high HbA1c subgroup, KICk-OFF was dominant i.e. provided more QALYs (+0.2012) at a lower cost (−£4,423) per person (96.4% chance of being below £20 000). In this subgroup results were robust to different treatment effect durations.
Conclusions
For the whole study population, whether KICk-OFF is cost effective depends on the long-term treatment effect duration. For the high baseline HbA1c subgroup, KICk-OFF was found to be cost effective.

DOI: 10.1530/endoabs.39.OC7.4

OC7.5

Investigating the impact of post-translational modification of Type 1 diabetes auto-antigens by tissue transglutaminase.

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Background
Post-translational modification (PTM) of antigens has been shown to play a role in the pathogenesis of autoimmune disorders. In coeliac disease (CD), tissue transglutaminase (tTG) deamidates gliadin peptides to activate the immune response against gut endomysium. CD is six times more prevalent in Type 1 diabetes (T1D) patients than in the general population.
Hypothesis
tTG also modifies auto-antigens implicated in the pathogenesis of T1D, leading to an autoimmune response to pancreatic β-cells.
Methods
20 randomly selected samples from the Bart's-Oxford cohort were used to study the effects of tTG PTM. tTG was incubated with the following auto-antigens, which had previously been shown to have high correlation with the development of T1D: glutamic acid decarboxylase isoform 65 (GAD65), full length islet antigen (IA-2), intracellular portion of IA-2 (IA-2ic), and both isoforms of zinc transporter 8 (ZnT8W and ZnT8R). Antigens were radiolabelled and incubated with tTG for 20 h at 27 °C in 100 mM Denver buffer, 3.33 nM $CaCl_2$, at pH 7.3. Antibody binding with incubated antigen was measured using a standard radiobinding assay. Site-directed mutagenesis was carried out in ZnT8W, changing glutamine (Q) to glutamate (E) at residue 375, to mimic the expected action of tTG incubation with wild type ZnT8W.
Results
tTG treatment of ZnT8W, ZnT8R and IA-2ic showed no significant change in antibody: antigen binding. Modest increases in binding were observed with tTG-treated GAD65 and full length IA-2 (6.5 and 14.5% respectively). Decreases in binding of antibody to tTG-treated ZnT8W compared with mutant ZnT8W Q375E in 3 samples (% reduction of 69.9, 42.1 and 19.5), where antibody binding should have been the same, questions what tTG modification events occurred, or whether these sera contained antibodies against the Q-X-P site.
Conclusion
In the case of GAD65, full length IA-2, and certain samples with IA-2ic, the strength of antibody: antigen binding increased after incubation with tTG. However, the exact PTM events occurring with tTG incubation for each antigen, as well as the exact sites of antibody: antigen binding in each sample, require further study.

DOI: 10.1530/endoabs.39.OC7.5

OC7.6

The evolving phenotype of transient neonatal diabetes 1: findings from the international register

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Introduction
Transient neonatal diabetes 1 (TNDM1) has an estimated incidence of 1 in 400 000 and is characterised by intra-uterine growth retardation and diabetes presenting soon after birth. Spontaneous remission of diabetes usually occurs within the first year of life. TNDM1 is caused by overexpression of imprinted genes at chromosome 6q24. Three causes have been described: paternal uniparental disomy for chromosome 6; paternally inherited duplication of 6q24; and maternal hypomethylation at the differentially methylated region at 6q24.
Aim
To document the evolving phenotype in TNDM1 with emphasis on growth, developmental progress, recurrence of diabetes and educational outcomes.
Methods
The international TNDM register includes details at presentation of 210 TNDM1 cases with consent for follow-up provided in 73 patients. Samples were referred to the Wessex Clinical Genetics Service or the Molecular Genetics Department at Exeter Clinical Laboratory Service. Confirmed cases were recruited prospectively. Follow-up questionnaires were sent to patients enquiring about: height, weight, medical problems, current diabetic status, treatment (if relevant), educational achievements and learning difficulties.
Results
Follow-up data were available for 22 patients. 5 (22.7%) had permanent relapse of diabetes and required treatment. In these patients the median age at relapse was 11 years (range 9.2–14 years). BMI SDS range was −0.6–1.1. Seventeen (77.3%) patients did not have diabetes at follow-up. One had experienced transient relapse. Median age at follow-up in this group was 9.2 years (range 3.6–22.3 years). Of the non-diabetic patients, 11 were of appropriate weight, four were overweight, one was obese and one was underweight. Learning difficulties were frequent (10/21 respondents). Significant speech delay was reported in 36% (8/22).
Discussion/conclusion
These data suggest that the recurrence risk of diabetes in TNDM1 is not associated with obesity. Learning difficulties are frequently present and we highlight speech delay as a frequent occurrence.

DOI: 10.1530/endoabs.39.OC7.6

Oral Communications 8

OC8.1

4 year outcome of combined 'en bloc' liver-pancreas transplant in two adolescents with cystic fibrosis

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Background
Cystic fibrosis related diabetes (CFRD), a common complication of CF, contributes to increased morbidity and mortality and is a poor prognostic indicator. Whilst liver transplant is a well-established treatment for end stage liver disease (ESLD) in CF, there are few reports of simultaneous pancreatic transplant in the paediatric population. We report the nutritional and endocrine outcomes of

two adolescent CF patients who underwent combined liver and pancreas transplantation.
Case Presentation
A 14 year male and 16 year old female CF patient presented with end stage liver disease and CFRD and became eligible for liver transplantation. Insulin requirements were 0.5 and 2.1 units/kg per day respectively. Both required pancreatic enzyme replacement therapy (PERT) with requirements of 9200 and 7600 IU lip/kg per day and supplemental overnight nutritional support. During combined liver-pancreas transplantation, intravenous insulin infusions were required to maintain euglycaemia and were able to be discontinued soon after surgery. Both patients remain off insulin beyond 4 years post-transplant, OGTT 120 min glucose levels (3.3 and 3.6 mmol/l respectively) and HbA1c (DCCT – 5.1 and 4.6%) were within normal range. PERT requirements decreased to < 1000 and 0 IU lip kg/day. Previous mid-upper arm circumferences increased from below 5th Centile prior to transplant to the 25 and 75 centile post-transplant. BMI (initially confounded by massive hepatosplenomegaly) prior to transplantation was 18.1 (z-score −0.4) and 20.2 (z-score −0.1). Post-transplant BMI peaked to 26.91 (z-score 2.09) and 23.4 (z-score 0.6).
Conclusion
These cases demonstrate that endocrine and exocrine functions were restored with subsequent improvement in nutritional status in both patients through combined liver-pancreas transplant. This was sustained beyond 4 years suggesting good prognosis for these patients. This procedure has technical advantages over isolated liver and pancreas transplantation, making it an appealing option to treat ESLD in the presence of CFRD.

DOI: 10.1530/endoabs.39.OC8.1

OC8.2

Using WhatsApp messaging to improve engagement of young adolescents with type 1 diabetes mellitus

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Introduction
We present the use of WhatsApp messaging to improve engagement of young adolescents with type 1 diabetes mellitus at Ealing Hospital. This virtual community allows patients to share information and expertise in self-management to improve motivation, self-care and knowledge, and also bridging gaps between appointments. Patients find the diagnosis of diabetes socially isolating, and are 2–3 times more likely to suffer psychological issues. Social media is a hugely untapped resource and more people worldwide now have access to mobile phones than toothbrushes.
Method
All children with type 1 diabetes aged 11 years or greater were invited to participate from March 2015. Patients required access to a mobile phone, which was compatible with the app. Informed consent was obtained from children and parents. Patient confidentiality is maintained as the group is a 'broadcast' rather than an 'open group,' therefore replies are directed to the diabetic team phone, not the whole group, ensuring quality control.
Results
16 patients are now members. Patients participated in the design process through a coproduction session and forum. Patients send messages to the group, such as snack advice and 'using new pens' to motivate each other. They write questions and send pictures for their peers, which are forwarded to the group. Qualitative data of patient and parent feedback has been overwhelmingly positive. One mother quoted 'This is what my son needs, he knows no one with diabetes and often feels he is the only one who has to inject then acts out.'
Conclusion
This innovative approach highlights the successful use of technology to improve patient engagement. Initial analysis of qualitative feedback has been overwhelmingly positive. Further data will continue to be collected to show this how the use of social media can improve care.

DOI: 10.1530/endoabs.39.OC8.2

OC8.3

Frequent patient contact to improve HbA1C- face-to-face or 'Virtual'?

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Background
National Paediatric Diabetes Audit report 2012–2013 showed an increase in the number of patients with HbA1C >80 mmol/l at our paediatric diabetes unit.
Aim
Two methods of intensive support for patients with high HbA1C were trialled-monthly clinics and weekly telephone contact.
Method
From January to June 2014 we offered monthly 'Target' clinic appointments to a cohort of ten patients with high HbA1C. Consent was obtained prior to attending this clinic. Group education sessions were offered as part of the clinic and individualised targets were set at each consultation. The 'Virtual' weekly telephone clinics were run from January to June 2015. Patients with the highest HbA1Cs from our entire clinic population were included. At each contact blood glucose was reviewed, insulin doses were adjusted and targets for the next week were set.
Results
Six out of ten patients in the Target clinic were girls. Median age was 10.4 years (range 9.4–13.7). Median duration of diabetes was 4.1 years (1.5–9.5). Median HbA1C at first appointment was 88 mmol/mol (74–109), after 6 months it was 82 mmol/mol (67–101). 18 patients were contacted in the weekly Virtual clinic. Median age was 15.6 years (11.1-18), 11 were male. Median duration of diagnosis was 6.8 years (1.1–13.6). Median HbA1C at the start was 93 mmol/mol (71–>130), after 6 months it was 75 mmol/mol (56–123). 33.4% of appointments in the Target clinic were missed compared to 46.5% in the Virtual clinic.
Discussion
Patients in the Virtual clinic were older, with longer duration of diabetes and higher HbA1C at the outset. This was however an 'unbiased' cohort because consent was not sought for participation in this clinic, telephone contact was made as part of normal clinical care. Despite these differences a bigger improvement in HbA1C was achieved through the Virtual clinic. Higher non-attendance rate in this clinic was anticipated as contact was more frequent and patients were likely to attach less importance to a Virtual clinic.
Conclusion
More frequent patient contact leads to improved glycaemic control. Telephone clinics are an effective and efficient method of delivering the sustained support required by patients with poor glycaemic control.

DOI: 10.1530/endoabs.39.OC8.3

OC8.4

Predictors of insulin resistance and the effect of Metformin treatment in obese paediatric patients

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Introduction
Paediatric obesity is a growing concern for the health service. There is currently no consensus for routine screening of metabolic profiles and medical treatment in obese paediatric patients.
Aims/methods
We aimed to determine medium-term outcomes of Metformin treatment on BMI, glucose and insulin levels in obese paediatric patients. In a retrospective review, data were collected from obese paediatric patients on Metformin for insulin resistance between October 9 and October 14. Changes in BMI SDS, glucose and insulin were analysed. Paired sample t-tests were used to compare pre- and post-treatment results (treatment washout period of 1 month).
Results
70 patients were treated with metformin (50=female) (35=British White, 18=Pakistani) at a mean age of 12.7 (6.1–17.2) years. Mean BMI 35.2 (24.2–48.5 kg/m^2) and BMI SDS 3.4 (2.2–4.7). All patients with a family history of T2DM had acanthosis nigricans (AN). All patients with acanthosis nigricans (n=43, 49% with no family history of T2DM) had insulin resistance with significantly higher basal insulin levels ($P<0.05$) than those without. All patients were normoglycaemic at start of treatment. Metformin was associated with reduced BMI z-score at 6–12 months (−0.1 SDS, $P<0.05$) and 18–24 months (−0.2 SDS, $P<0.05$). Reduction in fasting and postprandial glucose levels were (−0.1 mmol/l, $P=0.17$) and (−0.5 mmol/l, $P=0.17$) respectively. Metformin was associated with a reduction in fasting insulin (−3.0 mU/l, $P=0.44$), and significantly reduced 2 h insulin (−118.0 mU/l, $P<0.05$) after treatment for 12–18 months. In prepubertal children <10 years, fasting insulin increased (+9.3 mU/l, $P=0.16$), but postprandial insulin decreased (−33.8 mU/l, $P=0.42$).
Conclusions
Metformin treatment is significantly associated with reduction in BMI z-score from 6 months and reduced postprandial insulin levels after treatment. It should be

considered as a treatment modality in normoglycaemic obese paediatric patients for weight stabilisation and improvement of insulin resistance, which may have longer term implications on metabolic health.

DOI: 10.1530/endoabs.39.OC8.4

OC8.5

In children with T1DM already achieving target HbA1c levels, those with HbA1c <48 mmol/mol have no increase in hypoglycaemia.

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Introduction
There is concern that lowering the HbA1c target for children and young people with T1DM would increase the amount and severity of hypoglycaemia.
Aims
To examine the relationship between HbA1c and blood glucose (BG) levels, particularly hypoglycaemia, in children with T1DM treated to current target.
Methods
BG meter downloads (Diasend) were examined for the 3 months before the latest HbA1c level in children with HbA1c lower than 58 mmol/mol in the Oxford clinic. Average number of BG readings, percentage of in-target (between 4.0 and 7.0 mmol/l) and low (<4.0 mmol/l) BG readings, and mean BG levels were recorded.
Results
Between September and November 2014, 127 children (37.5% all patients) had HbA1c levels lower than 58 mmol/l (range 30–57 mmol/mol). 92 had BG meter downloads available (55M, 37F, age 2.3–18.2 year, × 11.8 year, duration 0.23–14.29 year, × 3.10 year). 23 (25%) used insulin pumps and 69 (75%) multiple daily injections (MDI). Number of BG tests per day was 0.5–11.9 (mean 5.5). HbA1c was related to mean BG level ($r=0.64$, $P<0.0001$), duration ($r=0.28$, $P=0.007$) but not to age. HbA1c was no different in those using MDI (49.5) than pumps (48.0, $P=0.3$). Percentage BG levels <4 mmol/l was not related to HbA1c ($r=0.06$). 39 had HbA1c levels </=48 mmol/mol and 53 had HbA1c > 48 mmol/mol, There was no significant difference between these groups in percentage BG <4 mmol/l (11% vs 13%, $P=0.16$) or percentage BG <2 mmol/l (0.1% vs 0.3%, $P=0.09$), but the group with the lower HbA1c levels had a significantly greater percentage BG levels in target (49% vs 33%, $P<0.001$). 1 child had a severe episode of hypoglycaemia.
Conclusions
In children already achieving target HbA1c levels, those with HbA1c </= 48 mmol/mol have no increase in hypoglycaemia, but have a greater percentage BG levels in target.

DOI: 10.1530/endoabs.39.OC8.5

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OC9.1

Steroid sick day rules: an audit of caregiver education and confidence levels

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Background
For patients on hydrocortisone (HC) steroid therapy, educating families on 'Steroid Sick Day Rules' (SSDR) is key in preventing adrenal crises.
Aim
To audit education provided to patients and their families in emergency management of known adrenal insufficiency against published standards.
Method
A questionnaire assessing information provision and confidence with SSDR was given to 49 caregivers of children on HC treatment within the local Paediatric Endocrine Clinic and those attending the Peripheral Joint Endocrine clinics between June 2014 and January 2015. Mean patient age 9.9 years (range 0.7–21years).
Results
The majority of families had received information on SSDR (94%) but only half reported having information on IM HC injections (53%). Most families were 'very confident' or 'somewhat confident' (51 and 27%) in how to increase their child's HC dose during illness. Confidence increased with number of years from diagnosis. Families were less confident with when (24% 'very confident' and 37% 'somewhat confident'); and how (23% 'very confident' and 23% 'somewhat confident') to give the IM HC injection. Confidence levels decreased with time from diagnosis. Caregivers who had previously (14%) given the IM HC injection were generally more confident in when and how to give the injection.
Discussion
Many cases of adrenal crises are preventable with pre-emptive corticosteroid supplementation. Education on SSDR plays a major role in managing patients with adrenal insufficiency.
Our results show good confidence levels regarding sick day rules and provision of information on oral dosing. Increasing confidence with time may be related to the amount of practice caregivers have had at applying sick day rules. There are lower levels of confidence and provision of information for IM injection. Decreasing confidence levels over time may be due to the length of time elapsing since an initial demonstration on how to administer the injection (usually given at the time of diagnosis).
Recommendation
It is important to provide separate written information on IM HC administration for SSDR. A regular refresher course should also be offered to ensure caregivers maintain confidence in managing their children during a time of stress or illness.

DOI: 10.1530/endoabs.39.OC9.1

OC9.2

Identifying critical periods for maintaining weight loss in obese children

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Background
Studies in adults have shown physiological protection of a 'set-point' for weight, explaining why obese adults who diet eventually regain weight.
Objective
We hypothesised that set-points for weight, and their physiological defence, are flexible in childhood but become fixed around puberty. We aimed to show that obese children who lost weight had less 'reflex' changes in satiety hormone profiles (that would drive weight regain), compared with adolescents who had experienced a similar degree of weight change.
Method
Prospective cohort study. 41 subjects; 21 obese pre-pubertal children (age 3–7 yrs; 11 male) and 20 obese adolescents (age 14–18 yrs; 10 male). Obesity defined as BMI >2.4 SDS. Subjects recruited as either 'reducers' (relative/absolute weight loss of ≧10% in the preceding 9–15 months) or 'maintainers' (controls).
Measures
Resting energy expenditure (REE), bioelectrical impedance, and fasting and post-prandial (every 30 min for 3 h) satiety hormone profiles.
Results
Post-pubertal adolescents had 31% lower Ghrelin concentrations (4–51%, $P=0.03$) and 50% higher Amylin concentrations than pre-pubertal children (18–91%, $P=0.001$). The association between Ghrelin, Amylin and GIP concentration and weight change was similar for both pre- and post-pubertal children ($P=0.79$, $P=0.39$, $P=0.79$ respectively). No associations were found for Peptide YY, Pancreatic Polypeptide, or active GLP1. Regarding satiety, post-pubertal reducers reported less hunger and higher satiety than pre-pubertal children ($P<0.05$). REE in pre-pubertal weight reducers and maintainers were similar (50 kcal lower, −143 to 242, $P=0.6$) but post-pubertal reducers had 250 kcal lower REE compared to post-pubertal maintainers (−68 to 572, $P=0.1$).
Conclusion
Satiety hormone profiles were similar between pre- and post-pubertal subjects, and contrast with adult data where weight reduction leads to sustained increases in Ghrelin and reductions in the other hormones. These findings indicate that the physiological mechanisms which act to protect against weight change in adults develop later than in the adolescent years.

DOI: 10.1530/endoabs.39.OC9.2

OC9.3

National audit of transition in endocrinology: joint between society for endocrinology and the british society for paediatric endocrinology & diabetes

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Background
Transition is an important stage in the care of a young person with a long-term endocrine condition.
Objective
To explore current services for young people (YP) with endocrine conditions from the perspective of paediatric and adult endocrinologists, and YP and their parents using their services.
Methods
There were two components:- i). service questionnaire for completion by paediatric and adult endocrinologists ii). 'Mind the Gap' questionnaire for completion by YP and parents.
Results
49 service questionnaires were completed (25 by adult endocrinologists) representing 35 centres across the UK and the Republic of Ireland. 233 YP (median age 17.3) and 200 parent questionnaires from 24 centres were also completed. Out of 16 You're welcome criteria (Quality Criteria for YP Friendly Health Services) the median number achieved by each centre was seven (range 3–12). Criteria recorded as achieved in $>80\%$ were YP being given the opportunity to be seen on their own, encouraging independence and discussing transition issues, $<20\%$ achieved giving YP a hand-held summary at the time of transfer, running clinics outside school/college hours and YP involvement in service evaluation and design. YP reported organising their own medications in 65%, being seen alone in 19% and contacting the hospital in 13%. YP identified the most important aspects of endocrine care (scoring greater than 6 out of 7) were three provider characteristics (staff that are knowledgeable, provide honest explanations and treat them with respect) and 1 process issue (having appointment times that are convenient). Gaps in care were identified in all areas but were greatest in 2 process issues (having appointment times that are convenient and not wasting their time) and 1 related to the environment not being suitable for their age.
Conclusion
Most services are achieving less than 50% of criteria associated with high quality care for YP. Despite services encouraging independence in being seen alone only 19% of YP report this occurring most or all of the time. The 'Mind the Gap' questionnaire is a useful tool to understand YP and parent experience.
Funded by Clinical Endocrinology Trust.
DOI: 10.1530/endoabs.39.OC9.3

Poster Presentations

POSTER PRESENTATIONS

P1

Mutations in HS6ST1 cause self-limited delayed puberty (DP) in addition to idiopathic hypogonadotropic hypogonadism (IHH)

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Background
Self-limited DP often segregates in an autosomal dominant pattern, but in the majority of patients the neuroendocrine pathophysiology and its genetic regulation remain unclear. By comparison, many genes have been identified where loss-of-function mutations lead to IHH. Despite likely overlap between the pathophysiology of DP and conditions of GnRH deficiency, few studies have examined the contribution of mutations in IHH genes to the phenotype of DP.
Methods
We performed whole exome sequencing in 111 members of 18 families from our patient cohort with DP. We filtered the results, seeking potentially pathogenic mutations, with a list of 25 genes identified in the published literature as causal in IHH. After follow-up targeted re-sequencing in a further 42 families (288 individuals), one candidate gene was identified. Developmental tissue expression studies and assessment of the enzymatic function of the mutant protein were performed.
Results
A rare variant in *HS6ST1* (Heparan sulfate 6-O sulphotransferase i) was identified, present in six affected members in one family and not present in 145 controls. No other pathogenic variants in IHH genes were identified. *HS6ST1* codes for an enzyme that modifies extracellular matrix components critical for normal neural branching. It is thought to be required for the function of FGFR1 and KAL1 *in vivo*, both of which are vital for GnRH neuronal development and normal hypothalamic-pituitary-gonadal axis function. Our variant is predicted to lie within a highly conserved coiled-coil domain and displays reduced sulphotransferase activity *in vitro*.
Conclusions
Mutations in *HS6ST1* contribute to the phenotype of both IHH and DP. Thus, it appears that misregulation of GnRH neuronal migration and differentiation may cause both IHH and DP. However, the overlap in the genetic basis for these two conditions appears from our study to date to be limited to a subset of IHH genes.

DOI: 10.1530/endoabs.39.P1

P2

Islet cell proliferation is inappropriately maintained in the pancreas of children with congenital hyperinsulinism in infancy

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Background
In diffuse CHI (CHI-D) insulin release is uncontrolled due to mutations in the *ABCC8*/*KCNJ11* genes. Increased rates of cell proliferation have also been reported, but the mechanisms responsible for this are unknown. We hypothesized that this may arise as a consequence of failure to terminate proliferation in the neonatal period. Here, we examined the proliferative index (PI) of islet cells in CHI-D patients and compared this with focal CHI (CHI-F) which is caused by loss of cell cycle repression in β-cells within the focal domain.
Methods
PI was assessed by Ki67 expression using tissue from CHI patients positive for mutations in the *ABCC8* gene - CHI-D ($n=10$), CHI-F ($n=6$), and neonatal ($n=12$), juvenile and adult control tissues ($n=5$). Analysis of digitized images was used to calculate the average PI (mean $\pm$ S.E.M).
Results
In CHI tissue – including the non-lesion domains of CHI-F, we found an inverse correlation between PI with age, but the rates of decline were markedly decreased when compared to control tissues. Thus, up to 8 weeks following birth $8\pm0.4\%$ ($n=5$) of cells were $Ki67^+$; $4\pm0.4\%$ ($n=3$) up to 7 months and 3% up to 10 months of age. Importantly, whilst there was an increase in Ki67 + cells within focal lesions (due to defects in p57kip2), there was little overall difference in the PI between the non-lesion domains of CHI-F and CHI-D; 4 ± 0.4 vs. 5 ± 1, respectively.
Summary/conclusion
In control and CHI tissues, we found an inverse correlation between the PI of the exocrine and endocrine pancreas and age. We suggest that enhanced rates of proliferation in CHI islet cells arise from failure to terminate proliferation by a mechanism that is not directly attributable to the genetic cause of disease.

DOI: 10.1530/endoabs.39.P2

P3

The relationship between catch up growth and adipokine profile in adolescent children born preterm

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Background
Data remain conflicting regarding the long-term metabolic consequences of prematurity and the impact of early nutrition and catch-up growth. Adiponectin and leptin are adipocyte derived proteins (adipokines) and are thought to be important regulators of insulin action.
Objectives
i) To investigate the influence of infant growth and contemporary body composition on adolescent adipokine secretion.
ii) To investigate the correlation between adipokine levels and insulin sensitivity.
Design, setting and participants
Participants were recruited from the Newcastle Preterm Birth Growth Study (NPBGS), a prospective, randomised study of infant growth. 102 underwent venepuncture and DEXA at a median of 11.5 years. *Z*-score weight changes between term and 12 weeks were compared with adolescent adipokine levels using multivariable linear regression to adjust for potential confounders (birthweight, gestation, fat mass index, sex and pubertal status). Insulin sensitivity was measured using HOMA 2.
Results
i) Overall, adipokine levels did not vary by sex. Stratification by pubertal status (Tanner stage 1 vs >1) showed significantly higher leptin levels in pubertal females than males and remained after adjustment for fat mass index. Infant growth patterns were not significantly associated with adolescent adipokine levels. Adiponectin levels were negatively correlated with adolescent fat mass index (Spearmans correlation $=-0.25$, $P=0.01$), while leptin was positively correlated (Spearmans correlation $=0.90$, $P=0.00$); these associations remained after multivariate adjustment.
ii) The correlations of leptin-adiponectin ratio (LAR) and leptin to insulin sensitivity (both Spearmans correlation $=-0.58$, $P=0.000$) were equal and stronger than that of adiponectin alone. (Spearmans correlation $=0.20$, $P=0.05$).
Conclusions
We have not shown an effect of early infant growth patterns on adipokine levels at adolescent follow-up and contemporary body composition appears more important. The sex difference in leptin levels in the pubertal cohort may reflect sex-based differences in body fat distribution, which only evolve at puberty. Our data indicate that the LAR is a useful surrogate marker of insulin sensitivity. The LAR could replace clamp methods and HOMA approximation when assessing insulin sensitivity in clinical research.

DOI: 10.1530/endoabs.39.P3

P4

Use of long acting somatostatin analogue (Lanreotide) in CHI – its pharmacokinetics and long-term follow-up study

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Background
CHI is a cause of severe hypoglycaemia in children. Diazoxide (K_{ATP} channel agonist) is used as first-line treatment but is known to cause severe hypertrichosis and reduced appetite in children. Diazoxide unresponsive CHI us treated with daily octreotide subcutaneous injections (3–4 times/day).
Objective and hypotheses
To evaluate the efficacy, safety and pharmacokinetics of long acting Somatostatin analogue (Lanreotide) therapy in CHI patients.
Method
Children with CHI >6 months of age either on high dose diazoxide (causing side effects), or daily octreotide were started on 30 mg Lanreotide administered every 4-weeks. Children >3 years of age had paediatric quality of life (PedsQL) with strengths and difficulties questionnaires (SDQ) pre- and 1-year post-Lanreotide. Plasma Lanreotide concentrations measured by radioimmunoassay collected at different time points after administration and subsequently prior to each dose for 6 months.
Results
30 children were commenced on Lanreotide and three had to stop treatment. Out of 27 children, 19 were on daily octreotide injections and eight on diazoxide. Five children have stopped overnight continuous feeds. 23 children had diffuse hyperinsulinism, three were protein sensitive and one had focal lesion (had three surgeries). Pharmacokinetic data on 21 children showed highest median value (25th–75th interquartile range) of Lanreotide concentration was 14.93 ng/ml (4.39–31.6) at +4 h of first dose. The median values (25^{th}–75th interquartile range) prior to 2nd, 3rd, 4th, 5th, 6th and 12th doses were 0.88 ng/ml (0.66–1.32), 1.09 ng/ml (0.89–1.35), 1.21 ng/ml (0.87–1.49), 0.79 ng/ml (0.67–1.55), 1.35 ng/ml (1.19–1.86) and 1.44 ng/ml (1.08–2.18) respectively. PedsQL showed significant change in total health and psychosocial score and significant reduction in overall stress in the SDQ after 1-year post-Lanreotide ($P<0.05$).
Conclusion
This study demonstrates that lanreotide can be used as an alternative to diazoxide and octreotide therapy in CHI patients with a significant improvement in blood glucose control and quality of life. There is cumulative effect in lanreotide concentration after each dose. Our 2.5 years follow-up data shows no adverse effects on growth.

DOI: 10.1530/endoabs.39.P4

P5

Junior KICk-OFF (kids in control of food)-developing structured education for primary school age children

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Background
Currently there are no evaluated diabetes teaching packages for primary school age children which meet their learning needs, styles and are delivered by trained educators. Sheffield children's Hospital produced and tested, as a randomized controlled trial (RCT), the KICk-OFF course for 11–16 year olds. This 5-day course based on carbohydrate counting and insulin dose adjustment showed significant improvement in HbA1c (9 mmol/mol, 0.8%) for those with poorest control.
Aims
Use the experience of KICk-OFF for a feasibility study to develop and pilot a junior curriculum and teaching materials before a future RCT.
Methods
Primary teachers and educationalists advised on curricula activities, timings and resources for key stages (KS) one (4–7 years) and two (7–11 years). A pilot course for each KS has been completed. Parents attended separate sessions. Familiar activities were used, i.e. puppets, models, card games, role-play, sorting activities, snakes and ladders. The curricula use the constructivist learning theory of building on knowledge.
Key outcomes:
- Produce curricula and resources for children age 4–11 years and their parents
- Observation by educationalists and videos to review sessions
- Qualitative assessments of learning via structured interviews
- Quantitative outcomes include HbA1c, number of blood tests pre and post course and their mean. Quality-of-Life measures for parents and children
- Knowledge assessment for KS2 children

Results
Comments from educationalist report include:
- Well designed and structured courses
- Activities and resources of high standard
- Highly skilled educators
- Children highly engaged, demonstrating new knowledge and skills
- Excellent work books (KS2) – attractive, clearly set out, age appropriate language

Analysis of qualitative and biometric outcomes is due November 2015
Discussion
Junior KICk-OFF courses were well received. Both children and parents were engaged in all the activities. Greater use of a combined approach to learning including more problem solving challenges could be explored further when the curricula are adapted prior to a RCT.

DOI: 10.1530/endoabs.39.P5

P6

Growth and metabolic phenotypes in patients with srs: a multi-centre cross-sectional observational study

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Background
Silver-russell syndrome (SRS; OMIM 180860) is a genetically and clinically heterogeneous low birthweight syndrome characterised by poor postnatal growth and a number of variable dysmorphic features. Small-for-gestational age infants in general have an increased risk of metabolic complications, some initially occurring in late childhood and adolescence.
Objective and hypotheses
To identify (a) response to GH based on genotype and (b) development of metabolic complications whilst on GH treatment or as young adults.
Method
A cross-sectional, observational multi-centre study across England, investigating patients >5 years with clinical or genetically confirmed SRS for response to GH and evidence of insulin resistance and hypertension on baseline screening.
Results
Thirty seven patients (18 H19; 9 mUPD7 and 10 clinical; 22M: 15F, mean age at assessment 11.74 years, range 5.0–39.1). GH treatment increased height SDS by 0.99 (0.56 s.d.) SDS after 1 year and 1.97 (1.16) SDS after 3 years; $P<0.001$). A significantly better response to GH treatment was seen in mUPD7 patients compared to H19 after 3 years (P 0.002). BMI increased by 0.41SDS (1.0; *P*,0.046) on GH treatment after 3 years. No significant difference between genetic subtypes seen. Mean % fat mass (assessed by Tanita scales) was 16.3% (5.26) with no significance between pubertal and pre-pubertal individuals. Baseline fasting lipid, insulin, glucose, leptin and adiponectin levels showed no evidence of insulin resistance or impaired fasting glycaemia ($n=30$) and OGTT data ($n=7$) showed no insulin resistance. Basal blood pressure measurements showed no evidence of hypertension (diastolic and systolic measurements <90 centile). Adrenarche was seen in seven patients and central precocious puberty requiring treatment in four patients.
Conclusion
GH treatment improves height SDS and BMI SDS in SRS patients with significant difference in height SDS increase between mUPD7 and H19 after 3 years of treatment. No evidence of insulin resistance or hypertension was seen on baseline screening.

DOI: 10.1530/endoabs.39.P6

P7

An assessment of the hypothalamic-pituitary-adrenal axis in children with prader-willi syndrome (PWS)

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Introduction
In children with PWS, dysfunction of HPA axis may contribute to the high incidence of sudden death. The prevalence and the extent of the dysfunction of HPA axis remain unclear.
Methods
18 (4M/14F) children with PWS, with a median age of 2.51 years (0.6,9.9), underwent insulin tolerance test (11/18, median age 3.8 years (2.1,9.9)) or glucagon stimulation test (7/18, median age 1.8 years (0.6,2.4)) as part of their

assessment before commencing GH treatment. Cortisol and GH were measured at 0, 15, 30, 45, 60, 90, 120, 150 and 180 minutes in relation to insulin/glucagon administration. Either cortisol peak of ≥550 nmol/l or cortisol increase of ≥250 nmol/l from baseline were considered as adequate cortisol responses. GH peak of ≥6.7 μg/l was considered an adequate GH response.

Results

Median baseline cortisol (at 0 minutes) was 390 nmol/l (22,646) and was negatively correlated with age (r, −0.569, P,0.014). Median peak cortisol was 709 nmol/l (389,1297) and was negatively correlated with age (r, −0.623, P,0.01). Median cortisol increase from baseline was 328 nmol/l (157,787). Median cortisol increment (ΔCortisol) was 1.95 (1.4,24.7), and it was positively correlated with age (r, 0.48, P,0.046). Of the 18 children, 16(89%) had adequate cortisol response. The 2(11%) children with inadequate cortisol response had baseline cortisol values of 208 nmol/l and 368 nmol/l and peak cortisol values of 389 nmol/l and 525 nmol/l, respectively. Median baseline cortisol in children with peak cortisol levels ≤550 nmol/l (n,4) and ≥550 nmol/l (n,14) was 220 nmol/L (22,368) and 441 nmol/l (133,646), respectively (P,0.016). Median baseline cortisol in the 5/18(28%) children with adequate and in the 13/18(72%) children with inadequate GH response was 502 nmol/l (360,571), and 350 nmol/l (22,646), respectively (P,0.039). Median peak cortisol in the same groups was 848 nmol/l (723,1050), and 645 nmol/l (389, 1297) (P,0.029), respectively.

Conclusion

The majority of children with PWS showed a normal function of HPA axis. However, the lower cortisol levels in those with GH deficiency may reflect a more generalised hypothalamic dysfunction. Although cortisol secretion decreases continuously with age, age-specific peak cortisol thresholds are required.

DOI: 10.1530/endoabs.39.P7

e-Posters

Adrenal

EP1

Variation in absorption and half-life of hydrocortisone: a need to consider plasma terminal half-life in dosing schedules

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Hydrocortisone therapy needs to be individualised in congenital adrenal hyperplasia (CAH) patients to avoid over and under replacement. Plasma cortisol concentration is determined by absorption and half-life of cortisol influence glucocorticoid exposure. Terminal plasma half-life is the time required to divide the plasma concentration by two and is important when absorption may vary.

