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Highlights

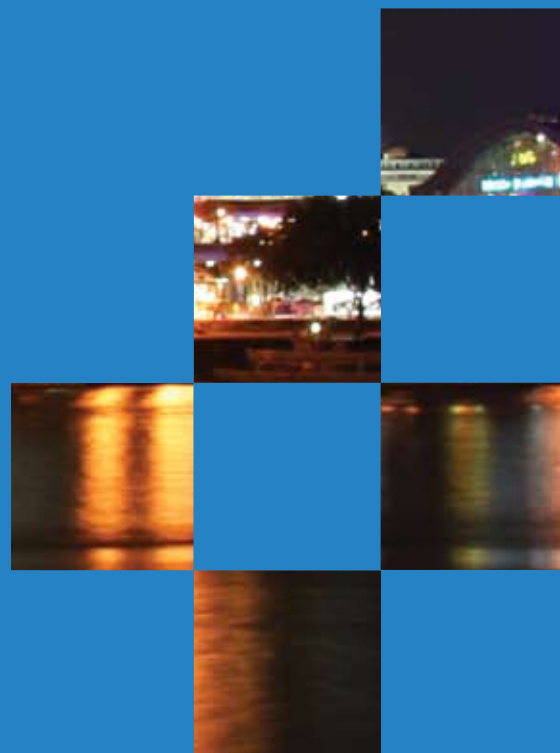
Highlights

6th International Paediatric Endocrinology Symposium

21-23 April 2010
Hilton Cologne Hotel
Germany

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Welcome to Cologne Highlights

Dear Colleagues

The 6th International Paediatric Endocrinology Symposium supported by an unrestricted educational grant from Ferring Pharmaceuticals has a unique place in history, apart from the excellence of its content. Nobody could have foreseen the consequences of the Icelandic *Eyjafjallajökull* volcanic eruptions for our travel across Western and Northern Europe. This was an unprecedented event in conference planning and all credit to the Ferring staff and their allied events organisers for having the confidence and courage to proceed with the 6th Symposium.

It turned out to be remarkably successful for two reasons: most of the delegates were from mainland Europe and were able to travel to Cologne overland; secondly, the absence of most of the speakers was nullified by superb video-conferencing that ensured our Faculty were almost present in person. There was minimal disruption to speaker/audience rapport. The main casualty of the 'ash cloud' was the cancellation of the Workshops, where lively interaction is key to their success. This has been one of the highlights of the Symposia in recent years and they will surely regain a position of pre-eminence in future Symposia.

The production of these highlights has even greater relevance in providing a distillate of the proceedings of the 6th Symposium. Delegates, if present and particularly those unable to make it, will find much of interest and value across a range of endocrine topics. To be able to cover major facets of diabetes, endocrinology of the neonate, growth hormone across a spectrum of disease, the adrenals, thyroid and gonads is no mean feat in less than two days. The synopsis of each of the seven sessions is punctuated with key messages and 'talking points' for the reader to take away. The stage is set to start planning the next Symposium, assisted greatly by helpful topic suggestions received from delegate feedback.

It remains for the Scientific Committee to thank the sponsors and conference staff for their supreme effort in ensuing that despite all the odds, the 6th International Symposium was an outstanding success.


The Scientific Organising Committee



Prof Henriette Delemarre-van de Waal, The Netherlands



Prof Lucia Ghizzoni, Italy



Prof Ieuan Hughes, United Kingdom



Prof Eckhard Schoenau, Germany

Diabetes and insulin in children

Co-chairs: Professors Henriette Delemarre-van de Waal and Eckhard Schoenau



Modulating the immune system in type 1 diabetes

While the symptoms of diabetes have become treatable to a certain extent, even intensive state-of-the-art insulin therapy cannot prevent the development of severe complications in the majority of patients. In the view of Professor Bart Roep (Leiden University, The Netherlands) there is therefore a vast and unmet clinical demand for disease intervention in diabetes, but no cure for type 1 diabetes exists as yet, and current therapy combats disease symptoms, not its cause.

The challenge is to determine which immune factors associate with beta-cell destruction or tolerance.

Professor Roep went on to explain that type 1 diabetes is a T-cell mediated autoimmune disease in which the insulin-producing pancreatic beta-cells in the islets of Langerhans are destroyed. Disease intervention therapies directed against T-cells have been shown to halt the disease process and delay recurrent beta-cell destruction after islet transplantation. However, the success rate of these therapies depends on the beta-cell mass and on immune status at the time of intervention. Induction or restoration of immunological self-tolerance requires reversal of the autoimmune processes which permanently destroy beta-cells, preferably before clinical manifestation of the disease, at a time when the beta-cell mass is still sufficient

to maintain normoglycaemia. The challenge, in Professor Roep's view, is to determine which immune factors associate with beta-cell destruction or tolerance, and to define what measures can suppress autoreactivity.

With insight gained from studies undertaken in recent years, new therapeutic strategies can be designed that selectively and safely interfere in the beta-cell destruction process. Recent efforts assessing efficacy of new drugs offer hope and provide impetus for future progress. Professor Roep believes it is conceivable that the immune processes causing type 1 diabetes may ultimately be controlled via therapeutic approaches that combine multiple agents, each with different modes of action. Ultimately this approach may minimise toxicities, offer synergies and prolong efficacy.



Single gene disorders causing diabetes

Turning to monogenic diabetes – frequently misdiagnosed as type 1 or type 2 diabetes – Professor Pål Rasmus Njølstad (University of Bergen, Norway) explained that this results from mutation in a single gene primarily affecting pancreatic beta or acinar cell function. The prevalence is 1–2 % of all diabetes. Knowledge of the genetic aetiology of monogenic diabetes has proved vital in improving diagnostics and treatment.

Monogenic diabetes should be suspected in subjects with diabetes and an unusual presentation or development.

Professor Njølstad went on to outline that monogenic diabetes can be divided into neonatal diabetes and maturity-onset diabetes of the young (MODY). The term neonatal diabetes is commonly used when diabetes occurs before the age of six months. Mutations in several beta-cell genes can cause neonatal diabetes, the most important being KCNJ11 and ABCC8. Children with a mutation in either of these genes can be treated with sulfonylurea rather than insulin¹ (avoiding the need for painful injections) and with better glycaemic control,² thus reducing the risk of long-term complications.

Some ten genes can cause MODY. Mutations in GCK lead to a mild form of diabetes that seldom requires treatment and late diabetes complications are rare. Two other common forms are due to mutations in HNF4A and HNF1A. These are clinically virtually indistinguishable and are commonly misdiagnosed as type 1 or type 2 diabetes. Sulfonylurea sensitivity means these forms can successfully be treated with low doses of sulfonylureas. Subjects with mutations in HNF1B or CEL often develop both exocrine and endocrine dysfunction requiring pancreatic enzyme supplement and insulin.

Professor Njølstad stressed that monogenic diabetes should be suspected in subjects with diabetes and an unusual presentation or development. Most will have a positive family history of diabetes and beta cell dysfunction, and be negative for antibodies associated with type 1 diabetes. In Professor Njølstad's view a precise diagnosis of neonatal diabetes or MODY is vital if optimal targeted treatment is to be instigated and late complications avoided. Research in this important area may ultimately cast light on diabetes as a whole and provide a model for 'translational' medicine in the future.

References

1. Sagen JV, Ræder H, Hathout E et al. Permanent neonatal diabetes due to mutations in KCNJ11 encoding Kir6.2. Patient characteristics and initial response to sulfonylurea therapy. *Diabetes* 2004; 53: 2713–18.
2. Pearson ER, Flechtner I, Njølstad PR et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006; 355: 467–77.



Neonatal endocrinology

Chair: Professor Ieuan Hughes

Calcium in the newborn: adjustments or disease

The neonatal period is increasingly seen as a critical time for numerous aspects of development. In the complex field of neonatal endocrinology Professor Lars Sävendahl (Karolinska Institutet, Stockholm, Sweden) set out to interpret the changes that occur in calcium and phosphate metabolism in the neonate once separated from the influence of maternal calcium. Professor Sävendahl explained that in the hormonal regulation of calcium balance two hormones increase serum calcium – parathyroid hormone (PTH) and vitamin D – and that calcitonin decreases serum calcium. In the pregnant mother calcium balance is well regulated, meaning that ionised calcium is very stable throughout pregnancy. Importantly vitamin D increases very early in pregnancy in parallel with a decrease in PTH, and calcium uptake from the gut is increased in the mother.