To ascertain a role for this measure we have studied 48 patients (21M) aged between 6.1 and 20.3 years with CAH due to CYP21A2 deficiency. Each patient underwent a 24 h plasma cortisol profile with the morning dose used to calculate absorption parameters along with an intravenous (IV) hydrocortisone (15 mg/m^2 body surface area) bolus assessment of half-life. Parameters derived were maximum plasma concentration (C_{max}), time of maximum plasma concentration (t_{max}), time to attaining plasma cortisol concentration less than 100 nmol/l and half-life of cortisol.

Mean half-life was 76.5 $\pm$ 5.2 (range 40–225.3) min, C_{max} 780.7 $\pm$ 61.6 nmol/l and t_{max} 66.7 (range 20–118) min. Time taken to a plasma cortisol concentration $<$100 nmol/l was 289 (range 140–540) min. Those with a fast half-life and slow t_{max} took longest to reach a plasma cortisol concentration less than 100 nmol/l (380 $\pm$ 34.6 min), compared to those with a slow half-life and fast t_{max} (298 $\pm$ 34.8 min) and those with a fast half-life and fast t_{max} (249.5 $\pm$ 14.4 min) ($P = 0.009$).

Both rate of absorption and half-life of cortisol in the circulation play important roles in determining overall exposure to oral glucocorticoid. Dose regimens need to incorporate estimates of these parameters into determining the optimum dosing schedule for individuals.

DOI: 10.1530/endoabs.39.EP1

EP2

Between patient and inter-time point variability in salivary cortisone: cortisol ratios

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Background

Salivary biomarkers are attractive diagnostic tools for paediatric practice, enabling non-invasive sampling at home. Salivary cortisol (SCl) and cortisone (SCn) are sensitive markers of adrenal insufficiency during inhaled corticosteroid treatment(1). SCn is reported to be the best correlate of plasma cortisol. Measurements of SCl may not be necessary, reducing cost and sample volumes. Eleven beta hydroxysteroid dehydrogenase type 2 (11BHSD2) regulates conversion of cortisol to cortisone. It is subject to genetic variability, and may become saturated at high cortisol concentrations. These factors could be important if only SCn is used as a biomarker of plasma cortisol for clinical decision making.

Patients and methods

We examined inter and intra-individual variability in SCl:SCn in 756 early morning saliva samples collected on 3 consecutive days (D1, D2, D3) from 269 (160 M) children with asthma, age 10 yrs (5–15), as reported previously(1).

Box-Cox transformations were applied to yield normally distributed data. Pearson correlation and variance component models were used to investigate intra and inter-individual variability.

Results

Mean SCl:SCn ratio for all samples was 0.177 (range 0.0274–3.57). There was a weak correlation between SCl:SCn on D1 vs D2, D1 vs D3 and D2 vs D3: 0.512, 0.580 and 0.585 respectively. 56% of overall variation was explained by between patient variation and 44% by inter-time point measurement error.

Conclusions

Statistically significant relationships are observed between measurements obtained from the same individual over time, and between individuals. However, the observed level of variability could influence clinical decision making for individual patients. These observations may indicate genetic heterogeneity in our population and /or saturation of 11BHSD2 at higher levels of SCl. We continue to measure both biomarkers on serial samples to mitigate these effects.

1. Early morning salivary cortisol and cortisone, and adrenal responses to a simplified low-dose short Synacthen test in children with asthma. Clin Endocrinol. 2014, 80, 376–83.

DOI: 10.1530/endoabs.39.EP2

EP3

Cortisol responses to the insulin tolerance test and glucagon stimulation tests in children with idiopathic short stature and idiopathic isolated growth hormone deficiency

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Introduction

The insulin tolerance test (ITT) and glucagon stimulation test (GST) stimulate the release of both growth hormone (GH) and cortisol. A normal cortisol response is considered to be $>$500 nmo/l, however there are no robust normative paediatric data. Cortisol results may generate anxiety and further investigations in short children, tested for GH deficiency, with no clinical suggestion of cortisol deficiency.

Aim

To describe cortisol response in the ITT and GST in children with idiopathic short stature (ISS) and idiopathic isolated growth hormone deficiency (IIGHD).

Methods

Between January 2011 and December 2014, 502 children underwent ITT or GST for investigation of short stature. Data from children with ISS (birth weight SDS >-2, peak GH $>$6.1 μg/l, no evidence of chronic illness and no steroid therapies) and IIGHD (peak GH $<$6.1 μg/l) were included.

Results

Data from 118 (76 M) patients, age 12.9 yrs (1.7–20.7) were studied. Results are given in

Table 1 Age, gender, baseline and peak cortisol levels in children and adolescents with ISS and IIGHD in insulin tolerance and glucagon stimulation tests.

		GST ($n=43$)		ITT ($n=26$)	
ISS		Males (23)	Females (20)	Males (19)	Females (7)
	Age (years) median, range	8.59 (1.73–18.51)	9.6 (2.11–16.16)	16.68 (7.22–20.67)	15.86 (11.69–17.81)
	Baseline cortisol (nmol/l) median, range	232 (149-643)	249.5 (131-419)	279 (105–532)	260 (152–657)
	Peak cortisol level (nmol/l) median, range	450 (228–1082)	608 (309–963)	552(408–668)	624(488–919)
IIGHD			GST ($n=19$)		ITT ($n=30$)
		Males (13)	Females (6)	Males (21)	Females (9)
	Age (years) median, range	8.17 (4.84–18.24)	12.3 (4.02–16.88)	14.8 (6.92–18.85)	14.23 (10.34–17.55)
	Baseline cortisol (nmol/l) median, range	264 (125–458)	364 (252–604)	287 (149–715)	199 (114–632)
	Peak cortisol level (nmol/l) median, range	585 (414–966)	668 (417–717)	555 (508–767)	579 (497–734)

Conclusion

These data suggest that the current definition of a normal cortisol response to the ITT and GST should be re-examined. In a larger cohort, the effect of age and gender could be explored, to refine guidelines for the diagnosis of adrenal insufficiency in childhood and adolescence.

DOI: 10.1530/endoabs.39.EP3

EP4

Discordance between the cortisol dose for replacement and that required for suppression of androstenedione (A4) and 17 hydroxy-progesterone (17OHP) in congenital adrenal hyperplasia

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Androstenedione and 17OHP are often used as measures of cortisol replacement in congenital adrenal hyperplasia (CAH) rather than cortisol itself. Very little is known of the dose response relationships between cortisol and A4 and 17OHP. We have studied the relationship between 24 h serum cortisol, 17OHP and A4 in 33 (18M) children with CAH due to P450c21 deficiency. 24 h serum cortisol and 17OHP profiles were constructed using 20 min sampling intervals and expressed as the mean value. A4 was measured at 0800 h.

There was a significant relationship between mean 24 h serum 17OHP and A4 concentrations ($r=0.62$; $P<0.001$). For every 1 nmol/l rise in 17OHP, A4 rose by 0.2 nmol/l. Both mean 24 h 17OHP and A4 concentrations showed suppression when the 24 h mean cortisol concentration exceeded 150 nmol/l, although 50% showed suppression with a cortisol <150 nmol/l. This threshold was a step threshold and four S.D. below the mean 24 h cortisol production of normal individuals.

These data demonstrate that there are not equimolar changes in A4 and 17OHP, and that suppression of A4 and 17OHP occurs at cortisol concentrations that are below those associated with normal cortisol secretion. If only A4 and/or 17OHP are used to assess cortisol replacement it will leave many individuals under replaced with cortisol and at risk of Addisonian crisis.

DOI: 10.1530/endoabs.39.EP4

EP5

Current dilution methods cause large variations and inaccuracies when making up 1mcg Synacthen dose

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Background

The low-dose short synacthen test (LDSST) is the most popular diagnostic test for adrenal insufficiency in UK. Although various dosing strategies exist 1 μg is most commonly employed but not commercially available. A BSPED survey revealed 14 different methods for diluting the 250 μg/ml ampoules. We investigated whether differing dilution strategies, made up using standard ward not laboratory equipment, result in differences in Synacthen dose administered.

Method

The ten most popular dilution methods were tested, encompassing different diluents (0.9% saline $n=9$, 5% dextrose $n=1$), single ($n=6$) and double ($n=4$) dilution strategies and initial quantities of Synacthen (0.1–1 ml) used. Each was made up five times by the same investigator and three samples taken from the resultant solution. Samples were frozen then batch analysed on an ACTH RIA validated for Synacthen. All samples were diluted down to 250 pg/ml (most sensitive part of the assay measuring range), with 0.9% saline and the variance calculated (coefficient variation (CV)).

Results

There was variation in the Synacthen detected from the three samples taken from the same solution (CV range 3.4–107.5%) suggesting mixing issues, the five preparations of the same method, suggesting batch to batch variation, and between the ten different preparation methods (CV range 22.9–89.8%). The method utilizing 5% Dextrose as diluent had 14 of its 15 samples off the top of the assay range. Estimates of the likely Synacthen dose, if administered to patients, range from <0.04 μg to more than 2 μg.

Discussion

Considerable variation was observed both within and between dilution methods. There are numerous variables which may affect the actual dose of Synacthen administered: pharmaceutical manufacturer variation, use of inaccurate ward equipment causing drawing up inaccuracies, volume inconsistencies and lack of adequate mixing. We recommend low-dose Synacthen be made up under laboratory conditions and call for a commercial preparation of 1mcg Synacthen.

DOI: 10.1530/endoabs.39.EP5

EP6

Not always CAH: urine steroid profiling in the investigation and diagnosis of adrenal causes of neonatal hyponatraemia and failure to thrive

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A 1 month old baby boy presented at a local district general hospital with failure to thrive. He was born to non-consanguineous Eastern European parents, with an 18 month old healthy sister. The term birth was unremarkable, with nil of note from the antenatal history. Initial clinical examination revealed a slightly low but stable blood pressure for age, but was otherwise normal.

Investigations

Biochemistry results showed low plasma sodium (125 mmol/l) and elevated potassium (6.1 mmol/l) concentrations. Urine sodium was <10 mmol/l. Blood glucose was stable (3.5–4.2 mmol/l). The plasma cortisol response to synacthen was assessed; baseline: 65 nmol/l, 30 min: 286 nmol/l. Based on these results, CAH remained a potential diagnosis and hydrocortisone and sodium supplementation were commenced. Additional blood tests (17-OHP, ACTH, renin activity, aldosterone) were requested and a spot urine sent for urine steroid profile (USP) analysis.

The USP showed normal cortisol metabolite excretion, and no biomarkers associated with CAH. However, the corticosterone metabolites tetrahydro-11-dehydrocorticosterone (THA), hexahydro-11-dehydrocorticosterone, 6-hydroxyTHA and 18-hydroxy THA were comparatively abundant in the absence of detectable tetrahydroaldosterone. This pattern is indicative of an aldosterone synthase, specifically corticosterone methyl oxidase type II, deficiency. Subsequent plasma renin activity (185 nmol/L per h) and inappropriately low aldosterone (1040 pmol/l) measurements supported this diagnosis. Whole gene sequencing of *CYP11B2* identified a known pathological change, c.554C>T (p.Thr185Ile), confirming aldosterone synthase deficiency.

Conclusion

The investigation of a young infant presenting with hyponatraemia is challenging, further complicated by the need to obtain sufficient blood samples and prioritise informative tests. Where a steroid disorder is suspected, a USP has great utility since the specimen is easily accessible and the test can identify/exclude a variety of disorders. Furthermore, where urgent samples are involved, analyses can be prioritised with a relatively rapid turnaround time. In this case, the USP diagnosis was made within 2 days of sample receipt, prompting fludrocortisone treatment and reduction of hydrocortisone.

DOI: 10.1530/endoabs.39.EP6

EP7

Improving patient safety: evaluating the introduction of the Annual Steroid Review and Emergency Alert Systems

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Introduction

Management of paediatric cortisol deficiency requires regular parent and child education and effective liaison with the emergency services. Best practice in the management of these patients is largely based upon local consensus. An annual steroid review service was introduced by the CNS team to provide education and improve parental understanding of the issues regarding cortisol deficiency in children. Emergency alert systems for the local children's emergency department (CED) and ambulance services were also introduced. The aim of this project was to evaluate the success of these changes in improving the safety of patients with cortisol deficiency at one centre.

Methods

Audit criteria were agreed based upon local consensus standards and expert committee reports.

All 91 patients receiving steroid replacement for cortisol deficiency attending paediatric endocrine clinic during June 2014- June 2015 were included. A service evaluation was also conducted in the form of a structured parental questionnaire.

Results

72.2% of patients had received an annual steroid review. 89% of questionnaire participants rated their experience of the annual steroid review as 'excellent' or 'good.' 100% of parents answered 'strongly agree' or 'agree' when asked if they understood their child's condition. 60.2% and 81.8% of patients had an active alert in place for the CED and ambulance service respectively.

Conclusion
Parental feedback of the annual steroid review was very positive, with improved parental education and confidence in managing their child's condition. Implementation of the ambulance alert system was largely successful, although administration must be improved to achieve universal coverage. The CED alert system should enable safe and effective emergency treatment of cortisol deficient patients. However, the current system did not identify all patients or specify 'cortisol deficiency' as required to ensure appropriate triage and management. This will be addressed with the CED and re-audited.

DOI: 10.1530/endoabs.39.EP7

EP8

Intravenous Etomidate in the management of hypercortisolaemia due to ectopic ACTH producing thymic neuroendocrine tumor

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Background
Ectopic-ACTH syndrome (EAS) is an extremely rare cause of Cushing's syndrome in young children. The intensity of ACTH secretion and hypercortisolaemia is greater in EAS than in Cushing's disease. Control of hypercortisolaemia represents a key management step while awaiting localization of the ACTH source or in preparation to surgery. Etomidate inhibits cortisol synthesis and its rapid onset of action makes it an ideal medication in severe hypercortisolaemia.
Clinical case
A 6-year-old girl presented with hypertensive encephalopathy on a 6-months background history of excessive weight gain. On examination, she had moon facies, centripetal obesity and abdominal wall striae. Investigations showed markedly elevated serum cortisol (>2500 nmol/l) with loss of circadian rhythm and unsuppressed ACTH (95 ng/l). MRI-brain showed evidence of posterior reversible encephalopathy syndrome and normal appearances of pituitary gland. MRI of adrenal glands was normal. CT chest identified an enlarged partially calcified nodular thymus.
In view of life-threatening clinical presentation, hypercortisolaemia was managed with intravenous Etomidate (2.5–3.5 mg/h) infusion with close monitoring of serum cortisol. Hydrocortisone (1 mg/h) was added when serum cortisol <200 nmol/l. The thymic mass was surgically excised and histology showed a highly infiltrative neuroendocrine carcinoma with positive immunohistochemistry for ACTH. Post-resection, etomidate was stopped and hydrocortisone was weaned to maintenance doses (12 mg/m^2 per day). Serum ACTH levels decreased to <15 ng/l. PET-scan suggested residual disease and trough serum cortisol were still elevated. Hypercortisolaemia was managed with etomidate and hydrocortisone infusions prior to bilateral adrenalectomy. Currently she is on hydrocortisone and fludrocortisone replacement, and undergoing chemotherapy for residual disease.
Conclusions
Etomidate is a useful therapeutic agent for rapid control of hypercortisolaemic crisis. Close monitoring of serum cortisol and level of sedation is required while on etomidate infusion. Complete block and replace with hydrocortisone when serum cortisol <200 nmol/l is more convenient than achieving partial blockade by altering the etomidate infusion rate.

DOI: 10.1530/endoabs.39.EP8

EP9

Slow progressing puberty and a secreting adrenocortical tumour in a teenager.

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Introduction
SACT are rare in childhood and present with variable signs depending on the type of hormone excess. We describe the unusual presentation of a teenager with SAT presenting with slow progressing puberty.
Methods
A pre-menarchal 13.5 years old girl with high BMI (28 kg/m^2) presented with slow progressing puberty. She started her puberty at least 3 years previously with breast changes, then progressed to develop pubic and axillary hair over 2 years before presentation. Her Tanner staging for puberty was B4,P4 without virilisation, acne and cushingoid features. There was a strong family history of PCOS and Type2 Diabetes. Investigations were done to rule out PCOS.
Results
Blood investigations showed raised levels of testosterone (3.6 nmol/l) and DHEAS (27 μmol/l). Abdominal US and MRI scan showed the presence of a left sided adrenal mass. 24 h urinary profile was suggestive of a SACT. The adrenal mass was removed surgically with intact capsule. Tumour size 125×95×75 mm, weight 585 g. Histology showed uncertain malignant potential with the presence of three potentially malignant absolute histological criteria (size/weight/presence of necrosis). She had a mild menstrual bleeding 1 month after surgery without further menses. PCOS was confirmed biochemically and by ovarian US morphology at the age of 15.5. At 2 year follow-up, there were no biochemical/radiological evidence of tumour relapse. She has recently developed glucose intolerance and started on Metformin. Current BMI is 27.4 kg/m^2.
Discussion
SACT is one of the most aggressive endocrine tumour with a poor prognosis. Distinction between adenoma and carcinoma is difficult and relies on tumour size, imaging and histopathological criteria. An early diagnosis of SACT is crucial but often delayed because of atypical presentation. Alertness should be maintained in using virilisation as a clinical criteria to exclude SACT when suspecting PCOS.

DOI: 10.1530/endoabs.39.EP9

EP10

Reducing the risk of adrenal crisis: a service improvement project assessing education on adrenal insufficiency

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Introduction
Parents/carers of children with adrenal insufficiency routinely receive training on the provision of emergency hydrocortisone. This service improvement project aims to assess patient and parent knowledge on their sick day rules, in NHS Tayside, with a view to improving the delivery of this information.
Methods
A 24 item postal questionnaire was constructed and distributed to parents of children with adrenal insufficiency. This included 11 sick day scenarios, where respondents provided their best answer via extended matching items. Responses were pseudo-anonymised and Caldicott guardian permission was obtained.
Results
children were identified as having adrenal insufficiency, of which seven responded (54%) – all had received training on sick day rules. Sick day rule knowledge was good with a mean score of 82% (54 out of a possible 66, range 32–62). Two children completed the questionnaire themselves with significantly lower scores (mean score 44/66, 67%, $P<0.05$). Parents were receptive to the idea of an online educational course and open days to reinforce knowledge. Parents also felt that there was a lack of awareness on adrenal insufficiency amongst other medical specialities.
Discussion/conclusion
We have demonstrated that parental sick day knowledge is currently good. Consideration should be given to how this information is delivered to children (especially as they transition to adulthood) as well as colleagues within other areas of the healthcare system.

DOI: 10.1530/endoabs.39.EP10

EP11

A case of acute muscular weakness from Ectopic ACTH secreting Neuroendocrine Tumour of the Thymus

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A 16 year old previously healthy boy from Manipur, India was admitted with rapid onset quadraparesis, vomiting and diarrhoea, on a background 3 month

history of increasing facial puffiness and progressive widespread rash. Investigations revealed hyperglycaemia, hypokalaemia and a raised ESR. The basal serum cortisol was 103 μg/dl ($n=7$–22 μg/dl) at 0800 h. 24-h urinary free cortisol failed to suppress with 8 mg of dexamethasone. Plasma ACTH and serum aldosterone were both markedly elevated at 263 pg/ml ($n=0$–40 pg/ml) and 528 pg/ml ($n=25$–31 pg/ml) respectively.
Imaging revealed mediastinal widening on chest radiography. A large thymic mass with focal liver lesions and vertebral sclerotic lesions was detected on CT. No abnormalities were detected upon MRI of the brain. Fine needle aspiration of the mediastinal mass revealed round cell lesions that morphologically resembled a neuroendocrine tumour.
The patient was diagnosed with an ACTH-secreting non pituitary tumour of the thymus, with infiltration of the liver and bone. Due to advanced disease progression he was not suitable for surgical resection. He was symptomatically managed with long acting Octeotride and followed up in clinic.
Neuroendocrine tumours (carcinoid and neuroendocrine carcinoma) of the thymus are extremely rare, and may present with Cushing's syndrome from ectopic ACTH excretion. It carries a worse prognosis compared to thymomas, requiring aggressive therapy, hence accurate early diagnosis is essential. Resection is the therapeutic modality of choice for thymic carcinoids that have not metastasised. Extrathoracic metastasis has been reported in only 20–30% of cases and are associated with poor prognosis. We present a rare case of ACTH secreting tumour from the thymus with extra-thoracic metastasis to the liver and bones. Subsequently, we review and discuss recent literature on the use of the somatostatin analogue Octreotide in symptomatic management of advanced carcinoid tumours.

DOI: 10.1530/endoabs.39.EP11

EP12

A case of a rare adrenocortical tumour mimicking neuroblastoma

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Presentation and investigation
A 10-month-old girl presented with a bluish lump on the left side of her abdomen which was increasing in size. An abdominal mass was palpable on examination. An ultrasound showed a large, partly calcified mass measuring 9×6×9 cm arising from the left adrenal gland. There were also calcified lesions in her liver and lungs suggesting metastsis. MRI confirmed the ultrasound finding plus detected an intraspinal deposit with some cord compression. Although, MIBG scan was negative and urine was negative for vanillylmandelic acid (VMA), this was thought to be neuroblastoma.
Treatment and progress
Following two cycles of chemotherapy, a repeat MRI showed a slight increase in size of the mass. She was given further chemotherapy (Kushner protocol which included mitotane) while further investigations were being carried out.
Initial urine steroid profile showed low steroid profile. Bloods showed low androgens suggesting this adrenal mass was a non-steroid secreting tumour. A Synacthen test was done which revealed adrenal insufficiency with low cortisol (max of 157 nmol/l and high baseline ACTH of 133 ng/l). She was started on hydrocortisone.
Further management
Initial subcutaneous biopsy of the skin lesions was inconclusive. Subsequent immunohistological analysis was positive for vimentine, cytokertin and synaptophysin which are indicative of adrenocortical carcinoma.
In view of this she underwent bilateral adrenalectomy. She has undergone T5–T8 laminoplasty and decompression to relieve the cord compression caused by the intraspinal metastatic lesion. There are residual metastases in the spine – which have remained stable over the years. She is now on a high dose of hydrocortisone (16 mg/m^2 per day) to keep her ACTH levels undetectable. She is also on maintenance fludrocortisone. She is currently doing well and leading an active life, with no evidence of disease progression.
Leaning points
Adrenocortical tumours in children are vanishingly rare. Nevertheless, this should be considered in any child with any adrenal mass. Adrenal function and reserve should be assessed in these children.

DOI: 10.1530/endoabs.39.EP12

Bone

EP13

Influence of skin colour, ethnicity, and genotype on the response to vitamin D treatment

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Background
Over-dosing and under-dosing of vitamin D in children and young people appears to be common, based on our audit of current practice. The contribution of ethnicity, skin colour, and vitamin D binding protein (VDBP) genotype has not been fully explored during vitamin D treatment.
Objective
To investigate how ethnicity/skin colour and genetic variation affect the response to 150 000 units of vitamin D administered to young adults of white Caucasian and South or East Asian origin.
Method
Prospective single centre clinical trial. Sixty healthy males aged 18 –25 years, white Caucasian ($n=30$) and South or East Asian ($n=30$) were recruited. Fasting i) blood samples for total 25-hydroxyvitamin D (25OHD), VDBP (Genways polyclonal assay), VDBP genotype, bone biochemistry, albumin, PINP and CTX, calculated free and bioavailable 25OHD and ii) urine for calcium:creatinine ratio were examined before and after an administration of single dose of 150 000 IU of vitamin D3. Anthropometry, skin colour grading, and vitamin D and calcium intake assessment were undertaken.
Results
All subjects achieved a $\geq$25 nmol/l increment in 25OHD level following vitamin D administration. Asians had significantly lower serum 25OHD and VDBP levels at baseline but similar estimated free and bioavailable 25OHD to whites. VDBP levels remained significantly lower in.
Asians post administration with no difference in total or free/bioavailable 25OHD compared to whites. No hypercalcaemia/hypercalciuria observed in any subject. Skin colour, race and VDBP genotype did not influence variation in treatment response.

	Serum total 25OHD (nmol/l)	Serum VDBP (μmol/l)	Calculated free 25OHD (nmol/l)	Calculated bio25OHD (nmol/l)	PTH (ng/l)
Baseline, *P value <0.05					
Whites	34.06 (12.30)	6.59 (3.03)	0.014 (0.008)	0.015 (0.007)	44.60 (14.24)
Asians	26.34 (13.72)	4.73 (2.27)	0.012 (0.007)	0.020 (0.010)	69.83 (38.62)
P value	0.04*	0.01*	0.37	0.26	0.002*
Post dosing					
Whites	90.79 (16.71)	6.495 (2.83)	0.037 (0.018)	0.015 (0.007)	49.37 (20.28)

Conclusion
Our results show that a single dose of vitamin D is sufficient and safe to increase the 25OHD level to >50 nmol/l irrespective of, and unaffected by, skin colour, ethnicity, and genotype.

DOI: 10.1530/endoabs.39.EP13

EP14

Increase in lean mass may augment gains in bone mass and size in patients with osteogenesis imperfecta treated with bisphosphonates

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Background
The role of bisphosphonates in improving bone mass in patients with osteogenesis impefercta (OI) is well established. However, the impact of bisphosphonate therapy on body composition in relation to increasing bone mass remains relatively unexplored.

Methods
Change in DXA-derived subtotal body (TBLH) and lumbar spine (LS: L1–L4) bone mineral content (BMC (g)), bone area (BA (cm^2)), areal bone mineral density (aBMD (g/cm^2)) adjusted for age and height, and age-adjusted volumetric bone mineral apparent density (BMAD), total body fat mass (g), and lean mass (g) were calculated in 26 children with OI after 1 year and in 17 children after 2 years of bisphosphonate therapy. Patients received i.v. pamidronate (3 mg/kg per day) over 3 days every 3 months.
Results
Age of first treatment ranged from 0.57 to 5.6 years (mean $\pm$ S.D. $=3.45\pm1.50$). 81% (21/26) had type 1 OI; the remaining patients had type 4 OI. There was no significant change in height or BMI SDS over 24 months. There was an increase in age- and height-adjusted TBLH BMC (95% CI: 46.9–232.5, $P=0.005$), BA (95% CI: 126.8–359.1, $P<0.001$), LSaBMD (95% CI: 0.02–0.216, $P=0.02$), and age-corrected BMAD (95% CI: 0.0001–0.013, $P=0.05$) over 12 months. From 12 to 24 months there was no change in the adjusted bone parameters. Total body fat mass (95% CI: 17.3–657.5, $P=0.04$) and lean mass (95% CI: 446.5–1490.8, $P=0.001$) significantly increased after 12 months of therapy but only lean mass continued to increase from 12 to 24 months (95% CI: 232.0–1702.3, $P=0.01$). In the first 12 months, change in lean mass was associated with an increase in TBLH BA (95% CI: 0.04–0.69, $P=0.03$) and TBLH BMC (95% CI: 0.22–0.77, $P=0.004$).
Conclusions
Pamidronate had the greatest impact on size- and age-adjusted total body and lumbar bone mass in the 1st year of therapy. Increase in muscle mass may augment overall increases in bone mass and size in children with OI. We speculate that improved mobility may underlie these findings.

DOI: 10.1530/endoabs.39.EP14

EP15

The precision of partial image analysis of trabecular bone micro-architecture by high-resolution magnetic resonance imaging in people with childhood-onset bone abnormalities

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Background
High-resolution magnetic resonance imaging (hrMRI) can assess trabecular bone microarchitecture but the number of image slices required for reliable assessment is unclear.
Methods
MRI was performed just below the growth plate of the proximal tibia from 20 healthy controls (all females; median age 21 years (range 18.35) and ten cases (3M:7F; median age 19.5 years (range 16.48) with known bone abnormalities including osteogenesis imperfecta and other endocrinopathies using a 3T-MRI with an isotropic resolution of 0.3 mm. Images were analysed using Matlab to generate the trabecular bone microarchitecture parameters, including apparent trabecular volume to total volume (appBV/TV), trabecular thickness (appTbTh), trabecular number (appTbN), and trabecular separation (appTbSp). The mean values obtained from 20 of the most central images (20IM) were compared to that for ten images (10IM), five images (5IM), and one image (1IM) from the centre of the total image set using linear regression analysis. ANOVA was used to compare the means between groups and Levene's tests used to assess the significance of the co-efficient of variations (CV) within subjects.
Results
The mean trabecular bone microarchitecture estimates from 10IM, 5IM, and 1IM were strongly and positively related to the estimates from 20IM for appBV/TV ($r=1.00$, $r=0.99$, and $r=0.97$, all $P<0.001$), appTbTh ($r=1.00$, $r=0.99$, and $r=0.97$, all $P<0.001$), appTbN ($r=1.00$, $r=1.00$, and $r=0.98$, all $P<0.001$), and appTbSp ($r=1.00$, $r=0.99$, and $r=0.98$, all $P<0.001$). The mean intra-subject CV (S.D.) for appBV/TV in healthy controls was 2.6% (1.1%) for 20IM, 3.0% (1.5%) for 10IM, and 3.1% (1.5%) for 5IM. Cases have higher mean appBV/TV CV (S.D.) at 3.7% (2.1%) for 20IM, 4.7% (3.0%) for 10IM, and 4.3% (3.1%) for 5IM; all $P>0.05$ when compared to that of controls. Furthermore, sub-analysis of the four cases with osteogenesis imperfecta, a more severe osteopathy, demonstrated even higher mean CV (S.D.) at 4.6% (2.7%) for 20IM, 7.1% (3.1%) for 10IM, and 5.9% (3.6%) for 5IM ($P=0.037$, $P=0.028$, and $P=0.017$ respectively).
Conclusions
These findings indicate that partial MRI sets can reliably represent a larger complete set of images when assessing trabecular bone microarchitecture parameters. However, in cases with severe abnormalities of bone health, a larger set of images may need to be analysed to improve precision.

DOI: 10.1530/endoabs.39.EP15

EP16

Metformin regulates the differentiation of murine mesenchymal stem cells via AMPK-independent suppression of p70s6-kinase

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Introduction
Metformin is widely used as oral anti-hyperglycaemic agent to treat type 2 diabetes, with increasing reports of an additional, potential bone protective role.
Objective
We investigated the role of AMPK in mediating the effects of metformin on the differentiation of mesenchymal stem cells (MSCs) to either osteoblasts or adipocytes.
Methods
Confluent murine MSCs (C3H10T1/2) were treated with metformin (500 μM), a known AMPK activator (A769662; 100 μM), or the p70S6K inhibitor (rapamycin; 10 μM), in both control and adipogenic-inducing environments (using pioglitazone; 10 μM) for 5 days. Nuclear extracts were separated by SDS–PAGE and immunoblotted with primary antibodies to peroxisome proliferator-activated receptor gamma (PPARγ; marker for adipogenesis), Runt-related transcription factor 2 (Runx2; marker for osteogenesis), phosphorylated-ACC (P-ACC (Ser79); marker for AMPK activity) and phosphorylated-p70s6k (P-p70s6k (Thr389); upstream regulator of mTOR signalling. Immunoblots were scanned using a Licor fluorescent reader. PPARγ and Runx2 activities were determined using Luciferase reporter assays and adipogenesis was quantified histochemically by staining neutral lipids with Oil red O.
Results
MSCs treated with pioglitazone demonstrated marked adipogenic phenotype staining positively with Oil red O. In contrast, treatment with both metformin and A769662 impaired adipogenesis. Pioglitazone induced an ($P<0.01$) increase in PPARγ expression, whilst metformin and A796662 suppressed PPARγ expression to basal levels, $P<0.05$ and $P<0.01$ respectively. Runx2 activity was significantly increased by metformin ($P<0.001$) and A769662 ($P<0.001$) but not Runx2 protein levels. As expected, A769662 promotes phosphorylation of ACC, but not so with metformin. Instead, metformin suppressed ($P<0.05$) the phosphorylation of p70s6k, as did A769662 ($P<0.05$) and rapamycin ($P<0.001$). Luciferase reporter assays confirmed the reciprocal action of metformin on adipogenesis and osteogenesis, namely suppression of PPARγ activity ($P<0.001$) and induction of Runx2 activity ($P<0.001$).
Conclusions
Metformin suppresses adipogenesis of C3H10T1/2 cells through the reciprocal regulation of PPARγ and Runx2. These results present novel mechanisms of action for metformin on MSC differentiation which is largely AMPK-independent, involving the suppression of p70S6K activity.

DOI: 10.1530/endoabs.39.EP16

EP17

The prevalence of fragility fractures in children with cerebral palsy in Manchester: a cross-sectional survey

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Background
Cerebral palsy (CP) is the most common physically disabling childhood motor disorder. Fractures in this group of children are common, however, prevalence and risk factors associated with fractures in children with CP in the UK is not known.
Aims
The aims of this cross-sectional survey were i) to determine the prevalence of fractures in children with moderate-to-severe CP in Manchester, ii) to determine the common sites of fracture, and iii) to identify risk factors associated with fractures.
Methods
This was a retrospective survey of a cohort of 96 children with CP and Gross Motor Functional Classification Score (GMFCS) levels III–V. Data were collected from Manchester database of children with CP, clinical health records, radiograph imaging and central database of fragility fractures in children with developmental delay. Sex, age, seizures, seizure medications, nutritional status, presence of contractures, hip dislocations, and fracture history were all collected and statistically analysed.
Results
Twelve children were found to have fractures, with a total of 23 fracture episodes, providing a prevalence of 12.5%. The median age of fractures was 6 years. Sixty-six per cent of the fractures were found to occur in children with a GMFCS level of V, with a 66% of fractures occurring in a child who was fed via a gastrostomy ($\chi^2=7.14$, df$=1$, $P<0.008$). The most common fracture site was around knee joint. Thirty per cent (GMFCS-5, $n=3$ and GMFCS-3, $n=1$) of the children had multiple fractures.
Conclusion
The prevalence of fractures in children with CP was found to be consistent with the figures in literature. Of the risk factors studied, the use of a gastrostomy-feeding device was the only variable found to be associated with an increased fracture risk. However, the presence of a gastrostomy may be a marker of the severity of the child's CP, predisposing them to fractures. Healthcare professionals and carers should be aware of the increased risk of non-traumatic fragility fractures in children with CP.

DOI: 10.1530/endoabs.39.EP17

EP18

Trends of use of bisphosphonates in children with secondary osteoporosis

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Aim
To review trends in bisphosphonate use in children with secondary osteoporosis attending a Tertiary Paediatric Endocrine Unit (2004–July 2015).
Methods
Data were gathered from a combination of a clinical and pharmacy database. Results reported as median (range).
Results
A total of 42 children (19M) commenced on bisphosphonates treatment over the 11-year period, median age 11.8 years (3.3–18.4). 19 were on pamidronate (3–6 monthly), 14 zoledronate (6–12 monthly), and one risedronate. I.v. zoledronate was introduced after 2011. Fracture and DXA data at start of therapy was available for 34 children. Fractures prior to treatment were: 12/34 (35.3%) vertebral fracture, 7/34 (20.6%) recurrent appendicular fractures (11 femoral, two tibial, four tibia/fibula, and four humeral), 11/34 (32.4%) single appendicular fracture (one radius/ulna, five femoral, two tibial, one radial, one navicular, and one phalangeal) in four children with immobility (two cerebral palsy, one maple urine syrup disease, and one spinal cord injury), two leukaemia, one duchenne muscular dystrophy, one juvenile arthritis, and one severe asthma on long-term oral glucocorticoid. DXA was assessed in 24/34 (70.6%) prior to commencement of bisphosphonates and was repeated during treatment in 12/24 (50%). Of those with no DXA prior to treatment, 8/12 were due children with immobility and/or significant learning difficulties.
Of the 12 patients with vertebral fractures, all were multiple. All were treated for painful compression fractures. 4/14 (28.6%) of those with vertebral fractures had repeat spine X-rays during treatment. None of them showed vertebral reconstitution but no new fractures were identified.
Conclusion
The number of children with secondary osteoporosis commenced on bisphosphonates therapy is increasing over the period of audit. This could reflect increasing detection of fractures in children with chronic disease, referral from other sub-specialties and increasing confidence in the use of bisphosphonates. Investigation and monitoring of patients is inconsistent, although the appropriate method to determine response following bisphosphonates therapy is unclear.

	2004–2005	2006–2007	2008–2009	2010–2011	2012–2013	2014–2015
n	3	5	4	8	8	14
Inflam-matory	–	2/5 (40%)	–	3/8 (37.5%)	–	1/14 (7.1%)
Immobility	–	1/5 (20%)	2/4 (50%)	3/8 (37.5%)	2/8 (25%)	9/14 (64.3%)
DMD	–	–	1/4 (25%)	1/8 (12.5%)	–	4/14 (28.6%)
Neoplastic	2/3 (66.7%)	2/5 (40%)	1/4 (25%)	1/8 (12.5%)	5/8 (62.5%)	1/14 (7.1%)
Other	1/3 (33.3%)	–	–	–	1/8 (12.5%)	1/14 (7.1%)

DOI: 10.1530/endoabs.39.EP18

EP19

Rickets due to dietary calcium deficiency in Manchester

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Background and aims
Rickets is a childhood condition resulting from impaired mineralisation of the growth plate, resulting in bony deformities. A retrospective survey was undertaken to identify causes of rickets in children treated at the Royal Manchester Children's Hospital from 2009 to 2014.
Methods
Cases of rickets were identified through a search of all paediatric radiology reports containing the words 'Rickets' or 'Osteomalacia' and confirmed with reference to relevant biochemical tests. Those with serum 25OHD concentrations <50 nmol/l were classified as vitamin D deficiency rickets and those with 25OHD >50 nmol/l and a history of inadequate dietary calcium intake as calcium deficiency rickets.
Results
Seventy-nine cases of rickets were identified of which 68 patients had nutritional rickets. Four children had rickets due to dietary calcium deficiency and the rest of the cases of nutritional rickets were primarily due to vitamin D deficiency (mean 25OHD 10.8 ± 10.3). Three of the cases with calcium deficiency rickets had cow's milk protein allergy and the fourth disliked and avoided dairy products. The relevant biochemical data are shown in the Table below.
Conclusions
Rickets due to dietary calcium deficiency has been reported in South Africa, Northern Nigeria, Bangladesh, and parts of India. Whilst vitamin D was the commonest cause of nutritional rickets in our survey, we also identified four cases of rickets due to dietary calcium deficiency. This survey highlights the importance of providing adequate calcium supplements in children with food allergies/intolerances.

Age (months)	Corr Ca (2.2–2.7 mmol/l)	Phos (0.95–1.5 mmol/l)	ALP (U/l)	PTH (1.6–6.9 pmol/l)	25OHD (50–75 nmol/l)
12	2.41	0.86	1781	NA	52
23	2.26	1.33	1149	26.5	134
25	2.34	0.98	538	21.1	70
133	2.20	1.08	1043	95.2	139

DOI: 10.1530/endoabs.39.EP19

EP20

Early onset cataract in an infant with activating calcium-sensing receptor mutation

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We present a 3-month-old boy who was born at term, to non-consanguineous parents by spontaneous vaginal delivery, weighing 4.19 kg. Newborn examination, including eyes, was normal. He was admitted at 7 days of life with focal seizures and hypocalcaemia, hypomagnesaemia, hyperphosphataemia, and inappropriately low parathyroid hormone (PTH) levels. He was treated with i.v. calcium and magnesium infusions and discharged on oral calcium, magnesium, and alfacalcidol. He was re-admitted at 5 weeks with recurrent focal seizures and hypocalcaemia. Parents noticed he had stopped fixing and following over the previous week. Eye examination revealed nystagmus and absent red reflexes. He was urgently reviewed by ophthalmology who confirmed presence of dense bilateral cataract.

An activating variant in the calcium-sensing receptor (CASR) gene was confirmed. He was commenced on a s.c. PTH infusion and weaned off intravenous calcium infusion. Alfacalcidol was stopped and colecalciferol was started. Thiazide diuretics were commenced to reduce renal calcium excretion. Seizures settled after resolution of hypocalcaemia. He was operated for cataract at nine weeks of life.

The CASR is a G-protein coupled receptor which senses extracellular levels of calcium ion. Activating CASR gene variants result in an increased calcium sensitivity in parathyroid and renal cells, which in turn reduces the parathyroid set point and reduces renal calcium reabsorption. The clinical presentation varies from mild paraesthesia to nephrocalcinosis, basal ganglia calcifications and seizures. Cataracts are a recognised complication of hypoparathyroidism. However, as far as we are aware, this is the first reported case of cataract in an infant with activating CASR mutation. We therefore suggest that evaluation for cataract is required in this subgroup of patients.

DOI: 10.1530/endoabs.39.EP20

EP21

Safe prescribing: vitamin D toxicity as a result of inadvertent overdose

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Introduction

Prevalence of vitamin D deficiency is well recognised and public awareness is being raised to encourage intake of vitamin D supplements. Optimal serum concentration of 25OHD for bone and general health has not been established. Desirable serum concentration of 25OHD had been proposed as >75 nmol/l and levels above 500 nmol/l are deemed toxic. Guidance is available on tolerable upper limit of vitamin D intake by US Institute of Medicine.

Case report

A 4-year-old boy presented with a history of vomiting, polydipsia, polyuria, weight loss, and worsening constipation. He had been taking a number of holistic medications including vitamin D and calcium supplements to help with his autism. Corrected calcium at presentation was 4.08 mmol/l, with low PTH of 0.6 pmol/l and undetectably high 25OH vitamin D level on the standard assay. He was initially managed with hyperhydration, calcitonin, and furosemide. Calcium level dropped to 3.15 mmol/l, however, there was a rebound rise in calcium levels and he was treated with pamidronate infusions. After 12 days of treatment, calcium level came down to 2.18 mmol/l. Results obtained by diluting initial blood sample revealed a very high 25OH vitamin D level of 1890 nmol/l. Further investigations revealed a normal MRI brain and mild nephrocalcinosis on USS of kidneys.

On further exploration, we discovered that he was prescribed one drop a day of concentrated solution of colecalciferol containing 2000 IU/drop but the child was being given at least 1 ml a day for 4 months, which amounts to 40 000 IU/day.

Conclusion

Though vitamin D toxicity is a rare occurrence, it is mainly due to inadvertent use of very high doses of vitamin D. When prescribing concentrated solutions, the dosage and risks should be carefully explained.

DOI: 10.1530/endoabs.39.EP21

Diabetes

EP22

Higher glycaemic response after British breakfast cereals in comparison to European breakfasts

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Introduction

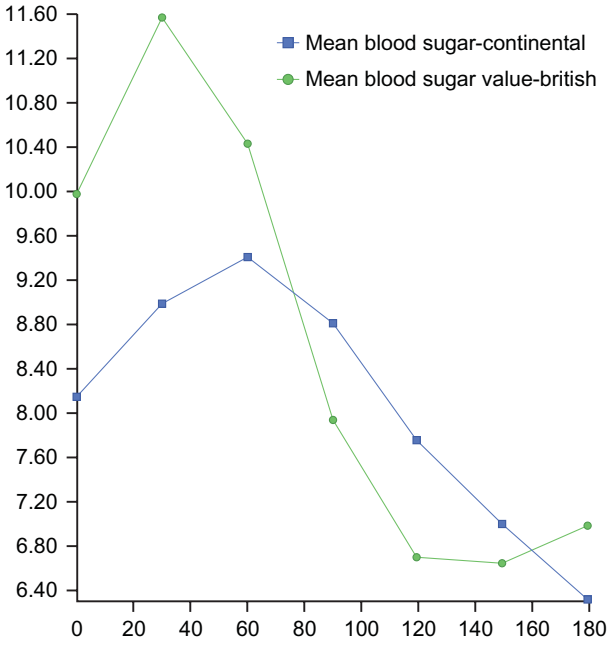
We hypothesised that children with type 1 diabetes would have more hyperglycaemia following a British as compared to a European breakfast.

Methods

Children were asked to take a continental breakfast and a typical British breakfast cereal on separate days. Pre breakfast glucometer readings were documented and then regular readings until lunchtime. The meals were prescribed by a dietitian; they were approximately carbohydrate matched but of different calorie content (more calorie in the continental breakfast). The quantities were allocated according to age bands.

Results

Eleven children participated. A statistically significant rise ($P=0.0085$) in blood sugar (see Table) was seen after the British breakfast compared to the European breakfast.



Conclusion

Dietetic advice should encourage continental type food as opposed to British breakfast cereals.

DOI: 10.1530/endoabs.39.EP22

EP23

Methods used in glycaemic monitoring in children and young people with diabetes in England and Wales

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Background

HbA1c remains the most powerful outcome measure for children and young people with diabetes. It is collected at every clinic visit and is used for individualised discussions around diabetes control and for national benchmarking. However, despite DCCT and IFCC standardisation, there is still no overall

consensus as to the most appropriate methodology, particularly when assessing patients with haemoglobinopathies that may affect HbA1c measurement.
Objective
To describe the methods of glycaemic monitoring in paediatric diabetes units (PDUs) across England and Wales.
Method
Cross-sectional surveys (electronic/paper) sent to all paediatric diabetes consultants in England and Wales through network coordinators. Data on frequency, timing and HbA1c measuring methods were collected from data submitted to the National Paediatric Diabetes Audit.
Results
59% ($n=101/171$) of PDUs responded representing 16 599 patients (96.9% type 1, 1.7% type 2, and 1.4% others). HbA1c methods for 3-monthly follow-up were: capillary point-of-care (POC) testing ($n=85$), laboratory capillary (Cap lab) ($n=7$), Cap lab/POC ($n=4$), and venous laboratory/POC ($n=5$). HbA1c were taken 95% on the day and 5% before the appointment. 78 units reported local laboratory HbA1c methods: ion-exchange affinity HPLC ($n=29$), capillary electrophoresis ($n=5$), immunoassay ($n=2$), ion-exchange HPLC ($n=39$), boronic affinity ($n=2$), and spectrophotometry ($n=1$). Full blood count was included with laboratory HbA1c regularly in 18/82 and selectively in 10/82. At annual reviews, laboratory venous HbA1c were always measured in 46/82 and selectively in 14/82. Selective screening for haemoglobinopathies was performed in 36/80. Methods of glycaemic monitoring in patients with haematological disorders, reported by 74 units, included, fructosamine ($n=51$), HbA1c ($n=32$), glucose pattern ($n=32$), average glucose ($n=30$), continuous-glucose ($n=29$), fasting glucose ($n=3$), total HbA1c ($n=8$), glycated protein ($n=4$), and none ($n=2$). Only 51/101 of respondents were aware of interferences in the methods affecting the reliability of HbA1c results.
Conclusions
There is considerable variation in the methods of glycaemic monitoring in paediatric diabetic patients nationally and lack of awareness of factors that may impinge on HbA1c results.
DOI: 10.1530/endoabs.39.EP23

EP24

A National survey of annual screening in diabetes clinics in the UK
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Screening for complications and associated conditions in children with type 1 diabetes is routinely performed in Diabetes Clinics. Though there are NICE recommendations screening tests, interpretation and management is varied as there is no strong evidence base in paediatrics. We conducted a survey across diabetes units to establish the prevailing practice.
Method
Survey monkey questionnaire was sent out to clinicians who care for children with diabetes in England and Wales. We received 85 responses in total with 77 complete responses.
Results
Sixty percent of respondents start screening at 12 years of age. 28% start screening from diagnosis irrespective of the age.
Microalbuminuria screening is varied across the regions. Majority (60%) use random urine sample 32% use early morning sample for initial testing. Few centres also do timed overnight testing. If the microalbuminuria is positive in the initial sample, majority recheck with early morning sample 67%. About 10% refer to nephrologists, with few centres (4%) starting medical management. ACE inhibitors are the most preferred treatment with some centres using AR blockers. One tertiary centre also considers renal biopsy.
Coeliac screening is performed annually in 70%, every three years in 14% and only if symptomatic in others. Thyroid screening is performed annually in 96%. Only 76% of respondents perform annual lipid profile. Diet and glycemic control is recommended in about 80% of units and about 25% of respondents use lipid lowering agents.
Seventy-seven percent units perform the same screening tests for both types 1 and 2 diabetes.
Conclusion
Our survey demonstrates that the practice of screening is widely varied across the regions and even within the same regional network. There is need to develop evidence based and practical national guideline to standardise practice across the networks which will help identify complications early, initiate appropriate treatment and save resources by minimising unnecessary investigations and referrals.
DOI: 10.1530/endoabs.39.EP24

EP25

Using co-production and graphic facilitation to improve patient experience in type 1 diabetes mellitus
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Introduction
Co-production refers to working in partnership with service-users to improve provision of services. Increasing evidence highlights that co-production can improve health care and result in financial savings. Service-users are involved in defining the problem or need, creating the solution, delivering it, and evaluating it. This approach demands longer-term engagement by service-providers but leads to sustainable change. Graphic facilitation is the use of large-scale imagery to focus groups towards a goal stimulating strategic dialogue. Patients feel their ideas are captured and validated helping a consensus to be gained.
Methods
Six patients and four members of staff from the Diabetes Service at Ealing Hospital attended the session. All participants were over 14 years old and informed consent was obtained. A graphic facilitator was present who documented the conversations as a pictorial storyboard, however did not take part in conversations. The session took part outside of any clinic area and refreshments were provided, this informal approach created a sociable environment, which was a useful way to move forward in co-design. Participants highlighted challenges faced by adolescents with diabetes initially through 'word maps' then focusing on ways to improve the service.
Results
Participants highlighted improvements to clinic structure using a more adolescent tailored consultation. Other topics included progressing forward a WhatsApp group. Further work is looking at setting up a clinic in a local school to reduce appointments and a cookery book. Following this session staff also undertook additional training in motivational interviewing to further enrich consultations. Qualitative data has highlighted improved patient satisfaction following this co-production. One patient quoted 'I felt valued and involved in decision-making to improve my care'.
Conclusion
Co-production and graphic facilitation are useful methods to improve services and patient-centred care. It may improve adolescent ownership of their condition, and further research is necessary to determine if this change is sustained.
DOI: 10.1530/endoabs.39.EP25

EP26

Ethnic variation in the correlation between waist-to-height ratio and total daily insulin requirement in children with type 1 diabetes: a cross-sectional study
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Introduction
Total daily insulin required to achieve glycaemic control in type 1 diabetes (T1D) depends on numerous factors. Correlation of insulin requirement to BMI and waist circumference has been variably reported in the literature, whilst that of WHtR has not been studied.
Aims
To study the correlation between daily insulin requirement (TDD) and WHtR in a multi-ethnic population.
Methods
A cross-sectional study of children (5–18 years) with T1D attending a diabetes clinic in a multi-ethnic population in Bradford, UK was conducted. Physical measurements were undertaken in the clinic setting and data collected from case notes and patients/carers. Ethnicity was classified using the Office of National Statistics recommended country specific ethnic group question. Deprivation was allocated using the index of multiple deprivation (IMD) based on current postcode.
Results
Sixty-nine patients with mean age 12.7 ($\pm$3.1) years, duration of diabetes 5.4 ($\pm$ 3.5) years, and HbA1c 80 ($\pm$18) mmol/mol were recruited. Nearly 54% ($n=37$) were white and 46% were non-white (29 Asian Pakistani, one Indian, and two mixed White Afro-Caribbean). The two ethnic groups had similar demographics and disease profile. Compared to whites, non whites had a higher prevalence of obesity (15% vs 5%, $P<0.01$), family history of T2D (49% vs 33%), microalbuminuria (22% vs 11%, $P<0.05$), and deprivation (mean IMD score 42 vs 30, $P<0.001$). WHtR and TDD were poorly correlated in the whole group. However, significant positive correlation was seen in whites ($r=0.583$, $n=37$,

$P<0.01$) and significant negative correlation seen in Asian Pakistanis ($r=-0.472$, $n=32$, $P<0.01$); significant negative correlation was also seen in subjects with relatives with T2D ($r=-0.86$, $n=6$, $P=0.02$).
Conclusions
The variation in correlations highlights that the two ethnic groups behave differently and should therefore be studied separately with regards to factors influencing insulin requirements with careful consideration to the presence of parental IR.

DOI: 10.1530/endoabs.39.EP26

EP27

Junior KICk-OFF – teaching and health care profession working in partnership to develop diabetes education

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Background
Structured education should be appropriate to the learning styles of participants. Health professionals and experts in education worked together to develop KICk-OFF for 11–16 year olds and similar experience has now been used in the development of Junior KICk-OFF for Key Stage (KS) 1 (4–7 years) and KS2 (7–11 years).
Method
The KICk-OFF team developed the curricula with input from teachers and an academic educationalist. Sections of the curriculum were tested initially within a primary school and then adapted to create full curricula for each KS group. The social constructivist approach was used emphasising a variety of tasks and assessment for learning approaches.
Two Junior KICK-OFF courses have been held to test out the material and curriculum. These were observed by the educationalist and videoed to allow further refinement of the curriculum and training.
Results
The education profession influenced Junior KICk-OFF through guidance on:
i) Age appropriate activities.
ii) Use of familiar school teaching resources e.g. puppets, story sacks, counting lines.
iii) Timings for activities.
iv) Use of the resources to produce a KS2 knowledge assessment.
v) Development of a peer review assessment system for quality assurance of courses.
Initial educationalist observation report showed:
i) Children found the course stimulating and enjoyable.
ii) The curriculum was well structured with a logical sequence of concepts and variety of tasks.
iii) Improvements in factual recall and understanding of concepts were demonstrated in assessment for learning activities.
Key points for enhancing the curriculum were:
i) Greater emphasis on the individual monitoring of progress.
ii) Courses could be longer.
iii) Emphasis of group rules for dominating individuals.
iv) More time for talking together to allow deeper thinking.
Discussion
Sharing expertise between professions has resulted in structured education courses tailored to the developmental age and learning needs of children within primary school.

DOI: 10.1530/endoabs.39.EP27

EP28

Is the glycaemic control in type 1 diabetes mellitus affected by Vitamin D status?

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Background
Animal studies have demonstrated relationships between Vitamin D and glucose homeostasis. There is paucity of evidence examining the relationship between the glycemic control in children with Type 1 Diabetes Mellitus (T1DM) and vitamin D status.
Objective
To determine the effects of vitamin D status on the glycemic control in children and adolescents with T1DM.
Methods
Retrospective data were collected on 348 children and adolescents with TIDM. The serum 25 (OH) Vit D concentrations were measured at diagnosis and as part of the annual assessment. Patients were catergorised as: Vitamin D deficient (25 nmol/l), insufficient (25–50 nmol/l) or sufficient (>50 nmol/l). Vitamin D deficiency was treated with 6000 units of cholecalciferol once a day or 20 000 units once a week for 6–8 weeks.
Results
The mean 25(OH) Vit D concentration was 54 nmol/l (+22.9). 52.4% of patients had normal vitamin D concentrations (94% white ethnicity, 2% somali), 39.2% were vitamin D insufficient (87% white ethnicity, 4% somali) and 8.4% were vitamin D deficient (79% white ethnicity, 7% Arabic, 7% mixed background). The mean HbA1C (mmol/mol) for the group with adequate, insufficient and deficient vitamin D concentrations were 72.36, 72.18 and 69.41 respectively. The mean HbA1C (mmol/mol) prior to treatment with vitamin D supplements was 70.85 (+18.9) and post treatment was 69.85 (+15.95) ($P=0.64$). There was no significant correlation between vitamin D concentrations and HbA1C ($r=0.05$, $P=0.2$).
Conclusions
Low Vitamin D concentrations are fairly prevalent in children with T1DM and much more common in ethnic minority groups. Glycaemic control does not seem to be influenced by the vitamin D status in our retrospective study. Long-term prospective studies are essential.

DOI: 10.1530/endoabs.39.EP28

EP29

Factors influencing type 1 diabetes control in children – a detailed local analysis of an NPDA dataset

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Background
National paediatric diabetes audit (NPDA) provides comparative data for local paediatric diabetes units (PDUs) on key care processes and overall HbA1c. More detailed analysis on other variables affecting HbA1c is undertaken at a national level, but not at an individual PDU level.
Objective
To determine the factors influencing glycaemic control (HbA1c levels) in young children and adolescents with Type 1 Diabetes Mellitus (T1DM).
Methods
Retrospective analysis of the local data collected for the NPDA 2014-15 in a medium sized PDU. Data was analysed using the SPSS statistical package.
Results
There were 181 patients (97 boys and 84 girls) aged 12.2±4.1 years (mean±S.D.). T1DM accounts for 96% ($n=174$) of cases. Non-T1DM patients ($n=7$) were excluded from the rest of the analyses. The average HbA1c is 8.6% (70.7±19.4 mmol/mol). 26.5% of children had an HbA1c level below 7.5% (58 mmol/mol). There was a linear relationship between age and HbA1c ($r=0.106$) indicating poorer control with advancing age. Adolescents, in particular, had poorer glycaemic control with a mean HbA1c 17.6 mmol/mol higher in 15–19 year olds compared to 0–5 year olds ($P<0.0001$). The mean HbA1c was significantly higher for those who had T1DM for 5 years and above (74.5±19.6 mmol/mol) compared to those with a duration <5 years (67.0±18.5 mmol/mol) ($P=0.01$). The average HbA1c for the Black population is (82.1±21.5 mmol/mol), significantly higher than and that for White population (69.7±19.5 mmol/mol) ($P=0.048$). This difference between the ethnic groups is more marked than the national data. Those on pump therapy (64.1±12.9 mmol/mol) have lower HbA1c levels than those on multiple daily injections (72.8±20.5 mmol/mol) ($P=0.003$). There is a tendency for those who are 'overweight' or 'obese' to have a higher HbA1c than those who have normal BMI ($P=0.3$). Age at first diagnosis and number of clinic visits per year did not seem to affect HbA1c.
Conclusions
Older children especially adolescents, black ethnic origin and a longer duration of diabetes adversely affect T1DM control and HbA1c. Those on insulin pump therapy had an improved control. Targeted measures to improve management in these at-risk groups, at a local level, are imperative. Careful analysis of NPDA data at a PDU level is a useful exercise to determine local priorities.

DOI: 10.1530/endoabs.39.EP29

EP30

Establishing a 'Pump School' in a large children's hospital

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Background
In 2013 the Diabetes Team at a large children's hospital commenced 'Pump School' for all children and young people (CYP) transitioning from multiple daily injections to insulin pump therapy (CSII) using Medtronic, Accu-chek, Animas and Omnipod pumps.
Aim
To provide CYP and their parents/carers with structured education to improve their outcomes including glycaemic control, hypoglycaemic episodes and quality of life (QOL).
Methodology
'Pump School' provides six 3-h sessions of structured, pump specific education, in small groups over a period of 3 months. Sessions are delivered by diabetes nurses supported by company educators/representatives. CYP and their parents undertake a CSII awareness and an assessment process prior to the programme, exploring expectations of CSII, knowledge of diabetes management and carbohydrate counting competency. Generic presentations on daily management with CSII were developed with specific CSII function and operational tools for the individual schools.
Data collection
HbA1c measurements using the DCA Vantage analyser and QOL questionnaires (Problem Areas in Diabetes (PAID) and Fear of Hypo) are taken at baseline and at 3 months, by each family, to evaluate the effectiveness of the programme.
Results
35 CYP have been enrolled, 14 on Medtronic, 11 Accu-chek, eight Omnipod, two Animas and 31 have 'graduated' with one individual dropping out after session 1.

Table 1

Mean value	HbA1c	Total daily dose (TDD)	PAID (max. score 80)	Fear of hypo (max. score 52)	No. weekly hypos
Baseline ($n=34$)	67 mmol/l (8.3%)	32.5 ui (7–95 ui)	15.8 (0–46)	8.2 (0–26)	3.1 (0–11)
3 months ($n=31$)	64 mmol/l (8.0%)	34.6 ui (8–90 ui)	11.6 (0–58)	5.1 (0–19)	2.6 (0–7)

Conclusion
Improvements were seen mainly in QOL with minimal changes in HbA1c. Plans are to audit whether improvements are sustained at 12 months and to evaluate the curriculum, involving other professionals from other disciplines within the team.

DOI: 10.1530/endoabs.39.EP30

EP31

Comparison of current trends in obesity in patients with type 1 diabetes in Nottingham with a historical cohort and 2013–2014 national child measurement programme data in the UK

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Aim
To compare the BMI z-score of children with type 1 diabetes (T1DM) in Nottingham with that of national and local background populations and to identify factors associated with increased BMI.
Methods
A retrospective observational cohort study of patients with T1DM aged 2–15 years under the care of the paediatric diabetes team at Nottingham Children's Hospital, between April 2013 and March 2014. Mean BMI-z-score for the year was computed in *R*, utilising publically available LMS data from the UK 1990 cohort. This was compared with BMI z-score of age-matched children from i) the National Child Measurement Programme (NCMP) ii) the Health Survey for England (HSE) data for the same year and iii) our 2008 audit data. Overweight and obesity was defined as a BMI $>$ 85th (BMI z-score >1.0) and $>$95th (BMI z-score >1.6) centiles, respectively.
Results
1140 clinic entries were analysed relating to 253 patients. The mean $\pm$ S.E.M. BMI-z-score was 0.62 ± 0.004, with 16% of patients being obese and a further 15.2% overweight, similar to national rates (15.2% and 14.2% (HSE)). Compared to previous data, obesity rates and mean BMI-z-score had improved (26.3% obese, $P=0.005$; mean BMI z-score 1.0, $P<0.001$). Younger age group female patients (2–10 years) had a higher mean z-score than males (0.63 ± 0.13 vs 0.44 ± 0.46, $P=0.24$) but this was not significant. No gender trend was noted in older children (11–15 years). 2–4 year old females (1.03 ± 0.16) had the highest z-score.
Conclusion
Obesity and mean BMI-z-score in T1DM in Nottingham have improved significantly and are now comparable to the national background population. In contrast to previously published evidence, the children with T1DM in Nottingham are not obese compared to the general population. This study does now allow any firm conclusions to be drawn, but possibilities for local improvement could include an increase in multidisciplinary support from dietitians and specialist nurses, targeted better management leading to fewer hypoglycaemic episodes and a general plateau in obesity.

DOI: 10.1530/endoabs.39.EP31

EP32

Diabetes distress in transitional age evaluated by 'problem areas in diabetes' in type 1 diabetic patients from Marrakech.

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Introduction
Type 1 diabetes (T1D) represents 5.3% of all types on diabetes. Its incidence is increasing around the world as it is in the Middle East and North Africa Region, where the incidence is at 1/100 000. T1D touches young subjects and is then established in a growing body. Transitional period is a crucial phase with physical and emotional distress. In Moroccan context, psychosocial difficulties are an additional challenge for these young patients.
Aim of the study
Evaluate diabetes distress in transitional age using 'problem area in diabetes' (PAID) in its Arabic transcultural adaptation.
Materials and methods
Problem area in diabetes questionnaire was self-administered in 50 type 1 diabetics that were followed up in the department of endocrinology in University medical hospital of Marrakech.
Results
Over the population evaluated; 54% were female. The median of age was 17, 54 years. 32% were younger than 15 years old and 68% were older. 84% were living in urban area. 78% of them were students. 90% were still living with their parents. 48, 6% had duration of diabetes <5 years and 56% had an A1c above 9%. 18% of patients had a PAID score above 40, which indicates a diabetic distress. 8% had a PAID score less than 10. And it was between 10 and 40 in 74% of the patients.
Conclusion
A high prevalence of diabetes distress had been observed in our population of patients. Non-access to care, limited resources, and social problems explain this result. This kind of studies allows a better understanding and support of those patients and should lead toward an improvement of transitional care in diabetes.

DOI: 10.1530/endoabs.39.EP32

EP33

Is the glycaemic control in type i diabetes mellitus affected by Vitamin D status?

Donatella Pintus, Dinesh Giri, Supriya Phanse, Fulya Mehta, Atrayee Ghatak, Princy Paul & Senthil Senniappan
Alder Hey Children's Hospital, Liverpool, UK.

Background
Animal studies have demonstrated relationship between Vitamin D and glucose homeostasis. There is paucity of evidence examining the relationship between the glycemic control in children with type 1 diabetes mellitus (T1DM) and vitamin D status.
Objective
To determine the effects of vitamin D status on the glycemic control in children and adolescents with T1DM.

Methods
Retrospective data were collected on 348 children and adolescents with TIDM. The serum 25(OH) Vit D concentrations were measured at diagnosis and as part of the annual assessment. Patients were categorized as: Vitamin D deficient (<25 nmol/l), insufficient (25-50 nmol/l) or sufficient (>50 nmol/l). Vitamin D deficiency was treated with 6000 units of cholecalciferol once a day or 20 000 units once a week for 6–8 weeks.
Results
The mean 25(OH) Vit D concentration was 54 nmol/l (±22.9). 52.4% of patients had normal vitamin D concentrations (94% white ethnicity, 2% somali), 39.2% were vitamin D insufficient (87% white ethnicity, 4% somali) and 8.4% were vitamin D deficient (79% white ethnicity, 7% Arabic, 7% mixed background). The mean HbA1C (mmol/mol) for the groups with adequate, insufficient and deficient vitamin D concentrations were 72.36, 72.18 and 69.41 respectively. The mean HbA1C (mmol/mol) prior to treatment with vitamin D supplements was 70.85 (±18.9) and post treatment was 69.85 (±15.95) ($P=0.64$). There was no significant correlation between vitamin D concentrations and HbA1C ($r=0.05$, $P=0.2$).
Conclusions
Low Vitamin D concentrations are fairly prevalent in children with T1DM and much more common in ethnic minority groups. Glycaemic control does not seem to be influenced by the vitamin D status in our retrospective study. Long-term prospective studies are essential.

DOI: 10.1530/endoabs.39.EP33

EP34

Heterozygous glucokinase splicing mutation – identical genotype with variable phenotype in a single family

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Background
Heterozygous loss of function glucokinase mutations causes MODY with fasting hyperglycaemia (>5.5 mmol/l). We report a 2 year girl with a glucokinase mutation who presented unusually with stress induced hyperglycaemia and normal fasting blood glucose levels.
Case report
She presented with wheeze and was started on Salbutamol. Her blood glucose rose to 16 mmol/l with ketonuria. The hyperglycaemia was disproportionate to the severity of the illness. Hyperglycaemia settled after medication was stopped and she had fasting blood glucose levels below 4 mmol/l. Two weeks later she had an OGTT. Fasting glucose was 3.3 mmol/l and blood glucose at 2 h was 8 mmol/l. When the results of the OGTT were discussed with mother she disclosed a family history of diabetes. Mother's uncle was diagnosed with type 2 diabetes, started on Metformin and was then well controlled with diet alone. Genetic analysis revealed a heterozygous GCK splicing mutation (c.483+2_483+16del15). His daughter and grandson had fasting hyperglycaemia and tested positive for the same mutation.
We tested our patient for this mutation in view of the impaired glucose tolerance and family history. She tested positive for the same GCK splicing mutation. Interestingly she did not have fasting hyperglycaemia which is unusual for MODY with glucokinase mutation. It further emerged that the child's mother had gestational diabetes and is awaiting genetic testing.
Conclusion
The molecular diagnosis of MODY is important to classify the diabetes, predict prognosis and screen asymptomatic family members. In this family four members carried the identical mutation but presented with varying phenotypes. We concur with the policy of central genetic testing for these patients.

DOI: 10.1530/endoabs.39.EP34

EP35

Retrospective baseline services audit regarding the nature of emergency department attendances by registered diabetic children

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Objectives
Many paediatric diabetes units in the UK have introduced 24 h telephone support to encourage self-management to reduce Emergency Department (ED) attendances and admissions. The UK national audit collects information on acute paediatric diabetic admissions; but there is no data available on ED attendances in this group. We undertook a retrospective audit of ED attendances as part of a baseline service evaluation of our newly introduced 24 h support service.
Methods
The details and outcomes of local ED attendances of children with type 1 diabetes ($n=177$) registered under the care of a large inner-city Paediatric Diabetes Unit between September 2011 and August 2014, were retrospectively reviewed with an electronic database.
Results
A mean of 39 children with T1DM (23% of those registered in clinic) attended the ED annually. The total number of episodes over the 3 years was 167. 72% were due to a 'diabetic' complaint. 30.3% of these accounted for their first diagnosis of T1DM. In those with an established diagnosis, 63/84 (73.8%) of attendances were due to hyperglycaemia, including DKA. 14.2% had hypoglycaemia and 12.2% had 'troubleshooting' queries. Importantly, 43/84 (51%) of cases had a concurrent illness, such as gastroenteritis, with their diabetic issue. 49/84 (56.3%) of cases were admitted, with a mean duration of 3.4 days. No trends were seen over the 3 years in any of the variables. Only 11.5% of these diabetes-related episodes were documented to have accessed the helpline.
Conclusion
Up to 23% of the cohort attended an ED. The vast majority of cases were related to glycaemic control. Only half had a concurrent illness. Half of the attendances were discharged back to the community. These could possibly have been avoided by early clinical advice. A targeted 24 h helpline could prevent them from presenting to ED, encouraging better self-management and glycaemic control.

DOI: 10.1530/endoabs.39.EP35

EP36

Quantity of patient contact with a paediatric diabetes service – is there correlation with HbA1c?

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Objectives
Best practice tariff guidelines recommend that paediatric patients with diabetes should have a minimum of four MDT clinic appointments, and an additional eight contacts with the diabetes service per year. This audit compares performance in a DGH against these recommendations. It seeks to determine whether there is a correlation between amount of contact with the service and average HbA1c level.
Methods
Analysis of a database recording contacts with a total of 159 children between April 2014 and March 2015.
Results
Of the 159 patients, 21 (13%) were newly diagnosed, 19 (12%) were transitioning to adult services, and one had care shared with another hospital. These were analysed separately. For the remaining children the median total number of contacts per year was 23. The median number of MDT contacts was 4/year, and of additional contacts was 18.5/year. Additional contacts included telephone calls, texts, school visits and home visits. 93% of these children were offered at least four MDT appointments per year, 100% were offered at least eight additional contacts with the service, and 100% had a total of at least 12 contacts. The median HbA1c was 61 mmol/mol and 35% of patients had HbA1c <58 mmol/mol (i.e. good control). There was no correlation between median HbA1c and total number of contacts per year ($P=0.18$).
Conclusions/recommendations
Compliance with best practice tariff guidelines was achieved in the majority of cases, although 7% were offered less than four MDT clinic appointments per year. In addition patients received on average 11 more contacts per year than the minimum requirement (these were mostly 'additional contacts'). There was no correlation between average HbA1c level and number of contacts per year. More comprehensive routine data collection will allow further analysis of the contacts taking place to ensure quality as well as quantity.