Stressing that in the fetus and neonate regulation of calcium and phosphorus levels is critical for proper bone development and mineralisation Professor Sävendahl

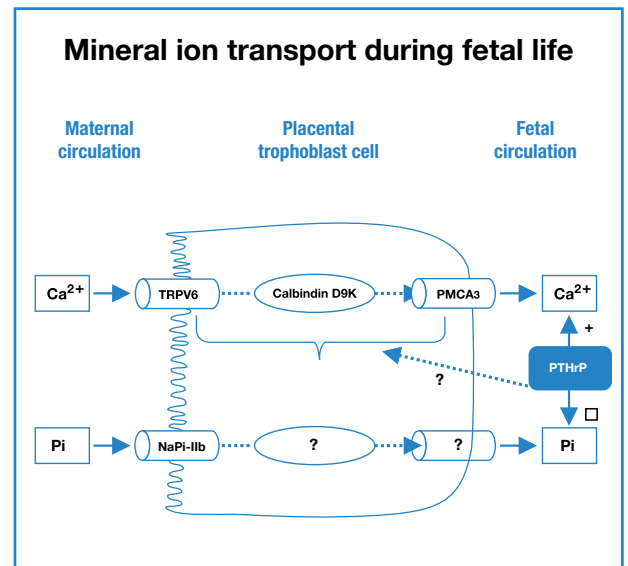
Regulation of calcium and phosphorus levels in the fetus and neonate is critical for proper bone development and mineralisation.

outlined the main regulators of fetal calcium balance: PTH, PTH-related peptide (PTHrP) and a PTH1 receptor which mediates both PTHrP and PTH actions. PTHrP plays an important role in transferring calcium across the placenta into the fetal circulation (Figure).¹ The placenta transports calcium to the fetus throughout pregnancy, the largest amount of fetal calcium accumulation occurring in the third trimester. As the fetus is dependent on maternal calcium turnover, untreated maternal hypocalcaemia therefore places the fetus at increased risk of hypocalcaemia in the neonatal period.

At birth, the body contains approximately 30 g calcium, which increases to approximately 1000 g in adults. At birth, the neonate experiences a sudden loss of the placenta as a source of mineral ion delivery and to maintain normal calcium homeostasis, a new dependence on intestinal absorption develops, as well as a need for regulation of the bone reservoir and renal reabsorption.

During lactation, maternal skeletal demineralisation is controlled by the breast itself. Production and release of PTHrP in the breast is stimulated by suckling and by prolactin. PTHrP also mobilises calcium from the maternal bone. In addition, prolactin (PRL) suppresses the pituitary-gonadal axis increasing maternal bone resorption, and stimulating osteoclast activity and mobilisation of calcium, which is then transferred via breast milk to the newborn.

Calcium intestinal absorption is affected by the type and amount of calcium ingested, noted Professor Sävendahl. It is also affected by the amount of intestinal calcium that is bound to dietary fats and proteins. Careful studies have demonstrated a physiological nadir of both total and ionised calcium at approximately 24 hours of life in healthy newborns.² Several factors can make the calcium nadir more dramatic including prematurity, maternal



Mineral ion transport during fetal life. Active calcium transport from the mother to the fetus during pregnancy results in higher calcium concentrations in the fetus than the mother. Adapted with permission from Mitchell and Jüppner.¹

gestational diabetes, and maternal vitamin D deficiency (since vitamin D is crucial for intestinal calcium absorption). The subsequent rise in serum calcium and the decline in serum phosphorus over the following days are a likely consequence of stimulation and maturation of the PTH response.

Professor Sävendahl's recommendations are that pregnant women should be encouraged to ensure exposure to sunlight and that vitamin D should be given during the last trimester of pregnancy to women with a history of insufficient dietary vitamin D and lack of sunshine exposure. He also recommends that daily supplementation with 400 IU vitamin D should be initiated within days of birth for all breastfed infants.

Doubts about sex assignment

'Is it a boy or a girl?' is one of the parents' first questions after birth. In neonates with disorders of sex development (DSD) the answer is not immediately clear but nevertheless, Western societies and civil laws require assignment of the newborn to the male or female sex. Professor Paul-Martin Holterhus (University of Kiel, Germany) stressed that this situation imposes enormous psychological distress on the families and represents a considerable challenge for the medical teams.

Professor Holterhus outlined that the bioethics working group of the German DSD network have proposed ethical principles to guide the management of DSD. These are to foster the well-being of the child and future adult, uphold the rights of the child to participate in decisions, and to respect the family (including the parent-child relationship). Because DSD is very complex, the consensus view is that that DSD should always be managed by interdisciplinary expert teams.

Outlining the historical background, Professor Holterhus noted that previously so-called 'optimal gender policy' maintained that newborns were psychosexually neutral at birth and that early corrective surgery would help the child and the parents facilitate stable gender identity. Later

It is vital that the endocrine basis of DSD and the role of androgen is considered in sex assignment and long-term decision making.

Interventions to improve glucose control in the potentially critical neonatal period should consider effects on long-term health as well as short-term outcomes.

however, under the so-called ‘full consent policy’, it was established that only the patient him or herself should make any decision as to gender assignment. However because the benefits to the small child, the teenager and the later adult differ, postponement of clinical decisions ignores potential interests of the neonate and the smaller child. The dilemma is that early clinical decisions (and early treatments), yet also their postponement, may both have consequences later in life. DSD should not equate to the genital malformation and its surgical ‘correction’ alone, in Professor Holterhus’s view. In addition, many other aspects must be considered, such as psychosexual development, dating, falling in love, marriage, raising children, preservation of fertility, etc.

The biological basis for sexual development starts with the sex-specific karyotype on fertilisation of the egg. Subsequent sex-specific development is controlled by genetic and hormonal pathways. The presence or absence of androgens determines the development of either male or female external genitalia. Later in life it has been shown that androgens influence functional and anatomical characteristics, as well as gender or sex-specific development of the brain. Sex-specific play behaviour in 46,XX CAH girls and undervirilised 46,XY girls indicates that the human brain is imprinted by androgens. This is supported by a high frequency of female to male gender role changes reported in 5-alpha-reductase 2 deficiency and 17-beta-hydroxysteroid dehydrogenase 3 deficiency (about 60%), both of which present with relevant concentrations of active androgens. Professor Holterhus therefore considers androgens to be important modulators of psychosexual development. More recently, genome-wide microarray analyses in DSD have demonstrated a long-term androgen memory at the transcriptome level in genital tissues and even the blood. Professor Holterhus’s view is therefore that it is vital that the endocrine basis of DSD and the role of androgen are considered in sex assignment and long-term decision making.

Dr Holterhus concluded that sex assignment should be based not only on the clinical, hormonal and molecular data in the context of the family but also on the psycho-social-cultural background. Sex assignment does not necessarily mean irreversible hormonal or surgical treatment in the neonate or in the small child. Making no definitive decision in the small child leaves options open for the future.

Blood glucose – too high or too low?

Speaking from the viewpoint of a neonatologist and expert in blood glucose homeostasis in the newborn, Dr Kathryn Beardsall (University of Cambridge, UK), began by outlining that historically in the intensive care

setting preventing hypoglycaemia has been the clinical focus, with hyperglycaemia considered a physiological response increasing non-insulin mediated glucose uptake and ensuring glucose availability for tissues such as the brain. However, hyperglycaemia has also been linked to adverse clinical outcomes and initial studies in adults have suggested that reducing hyperglycaemia with intensive insulin treatment could dramatically improve clinical outcomes.

In the neonate, where insulin is important in promoting growth and anabolism, the role of hyperglycaemia as a marker of relative insulin deficiency needs to be considered, as growth is an important factor in improving survival and long-term outcomes. With regard to long-term implications, catabolism and insulin deficiency may also impact on retinopathy, neurodevelopment and pancreatic development.

What constitutes optimal glucose control for children requiring intensive care and how this might be best achieved remains to be defined. Clearly the challenge is to maintain tight glycaemic control (4–6 mmol/L) without putting these babies at risk of hypoglycaemia, whether by manipulating glucose levels or nutritional intake. It is vital, in Dr Beardsall’s view, that interventions to improve glucose control in this potentially critical neonatal period should consider effects on long-term health as well as short-term outcomes.

References

1. Mitchell DM, Jüppner H. Regulation of calcium homeostasis and bone metabolism in the fetus and neonate. *Curr Opin Endocrinol Diabetes Obes* 2010; 17: 25–30.
2. Kovacs CS, Kronenberg HM. Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation. *Endocr Rev* 1997; 18: 832–72.