DOI: 10.1530/endoabs.39.EP36

EP37

Service evaluation of the 'Ready Steady Go' transition programme in type 1 diabetes in Southampton

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Background
Transition can be a difficult time for adolescents with chronic diseases leading to poor attendance in adult clinics and poor long-term health outcomes. The implementation of transition programmes like 'ReadySteadyGo' at University Hospital Southampton (UHS) aim to improve transitional care and outcomes for patients.
Aims
To assess the effect of a structured transition programme, 'Go' from 'Ready-SteadyGo', at UHS for patients with Type 1 diabetes.
Method
The cohort consisted of patients transitioned from paediatrics at UHS during 2011–2014, aged 17–19 yrs at transition ($n=74$). Group 1 transitioned during 2011 ($n=25$) receiving no structured transition: group 2 transitioned during 2012 and onwards ($n=49$) and received a structured transition programme, 'Go'.
Results
The average HbA1c of the cohort before transition was 9.6% (S.D. 2.1). After transition mean HbA1c in the cohort rose to 10.1% (S.D. 2.4, $P=0.026$). HbA1c in group 1 did not significantly increase after transition; in group 2 HbA1c rose 1.5% ($P=0.035$).
Patients attended on average 1 appointment less after transition however attendance as a percentage of appointments offered increased from 51% (S.D. 0.03) before transition to 73% (S.D. 0.04) after($P<0.001$). Attendance was better after transition in group 2 (74% vs 69% respectively). The percentage of documented conversations about contraception in girls before transition rose from 46%(S.D. 0.52) in group 1–79%(S.D. 0.42) in group 2 ($P=0.02$). Looking at diabetes related hospital admissions after transition, 84% (S.D. 0.07) were in those who had an HbA1c $>10\%$ before transition.
Conclusions
HbA1c at the beginning of 'Go' around 16 yrs of age was already high, and attendance in clinic was poor suggesting that transition programmes need to be implemented earlier. The implementation of a structured transition programme improved attendance in adult clinics and education around family planning in Type 1 diabetes. The implementation of the full "ReadySteadyGo" programme from 11 yrs will aim to continue improving transition outcomes at UHS.

DOI: 10.1530/endoabs.39.EP37

EP38

Continuous glucose monitoring: effects on metabolic control, fear and frequency of hypoglycaemic episodes

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Self-monitoring of blood glucose (SMBG) is an important part of diabetes management. Continuous glucose monitoring (CGM) provides real-time measurement of users' glucose levels. The advantage of CGM is the availability of constant information about glucose levels which helps to predict hyper and hypoglycaemia and to adjust the insulin doses accordingly. NICE guidelines recommend that children and young people with type 1 diabetes and persistent problems with hypoglycaemia unawareness or repeated hyper or hypoglycaemia should be offered CGM. In UK there is limited funding for CGM due to lack of evidence for benefits of use over SMBG in improving control. In our service within a large DGH, we have a cohort of 12 children who were funded for CGM use over a minimum of 12 months.
Aim
To assess the effects of CGM on metabolic control, fear and frequency of hypoglycaemic episodes and assess the overall compliance over a period of 12 months.
Methods
Data from 12 patients commenced on CGMS was collected. We compared their HbA1c, frequency of hypoglycaemic episodes over 12 months, as well as asking them to complete fear of hypoglycaemia questionnaires for before and after CGM use.
Results
12 patients (eight males), with median age 14.5 years (5–18 years) used CGM over a year. There was significant improvement in HbA1c within 1 month of usage and that improvement was sustained over 9 months. Number of hypoglycaemic episodes increased significantly at 6 months of usage but at 12 months there was no significant difference. There were some issues with non-compliance in 58% of patients.
Conclusion
In clinical practice, the use of CGM showed improvement in metabolic control within a short period of time but improvement was not sustained over 12 months. Fear of hypoglycaemic episodes were significantly improved following CGM usage.

DOI: 10.1530/endoabs.39.EP38

EP39

Young people with type 1 diabetes of non-white ethnicity and lower socioeconomic status have poorer glycaemic control in England and Wales – a national population-based study

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Introduction
The impact of ethnicity and socioeconomic status (SES) on glycaemic control in children with type 1 diabetes (T1D) is poorly understood in England and Wales.
Methods
We studied 18 478 children and young people with T1D aged <19 years attending diabetes clinics in England and Wales and included in the 2012–2013 National Paediatric Diabetes Audit (NPDA). Self-identified ethnicity was categorized as white, Asian, black, mixed, other and 'not stated' (those that chose not to divulge ethnicity). A small area measure of SES was estimated using postcode and the Index of Multiple Deprivation (grouped into quintiles). Multivariable linear regression was used to assess impact of ethnicity and SES on glycaemic control (mean HbA_{1c} levels) accounting for age, gender and diabetes duration. Associations between SES and HbA1c were also tested in models stratified by ethnicity. The impact of insulin pump use on the ethnicity/SES-HbA1c associations was tested in 13 962 children.
Results
All ethnic minorities had higher mean HbA_{1c} compared to white children, with the largest differences observed in black and mixed ethnicity children (7.84 mmol/mol, 95% CI 5.07–10.6 and 6.81 mmol/mol, 4.55–9.08 respectively). Lower SES was associated with higher mean HbA_{1c} with a dose effect. The lowest SES group (quintile 5) had on average 6.78 mmol/mol (5.63–7.95) higher mean $HbA1_c$ compared to the highest SES group, adjusted for ethnicity. Estimates for ethnicity were attenuated but remained significant on adjustment for SES. Having a lower SES was associated with higher mean HbA_{1c} irrespective of ethnicity in stratified analyses. However, being in the lowest SES group and of Asian (6.90 mmol/mol, 2.52–11.28), mixed (11.26 mmol/mol, 6.31–16.21) and other (8.85 mmol/mol, -0.05–17.5) ethnicity was associated with higher mean HbA_{1c} compared to being in the corresponding lowest SES group and white ethnicity (6.03 mmol/mol, 4.72–7.34). An interaction test between ethnicity and SES was statistically significant ($P=0.005$). Less non-white (white 20.3 vs Asian 12.1 vs black 5.5%) and deprived (least deprived 21.1 vs most deprived 13.2%) children were on insulin pump therapy. Both ethnicity and SES remained significant predictors of HbA_{1c} after accounting for insulin pump use.
Conclusion
The effect of ethnicity independent to deprivation on glycaemic control persists after adjustment for pump use, indicating that an alternative approach to intensive insulin therapy for the treatment of glycaemic control is required in these vulnerable children.

DOI: 10.1530/endoabs.39.EP39

EP40

Pancreatitis, adrenal insufficiency and autoimmune diabetes mellitus in a girl with probable sarcoidosis

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Case report
A 9-year-old girl of mixed ethnic origin presented with symptomatic hypercalcaemia with a 3-month history of weight loss and lethargy. Autoimmune

hypothyroidism had been diagnosed 10 months previously. Serum vitamin D concentration (11 nmol/l) was low and cholecalciferol 20 000 units daily for 7 days followed by 800 units daily was commenced. One month later, her symptoms worsened and she had developed anaemia and renal impairment. Hypercalcaemia was noted (Corr Ca 3.7 mmol/l, Phos 1.46 mmol/l, ALP 133 iu/l, Vitamin D 65 nmol/l, PTH 0.1 pmol/l (NR 1.1–6.9), 1,25 vitamin D_3 161 pmol/l (NR 43–143), urine Ca: Creat ratio 3.03). Intravenous fluids and one dose of calcitonin normalised the calcium concentration. Bisphosphonates were not used due to renal impairment. Elevated amylase (395 μ/l) and USS abdomen findings suggested pancreatitis. TSH was raised with normal T_4 (on 125 μg of Thyroxine), ACTH was undetectable and standard synacthen test was suboptimal (cortisol <50 nmol/l at 0 min and 320 nmol/l at 30 min). Hydrocortisone was commenced. MRI pituitary was normal and her adrenal antibodies were negative. Within few days, she developed diabetes mellitus requiring insulin therapy and GAD antibodies were strongly positive. Further investigations include negative mantoux, normal pelvis ultrasound and HR CT chest. The ACE levels (135 U/l (NR 10-43)) and ESR levels (26–35 mm/h) were elevated. Conjunctival biopsy did not reveal granulomas and bone marrow biopsy was normal. A probable diagnosis of sarcoidosis was made based on the constellation of clinical findings and she was treated with steroids and methotrexate. Pancreatitis resolved with conservative management.

Conclusions

Granulomatous diseases like sarcoidosis are rare causes of hypercalcaemia in children. Sarcoidosis causes hypercalcaemia by extra renal 1 alpha-hydroxylation of vitamin D causing high circulating concentrations of 1,25 vitamin D. It can be associated with multiple endocrine problems including hypothalamo-pituitary disease and autoimmune endocrinopathy.

DOI: 10.1530/endoabs.39.EP40

EP41

Variation in 24-h basal insulin requirements with age in children and young people with type 1 diabetes mellitus

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Introduction

Insulin requirements change with age, in part related to changes in Growth Hormone secretion. Little is known of the impact of age on the circadian variation in insulin secretion. We have studied changes in insulin basal rates as a proxy for insulin sensitivity in CYP with well controlled T1DM.

Methods

Insulin pump settings for total daily dose (TDD) and sensitivity ratio were obtained from 22 CYP with T1DM. Basal insulin requirements were calculated for four time blocks 0000–0600 h, 0600–1200 h, 1200–1800 h and 1800–2400 h. There were nine males/13 females aged 4–14.5 years. Height and weight data from the time of pump download were used to calculate BMI. Insulin settings were related to age, sex and BMI.

Results

TDD was 0.9 U/kg for males and 0.7 U/kg for females ($P=0.03$). There were no differences between the sexes for age, BMI or HbA1c. For every 1 year increase in age HbA1c declined by 0.13% ($P=0.02$). Sensitivity ratio was inversely related with age ($r=-0.65$; $P=0.006$) with no effect of sex or BMI. Total basal insulin increased with age.

The coefficient for this increase was highest (0.11) for the time period 0000–0600 h compared to the other time periods; 0600–1200 h (0.09), 1200–1800 h (0.05) and 1800–2400 h (0.08).

Discussion/conclusion

These data suggest that there is an age effect on the circadian variation in insulin sensitivity as reflected in basal insulin delivery rates. The change in insulin sensitivity decreases with age across the whole study population and is not influenced by sex or BMI. Although Growth Hormone has been implicated in the pubertal alterations these data would suggest that other factors, either intrinsic or extrinsic, may influence insulin sensitivity through childhood and adolescence.

DOI: 10.1530/endoabs.39.EP41

EP42

Challenges in diabetic care – the effect of implementing a New Patient Education Programme

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Introduction

Poor HbA1c in the first year following diagnosis of type 1 diabetes is a predictor of poor metabolic control and early development of complications. Achieving good glycaemic control requires compliant, well-educated patients. In October 2013, we introduced a revised and extended 'Newly Diagnosed Patient Education Programme' in which a total of 20 sessions are delivered by the multidisciplinary team.

Aim

To assess the effect of the new policy for newly diagnosed type 1 diabetics on their HbA1c in the first year.

Method

All type 1 diabetics diagnosed October 2013 to October 2014, who completed the new education programme were analysed and compared to a pre-intervention group diagnosed January to December 2010. Data obtained included HbA1c during the first year post diagnosis, patient demographics and psychosocial factors.

Results

patients (eight males, 16 females) were included in the study group compared to 17 (six males, 11 females) in the pre-intervention group. HbA1c at diagnosis was 11.4% for the study group compared to 10.2% in the pre-intervention group. Whilst at 6–8 weeks similar HbA1c levels were achieved (8.1% vs 8.0%), HbA1c at 12 months measured 8.1% vs 7.6%, but a similar percentage of patients in both groups achieved an Hba1c $<7.5\%$ (55% vs 53%).

Discussion

Psychosocial factors varied greatly between groups, with the study group having higher numbers of social risk factors (CAF 2 vs 0, split families 9 vs 3, domestic violence 3 vs 0, ongoing psychology support 8 vs 2, clinical depression 2 vs 0), impacting on diabetes management. It is encouraging that despite this, the percentage of patients achieving HbA1c levels $<7.5\%$ one year after diagnosis is similar between groups.

Conclusion

Current data highlights that the service is providing care to a socially challenging population and will need further consideration and tailoring. Long-term outcomes are awaited.

DOI: 10.1530/endoabs.39.EP42

EP43

The effects of CSII on glycaemic control, hypoglycaemia, DKA and BMI in paediatric T1D patients.

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Background

Current NICE guidance states that insulin pump therapy (CSII) can be considered in Type 1 diabetes (T1DM) patients who suffer disabling hypoglycaemia in an attempt to reach glycaemic control or whose HbA1C remains high (>69 mmol/l) despite careful management on multiple daily injections (MDI).

Aims

Our aims were to determine impact of CSII therapy on glycaemic control, BMI, incidence of severe hypoglycaemia and episodes of diabetic ketoacidosis (DKA).

Methods

Retrospective study on paediatric patients commenced on CSII between 2010 and 2014 at Nottingham Children's Hospital (NCH). Mean age at pump start, indications for therapy, duration of diabetes and HBA1c and BMI at baseline, 6 and 12 months post CSII, episodes of hypoglycaemia and DKA were collected.

Results

In total of 79 patients commenced pump therapy. 65 patients (35 male) were included with a mean age at diagnosis (5.9 ± 3.8), pump start (average 9.3 ± 3.5, range 1.8–15.6), duration of diabetes (3.4 ± 2.3, range 0.5–9.9) respectively. Indications for pump therapy included frequent hypoglycaemia (16), poor control on MDI (13) and not documented (22). There were no episodes of severe hypoglycaemia reported in the four years post pump therapy and the DKA hospitalisation rate was 4.6%.

Overall HbA1c improved at 6 months (62.95 ± 10.2 vs 58.95 ± 8.9, $P=0.02$) however this was not maintained at 12 months (61.51 ± 11.7, $P=0.45$). Subgroup analysis revealed that this improvement in HbA1c was only evident in the male population ($P=0.013$). Overall BMI did not differ at follow-up; similarly, subgroup analyses revealed male and female BMI did not differ from baseline.

Conclusion

In our cohort of patients ($n=65$) CSII therapy was only associated with short-term improvements in HbA1c of male patients. Further follow up is on going.

DOI: 10.1530/endoabs.39.EP43

EP44

Increased insulin requirement may contribute to higher BMI in children and young people with type 1 diabetes mellitus

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Background
Previous studies have reported that increased BMI and increase in insulin requirement are associated with more rapid disease progression following diagnosis in type 1 diabetes mellitus (T1DM). The recent UK National Paediatric Diabetes Audit (NPDA) 2013/14 reported that 37% of 0–11 year old children and 44% of 12 years and older children are currently overweight or obese.
Objective
Our objective was to evaluate factors associated with increased BMI SDS in CYP with T1DM following diagnosis.
Method
We examined the insulin requirement profiles defined by total daily insulin dose per kilogram body weight, BMI SDS, mean HbA1C over 12 months, age at diagnosis and pubertal status of 102 CYP with T1DM between April 2014 to March 2015 in a single paediatric centre.
Results
There were 59 males. 42 were on continuous subcutaneous insulin infusion (CSII), 56 were on multiple daily insulin regimen and four were on twice daily insulin regimen. Mean age at diagnosis was 7.79 years (range 0.16–16.91), mean BMI SDS was 0.89 (range -3.7 to $+3.32$), mean height SDS was 0.02 ± 2.97 and mean weight SDS was 0.73 ± 3.75. Mean diastolic blood pressure was 69 mm Hg (range 51–89), mean insulin requirement was 1.01 units/kg per day (range 0.38–2.43) and mean HbA1C was 8.0 (range 5.3–13.4). Out of 102 CYP, 24 were pre-pubertal, 28 were pubertal and 50 were post-pubertal. There was significant positive correlation between increased insulin requirement (units/kg per day) and HbA1c ($r=0.59$, $P<0.01$) and significant positive correlation between insulin requirement (units/kg per day) and BMI SDS ($r=0.23$, $P=0.02$). BMI SDS was not correlated with HbA1c. Multivariable linear regression analysis of factors affecting BMI SDS (age at diagnosis, HbA1c, gender, pubertal status and insulin in units/kg per day) showed that increased insulin requirement was a single independent factor affecting BMI SDS.
Conclusion
There is a significant relationship between increased total insulin requirement (units/kg per day) and increased BMI SDS in CYP with T1DM. Higher insulin requirement was also associated with poorer metabolic control following diagnosis

DOI: 10.1530/endoabs.39.EP44

EP45

Decorticate posturing in newly diagnosed case of diabetes ketoacidosis

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Diabetic ketoacidosis (DKA) is a common medical emergency in children. Altered consciousness in the form of mild disorientation or confusion can occur but frank coma is uncommon.[1] We present a case of a newly diagnosed Type 1 diabetes mellitus who presented in DKA and with glasgow coma scale (GCS) of seven. She developed decorticate posturing soon after she was commenced on resuscitation fluids.
Case
A previously well 15-year-old girl was rushed to hospital after she was found unconscious in toilet. She had diarrhoea and vomiting overnight following a take-away meal the previous day. On arrival her GCS was seven, blood glucose 25.4 mmol/l, ketones 5.4 and arterial gas showed a pH of <6.8, pCO2 1.5 kPa and incalculable base excess. Serum electrolytes results: sodium of 143 mmol/l, potassium 3.0 mmol/l, Chloride 120 mmol/l and bicarbonate 5 mmol/l.
She was commenced on fluid management as per BSPED DKA protocol but during administration of resuscitation fluids she developed decorticate posturing and GCS of four.
She was commenced on 3% hypertonic saline for suspected cerebral oedema. CT scan brain was reported as normal. She was ventilated and transferred to PICU. She made complete neurological recovery.
Discussion
Although DKA is a common paediatric emergency, the cause of the depressed conscious level is still under debate. Suggested causes include hyperosmolality, hyperglycemia, increased ketone production reduced glucose utilization and acidosis.[2]
In a study of a large number of episodes of DKA in children, it has been shown that conscious level is related to the degree of acidosis rather than to level of blood glucose or sodium or osmolality.[2]
Conclusion
Neurological deterioration in diabetes ketoacidosis could occur as a result of cerebral oedema. However, in our patient, we concluded that it was due to the severity of the metabolic acidosis.
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DOI: 10.1530/endoabs.39.EP45

EP46

Evaluation of a novel tool to adjust insulin boluses based on continuous glucose monitoring trend arrows and insulin sensitivity (trend arrow adjustment tool) in children and adolescents with type 1 diabetes using insulin pump therapy

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Background
Continuous glucose monitoring (CGM) measures interstitial glucose and display trends arrows, showing the direction and rate of change in glucose. Trend arrows allow the child/youth to take action to prevent hypo- and hyperglycaemia. Effective strategies for adjusting insulin boluses for trend arrows are lacking. The JDRF CGM Study Group recommended a 10/20% increase/decrease in the insulin dose. However this formula requires a mathematical calculation with each trend arrow, limiting the tool's uptake in paediatrics. We developed an alternative tool, based on the patient's insulin sensitivity factor.
Objective and hypothesis
To compare the effect of the trend arrow adjustment tool, the 10/20% adjustment and no adjustment for arrows; on postprandial glucose. To evaluate patient satisfaction and ease of use of both adjustment methods.
Method
A single blinded, counterbalance, treatment assignment crossover study of 20 subjects with type 1 diabetes. During a hospital assessment trend arrows were induced through exercise or oral carbohydrate. Subjects consumed a standardised meal with the insulin dose adjusted for trend arrows using the assigned method. Subjects used the assigned method during week 1, made no adjustment for arrows in week 2 and used the alternative method in week 3. CGM data was used to analyse postprandial glucose.
Results
Time with postprandial glucose in target range was equivalent with the trend arrow adjustment tool and the 10/20% adjustment. There was a trend towards more time in target range and less hypoglycaemia, with use of either tool compare to ignoring the arrows. Significantly more errors were made using the 10/20% method. Satisfaction and ease of use was greatest with trend arrow adjustment tool.
Conclusion
The trend arrow adjustment tool is a simple and well received method of adjusting insulin boluses for CGM trend arrows, which can be successfully used in the paediatric population.

DOI: 10.1530/endoabs.39.EP46

EP47

Characteristics of newly diagnosed children with type 1 diabetes – DKA vs Non- DKA presentation

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Background
Diabetic ketoacidosis (DKA) is a common presentation of newly diagnosed type 1 diabetes (T1DM) in children but increases the disease burden at diagnosis. In UK, average frequency of DKA presentation is reported as 25% with an international variation of 16 to 67%. Data on frequency variations within the UK is limited.

Aim
To compare the demographic and clinical characteristics of DKA vs non-DKA presentations in children <16 years at diagnosis of T1DM.
Methods
This was a retrospective audit of newly diagnosed children with T1DM over a 30 month period; (January 2013–June 2015), in a single paediatric diabetes unit.
Results
children presented with new onset T1DM. Median age was 8.0 years (range 2–16 years); 56% were females. 42% ($n=15$) presented in DKA (DKA+) and the rest with hyperglycaemia and +/− Ketosis (DKA−). Most DKA+ had either mild (40%) or moderate (33%) degree of DKA. There was no difference in the proportion of males (40%) or females (43%) presenting in DKA+ vs DKA−. Overall, 47% of children were diagnosed in a primary care setting, with no difference between the two groups. 19% had a family history of T1DM. Commonest symptoms were polydipsia (93%), polyuria (86%), and weight loss (66%) and were similar in both groups except abdominal pain which was more common in DKA+ group (33% vs 4.7%), ($P=0.059$). 100% of children of African ethnicity presented in DKA compared to33% of white British ethnicity, ($P=0.0261$). Mean length of stay was longer ($P=0.001$) in DKA+ (8.8 days; range 5–14) compared to DKA− (6.4 days; range 4–9). There was a trend for younger children to present in DKA with 66% of those aged 0–5 years presenting in DKA compared to 29 and 46% in 5–9 years and 10–16 years respectively (not statistically significant). There was no seasonal difference.
Conclusions
Rate of DKA at presentation of T1DM in our patients was higher than that reported in the literature. More patients were diagnosed in hospital than in primary care, highlighting the need to increase awareness amongst public and primary care health professionals to aid early diagnosis and reduce the burden of DKA. Particular attention in this regard should be paid to younger children and those from ethnic minorities.

DOI: 10.1530/endoabs.39.EP47

EP48

Use of U200 insulin degludec (Tresiba) and metformin in an adolescent with Type-1 diabetes-mellitus

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Background
Insulin dose requirements are higher during puberty and in overweight/obese individuals with type 1 diabetes mellitus (T1DM) due to insulin resistance. Through meta-analysis metformin has been shown to be beneficial as adjunctive therapy in T1DM adults independent of BMI. The large volumes of insulin required to administer higher insulin doses in insulin-resistant individuals have adverse effects on insulin absorption. Insulin degludec (Tresiba) U200 preparation allows lesser volume administration for the same dose. We describe a 16-year-old girl with T1DM whose basal insulin requirement decreased markedly when switching to insulin degludec (Tresiba) U200 with the addition of metformin.
Case
The patient was diagnosed with T1DM at the age of 5 years. GAD and islet cell antibodies were positive. HbA1c at diagnosis was 89 mmol/mol. Initial management was with multiple daily insulin (MDI) injections. At age 9 years she switched to continuous subcutaneous insulin infusion (CSII). At age 15 years she chose to change back to MDI due to recurrent skin abscess formation. The patient increased her basal insulin detemir (Levemir) doses from 0.6 U/Kg per day up to 1.9 U/kg per day over 8 months following the switch. During this period HbA1c increased slightly from 58 to 64 mmol/mol and BMI increased from 23.4 to 24.8 kg/m^2. There were no episodes of ketoacidosis. She was trialed on insulin degludec (Tresiba) U200 at 30% reduced dose (1.3 U/kg per day) with addition of modified release metformin. Over the first 4 weeks following switch, due to recurrent hypoglycaemia, her basal insulin requirement reduced further to 0.7 U/kg per day (60% reduction in basal insulin dose).
Conclusions
Insulin degludec U200 preparation can be useful in T1DM patients requiring high basal insulin doses. Metformin is a useful adjuvant therapy in post pubertal T1DM patients with insulin resistance. Close monitoring is required over first weeks of therapy with insulin degludec (Tresiba) and metformin.

DOI: 10.1530/endoabs.39.EP48

EP49

HbA1c: is it a reliable measure of glycaemic control in all patients with type 1 diabetes mellitus?

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Introduction
HbA1c levels are used as objective long-term measure of glycaemic control in patients with type 1 diabetes mellitus (T1DM). Regular HbA1c measurement helps us to formulate the management and education to the patients and carers. But, in rare cases, it might not prove reliable, as in our case report.
Case report
A 4 years old girl with known T1DM and autoimmune hyperthyroidism, had mitral valve repair for mitral valve regurgitation. She was admitted with hyperglycaemia and ketosis 5 months following cardiac surgery when she was noted to be jaundiced. Subsequent investigations revealed DAT negative micro angiopathic haemolytic anaemia with elevated reticulocytes (301×10^9/l), bilirubin (61 umol/l), LDH (1713 IU/l), normal hemoglobin electrophoresis, G6PD screen, negative CMV/EBV/Parvovirus PCR and absent thrombus on echocardiogram. She was noted to have lower HbA1c against the persistent hyperglycaemia on her glucometer. Hence, serum fructosamine level was requested which was reported high, in sync with the blood glucose levels. She is now being monitored in the diabetes clinic with fructosamine level along with HbA1c to assess the trend of her blood glucose level and table shows the serial HbA1c levels and Fructosamine levels.

Hb (g/l)	HbA1c (mmol/mol)	Fructosamine (micromol/l)	Mean blood glucose (mmol/l) for 2 weeks	Corrected HbA1c mmol/mol
59	37 (5.6%)	380	12.5	65 (8.1%)
94	35 (5.3%)	307	9.5	51 (6.8%)
86	40 (5.8%)	370	10.3	63 (7.9%)

Discussion
Fructosamine levels indicate the blood glucose control over the past 2–3 weeks. HbA1c and fructosamine are highly correlated with following formula. HbA1c = 0.017× fructosamine level (μmol/l) + 1.61. HbA1c measurement is not a reliable marker of glycaemic control in diabetics with condition associated with shortened red blood cell life span. Haemolytic anaemia should be considered if there is discrepancy between HbA1c levels and blood glucose levels and Fructosamine can be used a marker of glycaemia.

DOI: 10.1530/endoabs.39.EP49

EP50

Monitoring HbA1C in patients on continuous subcutaneous insulin infusion for the treatment of type 1 diabetes

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Abstract
Continuous subcutaneous insulin infusion (insulin pump therapy) is recommended as a treatment option for patients with type 1 diabetes where multiple-dose insulin therapy has failed. These patients are looked after by a specialist multi-disciplinary team and those receiving this treatment should have the commitment and competence to use the pump effectively.
We carried out a retrospective study on 33 paediatric type 1 diabetic patients on insulin pump therapy by comparing their HbA1C levels before and after starting the therapy. We also compared the change in HbA1C levels in males vs females and in different age groups.
Our patient group had an almost equal gender distribution. The age at diagnosis was <5 years of age in the majority (52%). The majority of patients were greater than 14 years when insulin pump therapy was initiated (43%).
We found an improvement of HbA1C of greater than 0.5% in 49% of our patient group. However in 42% there was no improvement.
We also noticed a greater improvement in boys and in those older than 14 years. We concluded that older children have a better outcome due to better understanding and ability to use the pumps effectively.

In the group of patients that did not show any improvement, we speculate a multifactorial cause including poor compliance, poor dietary control and likely lack of understanding. Through our multidisciplinary team we will focus on this group of patients on re-education of their management.

DOI: 10.1530/endoabs.39.EP50

EP51

High ferritin and glucose metabolism in diabetes – a case report.

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Iron is a transition metal that acts as an oxidant. There is evidence that systemic iron overload could contribute to abnormal glucose metabolism. Further research has showed that iron overload can result in an increased in type 2 diabetes irrespective of the cause of gene involved. Although the exact mechanism of iron-induced diabetes is uncertain, it is likely mediated by these three mechanisms: i) insulin deficiency, ii) insulin resistance, and iii) hepatic dysfunction.

Insulin stimulates cellular iron uptake through increased transferrin receptor externalisation. Thus, insulin and iron can mutually potentiate their effects, leading, after a vicious cycle, to insulin resistance and diabetes. Furthermore, a decrease in insulin resistance has been documented after iron depletion in type 2 diabetic patients. Majority of the current literature discusses the relation between high ferritin and type 2 diabetes but few describe the relation between elevated ferritin levels and type 1 diabetes.

In this novel case study, we question the significance of high ferritin levels and type 1 diabetes in an 11-year-old boy whose first presentation was with pain in his hands which worsen in hot weather and exercise. His high ferritin levels (300–630 μg/l) persisted and he presented again 7 months later with testicular pain and poor urinary stream and was reviewed by the Urologist. Four years later he presented with type 1 diabetes. To date he has displayed poor diabetic control and high ferritin.

In the UK, there is has been an increasing prevalence of type 2 Diabetes in children. We propose to monitor ferritin levels in this cohort of children as part of their annual review investigations.

DOI: 10.1530/endoabs.39.EP51

EP52

Multi factorial challenges in managing a patient with neonatal diabetes

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Neonatal diabetes mellitus (NDM) is a rare form of monogenic diabetes affecting 1 in 100 000 to 500 000 live births.

We report the case of a term baby born to a diet controlled gestational diabetic mother with a birth weight of 2.8 kg. Baby was persistently hyperglycaemic from day 1 of life, leading to a diagnosis of neonatal diabetes being considered. She was breast-fed on demand and although insulin pump therapy was discussed, it was felt not to be suitable, as language barriers would have meant that parents would have had difficulty recognising pump failure/alarms. Twice daily subcutaneous injections of Isophane Insulin (Insulatard) were commenced although there have been no studies on efficacy of Insulatard in neonates. The small doses of insulin required were administered by diluting the insulin with a suitable diluting medium. Providing training for the family on self-management called for significant input from the diabetes specialist nurses. Telephone follow up was challenging due to language barriers, resulting in the need for frequent home visits and hospital appointments for close monitoring. At 8 months of age our patient is thriving and developing well with no hospital admissions. She is on 0.2 units/kg per day of insulin with most recent glycated haemoglobin (HbA1C) being 48 mmol/mol. No known genetic mutation has been identified.

The management of neonatal diabetes is challenging for many reasons. Blood glucose monitoring can be technically demanding for carers and traumatic for infants. Insulin requirements and insulin sensitivity can be very variable. The small volumes of insulin required cannot be delivered using standard insulin formulations and these do not provide insulin delivery profiles that complement the feeding patterns and glycaemic excursions of newborns. Conventional insulin delivery devices are also often not useful. Our case highlights that physiological and pharmocological factors as well family and social factors that influence treatment planning.

DOI: 10.1530/endoabs.39.EP52

EP53

Too sweet for too long?

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Background

Cystic fibrosis related diabetes (CFRD) is associated with deterioration in clinical status. Lung function and nutritional status deteriorate up to 2–4 years before a diagnosis of CFRD based on the oral glucose tolerance test (OGTT). Timely detection and treatment is crucial.

Aims

To evaluate: i) adherence to CFRD screening guidelines and ii) whether identifying stages of progressive cystic fibrosis insulin deficiency (CFID) using the extended OGTT altered management. iii) trends in weight, BMI and FEV1 in CFRD as compared to CF controls.

Methods

Retrospective analysis using patients' records. Seven patients with CFRD were compared to matched CF controls using mean *z*-scores for weight, BMI and FEV1.

Results

Records of 59 children were analysed.

Screening:

Modality	Age (years)	*n*	% adherence to guidelines
HbA1c and random glucose	5–10	21	17 (80%)
OGTT	≥ 10	38	30 (70%)

Outcomes:

		Glucose (mmol/l)	
n (%)	**Result**	Peak	**2 h**
6 (20)	Normal		
11 (36)	CFID1	≥8.2	<11.1
6 (20)	CFID2	≥11.1	<11.1
7 (23)	CFID3	<7	≥11.1
0 (0)	CFID4	≥7 with fasting hyperglycaemia	

The mean weight and BMI *z*-scores for those with CFRD compared to controls were −0.64 vs −0.02 ($P=0.005$) and −1.26 vs −0.03 ($P=0.0001$). Mean FEV1 was lower in CFRD 1.87l (73.06%) compared to controls 2.35l (89.03%). Three patients with CFID3 and one with CFID1 later commenced insulin based on clinical grounds.

Conclusions

Adherence to screening guidelines needs to be improved. Patients with CFRD have a significant declining trend in weight, BMI and FEV1 compared to controls. Some patients with CFID were commenced insulin on clinical grounds rather than results of extended OGTT. Whether treatment at earlier stages of CFID will slow down the rate of decline needs to be explored, but we have reverted back to the standard OGTT for the present.

DOI: 10.1530/endoabs.39.EP53

EP54

A case of a retained needle from insulin pump therapy

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Background

Continuous subcutaneous insulin infusion (CSII) therapy is increasingly used for managing children with type 1 diabetes mellitus. Devices vary in design by

manufacturer; however in general terms insulin is administered from the pump via a subcutaneous plastic catheter or needle. If the pump or the circuit malfunction and interrupt the insulin infusion, it can put the patient at risk of hyperglycaemia.
Case
A 5-year-old boy with type 1 diabetes, well controlled with CSII (Roche Insight pump) presented with worsening hyperglycaemia. His father attempted to change the pump infusion circuit and noticed, on withdrawing the Rapid D cannula that the needle had detached and remained within the child's buttock. On review by the paediatric team the boy complained of mild discomfort in the area, and on examination he had localised erythema but the needle could not be palpated. A lateral X ray of his buttock revealed the needle within the subcutaneous tissue. This was removed surgically under general anaesthetic the following day. The child presented in an almost identical fashion 2 weeks later, with hyperglycaemia and no needle seen on withdrawal of the cannula. Again the needle could not be palpated, though was clearly seen on X ray, and required surgical removal. The incident and batch had been reported to the company after the first episode, but the father had accidently continued to use what was thought to be a faulty batch.
Discussion
We present a case where, on two separate occasions, the needle became detached from the infusion device and remained in the child's subcutaneous tissue. A recent case report documented two similar cases (Plager *et al*., 2015) though there are no other reported cases in the medical literature. This is a rare complication of pump therapy but importantly highlights the risk of foreign body from the infusion system especially as devices increasingly use finer infusion set needles.

DOI: 10.1530/endoabs.39.EP54

EP55

Acute kidney injury as a severe complication of diabetic ketoacidosis

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Background
Diabetic ketoacidosis (DKA) in children and young adults carries significant morbidity and mortality relating to complications such as cerebral oedema. Acute kidney injury (AKI) is a rare but potentially fatal complication of DKA. We present three cases of DKA complicated by AKI.
Case 1
A 9-year-old girl presented with severe DKA at diagnosis. She was treated with intravenous fluids and insulin as per protocol. She had oliguria and haematuria 36 h after admission. She was hypertensive with evidence of enlarged kidneys on ultrasound (USS). She was transferred to the renal unit where she needed two cycles of hemodialysis before making full recovery.
Case 2
A 14-year-old girl presented with severe DKA and altered consciousness at diagnosis. She developed oliguria 24 h after starting treatment for DKA. USS of abdomen showed enlarged kidneys. Her renal function improved with haemofiltration and recovered fully by 1 week.
Case 3
17-year-old girl with poorly controlled type 1 diabetes presented with severe DKA. She showed evidence of AKI with very high plasma creatinine, oliguria and low plasma phosphate. She was managed conservatively with individualised fluid plan and phosphate supplementation with recovery in 7 days.
Conclusion
Patients with severe DKA can develop AKI due to a number of possible causes, hypovolaemia being the most likely primary cause. Appropriate management of hypovolemia and electrolyte disturbance in these patients can be very challenging. These cases highlight the importance of early recognition of AKI (rising plasma creatinine, oliguria, haematuria) and discussion with paediatric nephrologist to formulate individualised fluid therapy in order to prevent deterioration in renal function. It is uncertain if recent modification in fluid management of DKA has led to a change in the incidence of AKI.

DOI: 10.1530/endoabs.39.EP55

EP56

Delayed referral of children with new onset type 1 diabetes

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Background
Type 1 diabetes (T1D) is characterised by autoimmune destruction of pancreatic beta cells leading to insulin deficiency. Prompt referral and treatment is important to prevent diabetic ketoacidosis (DKA) which remains the commonest cause of death in this condition. NICE guidance 2004, advises same day referral to specialist paediatric Diabetes team when childhood diabetes is suspected.
Aim
The aim was to audit the timeliness of referrals of children with suspected T1D to paediatric diabetes team, as well as reasons for any delay.
Method
This was retrospective case notes review of children diagnosed with diabetes mellitus (DM) between 1 January 2005 and 31 December 2014 and managed by Sandwell Paediatric Diabetes service. We reviewed demographic data, information on source of referral, date of initial presentation to a health care professional, date of insulin initiation, cause of delayed presentation (where applicable), date of initial diagnostic blood tests and mode of presentation.
Statistical analysis was carried out using Minitab 17.
Results
A total of 117 children were diagnosed with diabetes in the study period. 21 were excluded as 9 (7.7%) had T2DM, 1 (0.85%) had glucokinase deficiency and 11 (9.4%) children were diagnosed elsewhere and transferred later to our service.
96 children with T1D were included in the study. Mean age at presentation was 8.6 years (s.d. $\pm$3.8 years), 49 (51.04%) were males and 68 (70.83%) were White British. Main sources of referral were General Practitioners in 55 (59.14%) and emergency department in 24 (25.81%). 33 (34.37%) children presented in DKA. In a regression analysis, presentation in DKA was significantly associated with younger age at presentation ($P=0.033$) and delay in referral ($P=0.01$). There was no significant association between DKA at presentation and sex, ethnicity, family history of DM or source of referral.
There was a delay in referral in 35 (36.54%) children. 19 (79.17%) of these children presented in DKA. Mean duration of delay in presentation was 2.96 days (s.d. $\pm$3.183 days). The commonest reason for delayed presentation was delayed referral due to GP requesting fasting blood glucose in 71.4% (25/35)
Conclusion
In children suspected of having DM, requesting fasting blood glucose to confirm the diagnosis leads to delayed referral to Paediatric diabetes team putting the child at risk of developing DKA.

DOI: 10.1530/endoabs.39.EP56

EP57

Impact of best practice tariff (BPT) for accessing psychological service by diabetic children and young people

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Introduction
25 314 children and young people $<$18 years with diabetes in England and Wales have been looked after in 178 paediatric diabetic units (PDUs) across the country. In 2012–2013, BPT has been introduced with 13 mandatory requested criteria, one of them is; each patient should have an annual assessment as to whether input to their care by a clinical psychology input is needed, and access to psychological support as appropriate. Therefore we aimed to study the impact of this criterion on PDUs.
Methodology
Online survey was cascaded to diabetic lead consultants via diabetic network managers. Data collected in Spring 2014 and analysed in Summer 2014.
Results
Fifty eight units responded across England. They serve 9817 diabetic children. 51 were district hospitals (88%) and seven tertiary centres (12%). Ratio of a psychologist to diabetic children ranged from 0 to 1:350. Median ratio of psychologist to diabetic children was 1:130 in district hospitals and 1:100 in tertiary centres. 14 PDUs (13 district hospitals) have not had psychological assessment for all their diabetic children. Other 40 PDUs have been referring to psychological services; majority (54%) were referring more than 2 years ago, 34% between 1 and 2 years ago and 11% started referring just over last year. Most of units (67%) were referring to Children and Adolescents Mental Health Services mainly when problems arise. Since introduction of BPT, 91% of PDUs have made some change to their provided service, either by recruiting new psychologists to their teams (48%) or increasing the sessions of psychologists (43%). Psychological assessment at time of diagnosis has raised from 18.9 to 58% before and after BPT respectively, so the routine/annual assessment from 10.3 to 55.1%.
Conclusion
Majority of units either recruited new psychologists or increased sessions following BPT. More impact on district hospitals compared to tertiary centres. The psychological support is going to be provided more at diagnosis and annually.

DOI: 10.1530/endoabs.39.EP57

EP58

Acute hyperglycaemia in cystic fibrosis related diabetes: the role of insulin pumps

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Cystic fibrosis related diabetes (CFRD) is the commonest co-morbidity in CF leading to increased mortality rates. The pathophysiology includes pancreatic fibrosis, reduction in α and ß-cell mass, delayed insulin secretion and variable insulin insensitivity. Insulin production can fluctuate with progression over time to an insulinopenic state. We report two cases of young people with CFRD with high insulin requirements, poor glycaemic control and improvement with the introduction of insulin pump therapy.

Cases

Two 15-year-old females were diagnosed with CFRD following positive OGTT and elevated HbA1c (7.1 and 6.5% respectively). They were started on insulin (0.13 units/kg per day and 0.03 units/kg per day). Each subsequently presented on a weekend to their local A&E unwell with blood glucose >20 mmol/l, polyuria, polydipsia and negative ketones. They were advised that CFRD did not need acute treatment and discharged. On admission to their tertiary centre they required >2 units/kg per day of IV insulin sliding scale, suggesting probable hepatic insulin insensitivity and acute decompensation at a time of illness.

Case 1 opted for insulin pump therapy and case 2 opted for Multiple Daily Injections. Case 2, after initial improvement found adherence to be an issue, particularly given her eating patterns and multiple injection requirement. A decision was taken to support her request to start insulin pump therapy.

Improvement in HbA1c from pump start to 6 months was 8.0 to 7.7% (Case1) and 14.0–8.6% (Case 2). Δ BMI SDS 0.28–0.11 (Case1) and -2.44 to -0.93 (Case 2). Insulin requirements on the pump at 6 months were 0.5 units/kg per day (Case1) and 0.6 units/kg per day (Case 2). This was a 75% reduction in insulin requirements from acute presentation.

Each reported a subjective improved quality of life and reduced burden of diabetes with respect to CF care compared to injection therapy.

Discussion

Acute, symptomatic hyperglycaemia in CFRD should be acted on promptly. Hepatic insulin insensitivity in illness can lead to high insulin requirements which reduce with treatment. An insulin pump is a valuable tool in CFRD.

DOI: 10.1530/endoabs.39.EP58

EP59

Clinical examination of lipohypertrophy: best practice recommendations

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Forum for injection technique (FIT) recommendations for lipohypertrophy (LH) detection influenced clinical examination technique with the aim of improving practice and health outcomes for children and young people (CYP). Interactive LH workshops were developed to influence a change in care provision and facilitate swift integration into clinical practice.

The event was delivered to MDT representatives from the CYP diabetes network. A structured clinical examination was role modelled facilitated by four young male volunteers with diabetes. Two YP managed their diabetes on multiple daily injections (MDI) regime and two were on continuous subcutaneous insulin infusions (CSII). Opportunity to visualise and palpate sites for LH outwith the pressured clinic environment was universally appreciated by all attendee's. The use of head torches, safe skin marker pens, and application of ultrasound gel in liberal amounts was widely agreed to enhance detection. Attendee's were encouraged to examine with two fingers at a 30° angle and firm pressure which also facilitated identification. Most were able to distinguish between softer smoother areas and a transition to harder more rubbery skin. Both medical and nursing colleagues reported increased expectation to find LH as well as confidence using an agreed method base don best practice. Although the number of volunteers was small a difference in the shape formation of LH in patients on CSII (more diffuse and uneven) compared to those on MDI (more localised and discreet) was also observed and may have implications for practice. In conclusion health care professionals reflection on practice and agreement of tangible changes in detection of LH has the potential to reduce glycaemic variation ad hypoglycaemia.

DOI: 10.1530/endoabs.39.EP59

EP60

To pump or not to pump; paediatric insulin pump efficacy

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Background

Insulin pumps are used in the management of type 1 diabetes in children at Macclesfield District General Hospital (MDGH). There has been no study previously conducted at MDGH to check the efficacy of the insulin pumps against non-pump methods such as multiple daily injections.

Methods

Review on the number of admissions, type of admissions and insulin administration method were collected from the years 2012–2015. The types of admissions were grouped into preventable and non-preventable. Non-insulin pump methods were grouped as non-pump. Average HbA1C levels were collected using Accucheck. 85 patients between ages of 4 and 18 were identified, 50 of which were on a pump. The number of preventable admissions and average HbA1c levels of the pump group were then compared to the results of the non-pump group.

Results

Three patients were excluded when comparing HbA1c levels as no data on HbA1c could be found in the notes. The pump group had lower HbA1c levels, 82.01 ± 5.609 mmol/mol, compared to non-pump, 99.70 ± 11.299 mmol/mol. *P* value for average HbA1C was <0.167. Total preventable admissions were on average lower in the pump group than non-pump group, 36 and 51% respectively. *P* value for total *P* admissions was <0.463.

Conclusion

No significant difference in average HbA1c levels or total *P* admissions when comparing pump to non-pump was found. To reduce admissions and improve glycaemic control, comprehensive education, with the help of a multidisciplinary team is needed. Prospective studies testing insulin pump efficacy are warranted.

DOI: 10.1530/endoabs.39.EP60

EP61

CYPWMDN diabetes awareness education for schools – regional study day

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With the increase in incidence of type 1 diabetes in children and young people (CYP) and the use of intensive insulin therapies, paediatric diabetes teams are under increasing pressure to support school staff with the day to day management of their pupils with diabetes. The CYPWMDN have developed a study day to provide basic diabetes awareness education to all school staff in the West Midlands (WM) region. This work also meets the training and support responsibilities of diabetes teams in line with the statutory guidance for schools governing bodies, 'Supporting Pupils at School with Medical Conditions', (DfE, 2014).

The aims of this project have been to provide school staff with an awareness of:

i) All stakeholders responsibilities of managing a CYP with diabetes in school.
ii) The difference between Types 1 and 2 diabetes.
iii) Causes, signs and symptoms of diabetes.
iv) Treatment options.
vi) How to manage acute complications – hypo and hyperglycaemia.
vii) Dietary requirements – carbohydrate counting.
viii) Insulin pump therapy.
ix) Have a basic understanding of the practicalities of insulin administration and blood glucose/ketone monitoring.

To date we have run events, attended by over 136 school staff delegates and attended by over 82 schools in the WM Region. The group believe that this programme can be delivered by any team nationally with minimal need for training and/or explanation in to its use thus minimising development, planning provision and evaluation time.

Raising staff awareness of diabetes with school staff, improving their knowledge and confidence around diabetes can only enhance the experience of families with CYP with diabetes when they are dealing with the anxieties of a new diagnosis or a start/change in school/teacher. Parental confidence in the schools capabilities to care for their child throughout the school day is fundamental in both the emotional wellbeing and physical health of the child and parent.

DOI: 10.1530/endoabs.39.EP61

EP62

Frequency of Hypoglycaemia in Children and Young People's Diabetes Clinic

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Background
Hypoglycaemia is a common complication of diabetes which causes great anxiety in patients and their families. Asymptomatic hypoglycaemia can be debilitating, especially in young children. All patients who attend Children and Young People (CYP) Diabetes Clinic have their blood glucose tested. If hypoglycaemia is identified (Blood Glucose less than 4 mmol/l), the local hypoglycaemia hospital policy should be followed by staff to provide safe and effective treatment.
Aims
i) To record the number of children and young people in Diabetes Clinic who presented with hypoglycaemia over a six month period.
ii) To identify if the children and young people presenting with hypoglycaemia were symptomatic or asymptomatic.
iii) To ascertain if the local hospital hypoglycaemia policy was followed.
Methods
Retrospective analysis of patient attending the CYP Diabetes clinic records over 6 months period.
Results
During the six month period a total of 272 CYP attended Diabetes clinic. Of these 57 presented with hypoglycaemia (21%).
Majority of patients were on MDI (multiple daily injections) regime. There was no significant difference between the type of insulin regimen used and mean HbA1c, although those on BD (twice daily insulin regimen) have the highest mean HbA1c at 9.17%.
38% of CYP presenting with hypoglycaemia reported a complete lack of symptoms.
50% of CYP with measured severe hypoglycaemia and reported preserved hypoawareness, reported no symptoms in clinic. This suggests that modified hypoawareness can often go undetected by children and their responsible adults.
The local hospital hypoglycaemia protocol was rarely followed due to different reasons and requires revision to improve usefulness and suitability to meet both the clinical needs for appropriate hypoglycaemic treatment and acceptability for diabetes patients.

DOI: 10.1530/endoabs.39.EP62

EP63

Paediatric type 1 diabetes mellitus in The Gambia, West Africa – presentation and outcome

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In 2010 non-communicable diseases were shown to be the most important cause of mortality worldwide on the WHO global status report, with diabetes the 4th most common disease causing death. Type 1 diabetes Mellitus (T1DM) is the most common form of diabetes in children and young people. There is a paucity of data regarding T1DM in children in West Africa, in particular in The Gambia.
Aim
To explore the clinical presentation and outcome of children with T1DM admitted to The Edward Francis Small Teaching Hospital (EFSTH) in The Gambia, West Africa.
Method
Retrospective case note review of patients admitted to EFSTH over a 4-year period from January 2009 to December 2012.
Results
Nineteen children were admitted with a diagnosis of T1DM with or without diabetic ketoacidosis (DKA) within the time period, 15 of which were first presentations. 12 patients were documented to be in DKA on presentation, 9 that were new diagnoses of T1DM. 2 of the newly diagnosed patients, found to be in DKA were also found to have severe malaria. The most common presenting symptoms were abdominal pain, polyuria or fever, with only two patients reporting the typical clinical triad of polyuria, polydipsia and weight loss. Blood glucose measurement was performed in all patients but urinalysis only in 11 of the 19 identified. There was one mortality in the cohort of patients, the remaining 18 survived to discharge.
Although the incidence of T1DM in developing countries is known to be increasing the numbers in this study are small. This gives a glimpse into how varied and vague the presentation of T1DM is in The Gambia and how minimal the clinical resources are. Further study is needed on a wider scale to assess the true incidence and prevalence of the disease.

DOI: 10.1530/endoabs.39.EP63

EP64

Audit of DKA admission rates in children and young adults 2010–2015

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Introduction
The National Paediatric Diabetes Audit (NPDA) in 2012 reported a twofold increase in the incidence of diabetes ketoacidosis (DKA) admissions from 2005/6 to 2010/11 in children and young people with type 1 diabetes mellitus (T1DM). The paediatric diabetes best practice tariff (BPT) was introduced in 2012 to incentivise provision of high quality care to those under the age of 19.
Aims
We examined DKA admission rates in children and young adults in relation to the impact of the introduction of BPT.
Methods
A retrospective audit was performed on children and young adults aged up to 25 admitted with DKA from January 2010 to April 2015.
Results
There were 359 DKA admissions in children and young adults, 165 were new diagnoses (151 < 19, 14 19–25 year olds). 194 admissions were in known diabetics. The number of admissions for those in transition/young adult care was four times that in paediatrics. This was mostly due to a much higher repeated admission rate, up to a maximum of 26 times. There was no difference in DKA rates pre and post BPT introduction. Mean HbA1c on admission was 98 mmol/mol for all groups. All were seen within 8 weeks of admission in paediatrics; only 25% were seen within 6 months in young adult clinic due to non-attendance.
Discussion and Conclusions
DKA readmissions were much lower in paediatric vs transitional/adult care. There was no significant difference pre and post introduction of BPT for paediatrics, however, numbers were small. Also, pre BPT, paediatric care had focused resources on those with poor control, with frequent contact, admission for stabilisation and involvement of social care/CAMHS, where needed. A systemic family therapist has been a member of the diabetes team from 2009. This audit has highlighted deficiencies in transition and young adult care and calls for the extension of BPT to age 25, in order to focus provision of resources at this vulnerable time.

DOI: 10.1530/endoabs.39.EP64

EP65

CASE REPORT-chromosome 9p trisomy with insulin dependent diabetes

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Introduction
Chromosome 9p trisomy is a rare chromosomal syndrome in which a portion of the 9th chromosome appears three times rather than twice in cells of the body. Most often these children present with developmental delay, craniofacial malformation and growth deficiency. We present a case of insulin dependent diabetes in a 5-year-old boy known to have a diagnosis of Chromosome 9p trisomy.
Case
Born at 38 + 3, by normal vaginal delivery with birth weight of 2980 g (25th cent.), birth head circumference 33 cm (25th cent.). Mum – G2Po, TIOP 9/40 for

personal reasons, age 29 yrs; well during pregnancy. He is the first born of non-consanguineous parents.
Noted to have soft dysmorphic features at birth- left correctable talipes calcaneovalgus, apparent short penis, small cup like ears, marked tongue tie, no cleft palate, hypoplastic toe nails, widely placed nipples. Rest of the physical exam was normal.
Chromosomal analysis
Unbalanced male karyotype with two additional abnormal chromosomes. The larger of the additional chromosome appears to comprise of short arm and proximal long arm of chromosome 9- therefore trisomic for this region. No evidence of mosaicism. Parental studies showed that the abnormal chromosomes detected, is of de novo occurrence.
He was delayed in his motor, speech and language development. His cardiac ECHO was normal.
At 4 yrs age, he presented with h/o polyuria, polydipsia and weight loss in Diabetic Keto acidosis. He was commenced on CSII once his acidosis improved. He continues to remain on CSII with insulin requirement of around 0.5 U/kd per day.
Conclusion
There have been no reported cases of insulin dependent diabetes in this rare syndrome. Early management with CSII should be considered based on age and underlying degree of developmental impairment.

DOI: 10.1530/endoabs.39.EP65

EP66

Just a little prick; the effect blood glucose monitoring on diabetic control

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Brief overview
The control of diabetes is a somewhat constant chase, with optimal control being the goal. Indeed, there are many methods marketed claiming to improve control. This is with neglect to the most basic of techniques, blood glucose monitoring. This is highly dependent on individual and parent motivation levels.
Objective
The objective of this study is to answer the question, 'Does the frequency of blood glucose monitoring affect the control of T1DM in the Paediatric patients of Macclesfield DGH?'
Methods
Retrospective data for age, HbA1c levels, tests/day and preventable admissions was collected and analysed. The main independent variable was based on number of tests using the BA device per day (tests/day). The minimum recommendation for this is four tests/day, and as such patients will be separated by this value. Data were also separated based on groups of patients within NICEs target HbA1c levels of <58 mmol/mol.
Results
17/82 (21%) patients were performing the recommended minimum of four tests/day. The mean HbA1c for the ≥ 4 and <4 tests/day groups were 63.94 and 93.90 mmol/mol respectively. This was statistically significant ($P \leq 0.05$). 17/82 (21%) patients were below the target set by NICE. Mean number of admissions per patient were 0.12 and 0.51 for HbA1c values of <58 mmol/mol and ≥ 58 mmol/mol respectively. This was statistically significant ($P \leq 0.05$).
Conclusion
Regular blood glucose monitoring reduces HbA1c values and therefore preventable admissions when used correctly. Parent and patient education is a key part of inspiring motivation, potentiating lower HbA1c levels and therefore preventable admissions. Novel methods of control are needed to help overcome social barriers to optimal control.

DOI: 10.1530/endoabs.39.EP66

EP67

Severity of presentation with diabetic ketoacidosis at diagnosis of diabetes; India versus the UK

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Background
Diabetic ketoacidosis (DKA) is associated with significant morbidity and mortality. Comparison of healthcare systems often helps highlight areas of concern.
Design
In a short survey, we evaluated severity of DKA at presentation with diabetes by comparing clinical and biochemical data from clinic cohorts from paediatric diabetes units in Delhi, India and Manchester, UK.
Results
In the Delhi vs UK groups; there were no significant differences in pH (7.2 (S.D. 0.2) vs 7.2 (0.1)), blood glucose concentrations (28.8 (5.9) vs 26.7 (9.8) mmol/l) or HbA1c levels (10.4 (2.2) vs 10.4 (1.7)%) at diagnosis of DKA. However rate of readmission with DKA was greater (60.0 versus 10.7%).
Conclusions
Our data suggest a similar length of prodrome prior to first presentation with DKA between India and the UK and further highlights the need for DKA specific awareness campaigns in both countries.

DOI: 10.1530/endoabs.39.EP67

EP68

Non-adherence to treatment in teenagers with diabetes: how can we help?

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Introduction
Non-adherence to treatment is common in teenagers with type 1 diabetes (DM1). We aim to report on our experience, in a University teaching hospital, on factors leading to non-adherence, and describe strategies which improve compliance.
Discussion
There are numerous factors which account for why teenagers fail to adhere to treatment.
i) Lack of knowledge about the condition.
ii) Teenagers may not understand the importance of treatment. They view insulin administration as a burden as they do not perceive any immediate benefits.
iii) Affect and eating disorders
Exogenous insulin administration can lead to weight gain. Teenagers may choose to miss out their required insulin injections to fit into society's definition of 'healthy'.
i) Peer relationships and acceptance.
ii) Teenagers with DM1 feel that their life lacks spontaneity. Feelings of isolation and stigma can make them adopt avoidant behaviour.
iii) Family support and social situation.
Rebellion against parental control contributes to non-compliance.
There are strategies which can be employed to improve adherence. These are as follows:
i) More frequent follow-up for high risk groups.
NICE guidelines advise weekly contact with patients having HbA1c levels $>9.5\%$. Phone calls and home visits by diabetes nurses decrease acute admissions to hospital with diabetic ketoacidosis and hypoglycaemic episodes.
i) Family involvement.
The clinical psychologist aims to understand the difficulties of the teenager, and of their relatives. Interviewing them separately helps to recognise differences in their mindsets. Behavioural family systems therapy enhances family interactions and problem-solving skills.
ii) Motivational interviewing.
Motivational interviewing helps clinicians understand the inconsistencies in goal versus action in teenagers, with the aim of reiterating the importance of treatment. It has been shown to achieve better HbA1c levels.
Conclusion
Establishing treatment for teenagers with DM1 is challenging. It is essential for health professionals to understand the complex reasons behind non-adherence to successfully manage diabetes in teenagers.

DOI: 10.1530/endoabs.39.EP68

Gonadal, DSD and Reproduction

EP69

Changes in body composition during late puberty. The effect of sudden sex hormone withdrawal

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Aim
The sex hormones initiate profound physical and physiological changes during early puberty, but to what extent are they responsible for continuing the body composition changes of late adolescence? We aimed to examine the effect on body composition of sudden sex hormone withdrawal to gain insight into their action.
Patients and Methods
Thirty six healthy phenotypically and chromosomally normal postpubertal individuals aged 15–17 years with gender dysphoria (M = 11; F = 16) underwent Tanita body composition analysis at 0, 6 and 12 months during reproductive hormone suppression with triptorelin (Gonapeptyl Depot 3.75 mg) 4 weekly as part of the standard therapeutic protocol. Sex hormone suppression was assessed biochemically.
Results
The effect on body composition differed between males and females. Values quoted are group means. Females gained weight +3.5 kg due to fat deposition (3%), with a BMI increase of +1.2 kg/m^2 over the year. The BMI, however, fell in males by −0.25 kg/m^2; the small weight gain 0.4 kg being counterbalanced by a 1 cm height increase. Changes in fat free mass were small: −0.35 kg in females and none overall in males. Basal metabolic rate fell rapidly in females by 200 kJ/day. For males in contrast, although the fall was greater, −240 kJ/day, but this did not occur until the second 6 months on treatment.
Conclusions
The body composition changes on sex hormone withdrawal in mid-adolescence are much less marked than in the equivalent state in late middle age, and differed between the sexes. In particular the expected loss of the lipolytic and anabolic effects of testosterone were not seen. It is possible, therefore, that other factors, such as the relatively higher GH production inferred from the continued growth in males may preserve body normal body tissue balance, even in the absence of sex hormone secretion, and this requires further study.

DOI: 10.1530/endoabs.39.EP69

EP70

Chromosomal variations in children and adolescents with gender dysphoria: is routine karyotyping indicated?

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Background
Chromosome analysis is always indicated in disorders of sex development (DSD), but the need for karyotyping in gender dysphoria (GD) is less clear.
Aims and objectives
We therefore aimed to review the place of routine chromosome analysis in the management of GD in children and adolescents.
Patients and methods
Five hundred and twenty children and adolescents with GD have been referred at the time of reporting to the two endocrine clinics in London and Leeds forming part of the joint National Gender Identity Development Service since 2009. Chromosome analysis and physical examination are performed routinely to exclude a DSD.
Results
One *denovo* sex chromosome variation (47,XYY) was identified. The prenatal diagnosis of 47,XXX was confirmed in one other (total sex chromosome aneuploidy rate 1:260). Neither would have been suspected phenotypically nor did the finding have any bearing on the management of the GD. In addition, karyotyping revealed two individuals with balanced familial translocations and one with a small marker chromosome, none of which had any clinical consequences (total autosomal aneuploidy rate 1:173). The finding of these karyotype variations is within known population aneuploidy prevalence rates.
Conclusions
No additional chromosome variations were identified in children and adolescents with GD over and above the frequency expected within the general population. This differs from the situation in a DSD. Chromosome analysis in children and adolescents with GD may not, therefore, be routinely indicated.

DOI: 10.1530/endoabs.39.EP70

EP71

Standard GnRH analogue doses do not adequately suppress puberty in adolescent patients

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Introduction
Adolescents with persistent gender dysphoria (GD) receive GnRH analogues to achieve pubertal arrest. It is unclear whether this is adequate to achieve biochemical suppression of gonadotrophin (LH, FSH) and sex hormone production.
Methods
Gonadotrophins, testosterone and oestradiol were measured in GD patients (15–18 years) before and after monthly Gonapeptyl treatment (3.75 mg i.m.). Patients administered other analogues and/or cross-sex hormones were excluded. For data analysis, undetectable measurements were substituted for the assay's quantitation limit. Biochemical suppression was defined as undetectable gonadotrophins and oestradiol (natal females) or testosterone (males).
Results
Seventy four patients (25 males, 49 females) were treated with Gonapeptyl for a median of 7 months (IQR 6–8). Gonadotrophins were lower following treatment. However, most patients did not achieve complete biochemical suppression. In females, only 14 and 64% achieved complete LH and oestradiol suppression respectively. No males completely suppressed LH and only 20% had undetectable testosterone. FSH was not adequately suppressed in any patients. There was no correlation between age, treatment duration, or body size with responses to Gonapeptyl.

	LH (IU/l)		FSH (IU/l)		Testosterone (nmol/l)		Oestradiol (pmol/l)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Natal male	5.1 (3.0–6.8)	0.6* (0.4–0.9)	3.1 (2.1–5.8)	1.1* (0.8–1.5)	14.9 (10.7–18.6)	0.9* (0.4–1.3)	79 (69–115)	<44* (<44–<44)
Natal female	6.8 (4.0–10.3)	0.4* (0.2–0.6)	5.2 (3.7–6.6)	3.0* (2.0–4.1)	1.0 (0.8–1.3)	0.7* (0.4–1.1)	157 (99–316)	<44* (<44–49)

Results are median (interquartile range).
*P<0.01 vs pre-treatment.

Discussion/conclusion
The majority of patients did not achieve complete biochemical suppression of gonadotrophin or sex hormone production on Gonapeptyl treatment. The suppression was more marked in females than males. No effect was seen when adjusting for body size. The optimal treatment to arrest puberty in GD patients needs a consensus view. Pragmatically, a significant fall in testosterone or oestradiol accompanied by LH suppression and clinical pubertal arrest could be considered adequate.

DOI: 10.1530/endoabs.39.EP71

EP72

The role of a next generation sequencing panel in the diagnostic pathway in disorders of sex development

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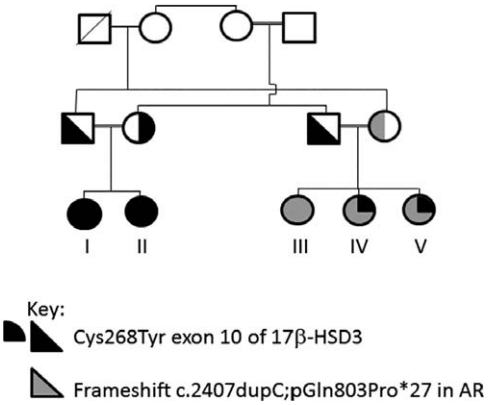
Background
Accurate genetic diagnosis is essential in disorders of sex development (DSD), guiding medical management and enabling optimal personalized care delivery.
Case presentation
Two siblings (I and II) with a family history of 17β-hydroxysteroid dehydroxygenase (17β-HSD3) deficiency presented postnatally with isolated labial swelling. Karyotype was 46,XY and urinary steroid profile (USP) normal. HCG-stimulated testosterone/androstenedione ratio was 0.17 (normal >0.8) in

patient II (unavailable patient-1). *HSD17B3* was sequenced. A homozygous missense p.Cys268Tyr mutation was identified in both children.
Patient V presented aged 1 week with bilateral inguinal masses. External genitalia appeared female, karyotype was 46,XY and USP was normal. Stimulated testosterone/androstenedione ratio was 3.27. Gonadectomy was performed at 18 months. Her siblings were referred for assessment. Both had female external genitalia, 46,XY karyotype, normal USP and baseline androstenedione concentrations that did not rise post HCG-stimulation. Patients IV and V were heterozygous for the *HSD17B3* p.Cys268Tyr mutation, whereas patient III was not a carrier. Targetted sequencing was therefore performed using a custom-designed TruSeq amplicon panel covering 32 genes associated with 46,XX and 46,XY DSD. A novel hemizygous frameshift mutation c.2407dupC; p.Gln803Profs*27 in the androgen receptor was identified in patients III–V.
Conclusion
These cases highlight the value of targeted sequencing panels in DSD. Biochemical tests can be equivocal, for example, performing a USP is not helpful in prepubertal children with 17β-HSD3 deficiency. Reaching the correct diagnosis in DSD is critical to subsequent management decisions, e.g. adult gonadectomy facilitates a more physiological transition through puberty in CAIS, whereas early gonadectomy or a block and replace regimen during puberty is required in patients with 17β-HSD3 mutations. Although a second hit was thought unlikely in patient V, high throughput sequencing is increasingly leading to the identification of patients with mutations in more than one gene, highlighting the need for periodic review of molecular testing results.



DOI: 10.1530/endoabs.39.EP72

EP73

Inter and intra-rater reliability of accuracy of testicular volume evaluation: a simulation study

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Background
Measuring testicular volumes by orchidometer is a standard method of pubertal staging in boys. A paucity of evidence exists as to its inter and intra-observer reliability and the impact of clinicians gender, experience and training on the accuracy of measurements. We are developing specifically engineered models with different testicular volumes to investigate inter and intra-observer reliability of testicular volume estimation for simulation training.
Methods
A pilot study was conducted using four child-sized manikins with 20, 10, 5 or 3 ml prosthetic testes attached. Observers were asked demographic data (gender, job title, endocrinology experience and specific training) then, using an orchidometer, anonymously recorded their estimation of the four manikins testicular volumes before and after a training session.
Results
There were 16 participants: ten junior doctors, four consultant paediatric endocrinologists and two specialist endocrine nurses. Twelve participants were female, four male. Thirteen repeated testicular volume measurements following training. Overall 46% of participants overestimated testicular volume, 7% underestimated and 46% were accurate. Males were significantly more accurate than females ($P=0.04$). Males accurately measured 62% of the time, over-estimated 31% and underestimated 6% compared to females (40, 51, 8% respectively). Larger volume testicles were more accurately measured: 20 ml volume had the smallest variability (CV 12%) and 3 ml volume the largest (CV 50%). Variation was higher at all volumes in the left testicle. Experience and training did not significantly impact on accuracy.
Discussion
There was considerable variation in the estimation of testicular volume between subjects and at lower testicular volumes. Males are more accurate with their testicular staging than females. Feedback from this pilot study has been used to further develop our specifically engineered prototypes ready for a larger study to be conducted with delegates at BSPED 2015.

DOI: 10.1530/endoabs.39.EP73

EP74

Mode of clinical presentation and delayed diagnosis of turner syndrome

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Background
Early diagnosis of girls with turner syndrome (TS) is essential to provide timely intervention and support. The screening guidelines for TS suggest karyotype evaluation in patients presenting with short stature, webbed neck, lymphoedema, coarctation of aorta or >two dysmorphic features (nail dysplasia, high arched palate, short fourth metacarpal or strabismus).
Objectives
The aim of the study was to determine the age and clinical features at the time of presentation to identify potential delays in diagnosis of TS.
Methods
Retrospective data on age at diagnosis, reason for karyotype analysis and presenting clinical features was collected from the medical records of 67 girls with TS.
Results
The mean age of diagnosis was 5.89 ($\pm$5.3) years and ranged from prenatal to 17.9 years. 10% were diagnosed antenatally, 16% in infancy, 54% in childhood (1–12 years) and 20% in adolescence (12–18 years). Only 42% of girls were diagnosed before 5 years of age. Lymphoedema (27.3%) and dysmorphic features (27.3%) were the main signs that triggered screening in infancy. Short stature was the commonest presenting feature in both childhood (52.8%) and adolescent (38.5%) years. 23% were screened because of delayed puberty and 15% due to irregular periods in the adolescence. At least 12% of girls fulfilled the criteria for earlier screening but were diagnosed only at a later age (mean age = 8.78 years). The actual duration of delay in children presenting with short stature could not be ascertained due to lack of height measurements prior to seeking specialist opinion.
Conclusion
Majority of girls with TS were diagnosed only after the age of 5 years. Short stature triggered evaluation for most patients diagnosed in childhood and adolescence. Lack of community height-screening programme and lack of awareness could have led to potential delays in diagnosing TS. New strategies for earlier detection of TS are needed.

DOI: 10.1530/endoabs.39.EP74

EP75

Intravaginal foreign body should be excluded in prepubertal cyclical vaginal bleeding without other evidence of precocious puberty

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Background
Isolated prepubertal vaginal bleeding can be secondary to various causes including Mullerian cyst, papilloma, foreign body and prepubertal menarche. There is no current consensus on the investigations for prepubertal girls with isolated vaginal bleeding with no other signs of precocious puberty.
Objective
The objective of our study is to evaluate the factors associated with persistent isolated cyclical vaginal bleeding including clinical presentation, gonadotrophin-releasing hormone (GnRH) stimulation test, genital examination under anaesthetic (EUA) and pelvic ultrasound findings.