Talking points

Asked about vitamin D supplementation in breastfed infants, Professor Sävendahl noted that guidelines from the American Academy of Pediatrics recommend starting vitamin D supplementation soon after birth. Traditionally treatment is started two, four or even six weeks after delivery which in Professor Sävendahl’s view is too late. Even more important is to ensure that vitamin D levels are sufficient in the pregnant mother. The non-breastfed infant is very dependent on vitamin D supplementation (all formula milks include vitamin D, though often in insufficient amounts). Calcium and vitamin D should also be supplemented in premature infants.

Questioned on the topic of prenatal programming in the human brain, Professor Holterhus emphasised that androgen is an important modifier and that development of gender identity must be influenced by more than behaviour. In Professor Holterhus’s view, severely virilised girls with 21 hydroxylase deficiency are a good example because they show androgenised behaviour.

Asked whether glucose control is important for controlling inflammation and therefore morbidity in retinopathy after intraventricular haemorrhage in newborns, Dr Beardsall noted that it has been suggested that insulin can reduce inflammatory processes and therefore may well be beneficial. However there is not data on this as yet.

Use of growth hormone in non-growth hormone deficient children

Co-chairs: Professors Henriette Delemarre-van de Waal and Ieuan Hughes

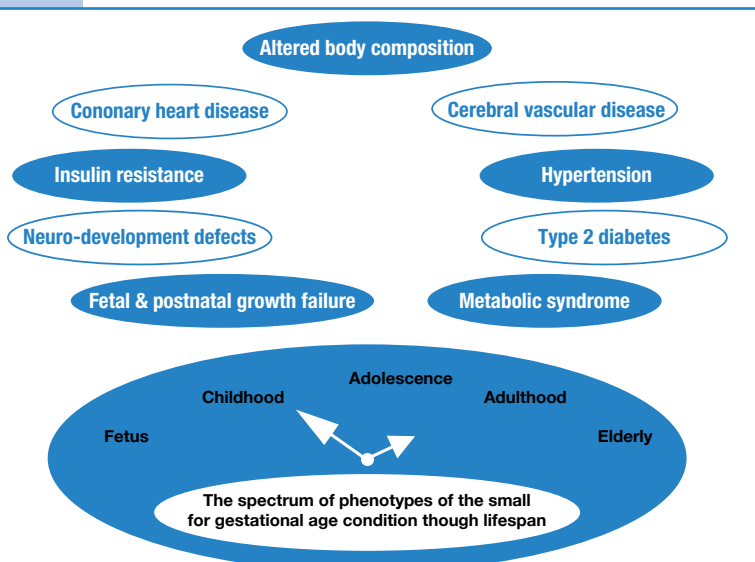
Growth and chronic inflammatory disease

Chronic inflammatory diseases are common in children. The prevalence of childhood inflammatory bowel disease (IBD) for instance is estimated at one in 500 in the UK, meaning there are currently around 10,000 children with IBD in the UK. Growth retardation can be a presenting symptom in over 30% of these children and subsequent short stature in adulthood may occur in over 15% of cases. Professor Faisal Ahmed (Royal Hospital for Sick Children, Glasgow) explained that the aetiology of growth retardation is multifactorial and it is very likely that pro-inflammatory cytokines play a major role, independent of other important factors such as nutrition and the use of drugs such as glucocorticoids.

The deleterious effects of cytokines on growth may be exerted via various mechanisms, either systemically or at the level of the growth plate. Efforts in controlling disease activity, supporting poor nutritional status, and avoiding long-term use of glucocorticoid therapy are paramount in managing children with poor growth. Chronic inflammatory disease is often associated with hypogonadism in adolescents but the evidence base for its management with sex steroids in this group of patients is minimal.

Professor Ahmed went on to outline results from studies that have shown that the use of recombinant growth hormone therapy has some benefit in addressing the growth retardation of chronic inflammatory disease. The rationale for the use of growth hormone is that exposure to pro-inflammatory cytokines plays a role in growth retardation. This has been explored most in juvenile idiopathic arthritis with improvements observed in both

The aetiology of growth retardation is multifactorial and it is likely that pro-inflammatory cytokines play a major role.



Pierre Chatelain 2008

A spectrum of phenotypes is associated with the small for gestational age condition throughout life.

Discussion around growth hormone therapy in ISS should focus more on the degree of shortness rather than its cause.

height velocity and height associated with an increase in IGF-1 and alkaline phosphatase levels.¹ Similar studies in cystic fibrosis show improvements in height velocity with growth hormone therapy, as well as in improvement in the number of pulmonary exacerbations requiring hospitalisation.² Growth hormone has also been shown to have anabolic effects in glucocorticoid-dependent children with IBD.³ Growth hormone therapy in chronic inflammatory disease may also have beneficial effect on body composition (lean mass, body fat, bone mineral content).²

Professor Ahmed stressed that a number of unanswered questions remain, such as the optimal dose, timing and duration of therapy and whether it should be combined with other interventions such as nutrition, sex steroids and recombinant human IGF-1. Dr Ahmed did not touch on improving disease and nutritional status, targeting cytokines, or the use of other alternatives to glucocorticoids, but he stressed that these are important areas which need to be considered first before endocrine interventions are considered.

Use of growth hormone in idiopathic short stature

When it comes to idiopathic short stature (ISS) there is little consensus about its definition or its management. Professor Jan-Maarten Wit (Leiden University, The Netherlands) outlined that it is generally accepted that ISS is made up of shorter height than the general population but with no clear identifiable abnormality (in the medical history, at physical examination, or on laboratory testing). More specifically this means normal birth size, good nutritional intake, absence of psychiatric disorder, normal body proportions and sufficient growth hormone, plus no evidence of endocrine deficiency or other disorders. A majority of those attending the ISS Consensus Meeting agreed that ISS can be subcategorised into familial short stature (short for population) and non-familial short stature (short for population and also short for target height range).⁴ Both familial and non-familial short stature can be associated with normal or delayed puberty.

Height in adulthood is determined by 'height' genes (as in pure familial short stature). Professor Wit went on to explain that during childhood so-called 'tempo' genes are also important. Since speed of maturation also runs in families there must also be 'slow' and 'fast' genes, though these have not yet been elucidated. Dr Wit hypothesises that most ISS patients have a combination of slow 'tempo' genes and short 'height' genes.

With regard to how to treat, in the United States and other countries growth hormone is registered for ISS, but not in Europe and many other countries. Growth hormone leads to a height velocity increment of 3–5 cm per year and a 3–7 cm adult height gain. The equivalent of 40–50 µg growth hormone per kg per day leads to an average of 7 cm height gain.⁵ Other predictors for a good adult height gain include the first year's growth responsiveness, initial bone age delay, the distance between height standard deviation score (SDS) and target height SDS, and age. However, a very high dose in young children does not increase adult height, due to advanced skeletal maturation. A treatment regimen of growth hormone in

Growth hormone treatment in the SGA infant rapidly improves height in childhood and may normalise final height if initiated soon enough and applied for long enough.

combination with GnRH analogues for three years leads to a 5 cm adult height gain, but possibly at the expense of a decreased bone mineral density in boys.⁶ Safety appears good during treatment, but longer follow up is needed. Professor Wit's view is that discussion around growth hormone therapy in short children should focus more on the degree of shortness rather than its cause.

Most children with ISS function normally, although they are sometimes juvenilised and short children are exposed to more stress, particularly being teased or bullied. In most studies no effect of ISS could be shown on quality of life or on psychological functioning, possibly partly due to the insensitivity of the psychometric tools but most likely because children are adaptable and will always make the best of their situation. Parental attitudes are important however, in Professor Wit's view.

Small for gestational age

Professor Pierre Chatelain (Hopital Mère-Enfant, Lyon, France) outlined the consensus definition of small for gestational age (SGA), namely any newborn with a birth weight and/or birth length below -2 SD for gestational age. Professor Chatelain also stressed that we now see increasing numbers of very low birth weight newborns (VLBW), defined as infants born with a birth weight below 1500 g (which may be SGA or appropriate or even large for gestational age), among which some will present with postnatal short stature. Although SGA is heterogeneous, a spectrum of phenotypes is associated with SGA throughout life, for example fetal and postnatal growth failure, metabolic syndrome during adulthood, etc (Figure).

The majority (85–92%) of SGA newborn infants catch up growth dramatically by two years of age, which in Professor Chatelain's view indicates that there must have been a major failure in the fetal growth process in these infants. He also stressed that parents should not be tempted to overfeed these children because the majority will catch up. Overfeeding at this young age could increase the risk of overweight and metabolic syndrome as an adult.