Method
We describe a retrospective case series of 14 girls with isolated prepubertal menarche from two centres between January 2007 and December 2014. All girls presented with persistent cyclical vaginal bleeding without signs of precocious sexual development.
Results
At presentation, mean age was 7.4 years (range 5.0–9.67), mean BMI was 19.6 (range 14.6–29.3), mean height SDS was 0.33 ± 1.35 and mean weight SDS was 1.01 ± 1.75. Vaginal bleeding was reported to be cyclical ranging from 1 week to 3 monthly, lasting 1–4 days in duration. GnRH stimulation test showed a mean LH peak of 3.1 U/l (range 0.3–14), mean peak LH/FSH ratio of 0.23 (range 0.07–0.66) and oestradiol levels were < 100 pmol/l in all girls. Pelvic ultrasound showed prepubertal uterus with no identifiable endometrial echo and bone age showed no advancement in all girls. EUA was performed in eight girls, this was normal in seven girls and one girl had a 1.5 cm foreign body found. The girl with the foreign body presented with cyclical vaginal spotting weekly for 6 months prior to the EUA.
Conclusion
Prepubertal girls presenting with persistent and cyclical vaginal bleeding should have baseline LH, FSH, oestradiol, adrenal androgens, GnRH stimulation test, pelvic ultrasound for endometrial echo and bone age following clinical evaluation to exclude precocious puberty. EUA should be considered in persistent isolated cyclical vaginal bleeding without evidence of precocious puberty to exclude other causes such as intravaginal foreign body.

DOI: 10.1530/endoabs.39.EP75

EP76

Causes of precocious puberty in children referred to an Endocrine Unit in Northwest of Turkey

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Background
Although data from developed countries about precocious puberty (PP) are abundant, data from developing countries are scarce. The aim of our study was to analyze the frequency of the variants of PP in children who had applied to our department.
Patients and methods
Retrospective analysis of 367 children (18 boys and 349 girls) with features of PP referred for evaluation to our clinic between the years 2006–2012 was performed.
Results
Premature telarche (PT) was diagnosed in 117 (30.5%) girls with the mean age of 3.9 ± 2.8 years. Their mean height SDS was within 0.3 ± 1.1 S.D. Premature adrenarche (PA) was diagnosed in 112 (30.5%) children (eight boys, 104 girls), having the mean age of 7 ± 1.2 years. Their mean height SDS was within 0.9 ± 1.0 S.D. Central precocious puberty (CPP) was diagnosed in 127 (34.6%) children (six boys and 121 girls), with the mean age of 8.3 ± 1.4 years. Mean height SDS in this group was within 0.9 ± 1.1 S.D. and was significantly higher than in the PT group. Of the patients with CPP, 95.3% (121 patients; six boys and 115 girls) were diagnosed as idiopathic. Organic causes for CPP were detected in only 6 (4.7%) girls (two hypothalamic hamartoma, 1 had tuberous sclerosis, 1 had meningomyelocele, 1 had traumatic barin injury). Peripheral precocious puberty (PPP) was diagnosed in 11 children (four boys and seven girls), having the mean age of 7.3 ± 2.2 years. The most common causes of PPP were congenital adrenal hyperplasia (CAH) (two boys and four girls), McCune Albright syndrome (three girls), testis tumour (one boy) and adrenal tumour (one boy).
Conclusion
The results of this study indicated that the most cases of PP are affected with CPP especially with idiopathic form of it, followed by PT. CAH might be the most frequent cause of PPP in our population as expected.

DOI: 10.1530/endoabs.39.EP76

Late effects of cancer treatment

EP77

Impact of haematopoietic stem cell transplantation with total body irradiation on apparent bone mineral density in childhood leukaemia survivors

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Background
Reduced bone mineral density (BMD) *z*-scores from Dual energy X-Ray absorptiometry (DEXA) have been reported in childhood HSCT survivors. However, BMD *z*-scores are unreliable in patients with short stature.
Objective
To investigate the influence of HSCT/TBI on size-corrected BMD in childhood leukaemia survivors.
Method
Post-pubertal leukaemia survivors (16–26 years) treated with HSCT/TBI (10–14.4 Gy) ($n=21$, ten male) at mean aged 9.3 (1.0–10.8) years were compared with patients treated with chemotherapy-only ($n=28$, 11 male). All had had endocrine evaluations and were on replacement hormones where appropriate. No patients were on long-term steroid therapy. Assessments: anthropometry (height, weight), DEXA scanning (Lunar Prodigy fan beam) [BMD-*z*-scores, bone mineral content (BMC), bone area (BA)] and vitamin D levels. Size-corrected BMD [i.e. Bone Mineral Apparent Density (BMAD)] were represented as total-BMAD ($BMAD_T$) = BMC/total body BA^2/height and Lumbar spine-BMAD ($BMAD_{L2\text{-}4}$) = $BMD_{L2\text{-}4} \times [4/(\pi \times \text{width})]$. Analysis: student's *t*-tests and Pearson's correlations (5% significance).
Results
HSCT/TBI compared with chemotherapy-only survivors had lower total BMD *z*-scores (−0.74 vs 0.19, $P=0.012$), but were lighter ($P<0.001$) and shorter ($P<0.001$). Total-BMD correlated positively with height-SDS, weight-SDS, fat and lean masses (all $P<0.001$). Size corrected BMD showed no mean(SD) differences between HSCT and chemotherapy-only patients: $BMAD_T$ (0.089 (0.008) vs 0.086 (0.007), $P=0.13$); $BMAD_{L2\text{-}4}$ (0.38 (0.057) vs 0.37 (0.056), $P=0.33$). There were no relationships between $BMAD_T$ or $BMAD_{L2\text{-}4}$ with age at or time from primary diagnosis in both groups; or with age at and time from HSCT/TBI in HSCT/TBI group. HSCT/TBI survivors showed no relationships between $BMAD_T$ or $BMAD_{L2\text{–}4}$ with serum Vitamin D ($P=0.13$, $P=0.21$) or presence of endocrine disorders (growth hormone deficiency ($P=0.16$, $P=0.46$), hypothyroidism ($P=0.53$, $P=0.58$), gonadal failure ($P=0.33$, $P=0.43$)).
Conclusions
BMD must be corrected for size for appropriate interpretation to avoid over-diagnosis of osteopenia. Oncology treatment effects on long-term peak bone mass need further evaluation.

DOI: 10.1530/endoabs.39.EP77

EP78

Endocrine sequelae beyond 10 years in survivors of medulloblastoma: comparison of three major treatment regimens

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Introduction
Improved survival following treatment for paediatric medulloblastomas has resulted in increased incidence of late effects, particularly endocrine sequelae. The complete picture of late effects, however, has been limited by short duration of follow up.
Aims 1
To establish the evolution of endocrine sequelae in patients treated for medulloblastoma
Aim 2
To compare the prevalence of endocrine dysfunction among three major treatment regimens.
Methods
Single-centre analysis of medulloblastoma treatment and endocrine sequelae in patients diagnosed between 1982 and 2002.
Results
A total of 109 patients were treated for medulloblastoma. Only 45 (41%) patients remained alive, and details of treatment and late effects were available for 35 of them (25 M). The median age at diagnosis was eight (range 2–14) years and median follow up was 18 (range 10–28) years. Growth hormone deficiency (GHD) was the most prevalent hormone deficiency (97%), followed by hypothyroidism (60%) and adrenocorticotrophic hormone (ACTH) deficiency (45.5%). The median time from end of treatment to loss of growth hormone was 1.7 (range 0.7–15) years; ACTH deficiency 2.9 (range 0.75–7.5) years; and hypothyroidism 4.1 (range 0.7–11.4) years. Twenty three per cent developed hypogonadism (17% primary and 6% secondary) whilst precocious puberty was seen in 20%. The total number of endocrine events was highest for patients receiving Packer regimen (cysplatin, Vincristine and CCNU with radiotherapy)

($n=10$) at 2.8 events/patient, followed by 2.4 events/patient for those receiving PNET3 with chemotherapy ($n=10$) and least in patients receiving PNET3 without chemo ($n=8$) at two events/patient. We also present the cause of death and prevalence of endocrine dysfunction among non-survivors.
Conclusions
Prevalence of endocrine sequelae in medulloblastoma survivors is high and evolution of endocrine dysfunction can occur as late as 15 years from treatment completion, hence long term close monitoring of growth, puberty and gonadal function is essential. Endocrinopathies appear to be more prevalent in those treated with concomitant chemotherapy and radiotherapy.

DOI: 10.1530/endoabs.39.EP78

Miscellaneous/other

EP79

The not so sweet truth of paediatric hypoglycaemia

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Introduction
Paediatric hypoglycaemia is a relatively common medical emergency. In order to allow identification of the underlying cause, investigations need to be performed urgently prior to treatment being given. If done correctly this can save the need for future investigations. A 'hyposcreen' costs ~£450 so careful consideration is needed to ensure correct patient selection, as inadequate investigations have further cost and patient safety implications.
Methods
Forty nine cases of proven or suspected hypoglycaemia (Glucose $\leq$2.6 mmol/l) were identified via the laboratory. Clinical notes, laboratory investigations, and results were reviewed.
Results
Forty two patients met the biochemical criteria for hypoglycaemia. Following review of individual clinical details it was agreed that only 48% of patients (20 patients; 15 neonates, five children) required investigation with a 'hyposcreen'. Of these 20 patients, three did not have any 'hyposcreen' investigations performed. In the remaining 22 patients the cause of hypoglycaemia was identifiable, but despite this six were investigated inappropriately. In total 23 patients were investigated but only two had a full 'hyposcreen' completed. A total of 5/23 (22%) patients investigated were admitted for a planned fast due to incomplete 'hyposcreens'. three patients did not become hypoglycaemic on fasting but despite this all five patients were investigated. None of these 'hyposcreens' were complete. Intermediary metabolites (96%), lactate (100%), cortisol (100%), insulin (87%) and growth hormone (87%) were taken most commonly with urine samples (48%) and ammonia (30%) taken least often. 35% cortisol, 20% insulin and 41% intermediary metabolite results were abnormal affecting ten patients, but only 4 had further investigations or follow up.
Investigations led to the diagnoses of pituitary aplasia (1), ketotic hypoglycaemia (3) and transient hyperinsulinism (1).
Conclusion
Investigations for hypoglycaemia are generally incomplete (91%) or inappropriate (27%). This has major cost implications for both the NHS and the individual who is investigated inadequately or incorrectly. We need to consider more stringent recommendations and dissemination of these to avoid inappropriate investigations and delay in diagnosis.

DOI: 10.1530/endoabs.39.EP79

EP80

Volumetric changes in the hippocampus and relationship to memory indices in children with hyperinsulinaemic hypoglycaemia and ketotic hypoglycaemia

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Background
Children with hyperinsulinaemic hypoglycaemia (HH) are at a high risk of brain injury, while children with ketotic hypoglycaemia (KH) are believed to be neurologically normal. Hippocampus is known to be susceptible to hypoglycaemia, and is one of the key structures in the memory system. Our objective was to ascertain if children with HH sustain greater hippocampal injury and memory deficits in comparison to children with KH.
Methods
Twenty one neurologically normal children between 5 and 16 years of age with HH and 14 children with KH were recruited from the endocrine and metabolic outpatient clinic database from 2009 to 2012. Cognitive assessment was performed using Wechsler Intelligence Scale for Children Fourth edition and Children Memory Scale. Conventional (T1, T2 weighted) MRI for visual inspection of hippocampus and fast low angle shot (FLASH) three-dimensional MRI for manual hippocampal volume measurement were acquired.
Results
HH group scored significantly lower in general memory (KH 110 vs HH 93.1, P 0.002), especially visual (KH 106.3 vs HH 94.8, P 0.022), verbal immediate (KH 110.5 vs HH 94.9, P 0.006) and verbal delayed memory (KH 108.7 vs HH 97.2, P 0.055) and also in Full scale IQ (KH 100.5 vs HH 89.3, $P=0.026$). On conventional MRI small hippocampi were seen in 28.5% with HH and 7% with KH, however no significant differences in hippocampal volumes were seen in the right (P 0.959) or left ($P=0.877$) hippocampus between the KH and HH groups. Hippocampal volumes did not correlate to memory indices in HH group. Three children in the HH group had >20–25% reduction in bilateral hippocampal volumes, however only one child had impaired memory.
Conclusions
Children with HH manifest significant impairment of memory that do not correlate with hippocampal volumes. Further studies are required to determine the neural substrate underlying these memory impairments.

DOI: 10.1530/endoabs.39.EP80

EP81

Pilot study on the utility and acceptability of video animation as a delivery method for educational materials for families and carers of patients with congenital hyperinsulinism in infancy

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Introduction
To prevent neurological damage caused by congenital hyperinsulinism (CHI), hypoglycaemia must be avoided and treated promptly. Education of parents, carers and families of patients with CHI (PCFs) about the causes and consequences of CHI may help to reduce severity of hypoglycaemia due to earlier correction of blood glucose levels. We aimed to determine whether video animations could be used to improve understanding of CHI among PCFs, and the acceptability of this delivery method among PCFs and health-care providers (HCPs).
Methods
Following PCF consultation, three video animations on aspects of CHI were produced and hosted on a single webpage. After watching the videos, participants completed an anonymous web-based questionnaire. Respondents were grouped according to whether they were HCPs ($n=8$) or PCFs ($n=12$) and data were evaluated using descriptive statistics.
Results
Biology knowledge was reported as below GCSE standard for 25% of PCFs. In seeking CHI-related information, 75% of PCFs used websites, 50% asked their HCP and 20% used social media. These data highlight the importance of simple, web-based materials for PCF education. After watching the videos, 73% of PCFs reported improved understanding of CHI and 82% of PCFs felt that the videos improved their confidence to explain CHI to others. The remaining PCFs had either extensive experience of dealing with CHI (>8 years) or a high level of knowledge about the condition already. Overall 100% of respondents would recommend the video animations to friends, relatives, or other HCPs.
Discussion/conclusion
The study revealed unprecedented support for the video animations and their ability to communicate complex scientific concepts to PCFs. We conclude that video animations are a useful way to deliver educational materials and the impact of these resources should be investigated in a larger cohort study. Moreover, video animation should be considered for delivery of education materials in other paediatric disorders.

DOI: 10.1530/endoabs.39.EP81

EP82

Development of a feasible intervention to support communication with young people

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Background
Many young people have inadequate follow up because they lose contact with adult care following transfer from paediatrics. There is a need to adapt communication interventions to help young people to determine and enact their preferred involvement in consultations with health professionals.
Objective
To develop interventions to support communication with young people in endocrine care and to assess the feasibility of implementation in routine consultations.
Design
Combined methods in three stages: i) Communication study: cross-sectional analysis of communication between healthcare professionals and young people in paediatric and adult endocrine clinics in two UK centres. ii) Development of interventions to address the preferences and perceived needs of young people. iii) Assessment of feasibility and acceptability.
Sample
Young people aged 11–25 years diagnosed with endocrine conditions including: Congenital Adrenal Hyperplasia, Turner Syndrome childhood cancer survivors, and hypothalamic pituitary conditions.
Methods
Analysis of activity in consultations as indicated by time talked and questions asked; communication behaviours assessed by the Paediatric Consultation Assessment Tool (PCAT); and shared decision making rated by the OPTION tool. Self report of patient satisfaction using the Medical Information Satisfaction Scale (MISS- 21). Semi-structured interviews to determine communication needs.
Results
There were wide variations between patients in the proportion of time talking and number of questions asked. Qualitative interviews indicated important gaps in knowledge and understanding. Young people, parents and clinicians participated in developing interventions directed at: i) pre-consultation preparation, ii) in consultation support for young people and clinicians, and iii) post consultation resources including a summary sheet, http://www.explain.me.uk/ web site and consultation recording. The interventions were acceptable and feasible for use in routine consultations.
Conclusions
A suite of interventions can be offered to support young people's active participation in consultations during transition to adult endocrine care.

DOI: 10.1530/endoabs.39.EP82

EP83

Determination of pancreatic hormones in children with different forms of hyperinsulinaemic hypoglycaemia

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Introduction
In congenital hyperinsulinism (CHI) hypoglycaemia results from a dysregulation of insulin secretion. We hypothesised that other pancreatic hormones may also be dysregulated in this condition.
Objectives
To proof the applicability of Luminex Multiplex method to measure pancreatic hormones (insulin, C-peptide, glucagon, amylin and PP) in the paediatric age. To elucidate the fasting response of these hormones in children with different forms of CHI.
Subjects and methods
12 children (seven females) with ages between 11 days of life and 13 years had the plasma pancreatic hormones extracted at normoglycaemia and at hypoglycaemia (end of fast). The patients have different CHI aetiologies, histology types and different response to treatments. The hormones were analysed using multiplexing manner on 0.025 ml of plasma.
Results
The concentration of glucagon (mean ± SDS) increases from 97 ± 239 pg/ml at normoglycaemia to 103 ± 260 pg/ml at hypoglycaemia (p0.21). Conversely, insulin decreases from 909 ± 441 to 503 ± 306 pg/ml (p0.004), respectively. Similarly, C-peptide descends from 1547 ± 1013 to 806 ± 366 pg/ml at normoglycaemia and hypoglycaemia, respectively (P 0.005). Amylin decreases from 35 ± 22 to 21 ± 9 pg/ml (P 0.014) whilst PP is almost unmodified: 84 ± 106 pg/ml at normoglycaemia and 86 ± 115 pg/ml at hypoglycaemia (P 0.65).
Conclusions
This assay demonstrates its suitability to determine pancreatic hormones in the paediatric age group. In children with CHI, glucagon's response to hypoglycaemia is impaired. No previous reports have determined amylin concentrations in CHI, and this study indicates that it decreases during hypoglycaemia to avoid its anorectic effect, although interestingly PP's concentrations remain stable despite hypoglycaemia.

DOI: 10.1530/endoabs.39.EP83

EP84

Congenital hyperinsulinism due to SUR1 (ABCC8) mutation in newborn twins: improvement of clinical outcome after eight years follow-up

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Introduction
Congenital hyperinsulinism (CHI), is the most frequent cause of persistent hypoglycemia in infancy. Mutations in the ABCC8 gene are responsible for 40–50% of CHI cases. Its management can be extremely complicated. The main goal of the treatment is to maintain normoglycemia, since hypoglycemia during infancy can have severe neurological consequences. Herein, we report 8 year follow up of twin patients who were diagnosed with CHI at neonatal period due to SUR1 (ABCC8) mutation.
Cases
Term male infants were born to consanguineous parents by caesarean section. Maternal antenatal screen was unremarkable. Insulin levels of the patients were 50.9 μU/ml and 51.9 μU/ml during hypoglycemia attacks (20–30 mg/dl). In genetic analysis of both patients, homozygous mutation 2371G > T, E791X, in the *ABCC8* gene was identified. Both parents were found to be heterozygous carriers of this mutation. One of the twins responded to diazoxide (20 mg/kg per day) and octreotide (25 mg/kg per day) treatment. The other patient underwent subtotal pancreatectomy (%95) at the age of 60 days; also medical therapy was required after surgery due to persistent hypoglycemia. Pathologic analysis revealed marked increase in endocrine cells in some sections throughout the pancreas. Medical therapy was stopped at 3 years of age in both patients. After 8 years of follow-up, psychomotor development and growth of the patients were normal. Neurological and intellectual abilities were also normal. Pancreas size of the patient who had pancreatectomy was found to be appropriate for his age in Magnetic Resonance Imaging after 8 years.
Conclusion
Despite severe clinical picture in neonatal period, these patients had no need of therapy after 3 years. Neurological and intellectual abilities can be sustained by aggressive hypoglycemia management. These patients may provide an understanding of the prognosis and treatment for patients who carry homozygous mutation 2371G > T, E791X, in the *ABCC8* gene.

DOI: 10.1530/endoabs.39.EP84

EP85

Digenic mutation resulting in a rare form of diazoxide responsive congenital hyperinsulinism

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Introduction
Congenital hyperinsulinism (CHI) results from unregulated insulin secretion from pancreatic β-cells, which leads to persistent hypoglycaemia. Mutations in nine different genes are reported and phenotypic variability exists both within and between the genetic subgroups. Variable penetrance has been described in some families with the same mutation; for example *HNF4A* mutations cause neonatal hypoglycaemia and/or maturity onset diabetes of the young (MODY).
Case
A male born at 35 weeks gestation with a birth weight of 4.3 kg (+3.6SDS) had recurrent hypoglycaemic episodes from day one of life. Investigations revealed a raised plasma insulin (1357 pmol/l) and C-peptide (3280 pmol/l) with supressed plasma free fatty acids and β-hydroxybutyrate during hypoglycaemia (glucose <0.5 mmol/l). Diazoxide (5 mg/kg per day) was started with a progressive increase to 20 mg/kg per day to maintain euglycaemia. His father was slim, had been diagnosed with diabetes mellitus in his thirties and was on Metformin. The paternal grandmother was also diabetic. There was no family history of hypoglycaemia. Sequence analysis identified a heterozygous *HNF4A* mutation (p.R245P) and two heterozygous *ABCC8* mutations (p.G92S; p.A1185V) in the proband. The p.A1185V *ABCC8* mutation had been inherited from his unaffected mother and the p.R245P *HNF4A* and p.G92S *ABCC8* mutations from his father. All three mutations are novel, affect conserved residues, and are predicted to be pathogenic by *in silico* analysis. It is therefore likely that the CHI in the proband is resulting from a dual aetiology. Identification of a *HNF4A* mutation in the father is consistent with a diagnosis of MODY. He has subsequently switched treatment to Gliclazide resulting in improved glycaemic control.
Conclusion
HNF4A CHI is often transient and responsive to diazoxide. In contrast recessively inherited *ABCC8* mutations usually cause diazoxide-resistant CHI. Interestingly, our patient is responsive to diazoxide despite the dual genetic aetiology. The mechanism(s) underlying the molecular interaction between *HNF4A* and *ABCC8* mutations are unclear.

DOI: 10.1530/endoabs.39.EP85

EP86

The use of glucagon in the treatment of hypoglycaemia due to congenital hyperinsulinism

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Background
Congenital hyperinsulinism (CHI) can cause severe hypoglycaemia with consequent adverse neurodevelopment. Continuous glucagon infusion (CGI) through intravenous and subcutaneous routes has been utilised to achieve glycaemic stability, but the efficacy has not been reported systematically in a CHI cohort.
Aim
We aimed to investigate the efficacy and safety profile of CGI in the management of hypoglycaemia due to CHI.
Methods
The efficacy of CGI was reviewed in a cohort of 31 children with CHI over a 5 year period by assessing the impact on glucose infusion rate (GIR), a marker of the severity of hypoglycaemia, within 48 h of treatment. Factors influencing the severity of CHI, such as K-ATP channel gene mutations, diazoxide unresponsiveness, requirement for second-line treatment with octreotide and sub-total pancreatectomy were also assessed in relation to CGI.
Results
In patients with CHI, CGI in a dose of 5 μg/kg per h administered either intravenously ($n=29$) or subcutaneously ($n=2$) reduced GIR from a mean (interquartile range) of 15.9 (8.1) to 11.5 (4.9) mg/kg per min ($P=0.001$ for difference). This reduction was independent of gender, K-ATP channel gene mutation status, resolution of hyperinsulinism, focal CHI and therapeutic response to diazoxide. The maximum dose of glucagon required to achieve euglycaemia (12.4 (15) μg/kg per min) was directly correlated with the pre-glucagon GIR ($R2=0.7$, $P<0.001$), as expected, but not to other factors determining the severity of hypoglycaemia. In 16 children where the duration of glucagon therapy was recorded, 33 (30) days of CGI helped maintaining euglycaemia along with other medical therapies. Only one child receiving subcutaneous glucagon developed a necrolytic migratory erythema (NME) skin rash.
Conclusions
CGI is effective in reducing GIR in patients with CHI in the short and long term management of children with CHI. Although generally safe, the possibility of NME rash should be considered as an adverse event with CGI treatment.

DOI: 10.1530/endoabs.39.EP86

EP87

An incidental finding of an abdominopelvic macrocystic lymphangioma in a girl with Turners syndrome

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Background
Cystic lymphangiomata are rare benign tumours of childhood resulting from an abnormal development of the lymphatic system, most of which occur in the head and axillary region, referred to as cystic hygromas. Lymphangioma arising in the abdomen are particularly rare and the symptoms are variable. They usually affect boys and can be associated with specific genetic abnormalities, most notably Turners syndrome.
Case
We report the case of a 14-year-old girl with Turners syndrome who was found to have a large abdominal lymphangioma after a routine renal ultrasound was performed. She was diagnosed with Turners syndrome on amniocentesis and was being followed up annually in outpatients. She had few features of Turners and was well apart from occasional abdominal pain. Renal ultrasound showed a large cystic structure measuring 17×6 cm in the right adnexa extending to the central abdomen. An MRI showed the cystic structure was separate from the right ovary and was highly suggestive of a lymphangioma. She was referred to the paediatric surgical team and the decision was made to excise the lesion.
Conclusion
Congenital abnormalities present outside the neonatal period as surgical disease, and although very rare intra-abdominal lymphangioma need to be excluded in the differential of an acute abdomen especially in girls of reproductive age.

DOI: 10.1530/endoabs.39.EP87

EP88

Usefulness of bedside ketone testing in the evaluation of children with hypoglycaemia

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Introduction
Bedside blood ketone measurement has often been used in the management of diabetic ketoacidosis. However there is no available data on its reliability in the evaluation of hypoglycaemia in children. We aimed to assess the reliability of bedside ketones (beta-hydroxybutyrate (BHB)) in the evaluation of hypoglycaemia in children.
Methods
We collected data on 20 children who had paired measurement of bedside and lab BHB at the end of a controlled fast. Bedside BHB was measured by finger prick at end of the controlled fast or at the time of hypoglycemia (blood glucose <3 mmol/l) using Precision Xceed Pro blood glucose and β-ketone monitoring system (Abbott Diabetes Care, Alameda, USA).Venous sample was sent simultaneously for measurement of BHB concentration using an enzymatic method (Randox laboratories, Crumlin, UK). Bland–Altman analysis and Regression analysis were used to compare bedside BHB measurement with the established lab BHB assay.
Results
The mean age was 3.8 years (M:F=14:6). Out of the 20 children, six children with CHI underwent fast to assess fast tolerance on treatment, six CHI children underwent fast when they came off diazoxide therapy and eight children underwent diagnostic fast for recurrent hypoglycaemia, which was subsequently

confirmed as ketotic hypoglycaemia. Both the measurements showed a good correlation on regression analysis ($r=0.98$, $P<0.01$). Using Bland–Altman analysis, the mean difference between the two assays was noted be minimal (0.11 (S.E.M. $\pm$0.107)).

Conclusion

In this study, we have demonstrated that assessment of bedside ketones using Precision Xceed Pro system is a reliable way of evaluating the ketotic response during hypoglycaemia in children. Bedside ketone measurement is a simple tool that would provide valuable insight into the aetiology of hypoglycaemia.

DOI: 10.1530/endoabs.39.EP88

EP89

Isolated postprandial hyperinsulinaemic hypoglycaemia in children

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Introduction

Isolated postprandial hyperinsulinaemic hypoglycaemia (PPHH) in the paediatric age has been exceptionally reported in the literature.

Objective

To describe the clinical and biochemical characteristics as well as the management of a cohort of children with isolated PPHH followed at a single tertiary paediatric centre.

Subjects and methods

Six children (three males) were collected. The clinical characteristics, diagnosis, management, and follow-up of patients with PPHH were retrospectively reviewed. The tests for diagnosis and monitoring were: 24 h blood glucose profile, continuous blood glucose monitoring system, diagnostic fast, prolonged oral glucose tolerance (OGTT) and mixed meal (MM). Management options included: dietary intervention, diazoxide and acarbose.

Results

Age ranged between 4.1 and 8.9 years at diagnosis, and auxology parameters in all children were within normality. Fasting tolerance was normal in all the patients, but a prolonged OGTT showed symptomatic hypoglycaemia (blood glucose <3.5 mmol/l) after 120 minutes with simultaneous detectable serum insulin concentrations. The mean follow-up was of 3.3 ± 3.1 years. Acarbose was started in four patients, demonstrating a favourable glycaemic and symptom–control effect, but only one patient remained on it on the long-term due to its side effects. Diazoxide was useful in one patient. The rest of the patients were managed on frequent feeds although, despite being on this, prolonged OGTT/MM evidenced persisting PPHH. Two patients spontaneously grew out of the condition on follow-up investigations.

Conclusions

Recognising hypoglycaemia in PPHH requires a prolonged OGTT. In those children with PPHH tried on acarbose, this proved to be beneficial although poorly tolerated. Patients managed exclusively on frequent feeds did demonstrate ongoing hypoglycaemia on prolonged OGTT. The aetiology of PPHH in these patients still needs to be deciphered.

DOI: 10.1530/endoabs.39.EP89

EP90

Case of raised creatinine in a newborn with congenital hyperinsulinism: diazoxide induced acute kidney injury

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Background

Congenital hyperinsulinism (CHI) is the result of unregulated insulin secretion from the pancreatic β-cells leading to severe hypoglycaemia.[1] Diazoxide is effective in virtually all forms of CHI except in those due to recessive (and some dominant) inactivating mutations in *ABCC8* and *KCNJ11* and in patients with focal CHI.[2] We report a case of CHI with acute kidney injury secondary to diazoxide.

Case presentation

A term male born to non-consanguineous Caucasian parents presented with hypoglycaemia on first day of life. Labetolol was administered during pregnancy for pre-eclampsia. The dopplers showed no end diastolic flow. He required up to 17 mg/kg per min of intravenous glucose. He had high insulin levels (26 mU/l) whilst hypoglycaemic (2.2 mmol/l). He was commenced on diazoxide and chlorothiazide. I.v. glucose was weaned off on day 8. On day 10, whilst on diazoxide, he had raised creatinine of 153 μmol/l. His blood pressure, urine output and weight remained satisfactory. There was no microscopic haematuria. Renal ultrasound scan was normal. Chlorothiazide was discontinued and diazoxide weaned off over the next 4 days. He maintained stable glucose levels and renal function improved following this intervention.

Discussion

Diazoxide is an antihypertensive antidiuretic benzothiadiazine. It acts on the pancreatic β-cells inhibiting insulin secretion. Tolerance to diazoxide is usually good. Renal side effects are rarely described. Diazoxide is also an arterial vasodilator, and in combination with diuretics, can induce acute changes in renal function with associated tubular sodium avidity (http://www.nature.com/nrneph/journal/v2/n2/full/ncpneph0076.html). Reported renal side effects of diazoxide include azotemia, decreased creatinine clearance, reversible nephritic syndrome and haematuria.

Conclusion

Raised creatinine can occur as a side effect of diazoxide. The half-life in children is 9–24 h and increases in patients with renal impairment (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1432880278807.pdf). This case highlights the importance of regular monitoring of renal function in patients with CHI on diazoxide.

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DOI: 10.1530/endoabs.39.EP90

Obesity

EP91

Leptin replacement improves central ventilation in a patient with congenital leptin deficiency: first report in childhood

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Background

Congenital leptin deficiency (CLD) is characterized by severe early-onset obesity due to hyperphagia and impaired satiety. The impact of obesity in obstructive sleep apnoea hypopnoea syndrome (OSAHS) was originally reported as mechanical, but recent data suggest that adipokines may influence central ventilation. We highlight that treatment with recombinant human leptin (RHL) in CLD with OSAHS improves ventilation before weight loss.

Case presentation

A 10 months old female of Pakistani origin was severely obese (weight: 17.85 kg ($+5.55$ SDS) and BMI: 29.35 kg/m^2 ($+5.25$ SDS)). Born at term to consanguineous parents. Mother reported rapid weight gain during 1st month of life, due to intense hyperphagia with food-seeking behavior. Family history showed a first cousin with CLD: genetic analysis confirmed the same homozygous leptin mutation. RHL replacement was started with good reduction of appetite. Oxicapnography was performed before starting treatment, showing normal mean saturations and CO_2 but clusters of deep desaturations (desaturation index (DI) 19.8/h of $\geq$4%). After 50 days of treatment polysomnography was performed showing a significant improvement in clusters of desaturation (DI 9.3/h) and a mixed pattern of both obstructive and central events with an apnoea–hypopnoea index (AHI) 13.7/h. At this stage the weight was stable at 26.9 kg ($+6.7$ SDS) and BMI was 34.8 kg/m^2 ($+6.6$ SDS). After 11 months of treatment a significant loss of weight was seen (weight: 19.62 kg ($+3.05$ SDS) and BMI: 25.5 kg/m^2 ($+4.5$ SDS)). Repeat polysomnography showed marked improvement with a DI 4.2/h.

Conclusion

To the best of our knowledge, this is the first report showing an improvement in ventilation, in a patient with CLD following treatment with RHL before significant weight loss. In mice, leptin microinjections into specific brain areas, are associated with increased pulmonary ventilation and enhanced bioelectrical activity of inspiratory muscles, suggesting that leptin may influence ventilation

through direct effect on respiratory control centres. Leptin may have central effects on ventilatory regulation, which need to be explored further.

DOI: 10.1530/endoabs.39.EP91

EP92

Psychological sequelae in obese paediatric patients and predictors for weight loss

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Introduction
There is limited data on the psychological sequelae of obesity in paediatric patients.
Aims/methods
We aimed to assess the prevalence of psychological comorbidities in obese paediatric patients. Internationally validated self-report questionnaires were offered to 19 patients and their parents from a tier three paediatric obesity clinics. These included the Paediatric Index of Emotional Distress (PI-ED); Beck Youth Inventory exploring self-perceptions of competency, potency, and self-worth; Pediatric Quality of Life Inventory (PedsQL); Parent-Proxy report (PedsQL Parent); and two in-house derived motivation questionnaires for parents and patients.
Results
Fourteen patients completed the PI-ED, of which more than half (57%) reported emotional distress (5, female and 3, male). 15 patients completed the Beck Youth Inventory of which 53% reported low self-esteem (4, female and 4, male). 17 patients had QoL scores below cut offs for the social and physical domains, as well as for overall psychosocial health and overall QoL (total score). The parents of these children also reported low scores for all domains except schooling. Those aged <10 years reported the highest QoL scores. Females reported significantly lower scores for emotional, social and overall QoL domains, particularly those between 10 and 15.9 years. Those who completed motivation scores reported medium to high motivation with a non-significant correlation between reduction in BMI SDS (*Z*-score) and increased patient and parent motivation scores ($P=0.19$ and $P=0.47$ respectively).
Discussion/conclusion
More than half of obese paediatric patients in our cohort experience a high prevalence of emotional distress and low self-esteem. Obese paediatric patients, particularly females between the ages of 10–15.9 years are the most vulnerable with reduced QoL. Initial observations may suggest high motivation scores are a positive indicator for weight change but more research should be carried out to establish a link.

DOI: 10.1530/endoabs.39.EP92

EP93

Obesity: a diagnostic dilemma

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Background
Pseudohypoparathyroidism type 1a (PHP1a) is a rare disorder caused by a maternally inherited mutation in the *GNAS* gene. PHP1a is usually diagnosed in childhood due to a distinctive phenotype that includes short stature, brachydactly, ectopic ossifications, and multi-hormone resistance. These features are associated with resistance to parathyroid hormone (PTH).
Case
We report the case of a 3.4-year-old boy who presented with a generalized tonic–clonic seizure. Investigations revealed hypocalcaemia (cCa 1.78 mmol/l, PO_4 2.01 mmol/l, PTH 68.2 pmol/l, and vitamin D 39 nmol/l). His seizure self-terminated and he was commenced on calcium and vitamin D supplementation. He was under review from the age of seven months with excessive weight gain 12.22 kg ($+3.01$ SDS), 72.0 cm ($+0.72$ SDS). At birth he weighed 3.40 kg (25th centile) and had a solitary episode of hypoglycaemia. In view of this he was thoroughly investigated and was referred for a tertiary opinion, but still no cause found. Genetics ruled out Beckwith Weiddeman and Prader–willi syndrome. His development progressed and despite strict dietary control he continued to gain weight. At 3.4 years he weighed 25.76 kg ($+4.34$ SDS) with BMI 25.71 kg/m^2 (>99.6th centile). He had a round face with short digits, and his hand X-ray was normal, but with an advanced bone age of 4.6 years. In light of hypocalcaemia and raised PTH a diagnosis of PHP was suspected, and when discussed with the family mum revealed areas of skin calcinosis. Genetic analysis showed he was heterozygous for an insertion of eight nucleotides at cDNA position 388 (c.388_389insGGTTCATC) in the *GNAS1* gene. This confirmed a diagnosis of Albright's hereditary osteodystrophy (AHO); PHP1a.
Conclusion
Although, a rare presentation Albrights should be suspected in early-onset obesity. Appropriate management ensures regulation of plasma calcium and other factors such as bone mass and TSH resistance. Follow-up should be comprehensive given the manifestations of the disease associated with being overweight.

DOI: 10.1530/endoabs.39.EP93

EP94

A modified macronutrient diet for children with Prader–Willi syndrome does work

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Background
Children with Prader–Willi syndrome (PWS) have a predictable pattern of weight gain, with obesity beginning in early childhood and worsening as they get older. They have low tone and as a result their energy requirements are lower (typically 60% estimated average requirement for energy (EAR)) than age matched controls. We present three case studies of children with PWS who have been following a modified macronutrient diet, with significant positive changes to their body composition and/or BMI. The modified macronutrient diet aimed to increase the proportion of energy from protein (25%) and fat (30%) and lower the proportion from carbohydrate (45%) compared to guidance for the general population, as well as having a high fibre content (>20 g/day). Individuals worked with their dietician to create personalised stepwise plans to move their current intake towards these levels. Follow-up measurements were taken between 9 and 12 months after starting the dietary changes.
Results
The first case is an 11-year-old boy and his BMI decreased from 26.7 (>99.6th centile) to 23 (98th centile). His fat mass decreased from 24.5 kg (41.4%) to 19.6 kg (35.2%) and muscle mass increased from 32.9 to 34.2 kg. The second case is an 18-year-old female and her fat mass reduced from 30.7 kg (43.6%) to 27.6 kg (39.2%) and muscle mass increased from 37.6 to 40.7 kg. A third case, a 5-year-old boy, is following the same diet but is too young to accurately measure bio-impedance with current equipment. Positive effects on BMI have been seen though from 22.1 kg/m^2 (above $+3.5$ S.D.) to 19.1 kg/m^2 (above 98th centile) over a 1-year period.
Conclusion
The results from these three cases indicate that an energy restricted diet with a well-balanced macronutrient composition and fibre intake improves both BMI and body composition in children with PWS compared to a simple energy-restricted diet.

DOI: 10.1530/endoabs.39.EP94

Other

EP95

Effect of dietetic management on weight in children with Bardet-Biedl syndrome

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Introduction
Bardet-Biedl syndrome (BBS) is a monogenic disease characterized by retinitis pigmentosa ($>90\%$), obesity (72–86%), insulin resistant diabetes, and hypogonadism. Weight management is challenging due to frequent association of learning and visual impairment. At our BBS MDT clinic, dietetic review is provided at each visit. Dietetic input focuses primarily on reduced fat and sugar content in diet and exercise is encouraged. Individualised written dietary plan is provided.

Aims
To assess the effect of dietetic input on BMI–SDS in BBS children.
Methods
All children attending our MDT BBS clinic between January 2007 and December 2014 with at least 3 years follow-up data were included. Paired *t*-test using SPSS was performed to compare the mean difference in BMI–SDS at baseline and follow-up.
Results
There were 48 children (median age 8.1 (range 0.9–15.1) years at baseline). The mean ($\pm$S.D.) BMI–SDS at baseline and after 3 years follow-up were similar 3.14 ($\pm$1.1) vs 3.18 ($\pm$0.9). Patients were grouped into group A, <5 years old at baseline ($n=10$) and group B, >5 years old at baseline ($n=38$). In group A at baseline the median (range) age was 2.4 years (1–4.4) and mean ($\pm$S.D.) BMI–SDS at baseline, 2, and 3 years were 3.8 ($\pm$1.7), 4.4 ($\pm$1.2), and 4.5($\pm$0.88) respectively. In group B at baseline the median age was 9.7 years (range 5.01–15.1) and mean BMI–SDS at baseline, 2, and 3 years were 2.8 ($\pm$0.68), 2.7 ($\pm$0.7), and 2.6 ($\pm$0.6) respectively. The reduction in BMI–SDS at baseline and 3 years was not statistically significant ($P=0.19$). Six children (12.5%) developed type 2 diabetes and one had hyperlipidaemia. Prevalence of hypertension was high at 33% ($n=16$) due to the associated renal problems.
Conclusion
Excess weight gain in early life may be attributed to delayed walking and difficulty in dietary restriction. Despite the increased risk of weight gain in later childhood associated with visual impairment, provision of individualised dietary plans are associated with a non-significant trend towards BMI–SDS reduction.

DOI: 10.1530/endoabs.39.EP95

EP96

A distinct population of islet cells defines diffuse congenital hyperinsulinism in infancy but not other forms of the disease

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Background/hypothesis
Congenital hyperinsulinism in infancy (CHI) mainly arises from mutations in ATP-sensitive potassium channel genes. However, the expression pattern of defects can be markedly diverse. In diffuse CHI (CHI-D) all islet cells express gene defects, whereas patients with focal CHI (CHI-F) only express defects in a localised region of islet cells due to loss of a maternally-imprinted locus. Here, we examined the properties of a novel population of CHI islet cells with enlarged nuclei.
Methods
Tissue was obtained from patients with CHI-D ($n=9$), CHI-F ($n=5$) and age-matched controls ($n=8$, 2 days to 36 months of age). High-content analysis of histological sections and serial block face-scanning electron microscopy were used to quantify nuclear enlargement and determined the extent of nucleomegaly.
Results
Islet cells with nucleomegaly have; i) an average area of $100.1\pm3.8\ \mu m^2$ ($n=105$), which was 4.3- and 5.3-fold larger than nuclei in endocrine ($n=173$) and exocrine cells ($n=115$) respectively; ii) an increased nuclear volume from $157.33\pm9\ \mu m^3$ ($n=22$) to $\sim420\ \mu m^3$; and iii) an endocrine phenotype as they stained positive for the neuroendocrine cell marker chromogranin ($n=398/405$ cells). The incidence of islet cell nucleomegaly was 6.4- and 8.4-fold greater in CHI-D ($0.67\pm0.11\%$ of islet cells, $n=40\ 320$) than in age-matched controls and CHI-F, respectively. Overall, $70.5\pm6\%$ of CHI-D islets contained at least one enlarged nuclei and $45.4\pm7\%$ of islets ($n=179$) were found to have more than one affected cell. As nuclear enlargement might be as a consequence of chromatin decondensation, we examined the correlation of Ki67 staining (as a marker of proliferation) with nucleomegaly. In controls (53%, $n=16/30$) and CHI-F (67%, $n=22/33$) nucleomegaly was positively-associated with proliferation, whereas only 9% of cells with nucleomegaly in CHI-D islets were Ki67 positive ($n=27/291$).
Summary
These findings suggest that nucleomegaly is pathognomonic with CHI-D and unrelated to cell proliferation in CHI-D islets.

DOI: 10.1530/endoabs.39.EP96

EP97

Body surface area estimation in girls with Turner syndrome: implications for interpretation of aortic sized index

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Background
Recent consensus recommends assessment of aortic dimensions with aortic sized index (ASI) normalized for body surface area (BSA) defined as absolute aortic dimension/BSA, in girls with Turner syndrome (TS) as young as 10 years. There are currently multiple formulae for estimating BSA without agreement on a preferred method. We assess the clinical validity of each formulae as this may have implications on interpretation of ASI.
Method
We calculated BSA using Dubois, Mostellar, Haycock (height and weight based) and Furqan (weight based) formulae from 114 girls with TS with height and weight measurements from 2273 outpatient visits. The mean of all four equations was used as gold standard and the mean error (lower limit and upper limit) for each individual formula calculated.
Results
All formulae were highly agreeable, with Mosteller (mean error -0.007, -0.021 to 0.007), and Haycock (mean error 0.001, -0.014 to 0.016) having all estimations accurate to within 5%. 3.9% of Dubios and 9.6% Furqan estimations of BSA had $>5\%$ error. Dubois underestimates BSA in heavier girls. Mostellar underestimates BSA in older, heavier, and taller girls. Haycock overestimates BSA in younger, lighter, shorter girls then underestimates but also overestimates in older, heavier, and taller girls. Furqan overestimates BSA in older heavier, and taller girls. Mean BSA (S.D.) in TS are: 8 years 0.90 cm/m m^2 (0.10); 10 years 1.01 m^2 (0.13); 12 years 1.19 m^2 (0.16); 14 years 1.37 m^2 (0.19); and 16 years 1.51 m^2 (0.21) ($P<0.0001$).
Conclusion
Our study demonstrated for the first time that Dubois, Mosttellar, Haycock, and Furqan formulae perform just as well for estimation of BSA in girls with TS, although under and overestimation can occur in specific situations. BSA increases in a non-linear fashion from the age of 8 years in TS. The clinical implications of this on interpretation of longitudinal changes ASI in growing children with TS need to be validated in future studies.

DOI: 10.1530/endoabs.39.EP97

EP98

Cardiovascular assessment in Turner syndrome: current practice in the UK

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Background
In 2007, the Turner syndrome (TS) consensus study group developed an international guideline for clinical care of girls and women with TS**.** Given emerging concerns of long term cardiovascular complications, the consensus recommends that cardiac MRI should be performed when girls are old enough to tolerate the procedure or at the time of transition and to be repeated at least every 5–10 years.
Method
We conducted a survey of cardiovascular (CVS) assessment in girls and women with TS in all tertiary paediatric endocrinology centres and all adult centres with dedicated TS clinical service in the UK.
Results
An online survey was sent to 49 consultants (20 paediatric and 29 adult). There were 26/49 (53%) responders. 13/26 (50%) provided care in childhood. At diagnosis of TS, echo (9/12, 75%) or echo and MRI (3/12, 25%) were performed. In adolescence, echo (6/13, 46%) or MRI (3/13, 23%) were performed for CVS re-evaluation. However, 4/13 (31%) were not re-evaluated in paediatric care. Median age of re-evaluation was 16 years (range 10–16) or at the time of transition. In adulthood, echo and MRI (10/13, 77%), MRI (2/13, 15%), and echo (1/13) were performed respectively at frequency of 5 years or less. Aortic sized index was provided in imaging reports of 5/10 (50%) and 13/13 of paediatric and

adult responders respectively. Blood pressure was measured in the paediatric clinic: annually 3/12 (25%), 6 monthly 6/12 (50%) and 3–4 monthly 3/12 (25%), whereas this was measured in the adult clinic: annually 10/13 (77%), 6 monthly 2/13 (15%) and at every clinic 1/13. Cardiovascular risk is discussed by the primary treating paediatrician in 7/11 (64%) and by the primary treating adult physician in 12/13 (92%). Written information on cardiovascular risks is provided in 3/10 (30%) and 2/12 (17%) of paediatric and adult clinics, respectively. In high-risk patients, a recommendation to carry medical bracelet/card is provided by 2/10 (20%) and 2/12 (17%) of paediatric and adult clinics respectively.

Conclusion

Despite existing consensus, this survey of clinicians providing care to individuals with TS in the UK demonstrate wide variation in cardiovascular assessment especially in adolescence. This variability may relate to access to local expertise and specialist investigations. Uncertainties surrounding the value of investigations to clinical outcome of aortic dissection especially in childhood may also be a factor.

DOI: 10.1530/endoabs.39.EP98

EP99

Positive thyroid peroxidase antibodies at diagnosis of type 1 diabetes mellitus is associated with earlier onset of thyroid disorders

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Aims

To assess the relationship between thyroid peroxidase (TPO) antibodies and the development of thyroid disorders in children with type 1 diabetes mellitus (T1DM).

Method

TPO antibody status and duration of diabetes at diagnosis of thyroid disorder were cross-sectionally examined in all children attending the Oxford T1DM service ($n=342$, male:female ratio 1:0.8).

Results

Twenty patients were identified with thyroid comorbidity, representing 5.9% of the clinic; with a female preponderance – M:F ratio 1:6. Most patients had hypothyroidism (90%, $n=18$) with 10% ($n=2$) having hyperthyroidism. In one patient the thyroid diagnosis predated the T1DM diagnosis by 5.6 years. She was discounted from further analysis, as were three patients in whom TPO antibody status at diagnosis of T1DM was unknown.

For the remaining patients ($n=16$) TPO antibody status at the time of diagnosis with T1DM was positive in $n=7$. In this group the duration from diagnosis of T1DM to developing thyroid disorders was 0–4.7years (mean 1.4), compared to 0.04–11.9 years (mean 8.1) in those with negative TPO antibodies at T1DM diagnosis ($n=9$). The P value was significant at 0.0005.

Most patients who developed thyroid disorders ($n=16$) were in the pubertal age range: 10–15 years – median age 11.5 years. This is likely to coincide with the onset of puberty.

Conclusion

Positive TPO antibodies at diagnosis in children with T1DM is associated with a significantly earlier onset of thyroid disease. This may warrant closer monitoring of symptoms, and increased biochemical monitoring if clinically indicated. Consistent with observations in non-diabetic populations, there is a higher incidence of thyroid disease in girls with T1DM, particularly around the time of puberty.

DOI: 10.1530/endoabs.39.EP99

EP100

Hypomagnesaemia due to lead poisoning in the context of a heterozygous *CLDN-16* mutation

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A 3-year-old boy born to non-consanguineous parents. He was diagnosed to have autism at 2 years of age. He had a history of pica. He was admitted with severe carpopedal spasms of hands and feet. Investigations revealed severe hypomagnesaemia, hypocalcaemia, hypokalaemia, hyponatremia, and moderately low vitamin D levels. Parathyroid hormone concentration was low. Urine analysis revealed loss of sodium, calcium, magnesium and sodium. Renal functions and renal ultrasound were normal.

He received multiple i.v. infusions of sodium, potassium, calcium, and magnesium and was started on oral calcium, magnesium, and colecalciferol. Hypocalcaemia resolved within few days. However, hypomagnesaemia was severe and persistent despite treatment and renal magnesium losses continued. Blood film revealed basophilic stippling of red blood cells suggestive of lead poisoning. Plasma lead concentration was extremely high and he received chelation therapy with dimercaptosuccinic acid, following which lead concentrations decreased. During chelation treatment, i.v. magnesium was switched to oral magnesium which could be gradually weaned and stopped after 10 weeks. Genetic studies revealed a previously described, but heterozygous mutation in *CLDN16* gene. Heterozygous carriers are not usually symptomatic.

Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive condition that is caused by homozygous mutations in the *CLDN16* gene, which encodes claudin-16, an important tight junction protein expressed in Henle's loop and distal tubule of the kidney. FHHNC is characterised by excessive renal magnesium and calcium loss, persistent hypomagnesaemia, nephrocalcinosis and renal failure. The overall prognosis is poor, and definitive cure is by renal transplantation. It is known that lead poisoning causes toxic effects to all organs, including the kidney, although magnesium loss has not been previously described in humans. In young rats, competitive antagonism between lead, calcium and magnesium has been shown in experimental studies. We suggest that, in our patient, lead poisoning resulted in hypermagnesuria in the context of a heterozygous *CLDN16* mutation.

DOI: 10.1530/endoabs.39.EP100

Pituitary and growth

EP101

Case series evaluating phenotypical and radiological signs of patients with *SHOX* mutation

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Background

Estimates for the prevalence of *SHOX* mutation in children with short stature vary from 2 to 15%. Unless specific clinical and radiological signs are sought these patients can be misdiagnosed as idiopathic short stature. An evidence based clinical scoring system has been published to identify these patients; more recently characteristic radiological signs have also been identified in bone age X-rays. To our knowledge there has not been a survey in the UK evaluating the prevalence of these features.

Aim

To evaluate the phenotypical and radiological signs of a cohort of patients with confirmed *SHOX* mutation, which may be used to identify patients with short stature for genetic testing.

Method

Multicentre retrospective case review in the South West region.

Results

Fifteen patients were identified from eight hospitals. Mean age at diagnosis was 8.75 years with mean height −2.63 SDS (range −4.8 to −0.77). 14/15 had a familial history of short stature (75% had first degree relative with Leri Weill syndrome/*SHOX* mutation). 9/15 patients had documented disproportion. 7/13 eligible patients had a sitting height/height ratio performed: 86% had a ratio >55.5%. Five had an arm span measured: 100% had an arm span/height ratio <96.5%. 73% had a BMI >50th percentile. Nine patients had clinical rhizomelia, four Madelung deformity, and four bowing of forearm. 11 patients had a bone age X-ray: eight showed signs of triangularisation, pyramidalisation, and/or lucency, one result was equivocal and two were too young for analysis.

Conclusions

Analysis of our cohort identified key features that would prompt *SHOX* mutation analysis in a child with short stature. This included a positive family history, disproportion, and characteristic signs on a standard bone age X-ray. Approach to measuring disproportion varied throughout the South West. We propose a simple screening tool to identify patients more likely to have *SHOX* mutation.

DOI: 10.1530/endoabs.39.EP101

EP102

Final adult height and childhood growth trajectories in a cohort of preterm infants

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Background
Many premature infants experience significant early growth failure in the weeks following delivery. Subsequent catch-up growth has traditionally been assumed to have occurred by early childhood. Most studies have focused on cohorts defined by birth weight, for example, <1500 g resulting in disproportionate numbers of small for gestational age (SGA) infants as opposed to those small solely as a consequence of prematurity. Few studies have examined growth compared to local term control populations.
Aim
To determine whether preterm appropriate weight for gestational age (AGA) children reach their expected adult height when compared to term controls.
Methodology
This UK based prospective longitudinal cohort study, recruited 204 preterm children born at a tertiary neonatal unit during 1994 and a group of 50 matched controls. Growth parameters have been assessed annually until the completion of growth.
Results
The final height SDS of children born prematurely ($n=80$) was not significantly different to term controls ($n=30$) (0.45 term vs 0.10 preterm, $P=0.156$). However, catch-up growth continued throughout the whole of childhood. There was a non-significant trend towards the most preterm children, born at <29 weeks gestation, having a lower final height SDS (mean final height SDS −0.35, $P=0.075$). Children born both preterm and SGA ($n=7$) were however, significantly shorter than their peers and their parents regardless of the degree of prematurity (mean final height SDS −0.98 (SGA) vs 0.18 (AGA), $P=0.01$).
Conclusion
The preterm AGA population achieve a comparable adult height to children born at term, however, catch-up growth continues for much longer than traditionally thought.

DOI: 10.1530/endoabs.39.EP102

EP103

Does better adherence to GH treatment using jet rather than needle delivery translate into improved growth outcomes?

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Introduction
We wanted to assess whether our report of better adherence to GH therapy using jet (ZomaJet) rather than needle delivery in a large nationwide cohort, translated into better growth outcomes.
Aims and hypothesis
To retrospectively audit growth markers in our local split-site (GOSH/UCLH) cohort of children, starting GH using Zomajet between 01.01.2010 and 31.12.2012, for whom we had previous adherence (PDC) scores.
Methods
Of 75 local patients identified from the national cohort, 55 met the eligibility criteria for indication (GHD) and age (<16 years). Patients with PDC score >0.8 were considered adherent. Age and sex-SDS for height (HTSDS), IGF1 (IGF1SDS), and height velocity (HVSDS) were compared between and within adherent (n 33) and non-adherent (n 22) groups after 1 year and at end of assessment period with nonparametric statistics. Data is presented as median and range.
Results
There were no significant intergroup differences in baseline age, height, IGF1, mid-parental height (MPH) SDS, GH starting dose or duration. Eight patients in adherent and one patient in non-adherent groups switched to needle devices. Increments in HTSDS, HVSDS, and IGF1SDS at 1 year and end observation were similar between groups ($P>0.05$) with significant comparable gains in nine patients (six adherent) achieving adult HTSDS close to individual target MPHSDS ($P<0.05$). Significant longitudinal intragroup improvements occurred for adherent patients in HTSDS (n 27), IGF1SDS (n 14), and HVSDS (n 19) ($P<0.05$; see Table 1), but not for non-adherent patients ($P>0.05$).

Adherent patients	Treatment start, median (range)	1 year of treatment	Observation period end	*P* value (Friedman)
HTSDS	−1.73 (−3.88 to 2.43)	−0.99 (−3.62 to 0.98)	−0.67 (−3.48 to 2.24)	<0.01 S
HVSDS	−1.92 (−6.70 to 4.68)	1.21 (−2.53 to 6.52)	1.08 (−5.03 to 11.11)	0.03 S
IGF1SDS	−2.70 (−4.10 to 1.30)	−0.45 (−2.90 to 3.90)	0.05 (−3.20 to 5.20)	0.02 S

Conclusion
Improved adherence with Zomajet may translate into better height outcomes. This hypothesis will be explored in a larger local dataset comparing jet with needle devices.

DOI: 10.1530/endoabs.39.EP103

EP104

Overcoming the need for a second test: an evaluation of anthropometric, biochemical, and radiological parameters in the diagnosis of GH deficiency

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Background
The investigation of short stature includes evaluation of a number of clinical, radiological, and biochemical factors. This often includes dynamic function testing to rule out abnormalities of the hypothalamic–pituitary axis to rule out GH deficiency (GHD). NICE guidance advises that two GH stimulation tests demonstrating subnormal GH peak <6.7 μg/ml (20 mU/l) is required to confirm the diagnosis of GHD.
Objectives
To interrogate various clinical and biochemical parameters to reduce the need for dynamic function testing in the diagnosis of isolated GHD (IGHD) vs idiopathic short stature (ISS).
Methods
A retrospective case-review of all patients in a single centre from 2002 to 2014 undergoing two provocation tests.
Results
138 patients underwent GH testing, 32% (45) had a normal GH peak (>6.7 μg/l) on repeat testing.

	IGHD	ISS	*P* value
Gender	27F: 66M ($n=93$)	13F: 32M ($n=45$)	
Mean			
Age at first assessment	8.1 (0.95–16.29; SD 4.2)	7.9 (1.09–14.1; SD 3.7)	NS
BA delay	−1.1 (−5.2 to 2.8; SD 1.33)	−0.86 (−5.8 to 1.5; SD 1.2)	NS
Low IGF1	37 (39.8%)	10 (22%)	NS
HV SDS pre-test	−0.86 (−5.9 to 5.1; SD 2.1)	−0.5 (−5.3 to 11.85; SD 3.3)	NS
HV SDS 1 year post test	2.36 (−4.3 to 13.6; SD 3.5)	0.6 (−5.2 to 7.2; SD 3.5)	0.016
Final height SDS	−0.92 (−5.6 to 1.8; SD 1.9)	−1.19 (−2.2 to 0.6; SD 0.9)	NS

Conclusions
Approximately one-third of patients who undergo dynamic function testing for GHD will have a normal GH peak on re-test. We have previously shown that there is no cut-off on the first test that will predict an abnormal second test. There is no difference between IGHD vs ISS in terms of mean BA delay, IGF1 levels and pre-test HV SDS which improves the pre-test probability of having a low GH peak on

two tests. There is a significant difference between HV SDS between IGHD and ISS 1 year after dynamic testing, reflecting the effect of GH treatment in IGHD. There appears to be no significant difference in final height outcomes in either group. At present, undertaking two GH stimulation tests appears to be the best way to distinguish IGHD from ISS.

DOI: 10.1530/endoabs.39.EP104

EP105

Childhood somatotroph pituitary adenomas due to aryl hydrocarbon receptor interacting protein (*AIP*) gene mutations

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Introduction
Two childhood cases of somatotroph pituitary adenomas caused by aryl hydrocarbon receptor interacting protein (*AIP*) mutations highlight the importance of screening for familial isolated pituitary adenoma (FIPA) genes and wider family implications.
Case 1
A 13.5-year-old girl presented with 5 years growth acceleration and size ten feet, with no headache or visual disturbance. Examination: coarse facial features, large hands and feet, height SDS +2.8. Investigations: marked IGF1 elevation (208 nmol/l (23–90)), oral glucose tolerance test (OGTT) showed elevated baseline GH (>40 μg/l) and unsuppressed nadir (19.1 μg/l). An 18 mm pituitary mass with suprasellar extension was surgically resected. Unfortunately post-operative sphenoidal abscess resulted in permanent left temporal upper quadrantanopia. Following surgery, height velocity and IGF1 normalised, other pituitary function is normal and no medical treatment required. A heterozygous frameshift *AIP* mutation c.376_377del;p.Q126fs was identified, diagnosing FIPA.
Case 2
A 10.3-year-old boy presented with daily headaches and sudden onset blurred vision, with recent growth acceleration and increased shoe size. Examination: height SDS 2.8 with blurred temporal visual fields. A 23 mm pituitary adenoma with suprasellar extension was identified on urgent MRI and resected transsphenoidally. Post-operatively: histologically immunopositive for GH, elevated IGF1 (91.4 nmol/l), elevated baseline GH (41.2 μg/l), and OGTT nadir (17.5 μg/l), pituitary function otherwise normal. Long-acting somatostatin analogue was commenced. Targeted genetic testing of the *AIP* gene identified a disease-causing missense mutation c.811C>T;p.R271W.
Family testing was important as *AIP* mutations show autosomal dominant inheritance with 30% penetrance. In both cases the mother proved to be AIP carrier and siblings are under investigation.
Summary
About 50% of identified AIP-kindreds have no known family history. Childhood-onset isolated GH-secreting tumours may be index cases of FIPA and should prompt *AIP* mutational analysis. This facilitates management focussed on GH excess allowing discontinuation of other endocrine tumour screening and prompts cascade screening of family members to allow early identification of GH excess in family members.

DOI: 10.1530/endoabs.39.EP105

EP106

Acid-labile subunit deficiency: a case report

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Background
Acid-labile subunit (ALS) protein plays a vital role in maintaining the serum IGF by prolonging the half-life of IGF/IGFBP binary complex. ALS deficiency due to IGFALS gene mutation results in primary IGF1 deficiency and associated with growth impairment, insulin resistance and occasionally delayed puberty.
Case report
A 9-year-old boy was referred for short stature (height −1.8 SDS and weight −1.8 SDS). He is the sixth of non-consanguineous parents of Asian origin. His birth weight was 2.9 kg (−1.3 SDS). His older sister (18 years) was diagnosed with idiopathic short stature with final adult height of −3.9 SDS. His mother measures 160 cm (−0.6 SDS) and father 174 cm (−0.6 SDS) and his mid-parental height 170.5 cm (−0.8 SDS). There was strong family history of type 2 diabetes. He later became overweight and had developed marked acanthosis nigricans. Pubertal assessment showed pubic hair Tanner stage 1, genital stage 2 testicular volume 6 ml bilaterally. Despite pubertal progression, his height velocity remained at 5.3 cm/year (−1.7 SDS).
Investigations for short stature showed persistently low IGF1 (<3.3 nmol/l, normal range 8.5–60), normal thyroid function. Insulin Tolerance test on two occasions failed to produce hypoglycaemia. Glucagon stimulation test showed normal GH peak (8 μg/l). Pubertal response was noted in LHRH test. Oral glucose tolerance test (OGTT) found to be normal with insulin resistance (HOMA-IR 19.9). Subsequent OGTT was impaired and whole exome sequence identified mutation in *IGFALS* gene.
Conclusion
ALS deficiency is a rare condition and it is associated with short stature and insulin resistance. Insulin insensitivity may be due to increased GH, impairing insulin action by lipolytic effect or by impairment of insulin signalling. Decreased IGF1 levels may also be playing a role in Insulin resistance. Despite the marked reduction in IGF1, the growth impairment can be moderate.

DOI: 10.1530/endoabs.39.EP106

EP107

Manifestations of overt diabetes on GH treatment

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GH therapy has been reported to increase insulin resistance, but overt diabetes is rare. We present a young girl who developed symptoms of diabetes whilst on GH therapy with resolution of symptoms and normalisation of blood glucose profile on reducing the dose of GH.
Case report
A 14-year-old girl with background of prematurity, learning difficulty, cerebral palsy, scoliosis, and pan hypopituitarism presented with chest infection, high blood glucose levels (32 mmol/l) and polyuria. She was on hormone replacement therapy with GH, thyroxine, and hydrocortisone. She was commenced on basal bolus insulin regimen but insulin doses needed to be increased rapidly to around 2 units/kg per day, due to persistently elevated blood glucose readings.
Her HbA1c was 75 mmol/mol, but islet cell and glutamic acid decarboxylase antibodies were later found to be negative. Looking back at her auxology data, it was noted that there had been difficulty in getting an accurate height measurements in clinics due to scoliosis. She had been on GH treatment dose at 32 μg/kg per day for past 2 years. Her latest IGF1 levels were markedly elevated at 1363 μg/l (RR 230–950 for her age). In view of her diagnosis of diabetes, the dose of GH was reduced to adult replacement dose. Within 6 weeks her bolus insulin was stopped due to recurrent severe hypoglycaemia. 12 months later her long acting insulin analogue could be stopped. Her blood glucose profile remained stable in near normal range with latest HbA1c of 37 mmol/mol.
Conclusion
GH treatment has potential to cause insulin resistance. For children with disability assessing height velocity can be a challenge and clinicians should be vigilant about reducing the dose of GH to adult replacement dose in a timely manner.

DOI: 10.1530/endoabs.39.EP107

EP108

Achieving a consensus on managing idiopathic thickening of the pituitary stalk through a national multidisciplinary forum, meeting virtually

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Objectives
In 2010 we piloted a national multidisciplinary (MDT), meeting virtually to improve management of rare suprasellar (HPAT) tumours. In 2014 we reported centralised treatment decision-making in craniopharyngioma and now wished to

examine whether centre based management of idiopathic thickening of the pituitary stalk (iTPS) differs and can be streamlined by wider debate. This might also inform current commissioned BSPED and CCLG guidance.
Methods
We assessed centre uptake of HPAT MDT recommendations of 20 iTPS cases from five centres between 1.1.12 and 1.6.15 and their endocrine outcomes by case note review. MRI 3D volume was analysed with ITK-SNAP v 3.2.0 (www.itksnap.org) Software and with centralised radiology review.
Results
Patients presented at mean age 8.9 (range 3–16) years with low height −0.8 (−4.5 to 1.1) and weight −0.2 (−3.63 to 2.26) SDS but higher BMI +0.44 (−1.59 to 2.43) SDS. 75% (15) had polydipsia but 80% (16) confirmed DI, 55%(11) were GHd with ACTHd (4), TSHd (2), or Gnd(1) and two had visual dysfunction. One centre presented two biopsied histiocytosis cases. In 60% (12) a watch and wait strategy was recommended, and centres deferred GH replacement in 50%. All underwent PST, serum HCG and AFP, but only 55% had CSF markers, 66% plasma ACE, and 77% skeletal surveys and ophthalmic review. MDT discussion influenced management in 40% and debate in 60%. At an average 2 (0.26–4.5) years follow up, three more (15%) developed TSHd and ACTHd but not DI or GHd. Height 0.2 (−3.4 to 2.3) SDS improved and BMI +0.46 (−3.1 to 3.7) were unchanged. 8 (40%) cases remained idiopathic with stable scans, TPS disappeared in 2 (10%) within 2 years, decreased in 3 (15%), worsened in 1 (5%) and 20% awaited scans. MRI 3Dvolume did not correlate with initial endocrinopathy.
Conclusion
Centres have valued the opportunity to discuss this rare and complex condition where management is controversial and differs. This forum has enabled wider discussion, consensus and audit of practice and outcomes which can inform national guidance.

DOI: 10.1530/endoabs.39.EP108

EP109

A rare case of congenital hyperinsulinism associated with hypopituitarism due to pituitary stalk interruption syndrome

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Introduction
Congenital hyperinsulinism (CHI) is a rare genetic disorder that is characterised by persistent hypoglycaemia in infants and children. We are reporting a rare case of diffuse CHI who was also found to have hypopituitarism and several other congenital anomalies. A similar association has not been reported in literature.
Case
A female baby was born at 42 weeks gestation with a birth weight of 4.185 kg (1.72 SDS). She suffered shoulder dystocia and was ventilated for 12 days. Her persistent hypotension, hyponatraemia, and hypoglycaemia triggered further investigations. She was noted to have low free T_4 (5.3 pmol/l), undetectable TSH (<0.03 mU/l), and plasma cortisol (<50 nmol/l). She was commenced on levothyroxine and hydrocortisone. Her glucose requirement remained high at 20 mg/kg per min and the hypoglycaemia screen revealed raised insulin (90 pmol/l) and suppressed free fatty acids and ketones during hypoglycaemia confirming CHI. The hypoglycaemia was initially managed with high concentration dextrose infusion and i.v. glucagon. She was subsequently started on diazoxide but developed cardiac failure; therefore it was replaced by s.c. octreotide injections. This was later discontinued due to liver dysfunction. Genetic analysis was negative for *ABCC8*, *KCNJ11*, and *HNF4A* mutations and microarray was normal. She was also noted to have pulmonary stenosis requiring balloon dilatation, unilateral choroidal coloboma, and facial dysmorphic features including single median incisor. MRI brain showed hypoplastic anterior pituitary gland with absent posterior pituitary and the ^{18}F-DOPA PET–CT scan showed a diffuse pancreatic lesion. She is now 3-year-old and manages with continuous gastrojejunostomy feeds, hydrocortisone, levothyroxine, and GH.
Conclusion
We report a rare association of diffuse persistent CHI and hypopituitarism in a patient with several other associated anomalies with probably an unidentified genetic aetiology. The described case highlights the importance of maintaining a high degree of suspicion for alternative diagnoses in infants diagnosed with hypopituitarism but have persistent hypoglycaemia.

DOI: 10.1530/endoabs.39.EP109

EP110

Radiolucent hand outline: a simple intervention to improve quality of bone age X-rays

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Background
X-rays of the left hand and wrist are used to assess skeletal maturity. The Tanner-Whitehouse 3 (TW3) scoring method provides a framework for calculating bone age but specifies exact hand position. We noted a number of poor quality films, caused by difficulty with hand placement, e.g. scrunching of the fingers. This compromises the ability to score accurately and in a proportion necessitates re-X-ray, resulting in additional time, cost and radiation exposure. We introduced a simple radiolucent hand template to assist in positioning of the patient's hand and assessed changes in X-ray quality and need for re-X-ray.
Method
The position of fingers, thumb and overall clarity of bone age X-rays were prospectively scored by a single Auxology Nurse blinded to whether or not the template was used. In the absence of a validated tool to assess quality a 1–3 scale (poor, adequate, and good) was devised. A radiolucent hand template was used in the intervention group. The need for re-X-ray was determined by set criteria.
Results
There were no significant differences between the control ($n=259$) or intervention groups ($n=56$) in terms of gender. The intervention group were slightly younger ($P=0.03$). Patients age ranged between 0.9 and 18.48 years (mean$=9.99\pm3.84$). The intervention improved scores. Fewer patients scored <3 for the position of fingers (14.67 and 10.71%, $P=0.38$), thumb (10.04 and 1.79%, $P=0.06$), and overall clarity (29.73 and 23.21%, $P=0.41$) for the intervention and control groups respectively. The template significantly reduced the numbers requiring repeat X-ray. No patient required a re-X-ray from the intervention group, compared to 28 in the control group ($P=0.007$).
Discussion
Achieving good quality bone age X-rays may be more difficult than previously assumed. The use of a simple radiolucent hand template has been shown to improve the positioning of the hand and significantly reduce the need for re-X-ray.