Professor Chatelain went on to outline that it is now well established that boys born SGA have an increased risk of intellectual and psychological dysfunction,⁷ and present as a group with a lower cognitive ability in mathematics and in reading comprehension. Parents should be aware of this possibility and the children given support if necessary, particularly at school.

A recent consensus statement⁸ recommends early surveillance in those children who fail to catch up, as well as early neurodevelopmental evaluation and intervention in at-risk children. Growth hormone treatment in the SGA infant rapidly improves height in childhood and may normalise final height if initiated soon enough and applied for long enough. Professor Chatelain also explained that the 'catch-down phenomenon' means a loss in height and that the growth benefit can be substantially impaired if growth hormone treatment is interrupted before final height is reached and that at least some growth hormone treatment is required during puberty to maintain the prepubertal height benefit.

Efficacy of growth hormone is very sensitive to dose in the first three years of treatment so starting dose should be

individualised according to efficacy and safety and also the most appropriate in terms of cost. Professor Chatelain stressed that it is most important not to fail the patient in the first year of growth hormone therapy. Further progress is expected from ongoing pharmacogenomics studies to identify genes and gene polymorphisms that modulate responsiveness to growth hormone treatment in all indications, including SGA.

Talking points

Professor Wit confirmed that a large number of children with ISS are receiving growth hormone therapy in the US, as well as many children who do not fit the criteria for therapy (height < -2.25 SDS). He has not seen any good data on treatment of ISS since it was accepted as an indication by the FDA, and does not expect there to be any.

With regard to constitutional delay and at what point a child with normal weight and length at birth becomes short, Professor Wit stressed that children can have positive family history for delayed puberty but still enter puberty at normal age. Conversely children can have delayed puberty but have no positive family history. Family history is therefore just one factor that increases the likelihood of ISS. Also, Professor Wit emphasised that delay in bone ageing and delay in puberty are two separate phenomena.

Professor Chatelain added that use of bone ageing will over-predict final height in short SGA children. With regard to the effect of growth hormone on late complications such as metabolic syndrome, Professor Chatelain noted that there is now evidence that when therapy is stopped the transient hyperinsulinism observed during treatment appears to return to the normal range or to the prepubertal condition. Fat mass and tissue fat seem to improve with growth hormone therapy and body composition appears to move away from that known to be associated with high-risk metabolic syndrome. More long-term follow-up data is needed, though currently growth hormone therapy does not appear to increase the risk of metabolic syndrome and, if anything, may even mitigate the risk because of this positive effect on body composition.

References

1. Bechtold S et al. Growth hormone increases final height in patients with juvenile idiopathic arthritis: Data from a randomised controlled study. *J Clin Endocrinol Metab* 2007; 92: 3013-18.
2. Hardin DS et al. Growth hormone treatment improves growth and clinical status in prepubertal children with cystic fibrosis: results of a multicenter randomised controlled trial. *J Clin Endocrinol Metab* 2006; 91: 4925-9.
3. Mauras N et al. Growth hormone has anabolic effects in glucocorticosteroid-dependent children with inflammatory bowel disease: a pilot study. *Metabolism* 2002; 51: 127-35.
4. Cohen P et al. Consensus statement on diagnosis and treatment of children with idiopathic short stature. *J Clin Endocrinol Metab* 2008; 93: 4210-17.
5. Wit JM et al. Final height gain by GH therapy in children with idiopathic short stature is dose dependent. *J Clin Endocrinol Metab* 2002; 87: 604-11.
6. van Gool SA et al. Final height outcome after three years of growth hormone and gonadotropin-releasing hormone agonist treatment in short adolescents with relatively early puberty. *J Clin Endocrinol Metab* 2007; 92: 1402-08.
7. Lundgren EM, Tuvemo T. Effects of being born small for gestational age on long-term intellectual performance. *Best Pract Res Clin Endocrinol Metab* 2008; 22:477-88.
8. Clayton PE et al. Consensus statement: Management of the child born small for gestational age through to adulthood. *J Clin Endocrinol Metab* 2007; 92: 804-10.

The thyroid

Chair: Professor Lucia Ghizzoni

Cancer consequences of the Chernobyl disaster: 20 years on

Following the Chernobyl nuclear accident in April 1986, a sharp increase in the prevalence of childhood thyroid carcinoma was observed in Belarus, Ukraine and, to a lesser extent, the Russian Federation, with close to 5000 cases observed across the three countries. Professor Rossella Elisei (University of Pisa, Italy) explained that most cases were reported in children under the age of ten years and, in particular, in children who were under five years old at the time of the accident. Cases of differentiated thyroid cancer (DTC) have also been diagnosed 20 years after the Chernobyl accident in children who were in utero at the time of the explosion.

The radiation emitted after the accident consisted mainly of isotopes of iodine. The thyroid gland has a specific and high sensitivity to radiation, particularly radioiodine, and there is a direct relationship between radiation dose and the incidence of thyroid cancer. The mean latency period between radiation exposure and the diagnosis of DTC is about 9–10 years, much shorter than seen after external radiation therapy. Compared to naturally occurring childhood thyroid carcinomas, post-Chernobyl thyroid carcinomas were much less influenced by gender, were virtually always papillary, and had higher aggressiveness at presentation.

Post-Chernobyl thyroid cancers are as curable as naturally occurring thyroid cancer if adequately treated.

A difference was also observed in the prevalence and type distribution of RET/PTC rearrangements due to chromosome inversion, with post-Chernobyl thyroid cancer showing a higher prevalence of RET/PTC, in particular of RET/PTC3. Despite all these differences, Professor Elisei stressed that post-Chernobyl thyroid cancers are as curable as naturally occurring thyroid cancer if adequately treated. Incidence in children has now returned to that

before the Chernobyl accident, but adults who were children or adolescents at the time of the accident remain under observation.

Update on the management of congenital hypothyroidism

Moving on to congenital hypothyroidism, Professor Heiko Krude (Charité University Medicine Berlin, Germany) began by noting that worldwide this is one of the most frequent treatable causes of mental retardation. However the formerly disastrous outcome for affected children has improved radically with the advent of neonatal screening programmes established to diagnose an elevation of thyroid stimulating hormone (TSH) within the first days of life, with a chance of these children leading a completely normal life.

Questions regarding screening-based treatment of congenital hypothyroidism are nowadays related to setting the TSH cut-off levels that confirm diagnosis and the initial dose of L-thyroxin treatment. Professor Krude explained that while cut-off values were initially set at 50 mU/L, more recently some publications advocate even lower values of 5 mU/L to avoid false negative results.¹ However this may lead to a large number of inappropriate diagnoses with only mildly elevated TSH values in children with normal T4 and T3 concentrations. The fear of underdiagnosis therefore harbours the danger of overdiagnosis in Professor Krude's view.

Concerning the best dose of L-thyroxin, results from several adult outcome studies in patients treated during the first years of congenital hypothyroidism screening with an average dose of 25 µg L-thyroxin show an almost normal outcome in these adult patients. However there is a gap of eight IQ points compared to 'normal' control groups. Professor Krude stressed that the question is still open as to whether a higher initial dose, e.g. 50 µg, might result in a better IQ outcome. Only one prospective randomised study is under way comparing 37.5 and 50 µg L-thyroxin as an initial dose.² The preliminary results of this small study cohort are so far in favour of the higher L-thyroxin dose.