DOI: 10.1530/endoabs.39.EP110

EP111

Cost feasibility study: performing GH stimulation test only not full anterior pituitary function tests for simple short stature

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Background
Currently we investigate children with possible GH deficiency, but who are healthy, with a normal short stature screen, and without suspicion of other pituitary dysfunction ('simple short stature'), with full dynamic anterior pituitary function tests (APFT). An abnormal GH peak leads to a second GH stimulation test. We studied the cost implications of only performing a GH stimulation test initially, followed by full APFT if the initial GH peak was low, to ascertain the risk of missing or delaying the diagnosis of significant pituitary pathology.
Methods
Retrospective case notes review of all patients having APFT to investigate 'simple short stature' from January 2011 to December 2014. Results were examined to determine the response to GH stimulation, abnormal or suboptimal results of other pituitary hormones and their clinical significance. The costs of performing the different tests were calculated and the potential cost savings over the 4 years determined.
Results
Fifty-five patients had an APFT for 'simple short stature' of which 11 had an abnormal GH peak. GH deficiency was confirmed on second testing in four, and in two patients whom only needed a single test for diagnosis. Five patients had other minor biochemical abnormalities, none of which were investigated further as they were deemed clinically insignificant. Testing using the current approach cost £24 255.71 over 4 years, the proposed change would cost £14 289.80 (with full anterior pituitary baseline bloods) or £8575.30 (with IGF1 and GH only), resulting in a cost saving of £9965.91 or £15 680.41 (£181.20 or £285.10/patient).

Discussion
Performing GH stimulation only, at the point where dynamic testing is first indicated to investigate simple short stature, would yield considerable financial savings, a reduction in false positive results and all without missing any other significant pathology. A change of practice is being instigated locally in light of these findings.

DOI: 10.1530/endoabs.39.EP111

EP112

Skeletal disproportion in Turner syndrome

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Aims
The aim of this study is to evaluate sitting height (SH) and leg length (LL) in girls with Turner syndrome.
Methods
Retrospective study of SH and LL SDS, using SH–LL SDS (~0 in a proportionate child) as a measure of disproportion in 76 girls with Turner syndrome. Eligible girls were aged at least 4 years, had not started recombinant GH, and had no other chronic disease. 40 girls with measurements prior to pubertal induction and at adult height (AH) were assessed. Results as mean ± S.E.M.
Results
Of the 76 girls (9.3 ± 0.38 years), Ht SDS was −2.83 ± 0.10 with disproportionately shorter legs (LL SDS −3.65 ± 0.13) compared to their spine (SH SDS −1.64 ± 0.10) ($P<0.0001$). Thirty-five girls (46.1%) had SH–LL SDS > +2.0. Age was negatively associated with SH SDS ($r=-0.41$, $P<0.0001$) and SH–LL SDS ($r=-0.20$, $P=0.08$) but was not associated with Ht SDS or LL SDS. Ht SDS, SH SDS, LL SDS, and SH SDS–LL SDS did not differ between girls with 45X ($n=27$) and those with other karyotype ($n=49$).

	Before pubertal induction	At adult height	*P* value
Age (years)	13.0 ± 0.25	17.5 ± 0.23	<0.0001
Ht SDS	−2.29 ± 0.16	−1.86 ± 0.17	<0.0001
SH SDS	−1.42 ± 0.16	−1.05 ± 0.12	0.001
LL SDS	−2.90 ± 0.17	−2.02 ± 0.19	<0.0001
SH–LL SDS	1.48 ± 0.17	0.97 ± 0.16	0.002

Conclusion
Our data suggests that an assessment of skeletal disproportion is important in the evaluation of a short girl. The diagnosis of TS may be more likely in a short girl with significantly lower leg length compared to sitting height, although this needs to be validated in larger group of girls with short stature. At adult height, with current oestrogen replacement regime, disproportion was still present but less pronounced. There is a need to evaluate treatment factors and their impact on disproportion in girls with TS, especially oestrogen replacement.

DOI: 10.1530/endoabs.39.EP112

EP113

Endocrine outcomes in hypothalamic hamartoma: a single-centre study

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Background
Hypothalamic hamartomas (HH) are congenital, benign tumours consisting of disorganised neuronal cells within the hypothalamus. They usually present with precocious puberty, seizures, behavioural abnormalities, either in isolation or combined.
Aims
To look at the endocrine outcomes of patients with HH.
Methods
A retrospective casenote review of all patients diagnosed with HH over a 20-year period within a single endocrine centre.
Results
In total, data on 13 patients was available (9F:4M). Mean age of diagnosis was 3.8 years (range 0.08–9.5). Nine patients (7F:2M) had central precocious puberty (CPP) and two additionally had GH deficiency (GHD) at presentation. Three patients had surgery (for intractable seizures) and subsequently developed diabetes insipidus (transient), hypothalamic obesity, and behavioural changes. One child was found to have a *GLI3* mutation associated with Pallister–Hall syndrome.
Treatment for CPP was with regular GnRH analogue treatment, titrated to clinical symptoms. Treatment halted pubertal progression in all cases and reduced bone age advancement in 6/13 patients. Final height data were available on seven patients – mean final height SDS 0.02 (range −1.52 to +2.06). Most patients (5/7) achieved height within the expected mid-parental target range. 6/7 were overweight (mean BMI +2.36; range 1.39–3.01). For the seven patients who completed puberty, one was severely obese with 3.01 S.D., five were overweight with BMI SDS >2 and one had a normal BMI SDS at final height.
Menses occurred in all female patients ($n=3$) once GnRH therapy was withdrawn at an appropriate age. No information was available about fertility.
Conclusion
Most studies on HH have focussed on neurological/behavioural outcomes or endocrine presentation. Here, we show that final height in the majority of patients is not adversely affected compared to the general population and that the main endocrine abnormalities at diagnosis are CPP and GHD with excessive weight gain being a long term problem.

DOI: 10.1530/endoabs.39.EP113

EP114

Growth monitoring in girls attending a tertiary paediatric ENT service with middle ear disease

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Background
Recurrent middle ear disease may lead to poor growth or may suggest an underlying diagnosis associated with short stature. The aim of the study was to describe stature in a cohort of girls attending a paediatric ENT service.
Methods
Height and weight was measured in all girls attending ENT clinics over an 8 week period ($n=83$). A mid-parental height (MPH) was calculated from reported parental heights. The final ENT diagnosis was catergorised as: otitis media with effusion (group 1); recurrent acute otitis media (group 2); cholesteatoma (group 3); or otitis media with perforation (group 4).
Results
For the whole group the median age was 5.89 years (0.82, 14.49), median height SDS was 0.09 (−4.13, 2.86), median BMISDS was 0.44 (−2.49, 4.12). 2/83 girls (2.4%) had both height <−2S.D. and >1.5S.D. lower than MPHSDS, (Trisomy 21, short stature under paediatric review). An additional 7/83 (8.4%) had height >1.5S.D. lower than MPHSDS. The median age, either height parameter effected, ($n=9$) was 5.67 (2.38, 14.49); median height SDS −0.76(−4.13, −0.28) and median BMISDS −0.33(−1.53, 2.37).

	Group 1	Group 2	Group 3	Group 4
Number	52	23	7	1
Median age (range)	6.02 (0.82, 14.49)	4.13 (1.45, 9.80)	9.28 (4.65, 11.64)	3.72
Median height SDS (range)	0.15 (−4.13, 2.86)	−0.34 (−1.26, 1.39)	0.27 (−1.35, 0.67)	0.43
BMISDS (range)	0.51 (−1.53, 4.19)	0.23 (−2.85, 2.71)	0.45 (−1.01, 2.22)	2.18
Median height SDS-MPHSDS (range)	−0.04 (−3.91, 2.92)	−0.62 (−2.11, 2.62)	−0.17 (−1.30, 2.38)	−0.10

Conclusion
Most girls attending an ENT tertiary service with middle ear disease had a height within the normal range. However, 10.8% may be shorter than their genetic potential.

DOI: 10.1530/endoabs.39.EP114

EP115

Growth monitoring and use of growth hormone in children with renal failure

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Background
Chronic renal failure can cause significant growth impairment. Many factors contribute towards growth failure and it has a significant impact on morbidity, mortality and quality of life. Patients who undergo renal transplantation experience some 'catch-up' growth but most patients do not reach their target height. It is important that growth is monitored regularly and growth failure addressed, including offering patients growth hormone (GH) where appropriate.
Objective
We appraised our current practice to see how well we are monitoring growth in renal failure patients and if we are offering GH to eligible patients.
Method
We defined standards from NICE guidelines and Bristol guidelines endorsed by BSPED. We collected data from 76 patients on haemodialysis, peritoneal dialysis or post-renal transplant.
Results
We found 16/44 (36%) post-transplantation and 20/32 (62%) dialysis patients had growth failure as defined by height $<2^{nd}$ centile, slightly higher than quoted in the literature (29 and 41% respectively). 53/76 had growth charts in their notes, and 39/53 had their height and weight plotted regularly. 12 patients were potentially eligible for GH and not previously offered it. 11 patients were on or had previously received GH and were managed in line with NICE guidance.
Conclusions
Growth monitoring needs to be improved in renal failure patients. Growth failure should be highlighted in the problem list and addressed at clinic visits to improve their growth. 12 patients need discussing jointly by the nephrology and endocrinology teams and considering for GH. Patients on or who have had GH are managed appropriately.
Impact on Practice
Four patients in the post-transplantation group (first group reviewed) have been offered GH and two families accepted it. Eight patients are currently being reviewed. Growth charts have been placed in all patient notes. Findings have been shared with the nephrology team in a local meeting to improve awareness.

DOI: 10.1530/endoabs.39.EP115

EP116

GH deficiency and phenotypic features in four cases of 22q11.2 deletion syndrome

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Background
22q11.2 deletion syndrome (22q11DS) displays a wide phenotypic spectrum and is the most common deletion syndrome with an estimated incidence of one in 4000 children. Short stature is a phenotypic feature of the spectrum; uncommonly, GH deficiency (GHD) has been identified as a cause of short stature within this population.
Patients and methods
We describe a case series of four 22q11DS patients with concurrent GHD that have been followed up in our paediatric endocrinology clinics; we present clinical, auxological, biochemical, and neuro-radiological data.
Results
All four patients had heights below the 0.4th centile. They subsequently underwent GH provocation testing (Table 1) and were diagnosed with GHD. No other pituitary hormone deficiencies were identified. Three of the four patients had familial 22q11 deletions (Patients 1 and 2 were siblings). All four patients had dysmorphic features and congenital heart disease. Patients 2 and 3 had small anterior pituitaries. Patient 4 had cryptorchidism, which was later surgically corrected. The patients were all commenced on GH replacement therapy, with an excellent response.

Table 1

Patient	Age (years)	MRI appearance	Source of 22q11 deletion	GH peak (μg/l)	IGF1	IGFBP-3
1	3	Right-sided polymicrogyria	Paternal	5.8	7.1 pmol/l (4–20)	*
2	3	Small anterior pituitary and right-sided polymicrogyria	Paternal	3.2	19 pmol/l (4–20)	*
3	2.7	Small anterior pituitary, normal posterior pituitary and stalk	Sporadic	5.0	29 ng/ml (49–289)	1.55 mg/l (0.9–4.3)
4	7.16	N	Maternal	6.5	30 ng/ml (45–302)	1.78 mg/l (1.6–6.5)

*N/A, N – normal but specific report not available, M-mother, F-father

Conclusion
Our data suggest that 22q11DS patients with short stature should be appropriately investigated for GHD if they manifest poor growth; early treatment with r-hGH may help optimise height.

DOI: 10.1530/endoabs.39.EP116

EP117

Brain or the kidneys? Nephrogenic Diabetes Insipidus with loss of Pituitary brightness on MRI.

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A 6 month boy with chronic vomiting and severe weight faltering (birth weight 50th to 75th centile dropped to 0.4th centile) originally attributed to gastro-oesophageal reflux was admitted after a period of poor urine output and found to have severe hypernatraemia (Na 168 mmol/l, K 4.1 mmol/l, Urea 16.2 mmol/l, Creatinine 54 umol/l) with high plasma osmolality (330 mosm/kg) and inappropriately low urine osmolality (130 mOsm/Kg). Renal USS was normal with slightly small kidneys.
Thyroid function tests were TSH 2.7 miu/l & free T4 9.2 pmol/l suggesting a pituitary problem and so hydrocortisone, thyroxine and DDAVP were commenced. Urine output was high at up to 8 ml/kg per h even after DDAVP introduction with eventual rise in Sodium to 187 mmo/l.
The child was transferred to the regional centre for assessment.
An MRI Brain showed loss of posterior pituitary bright signal with prominent sulci (felt to be secondary to marked dehydration) supporting a diagnosis of central DI. DDAVP was continued, as the initial poor response to DDAVP was blamed on the acute renal insult. Subsequently electrolytes improved, this was felt to be due to fluid management rather than DDAVP response as polyuria persisted.
DDAVP trial: PRE-DDAVP osmolalities: Urine: 143 mOsmol/kg, Serum: 301 mOsmol/kg.
Post DDAVP urine osmolality: 142 mOsmol/kg.
A Standard Synacthen test showed normal peak Cortisol response (789 nmol/l) and repeat Thyroid function tests were TSH 3.39 miu/l & free T4 17.4 pmol/l hence Hydrocortisone and Levothyroxine were stopped.
A diagnosis of Nephrogenic DI was made and DDAVP was stopped. Chlorothiazide and Amiloride have produced gradual improvement of polyuria and weight on low Renal solute formula alongside liberal intake of water (180 mls/kg per day). Indomethacin was discontinued because of vomiting.
Clinical lesson: the loss of posterior pituitary bright spot is not always indicative of cranial DI as it can occur after exhaustion of vasopressin reserves in a child with Nephrogenic DI.

DOI: 10.1530/endoabs.39.EP117

EP118

Mosaic form of Turner's can be associated with normal stature and spontaneous puberty: a case report.

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Background
Turner's syndrome is the most common sex chromosome abnormality in females resulting from a 45,X cell line. A mosaic chromosomal complement (e.g. 45,X/46,XX) is detectable in over half of all patients with Turner's. Characteristically girls with Turner syndrome have a short stature attributable to the presence of *SHOX* (short stature homeobox-containing gene on the X chromosome) gene. Most affected women have no pubertal development and primary amenorrhea due to premature ovarian failure. There is a paucity of literature reporting Turner girls with normal height and spontaneous puberty. We describe a girl with mosaic form of Turner's with normal stature achieving spontaneous puberty.
Case
An 11-year-old girl was diagnosed with Turner's syndrome by amniocentesis and confirmed postnatally. Amniocentesis was performed due to maternal age. A karyotype of 45,X(19)/46,XX(11) confirmed a mosaic form of Turner's. Phenotypically she has dysplastic nails and a left accessory nipple. However, her renal ultrasound scan and cardiac ECHO were normal. Her thyroid function is normal. She receives support for mathematics. There are no other known learning difficulties. Dad is 180.34 cm. Mum is 170 cm. The mid-parental height is 168 cm and target centile range is between the 25th and 98th.
Our patient's height remains on the 91st centile. Her weight is on 25th centile. Pubertal changes occurred at 10 years of age with spontaneous menarche at 10.6 years. Baseline gonadotropins were elevated; FSH of 8.9 iu/l, and LH of 2.6 iu/l An GnRH test performed at 15 months of age showed an exaggerated FSH response. Her Anti-Mullerian Hormone is 16.36 pmol/l (2.56–17.0 pmol/l) suggesting low ovarian reserve. Family have been counselled regarding the possibility of premature ovarian failure.
Conclusion
Mosaic forms of Turner's syndrome may not show problems related to growth. Antenatal screening may change our perception of Turner's aiding appropriate counselling and follow up.

DOI: 10.1530/endoabs.39.EP118

Thyroid

EP119

Auditing the congenital hypothyroidism (CHT) screening programme in the North East and Cumbria region

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Introduction
UK Screening for CHT was introduced in 1981 to facilitate early detection, treatment and prevent associated morbidity and mortality. Screening in the North East and Cumbria is coordinated by the XXXXXX. A locally defined threshold of TSH >6 mU/l constitutes a positive screening test in contrast to national guidance of >10 mU/l. We explored the longer-term outcomes of infants identified by the screening programme.
Aim
The aims of this audit were to one. Determine the outcome and final diagnosis of patients screening positive for CHT in our region, two. Establish the overall prevalence of patients with CHT in the North East and North Cumbria region, three. Determine the outcomes of infants with screening TSH levels between 6–10 mmol/l.
Methods
Full caldicott approval was obtained. All patients screened by the service born between 1 April 2005 and 1 January 2011 were included. Mean blood TSH >20 mU/l on first screen or >6 mU/l in those subject to repeat testing in the 6–20 range constituted a positive result. Case notes of identified patients were reviewed.
Results
107 patients screened positive on first or repeat testing. We obtained results for 93 patients. 76% patients receiving thyroxine at 3 years of age and beyond had permanent CHT and 17% had transient hypothyroidism. 5% ($n=5$) patients had normal thyroid function, 1% ($n=1$) possible transient hypothyroidism due to a variant in the TSH receptor and the remaining 1% ($n=1$) hyperthyrotormaninam which resolved. Only 27% ($n=17$) of patients underwent thyroid imaging of which 71% revealed a radiologically normal thyroid gland. Abnormalities were identified in 29% of which three patients had thyroid agenesis and one demonstrated thyroid dyshormonogenesis. Of those with a TSH 6–9.9 mU/l ($n=16$) 62% did not have permanent CHT compared to 21% ($n=15$) of those with a TSH >20 mU/l
Conclusion
The estimated incidence of CHT in the North East and Cumbria is one in 3000. This is in keeping with the national incidence as estimated by the newborn screening programme. 9% of infants with permanent CHT screened in the North East and Cumbria region would not have been identified if the recommended national cut off (10 mU/l) had been used. Although only a minority of babies underwent imaging, no baby in the 6–10 mU/l category had demonstrable dysgenesis or dyshormonogenesis. It remains to be determined whether these babies have benefited from thyroxine intervention.

DOI: 10.1530/endoabs.39.EP119

EP120

Combined hypothyroidism and hypoparathyroidism in an infant following maternal administration of Iodine^{131} in early pregnancy

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Background
In adults, hypoparathyroidism is a rare, but recognised complication of radioactive Iodine therapy. Hypothyroidism has been reported in neonates who have been exposed to Iodine^{131} in-utero, however, only one case of neonatal hypoparathyroidism secondary to maternal Iodine^{131} therapy has been described in the literature. To our knowledge this is the first case in the UK.
Case presentation
A 27-year-old woman received two doses of Iodine^{131} therapy following total thyroidectomy for thyroid carcinoma. The first dose was given approximately 3 months prior to conception and the second dose at an estimated 10–12 weeks gestation. The mother was on 200 mcg levothyroxine at the end of pregnancy. The infant was born weighing 3400 g at 39 weeks gestation with severe clinical and biochemical features of hypothyroidism, (capillary TSH >150 mU/l on day 1 of life, 268 mU/l day 6). She was normocalcaemic on day 1 (2.21 mmol/l) but became hypocalcaemic by day 2 (1.43 mmol/l, PTH <1.2 pmol/l), with normal vitamin D levels. Initial treatment was with levothyroroxine (25 mcg) and calcium alone. Plasma calcium normalised; supplements were reduced then discontinued (day 25) with ongoing monitoring. She became hypocalcaemic again (day 37) and 1 Alpha Calcidol was commenced. At 6 weeks of age the patient had a cardio-respiratory arrest following RSV positive bronchiolitis and hypocalcaemia. She continued to have refractory hypocalcaemia despite increasing calcium and vitamin D supplementation. There was evidence of 'seizures' and possible tetany, although the cause was unclear – hypocalcaemia or CNS ischaemic insult – and the child was left with severe neurological impairment.
Conclusion
Radioactive Iodine^{131} may occasionally be given inadvertently to pregnant women despite rigorous protocols in place to prevent such an occurrence. Whilst Iodine^{131} is known to have an impact on thyroid tissue, the parathyroid glands can also be affected. The severity of this infant's hypothyroidism also questions maternal compliance with her own thyroxine medication. Neonatal hypoparathyroidism is a very rare complication of radioactive Iodine^{131} during pregnancy. Monitoring of both thyroid and parathyroid function in at-risk infants after birth is recommended.

DOI: 10.1530/endoabs.39.EP120

EP121

Massive pericardial effusion secondary to undiagnosed severe hypothyroidism in a child with neurodisability

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A 9-year-old boy presented to his local hospital having had a respiratory arrest at home. He had a background of a chromosomal microdeletion, and there had been several days of cough and coryza. CPR was underway and upon arrival in A&E he was resuscitated and retrieved to PICU. The working diagnosis was lower respiratory tract infection.
On day 4 of his PICU stay, with progressive signs on his chest *X*-ray, an ultrasound scan was performed. This confirmed bilateral moderate pleural effusions and, surprisingly, a large pericardial effusion. A percutaneous

pericardial drain was inserted and 750 mls of serous fluid was drained over 24 h with smaller volumes thereafter. Following drainage, the patient's ventilation became easier and he made slow but steady progress towards extubation and PICU discharge.

The aetiology of the pericardial effusion was unclear. The fluid was acellular with a high protein concentration. Extensive microbiology and virology testing was negative; his heart was structurally and functionally normal; immunology testing for inflammatory conditions was negative and there was no known association with his particular genetic condition. Thyroid function tests however revealed gross hypothyroidism with a TSH >100; mU/l and free T4 <5 pmol/l. Furthermore, his anti-thyroid peroxidise antibodies were >1000 U/ml, in keeping with severe autoimmune hypothyroidism. Thyroxine replacement was commenced and he was discharged home after a total of 4 weeks in hospital.

This case highlights the difficulty in recognising symptoms of hypothyroidism in a child with neurodisability, both for caregivers and medical professionals. In hindsight, symptoms such as dry skin, cool peripheries and worsening of his usual constipation were forthcoming and the medical team recognised a relative bradycardia and hypothermia during his early stay.

Small asymptomatic pericardial effusions occur often in association with hypothyroidism but large clinically significant effusions are very rare. The fluid builds up slowly due to increased capillary leak of albumin and large volumes can be accommodated over time by stretching of the pericardium, protecting the system from tamponade. Hypothyroidism should be considered in the differential diagnosis of any child presenting with an otherwise unexplained pericardial effusion.

DOI: 10.1530/endoabs.39.EP121

EP122

Scottish mothers and babies at Yorkhill (MABY) thyroid health study – preliminary report

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Introduction

Iodine is essential for thyroid hormones synthesis, and fetal/infant neurodevelopment. There is increasing evidence of iodine insufficiency among British women. The MABY study is a longitudinal cohort study assessing the iodine and thyroid status of pregnant women and their offspring.

Methods

Healthy women were recruited (target 697 mother/infant pairs) from antenatal clinics at gestational week (GW) 28 ± 1. Blood and urine were collected at GW 28, 36; and from infant and mother postnatally (week 1). Optional maternal hair and breastmilk samples were collected. A validated iodine-specific food frequency questionnaire (FFQ) was completed at G28 and postnatally. Infant thyroid function was assessed through neonatal capillary TSH and urinary iodine status (UI) by Sandell-Kolthoff method.

Results

Over 6 months, 50% of eligible women approached were enrolled ($n=191$) (median age 33 years, IQR 30–35). Median (IQR) iodine intake at recruitment (100% FFQ completed) was 142 (94–112) ug/d, up to 191 (121–269) ug/day when iodine-containing supplements (reported by 37%) were included. Urine and blood samples were collected from 99 and 93% (GW28) and 94 and 93% (GW36), respectively. To date, 70 women have given birth, with 62 infants (40F:22M) followed-up (eight excluded based on GW, pregnancy complications or drop-out). Median (IQR) birthweight and gestational age were 3515 g (3275–3899) and 40^{+2} weeks (39^{+3}–41^{+1}). Postnatal maternal sample/data collection ($n=62$) was: 97% FFQ, 92% urine, 98% blood, 57% hair and 30% breastmilk. Infant urine and blood spots were obtained from 75 and 77%. Infant TSH results ($n=60$) showed four (7%) infants >2 mU/l, none >3 mU/l. Preliminary UI analysis indicated a maternal median (IQR) UI of 109 ug/l (54–189) at GW28 ($n=58$); 150 ug/l (93–231) at GW36 ($n=53$), and 58 ug/l (19–163) postnatally ($n=53$). Neonatal UI was 117 ug/l (64–188).

Conclusion

Enrolment and retention for the MABY study is encouraging with $>25\%$ of the target number recruited so far. Preliminary data are consistent with other iodine studies in the UK.

DOI: 10.1530/endoabs.39.EP122

EP123

Apraxia of eyelid and hypothyroidism

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Apraxia of lid opening is defined as non-paralytic motor abnormality characterized by difficulty in lid opening after lid closure.

A 10-year-old presented to the ophthalmologist with history delayed opening the right eye after blinking. There was slight delay in opening of right eye after a blink during examination. There was no lid retraction. Visual acuity was normal in both eyes. Initial work up showed normal full blood count, urea and electrolytes and coeliac screen. Acetylcholine receptor antibodies were negative. The antinuclear antibodies titre was positive. While she was under regular review by ophthalmologists, she presented 18 months later to the children assessment unit with a diffuse painless neck swelling and tiredness. She had a diffuse non tender neck swelling with no palpable cervical lymph nodes. The rest of her clinical examination was normal. Thyroid function test done on clinical suspicion of hypothyroidism showed thyroid stimulating hormone was 144, T3 4.3, T4 4.7; thyroid peroxidase antibody was markedly raised at 1400. Coeliac screen, full blood count, urea and electrolytes are normal. She was started on thyroxine 50 micrograms once daily. Her thyroid function and goitre size and energy improved remarkably following administration of Thyroxine. The apraxia of the eyelid improved within four months of thyroxine therapy. She was reviewed by ophthalmologists nine months after starting thyroxine. She was found to be asymptomatic and discharged from their care.

There is lack of evidence in literature regarding an association between apraxia of lid opening and hypothyroidism. More research studies is needed to understand the association between these two conditions.

DOI: 10.1530/endoabs.39.EP123

EP124

Hypothyroidism presenting as child psychosis. A rare finding.

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15-year-old girl presented to the psychiatrist with behavioural problems, fluctuation in mood, paranoia, low self-confidence and school refusal. She presented to her GP 4 months later with history of increased body hair and irregular menstrual pattern. Her sex hormone binding globulin was low. Luteinising hormone, follicular stimulating hormone and testosterone levels were normal. Pelvic ultrasound showed both ovaries contain multiple follicles suggestive of polycystic ovary disease. She was diagnosed with polycystic ovarian disease and started on combined oral contraceptive pills. Baseline blood tests done prior to starting Quetiapine (antipsychotic) by psychiatrists 9 months after onset of her symptoms showed thyroid stimulating hormone was markedly raised at 165 and T4 was <1.9. She was referred to the paediatric team with these results.

She was seen by the paediatric team with history of cold intolerance, ongoing behavioural problems, scalp hair loss, increased tiredness and increased body weight. She was 72.1 kg (91st–98th centile), height 152.5 cm (2nd–9th centile), BMI 31.6. She had a small diffuse goitre with no palpable cervical lymph nodes and dry skin on examination. The rest of her examination was unremarkable. Her Luteinising hormone, Follicular stimulating hormone, Liver function tests, coeliac screen, prolactin, thyroid peroxidase antibodies and testosterone levels were normal. MRI head showed no space occupying lesions or haemorrhage and normal pituitary fossa.

She was started on Thyroxine 50 μg and later increased to 75 μg. There is marked improvement in thyroid function and behaviour. Quetiapine was stopped within two months of thyroxine therapy.

We found two reports of child psychosis due to hypothyroidism in literature. It is well recognised in adults but rare in childhood. Children presenting with behavioural problems should be checked for possible organic causes especially metabolic conditions such as hypothyroidism as this could be the first presenting feature has seen in this case.

DOI: 10.1530/endoabs.39.EP124

EP125

Clinical review of the identification and management of infants born to mothers with thyroid disease – is there a role for routine testing of maternal TRAB in the current practice?

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Introduction
Infants born to mothers with a history of thyroid disease may be at risk of developing neonatal thyrotoxicosis. Although rare, affecting approximately 1% of infants, maternal thyroid disease can have serious consequences including intrauterine death or neonatal death. Maternal Grave's disease poses significant risk due to trans-placental passage of TRAB.
Methods
Mothers with thyroid disease and their subsequent infants were audited retrospectively against local guidance between 1 March 2014 – 1 March 2015. In addition, maternal thyroid antibody status was also collated in order to determine the extent current testing.
Results
The exact aetiology of maternal thyroid disease was only documented on 16% of neonatal alert forms and 79% of infants notes. There was no evidence that any infants were affected with symptomatic thyroid disease during this audit period. Three asymptomatic infants, however, had abnormal TFTs on day 6. TRAB were only tested in 61% of hyperthyroid mothers and only 70% of those with Graves disease were tested. 0% of these had their TRAB documented on the neonatal alert form or infants notes.
Discussion/conclusion
This audit highlights the importance of accurate identification of maternal thyroid aetiology on the neonatal alert form and newborn review in order to identify and manage risk, especially to infants of mothers with secondary hypothyroidism. Therefore pre-alert of all mothers with thyroid disease is currently deemed necessary. The introduction of TRAB testing for all hyperthyroid mothers (present or current) would greater identify infants at risk and remove the need to identify mothers with primary hypothyroidism to the neonatal team.

DOI: 10.1530/endoabs.39.EP125

EP126

Neonatal thyrotoxicosis – a single centre case series

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Introduction
Neonatal thyrotoxicosis is rare and occurs with transfer of Thyrotropin Receptor Antibodies (TRAb) across the placenta in a mother with a history of Grave's disease. The neonatal mortality rate can be as high as 20%, usually secondary to cardiac failure. Therefore prompt diagnosis and treatment is essential.
Methods
We report a series of seven infants with neonatal thyrotoxicosis seen in the Endocrine clinic between 2011 and 2015. Maternal Grave's disease was confirmed as the cause of maternal hyperthyroidism in five of the cases. Data were collected for clinical and biochemical status, antibody status, type and length of treatment and complications of treatment.
Results
Two babies were asymptomatic and did not require any treatment. Other symptoms included jitteriness, agitation and tachycardia (4/5), poor weight gain (2/5), tachypnoea and cardiomegaly (1/5), temperature instability, diarrhoea, and an enlarged spleen (1/5). TRAb antibodies were measured and raised in five babies. TPO antibodies were positive in 3/6 of the babies tested. Treatment with Carbimazole (CBZ) was required in 4/7 babies on average for 57 days. Propranolol was required in 5/7 babies for control of thyrotoxic symptoms. Length of treatment was on average 16 days (range 7–37 days). In babies treated with Carbimazole and/or Propranolol the Free T4 concentrations normalised within 23 days of treatment. TSH normalised on average within 10 weeks of treatment when anti-thyroid treatment was given and within 30 weeks without treatment (2/7 babies). Side effects of CBZ included a florid, macular-papular rash (two babies) and neutropenia (on day 73) was documented in one baby. CBZ was discontinued in this instance.
Discussion/conclusion
Propranolol and CBZ treatment is effective, with improvement in clinical and biochemical status. Despite FT4 normalisation, TSH takes many weeks longer to respond. CBZ side effects do occur and neonates should be monitored closely with appropriate parental counselling and team contact details provided.

DOI: 10.1530/endoabs.39.EP126

EP127

Combination T_3/T_4 therapy in paediatric patients with autoimmune hypothyroidism unresponsive to T_4 therapy alone

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Introduction
We do not fully understand why some hypothyroid patients complain of persistent symptoms despite normalisation of TSH with levothyroxine therapy. Recent evidence in adults suggests that polymorphism in deiodinase2 enzyme could lead to lower level of T_3 in some tissues and persistence of symptoms. A combination therapy with T_3/T_4 may improve symptoms especially psychological well-being, mood and memory in such patients. Combination therapy is used in adults but rarely in children.
Methods
We describe two patients with autoimmune hypothyroidism who responded well to combination therapy with T_3 and T_4.
Results
Case 1: Despite normalisation of TSH, HT complained of low mood, poor memory and tiredness, affecting her school performance. With increasing doses of levothyroxine, she had transient symptomatic relief only. After exclusion of alternative causative pathology, liothyronine (T_3) was added with significant improvement of her symptoms and patient-reported quality of life.
Case 2: BB also continued to be symptomatic despite increasing doses of levothyroxine, and the TSH continued to be marginally high. T_3 was added to her therapy with good effect and patient-reported improvement in quality of life.

	At Diagnosis		On T_4 treatment			On T_3/T_4 treatment			Current treatment		
Patient	fT_4 (9–19 pmol/l)	TSH (0.3–3.8 mu/l)	T_4	TSH	T_3 (1.3–2.5 nmol/l)	T_4	TSH	T_3	T_4 (mcg)	T_3 (mcg)	QOL for patient and family
Case 1 14.4 years	Unknown	Unknown	24.1*	<0.03*	2.3	14.3	0.88	2.6	75 OD	10 TDS	Improved
Case 2 12 years	5.70	296	11.6	14.01	1.5	8.8	2.91	1.6	75 OD	10, 20 BD	Improved

*Noted to be overtreated

Discussion/conclusion
Our paediatric patients with autoimmune hypothyroidism showed a good symptomatic response to T_3/T_4 combination treatment after a limited response to T_4 alone. Both patients opted to continue combination treatment despite increased frequency of dosing.

DOI: 10.1530/endoabs.39.EP127

EP128

Audit on CH diagnosis and management in UHNM

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Background
CH has an incidence of 1 per 3500 live births per year. Early diagnosis and treatment are essential to prevent severe morbidity of mental retardation and developmental delay in children. The newborn screening programme has played a major role in management of CH.
Objectives
The aim of the first audit was to identify our practice in management of CH once the newborn screening laboratory notified about an abnormal result. Following the first audit, there were recommendations that were implemented in accordance with the BSPED and newborn screening program guidelines. We re-audited the following year after the recommendations to assess any improvement in our practice.
Method
The first audit was a retrospective case notes review for a period from 1 January 2005 to 31 December 2013. Data for when the notification was received form the screening laboratory in terms of day of life of the child, first clinical review, thyroid function test (TFT), radioisotope scan or US of thyroid, day of starting Thyroxine, starting dose of thyroxine, time for normalisation of TFT and out patient clinic follow up were noted. Whether maternal history and maternal TFT were done were also noted.

After the first audit a template was designed to clerk neonates referred for CH. After a year of using the recommended clerking template a re-audit was done to assess improvement or otherwise.
Re-audit period was from 1 January 2014 to 31 December 2014.
Results
Recommendation from the previous audit included designing a check list perform a with all the main domains of the standard guidelines. The re-audit showed that our service is improved in certain aspects. All patients started on treatment within 2 days of notification. 85% of patients seen in OPD within 2 days. All patients had maternal history documented, maternal thyroid status checked and outcome faxed to screening laboratory. OPD follow up improved as 71.4% of patient attended all the scheduled first year appointments.
Recommendation
Add scheduled out patient appointments to the CH proforma and give parents a copy. Phone message reminder system regarding clinic appointments. Contact the parents in advance to confirm the appointments.

DOI: 10.1530/endoabs.39.EP128

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