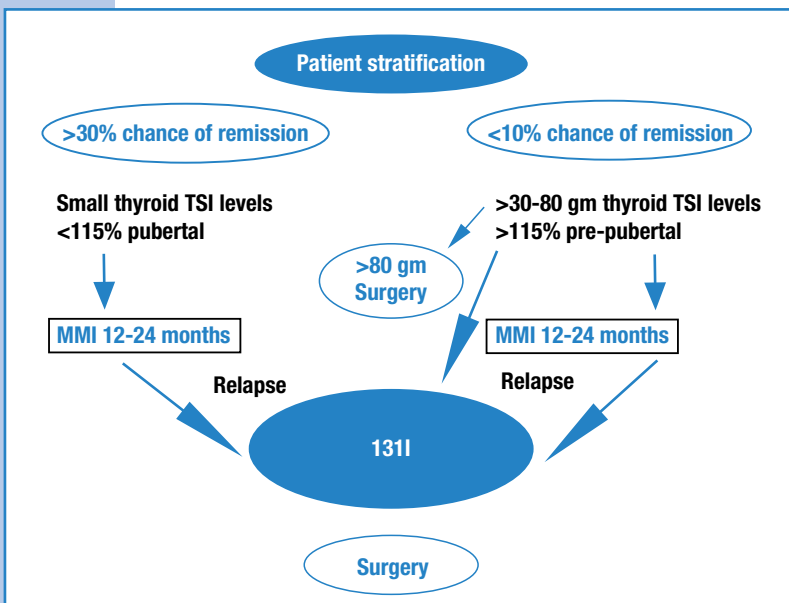
Graves' disease in children

Graves' disease is an autoimmune disease where the thyroid is diffusely enlarged and overactive, producing excessive amounts of thyroid hormones and causing hyperthyroidism. Discussing the treatment of paediatric patients with Graves' disease Professor Scott Rivkees (Yale University School of Medicine, US) outlined that this

The fear of underdiagnosis of congenital hypothyroidism harbours the danger of overdiagnosis.

varies considerably among institutions and practitioners. Children have lower remission rates than adults and lasting remission occurs in only a minority of paediatric patients with Graves' disease, including children treated with anti-thyroid drugs (ATDs) for many years.

In determining the initial treatment approach, Professor Rivkees stressed that the patient's age, clinical status, and likelihood of remission should be considered. Factors associated with a more favourable chance of remission include children who present with smaller rather than larger thyroids. Normal thyroid stimulating immunoglobulin (TSI)



Patient stratification in relation to projected outcome for children with Graves' disease. If patients relapse after 12–24 months of MMI they can move on to iodine-131 or surgery. Another option would be to continue with MMI until the child is old enough for iodine-131. If MMI is continued in these circumstances side effects can occur with long-term use so continued vigilance is needed. Eventually these individuals will need definitive therapy.

In determining the initial treatment approach in Graves' disease the patient's age, clinical status, and likelihood of remission should be considered.

levels are also a predictor of remission, as is older age (i.e. teenagers as opposed to younger children).

There are three treatment approaches: surgery, medical therapy and radioiodine treatment (iodine-131). In most circumstances, the ATD methimazole (MMI) for 1–2 years should be considered as first-line treatment for the majority of children. If clinical characteristics suggest a low chance of remission, MMI, iodine-131, or surgery can be considered initially. The ATD propylthiouracil (PTU) is associated with an unacceptable risk of hepatotoxicity in children and the current recommendations are that PTU should never be used as first-line therapy.³ PTU should only be considered in rare circumstances, such as preparation for surgery in a patient allergic to MMI, or in the first trimester of pregnancy. Any children currently on PTU therapy should be switched to alternative therapies.

If remission (defined as normal thyroid function off ATDs) is not achieved after one or two years of ATD therapy, iodine-131 or surgery should be considered, depending on the age of the child. Alternatively, MMI can be continued for extended periods, as long as adverse drug effects or toxic reactions do not occur and the hyperthyroid state is controlled. With regard to how long to treat, Professor Rivkees noted that there is little evidence of increased remission to support treatment with ATDs beyond 1–2 years. However it is safe to continue therapy, particularly in young children, to allow easier surgery when they are older and until they become candidates for radioiodine therapy.

When iodine-131 is used the dose should be > 150 uCi/g of thyroid tissue. Professor Rivkees stressed that the goal of iodine-131 therapy in children should be the hypothyroid state, not euthyroidism. It is recommended that iodine-131 be avoided in children less than five years of age, and doses greater than 10 mCi should be avoided in children between five and ten years of age. Professor Rivkees also noted that there are no reports of thyroid cancer attributable to radioactive iodine therapy in children treated with > 150 uCi/g of thyroid tissue.

With regard to whole-body irradiation, there is no evidence for an increase in cancer deaths or thyroid or other cancers associated with iodine-131 in adults. There is very little data in paediatrics, but theoretically projected cancer risks based on whole body radiation exposure long term show an increase in children aged five or younger. On this basis, Professor Rivkees recommends avoiding radioactive iodine in children younger than five and that modest doses of < 10 uCi should be used in children between the ages of five and ten.

When definitive therapy is required in young children (less than five years old) surgery is preferred and near total or total thyroidectomy is recommended as this is associated with very low relapse rates. The complication rates for thyroidectomy are higher in children than adults,⁴ and surgery should therefore be performed by a high-volume thyroid surgeon. Due to the scarcity of paediatric endocrine surgeons, a multidisciplinary collaborative approach between high-volume thyroid surgeons in conjunction with a specialist paediatric surgical team should be considered.

Talking points

Asked whether the population should carry iodine tablets in case of emergency, Professor Elisei noted that the WHO is currently running a programme to define guidelines for European countries with the idea of having iodine tablets available in future. Professor Elisei stressed however that most important is basic iodine prophylaxis – if the thyroid is full of iodine it will be less prone to take up radioactive iodine.

On the question of elevated TSH in obese children Professor Krude noted that this seems not to reflect a primary defect in the HPA axis, or a primary defect in thyroid function. It has been shown that if obese children reduce their weight by 10–20 kg, elevated TSH normalises, showing that elevated TSH is a secondary effect of obesity and not its cause.

With regard to whether fetal goitre on prenatal ultrasound should be treated in utero Professor Krude would not treat a child with a clear-cut diagnosis of thyroid peroxidase defect. However, sometimes the goitre is so big that there is concern about the natural course of delivery and this might be a reason to treat in utero to reduce goitre size. Fetal goitre also occurs in children of mothers with autoimmune disease of the thyroid and in such cases Professor Krude recommends treating the mother's condition to optimise the situation for the fetus.

Asked about the effect of MMI in utero during pregnancy Professor Rivkees conceded that this is an area of controversy. There is concern about MMI embryopathy and other minor malformations but to date there are very few reports of teratogenic effects related to PTU. The current recommendation is to avoid MMI and use PTU in the first trimester. Past the first trimester the recommendation is to switch from PTU to MMI to minimise the risk of liver failure in the mother. These recommendations are based on incomplete data however.

On the question of MMI and autoimmune antibody production Professor Rivkees noted that TSI levels in children may decrease slightly over the first six months of treatment, however in more than 90% of patients TSI will remain at elevated levels.

As to whether ocular disease is a contraindication for treatment Professor Rivkees stressed that Graves' ophthalmopathy is much less common in children than in adults. For adults with severe eye disease it is recommended that radioiodine is avoided altogether or used with adjunctive prednisone therapy. Studies where children have been treated with radioiodine for mild eye disease have shown improvement and only one child had worsening of eye disease 7–8 years after treatment. Ophthalmopathy is not therefore a contraindication. Children with moderate eye disease should have adjunctive therapy with prednisone 0.5 mg/kg/day for six weeks.

References

- Leonardi D, Polizzotti N, Carta A et al. Longitudinal study of thyroid function in children with mild hyperthyrotropinemia at neonatal screening for congenital hypothyroidism. *J Clin Endocrinol Metab* 2008; 93: 2679–85.
- Selva KA, Harper A, Downs A et al. Neurodevelopmental outcomes in congenital hypothyroidism: comparison of initial T4 dose and time to reach target T4 and TSH. *J Pediatr* 2005; 147: 775–80.
- Rivkees SA, Mattison DR. Ending propylthiouracil-induced liver failure in children. *N Engl J Med* 2009; 360: 1574–5.
- Sosa JA, Tuggle CT, Wang TS et al. Clinical and economic outcomes of thyroid and parathyroid surgery in children. *J Clin Endocrinol Metab* 2008; 93: 3058–65.



Key topics of interest

Chair:
Professor Eckhard Schoenau

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) can be defined as a hyperandrogenic disorder, the classic

phenotype consisting of obesity, anovulation and irregular menstruation. However Professor Renato Pasquali (St Orsola-Malpighi Hospital, Bologna, Italy) stressed that features of the PCOS phenotype differ at different ages in an affected female. Low birth weight can be a factor, as can macrosomia, and in childhood precocious puberty may occur. During adolescence signs of androgen excess, particularly hirsutism, but also acne and alopecia may be the dominant feature, while in adulthood infertility, particularly in the early adult years, becomes important. Later in adulthood metabolic alterations may occur, including obesity, glucose intolerance, and type 2 diabetes. Postmenopausally metabolic and cardiovascular diseases prevail.

The concept of fetal programming of PCOS by androgen excess has been outlined in a number of experimental, clinical, and genetic association studies. Initial findings from these studies show that prenatal androgenisation of the female fetus may programme differentiating target tissues towards the development of the PCOS phenotype in adult life,¹ though it is as yet unclear whether this occurs in humans. However, recent longitudinal studies performed in humans do not support the hypothesis that maternal androgens may directly programme PCOS in the offspring of humans.²

Increased testosterone levels are very common in the presence of anovulation, and hyperandrogenism may be variably associated with reduced GnRH sensitivity to progesterone-mediated slowing during adolescence.³ In addition to androgen levels, insulin resistance may modulate hypothalamic (GnRH) sensitivity to negative feedback to progesterone sensitivity thus influencing whether hyperandrogenic girls go on to develop the full clinical spectrum of PCOS. In addition, these effects can be amplified by the onset of obesity. It has been suggested that the pandemic of obesity may explain the very high prevalence of PCOS worldwide. Unfortunately there are no specific epidemiological studies to answer this important question. Professor Pasquali stressed that weight loss improves the PCOS phenotype (particularly with regard to androgens, menstruation and ovulation) provided that weight loss is sustained.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is the name given to a group of enzyme disorders causing impairment of cortisol synthesis and hence increased ACTH production by the pituitary gland, resulting in adrenal hyperplasia. By far the commonest enzyme defect is 21 hydroxylase (21 OH) deficiency. Dr Malcolm Donaldson (Royal Hospital for Sick Children, Glasgow, UK) noted that the epidemiology of 21OH-deficiency CAH is well documented with an overall worldwide incidence around 1 in 15,000–18,000 but

a much higher prevalence in certain populations (e.g. Yupik Eskimos).

In terms of genetics, the gene for 21OH deficiency has been mapped to chromosome 6p21 between the HLA-B and HLA-D loci. The active gene is flanked by a pseudogene (CYP21A). Broadly speaking, there are three types of genetic lesion in 21OH deficiency; deletion of the active 21 B gene; a substitution of all or part of the active 21 B gene by the pseudo-gene 21 A; and point mutations within the 21 B gene. In non-consanguineous families most affected individuals are compound heterozygotes. Generally speaking the phenotype in 21OH deficiency correlates well with the genotype.

With regard to the physiopathology in CAH, the defects in steroidogenesis and degree of glucocorticoid, mineralocorticoid and androgen derangement depend on the site of enzyme block. It is now recognised that severe cortisol deficiency affects the adrenal medulla with epinephrine deficiency leading to impaired gluconeogenesis and hepatic glucose output.⁴ This is an additional factor in the hypoglycaemia seen in CAH, and has important implications for its management.

Dr Donaldson explained that the features of the different phenotypes in the classical 21OH deficient form of CAH depend on gender and phenotype (either salt-losing or simple virilising). In **salt-losing males** presentation is that of mineralocorticoid (aldosterone) deficiency; presentation is within the neonatal period (usually from 5–10 days of age) with poor feeding, failure to thrive, vomiting, listlessness and paradoxically wet nappies (because the child cannot concentrate the urine). Biochemistry shows low sodium and high potassium, and normal cortisol levels which do not rise in response to stress and are thus inappropriate. The neonate may also be hypoglycaemic and it is therefore important to measure glucose in this situation.

The severely affected **salt-losing females** will by contrast present at birth with androgen excess (the effect of prenatal androgen) causing ambiguous genitalia (enlargement of the clitoris to form an enlarged clitoro-phallus), rugosity and fusion of the labia majora to form a scrotum. There are however no palpable gonads because this is a genetic female with intra-abdominal ovaries

Simple virilising males and females present with the features of androgen excess; there is longstanding tall stature, advanced bone age, and sexual precocity with penile/clitoral enlargement and pubic hair, as well as greasy hair and skin.

Concerning the clinical diagnosis, CAH should always be suspected: in a newborn girl with any degree of virilisation or genital anomaly; in any newborn who is not thriving even if plasma electrolytes are normal at presentation; in phenotypically male newborns without palpable gonads; and in older children with genital anomaly and sexual precocity (especially if virilising). The aim of biochemical investigation is to confirm the clinical diagnosis by measuring plasma 17OHP (the key hormone for 21 OH deficiency) and other steroid precursors. Plasma renin activity/electrolyte concentration will reflect impairment of

Weight loss improves the PCOS phenotype (particularly with regard to androgens, menstruation and ovulation) provided that weight loss is sustained.



the mineralocorticoid axis, and the urinary steroid profile is useful for defining the specific enzyme block. In certain cases genetic confirmation may be required but this is not regarded as mandatory in all 21OH patients in the UK.

With regard to monitoring Dr Donaldson recommends seeing patients every four months to measure growth – height, weight and height velocity. The ten key points Dr Donaldson recommends bearing in mind at every patient visit are set out in the Box.

Features of the different phenotypes of classical 21OH-deficiency congenital adrenal hyperplasia depend on gender and phenotype (either salt-losing or simple virilising).

With respect to linear growth and body composition the aim is to give sufficient glucocorticoid to suppress ACTH and thus minimise hyperandrogenism but not to give too much glucocorticoid since this will cause hyperphagia with obesity, which in turn leads to increased growth rate and advance of the bone age. Most children do fairly well on hydrocortisone 10–15 mg/m²/day (given in two or three divided doses) and fludrocortisone 150 µg/m²/day. In adolescence obesity tends to become more of a problem and at puberty the reproductive endocrine

aspects are important. Uro-genital complications in girls become of more pressing importance and psychological and psychosexual problems come to the fore, particularly in girls because of the genital anomaly. With regard to treatment, boys generally do well with the same regimen as in childhood (hydrocortisone 10–15 mg/m²/day and fludrocortisone 100–150 µg/m²/day). In girls who are in late puberty or who have reached menarche there is a case for switching from hydrocortisone to prednisolone in the dose of 4 mg/m²/day instead of hydrocortisone but Dr Donaldson tends now to continue with hydrocortisone. He cautions against the use of the potent glucocorticoid dexamethasone, which in his experience has caused unacceptable striae and weight gain, even in the lowest doses.

Compliance is also a problem in adolescence, and marked pigmentation in an individual receiving an appropriate dose of glucocorticoid should always raise suspicion of this.

With regard to surgical management in girls with 21OH deficiency, the tradition in the UK has been to perform clitoral reduction with excision of the corpus spongiosum, preserving the delicate neurovascular bundle and glans so that sensitivity during intercourse will be preserved. This has usually been practised towards the end of infancy. However, many centres are now moving towards not performing surgery at all if possible due to unsatisfactory results in adults, or delaying surgery until later in childhood.

Ten key factors to bear in mind at every clinic visit

With the patient:

- Height and weight velocity since the last visit
- Glucocorticoid dose/m² and the last time it was increased
- When was bone age last assessed?
- When was capillary/serum biochemistry (steroids, ACTH, renin) last undertaken and what was the result?

Then, and only then, invite the family into the consulting room and:

- Confirm current doses of glucocorticoid and mineralocorticoid with the parents
- Ask about compliance, lifestyle (school attendance, activities)
- Look for signs of overtreatment (striae, weight gain) and undertreatment (pigmentation, thin build, virilisation)
- Take the blood pressure
- Assess pubertal status (examine breasts, pubic/axillary hair, testicular palpation)
- Provide education regarding emergency management (i.e. increase oral medication and give intramuscular hydrocortisone in an emergency), and provide CAH cards to patients/parents to be shown to the doctor if they present to an emergency department (e.g. when on holiday)

Similarly, vaginoplasty used to be performed at the time of cliteroplasty (i.e. towards the end of infancy) but the current trend is to delay this procedure. This is because vaginal stenosis is a common complication of early vaginoplasty, and late vaginoplasty could be less problematic – although this remains to be shown.

Dr Donaldson went on to outline a number of problems and controversies. In the unborn child, maternal dexamethasone will greatly reduce virilisation of a female fetus in utero and thus avoid the need for subsequent surgery. However this will mean treating 7/8 unaffected fetuses in order to benefit one fetus, and there are concerns about the possible long-term neuro-cognitive and blood pressure programming effects of intrauterine dexamethasone exposure.

In childhood obesity is a problem, particularly in girls; this is because of the slightly supraphysiological doses of glucocorticoid that are required to suppress ACTH. Precocious/early puberty will occur in salt losers with 21OH deficiency if compliance is poor, and is an almost constant event in simple virilisers. Very rarely a girl with severe 21OH deficiency can be misdiagnosed as a boy and not confirmed as a genetic female until the age of three or later, by which time the child has developed in the male gender role.

In adolescence there can be problems with compliance, and polycystic ovary syndrome is frequent in girls. The perception of sexuality in the adolescent girl is bound to have been affected by the genital anomaly itself as well as the treatment. As adults severe salt losers will have diminished fertility and the effect of genital anomaly and the complications of surgery have a major effect on the subsequent sex life of affected women. For this reason prenatal treatment with dexamethasone in at-risk children is an attractive as well as a potentially problematic option, in Dr Donaldson's view.

Talking points

Asked about active and inactive obesity in PCOS Professor Pasquali stressed that the most important point is to achieve weight loss and decrease BMI, by whatever means (whether diet or exercise). This improves the phenotype.

Professor Schoenau raised the question of salt losing after puberty. Dr Donaldson indicated that if males receive no treatment at all and have plenty of salt in the diet they can get by. This is not encouraged however as they render themselves likely to adrenal crisis and, due to unsuppressed ACTH, they will develop irregular testes due to stimulation of adrenal rests, with subfertility. He therefore encourages families to persevere with treatment into adulthood. For females with CAH it is essential that they continue treatment.

Dr Donaldson emphasised that adrenal ultrasound is not informative in the newborn because it is not sensitive enough to detect moderate adrenal enlargement, even with a very good ultrasonographer and a good machine. Responding to a question from Professor Lucia Ghizzoni, Dr Donaldson noted that the different components of monitoring of steroid dose in patients with CAH can be considered as pieces of a jigsaw puzzle. These pieces include the biochemistry, bone age, growth velocity, height, weight, BMI and physical appearance of the child. He agreed that concentrating exclusively on the biochemistry and attempting complete suppression of adrenal steroids could end up with a Cushingoid patient. Dr Donaldson went on to stress that while it is clear that in utero virilisation causes well defined problems the effects of giving dexamethasone for a short time to the unaffected fetus are as yet unclear. The consequences of virilisation should not be underestimated and it is the physician's duty to explain the situation fully to families and allow them take their own decisions.

Age-related changes in the PCOS phenotype

Pre-adolescence	Low birth weight or macrosomia Precocious pubarche
Adolescence	Hirsutism (acne, alopecia) Menstrual irregularities Obesity
Adult age*	Infertility Obesity Androgen excess Type 2 diabetes and metabolic alterations
Post-menopause	Type 2 diabetes Cardiovascular disease (?)

*Often influenced by pharmacological treatment (e.g. oral contraceptives)

References

1. Xita N, Tsatsoulis A. Fetal programming of polycystic ovary syndrome by androgen excess: evidence from experimental, clinical and genetic association studies. *J Clin Endocrinol Metab* 2009; 91: 1660-6.
2. Hickey M, Sloboda DM, Atkinson HC et al. The relationship between maternal and umbilical cord androgen levels and polycystic ovary syndrome in adolescence: a prospective cohort study. *J Clin Endocrinol Metab* 2009; 94: 3714-20.
3. Blank SK, McCartney CR, Chhabra S et al. Modulation of gonadotropin-releasing hormone pulse generator sensitivity to progesterone inhibition in hyperandrogenic adolescent girls – implications for regulation of pubertal maturation. *J Clin Endocrinol Metab* 2009; 94: 2250-1.
4. Weise M, Mehlinger SL, Drinkard B et al. Patients with classic congenital adrenal hyperplasia have decreased epinephrine reserve and defective glucose elevation in response to high-intensity exercise. *J Clin Endocrinol Metab* 2004; 591-7.

Late morbidity from cancer treatments

Chair: Professor Eckhard Schoenau

The effect of chronic disease on bone development

Before discussion of late morbidity from cancer treatments, the question of bone development and how it is affected by chronic disease was addressed by Professor Eckhard Schoenau (University of Cologne, Germany), who noted that low bone mass has been discussed as a risk factor for osteoporosis and fractures for the last 20–30 years. He went on to outline that bone mass is dependent on many factors, such as chronic inflammation, decreased physical activity, low lean body mass, nutrition, growth rates, development of puberty, and medications and their side effects (Figure).¹

Professor Schoenau explained that bone mass is a function of bone growth in length, bone strength and geometry (dependent on the muscle system) and mineralisation. Clinically low bone mass means osteopenia (either because the bone is not stimulated, or due to bone loss because of bone resorption), and rickets and osteomalacia (when there is insufficient calcium and phosphate to mineralise the bone).

Bone mass is a function of bone growth in length, bone strength and geometry (dependent on the muscle system) and mineralisation.

Chronic diseases, such as growth hormone deficiency, cerebral palsy, juvenile idiopathic arthritis, and cystic fibrosis all adversely affect bone development. In patients with cystic fibrosis bone mass, bone strength and muscle area are decreased. Data show that bone problems in cystic fibrosis are due to impaired muscle development,² and illustrate a new diagnostic approach to paediatric bone diseases based on analysis of the balance between bone strength and physiological challenge to bone strength. Other chronic diseases in childhood have been analysed in a similar way. Physiotherapy and physical activity should therefore include aspects of muscle training to optimise prevention of osteoporosis in patients with chronic disorders.

Professor Schoenau emphasised that it is vital to select the optimal diagnostic tool to answer clinical questions (particularly to use paediatric reference data), to identify the reasons for 'low bone mass', and then to choose the requisite therapy for growth, muscle, and nutrition, as well as for the bone.

Late morbidity from cancer treatments: growth and puberty

Moving on to the effects of cancer on growth and puberty, Professor Jürgen Brämwig (University Children's Hospital Münster, Germany) explained that cancer survivors are at high risk of developing late complications in the endocrine system. Anterior pituitary hormone secretion is frequently affected following surgery or radiation damage to the hypothalamic-pituitary axis. Growth hormone deficiency is the most common endocrinopathy, its severity correlating with the total radiation dose and the length of follow-up. Growth hormone therapy will restore growth during childhood and adolescence and adult height will be within

the target range. Professor Brämwig noted that growth hormone deficiency will generally persist into adulthood so after appropriate testing and reconfirmation of the diagnosis, growth hormone therapy should be continued life-long.

Early, delayed or absent puberty are all associated with CNS tumors, surgery and radiotherapy in the hypothalamic-pituitary area. In addition, chemotherapy and direct or indirect gonadal irradiation can damage the female and male gonad and appropriate substitution therapy can initiate pubertal development during adolescence. In adulthood infertility or reduced rates of fertility are observed in patients suffering from direct gonadal damage as documented by hypergonadotropic hypogonadism. Spontaneous recovery of hypergonadotropic hypogonadism is rarely seen in female patients, but occasionally observed in male patients during long-term follow up. In male and female patients with hypogonadotropic hypogonadism following surgery or radiotherapy to the hypothalamic-pituitary area fertility is also reduced, but gonadotropins are a therapeutic option. Surgery, radiotherapy and chemotherapy can alter pubertal development and fertility by damaging the hypothalamic-pituitary axis (hypogonadotropic hypogonadism) or the gonad (hypergonadotropic hypogonadism). Timely assessment will identify those patients who will benefit from medical intervention.

Late morbidity from cancer treatments: fertility issues

Discussing the pathophysiology of puberty, the functional development of the testis and the endocrine consequences of curing childhood cancer, Professor Christopher Kelnar (University of Edinburgh, UK) outlined that over the last 30 years survival rates in children with cancer have dramatically improved, largely attributable to advances in chemotherapy and radiotherapy. As many as 70% of children with cancer will now survive ten years or more. The majority are fertile but risk factors for sub-/infertility include particular chemotherapeutic agents/regimens (for example for Hodgkin's disease) and radiotherapy – testicular, pelvic, abdominal or total body irradiation (TBI) – and questions regarding their ability to achieve normal reproductive potential are assuming greater importance. Few things are more important to these young people as they get older than their fertility, in Professor Kelnar's view.

Chemotherapy and direct or indirect gonadal irradiation can damage the female and male gonad and appropriate substitution therapy can initiate pubertal development during adolescence.

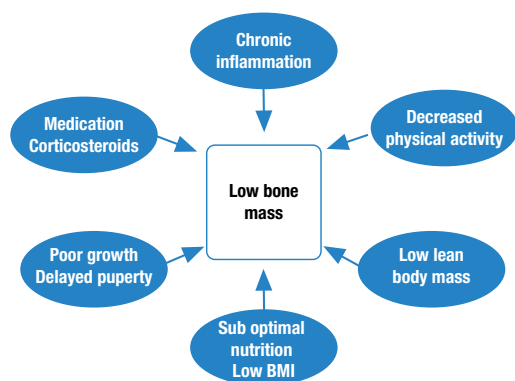
Regarding ovarian susceptibility, in a girl aged ten radiotherapy will deplete her primordial follicle population to the extent that she will undergo menopause at the age of 13 rather than 50. The naturally declining number of oocytes in the ovaries mean that in older females smaller doses will cause sterility compared to younger females, therefore 19 Gy radiation will sterilise a girl aged seven years, but only 11 Gy is required to sterilise a woman treated in her 40s. In terms of hormone levels, radiotherapy will result in elevated FSH, reduced oestradiol, and reduced inhibin B.

Boys are also susceptible to chemotherapy and radiotherapy, depending on the chemotherapeutic

The prepubertal testis is not quiescent, which explains its susceptibility to damage from gonadotoxic cancer therapies leading to infertility.

agent (or combination) and the dose. The germinal epithelium is more vulnerable than the Leydig cells to gonadotoxic chemotherapy. The same also applies to susceptibility to damage from radiotherapy (radiation dose and fractionation schedule are therefore very important). Treatment of childhood cancer significantly impairs spermatogenesis (overall 26% azoospermia; 19% oligozoospermia; 35% normal semen analysis). However childhood cancer treatments do not seem to damage sperm DNA integrity and assisted conception is a safe option.

Whole abdominal irradiation in childhood is associated with > 95% risk of premature ovarian failure, as well as a lack of response of the uterus in terms of growth and subsequent endometrial response to sex steroids. Professor Kelnar emphasised that uterine volume correlates with age at irradiation. Radiotherapy at a younger age will therefore mean a smaller uterus with all that implies. Following TBI, the risk of irreversible ovarian failure is much less predictable. Physiological sex steroid replacement therapy after TBI improves uterine bloodflow and the endometrium. Although these women may benefit from assisted reproductive techniques they have increased risks of pregnancy loss and prematurity.



Factors associated with low bone mass in children.

Strategies for fertility preservation in young females include oophoropexy (moving the ovary out of the radiation field), embryo cryopreservation and, experimentally, cryopreservation of oocytes³ or ovarian cortical strips. This entails laparoscopically removing ovarian cortical strips rich in primordial follicles, though with haematological malignancies there is a theoretical risk of ovarian contamination. So far in Edinburgh this technique has been offered to 36 women (aged 5–35 years), though none has yet requested reimplantation of the ovarian tissue (only two have confirmed ovarian failure).³ Professor Kelnar cautioned that women can become pregnant

spontaneously despite all the treatment they have undergone and despite adverse biochemical signs, and this can complicate matters when counselling patients about what the future holds. Newer techniques such as antral development from in vitro-grown human primordial follicles show promise.⁴

Professor Kelnar went on to stress that the prepubertal testis is not quiescent, which explains its susceptibility to damage from gonadotoxic cancer therapies leading to infertility. In a primate model, continued replication of spermatogonia in GnRHa-treated marmosets⁵ makes it unlikely that gonadal protection strategies with GnRHa will be successful in boys (unlike in the a model). More understanding of the physiology of spermatogonial regulation is required before gonadal protection strategies for the childhood human testis can be considered.

In boys, sperm retrieval and banking should be offered if testes are > 10 ml and chances of infertility are high. In terms of experimental techniques, intracytoplasmic sperm injection (ICSI) and germ cell transplantation, as well as testicular biopsy and cryopreservations are under investigation. Hormonal manipulation does not appear to hold promise, though much work is ongoing to elucidate what factors influence spermatogonial proliferation and maturation in the prepubertal testis. Certainly GnRH analogue suppression does not seem to be a potentially viable way of protecting the prepubertal gonad.

Talking points

Responding to a question from Professor Delemarre-van de Waal regarding bisphosphonates and bone structure Professor Schoenau noted that most experience is in patients with osteogenesis imperfecta, stressing that osteoclasts are necessary for bone remodelling, adaptation and repair. It is clear that osteogenesis imperfecta patients treated with bisphosphonates have more 'bad' bone but this is preferable to no bone at all.

Regarding insufficient vitamin D in childhood and in the elderly Professor Schoenau stressed that simply giving vitamin D in the hope of developing strong bones is not enough: osteoporosis patients have no bone to mineralise. Also physical activity is required to stimulate bone formation.

Professor Brämswig noted that both the quiescent testis and the pubertal testis are affected by chemotherapy – cyclophosphamide given to a five-year-old boy has the same effect as it would in a 14-year-old boy in puberty. Professor Delemarre-van de Waal added that the effects of chemotherapy are dose dependent in prepubertal boys.

Asked about the possibility of maturing immature sperm in vitro (similar to experiments with oocytes) Professor Kelnar outlined that it is not currently possible to mature the more primitive precursors of sperm. One potential way forward is to use stem cells to make germ cells, though the ethics are complex.

References

1. Viswanathan A, Sylvester FA. Chronic paediatric inflammatory diseases: effects on bone. *Rev Endocr Metab Disord* 2008; 9: 107-22.
2. Kelly A, Schall JI, Stallings VA, Zemel BS. Deficits in bone mineral content in children and adolescents with cystic fibrosis are related to height deficits. *J Clin Densitom* 2008; 9: 107-22.
3. Anderson RA, Wallace WHB, Baird DT. Ovarian cryopreservation for fertility preservation: indications and outcomes. *Reproduction* 2008; 136: 681-9.
4. Telfer EE, McLaughlin M, Ding C, Thong KJ. A two-step serum-free culture system supports development of human oocytes from primordial follicles in the presence of activin. *Hum Reprod* 2008; 23: 1151-8.
5. Kelnar CJH, McKinnell C, Walker M et al. Testicular changes during infantile 'quiescence' in the marmoset and their gonadotrophin dependence: a model for investigating susceptibility of the prepubertal human testis to cancer therapy? *Hum Reprod* 2002; 17: 1367-78.

The adrenals

Co-chairs: Professors Ileana Hughes and Lucia Ghizzoni

The safety of inhaled glucocorticoids

In humans, glucocorticoids synthesised in the adrenal cortex regulate a broad spectrum of physiological functions essential for life. Professor George Chrousos (University of Athens, Greece) explained that glucocorticoids play an important role in basal and stress-related homeostasis and also regulate approximately 20% of the genes expressed in human leukocytes. Glucocorticoids are involved in the function of almost every cell in the organism and play a pivotal role in growth, reproduction, intermediary metabolism, and immune and inflammatory reactions, as well as in central nervous system and cardiovascular functions.

Despite the fact that inhaled steroids given correctly are extremely safe, patients require careful monitoring.

Physiological amounts of glucocorticoids are also essential for normal renal tubular function and thus for water and electrolyte homeostasis. Furthermore, glucocorticoids are one of the most widely used therapeutic compounds, frequently used in the treatment of inflammatory, autoimmune and lymphoproliferative disorders. Both excess and deficiency of glucocorticoids are associated with disease, i.e. Cushing syndrome or Addison's disease.

At the cellular level, the action of glucocorticoids is mediated by an intracellular protein, the glucocorticoid receptor (Figure).¹ The human glucocorticoid receptor belongs to the steroid/thyroid/retinoic acid nuclear receptor superfamily of proteins and functions as a ligand-dependent transcription factor that regulates the expression of glucocorticoid-responsive genes either positively or negatively. Professor Chrousos outlined that the effector domains of the glucocorticoid receptor mediate transcriptional activation by recruiting coregulatory multi-subunit complexes that remodel chromatin, target initiation sites, and stabilise the RNA polymerase II machinery for repeated rounds of transcription of target genes. Alternatively, the glucocorticoid receptor may act via interactions with other transcription factors, such as NF- κ B, STAT5 or AP1, positively or negatively modulating the actions of these factors on their own target genes.

The discovery and clinical use of topical glucocorticoids that are not appreciably absorbed into the systemic circulation or which are metabolised into inactive compounds as soon as they cross into the blood stream represents a major advance in the history of therapeutics. This has been particularly so in the treatment of bronchial asthma with inhaled glucocorticoids and both the natural history and prognosis of this common and potentially devastating condition have profoundly improved since inhaled glucocorticoids became available. Inhaled glucocorticoids almost never cause cortisol excess because the dose is topical and very little is absorbed, except if patients exceed the recommended dose.

Several generations of inhaled glucocorticoids are now on the market with generally small differences from each other. The differences concern primarily their chronic systemic side effects, i.e. Cushing type manifestations (growth suppression, obesity, metabolic syndrome, osteoporosis, etc) and suppression of the hypothalamic-pituitary-adrenal axis (HPA) axis.

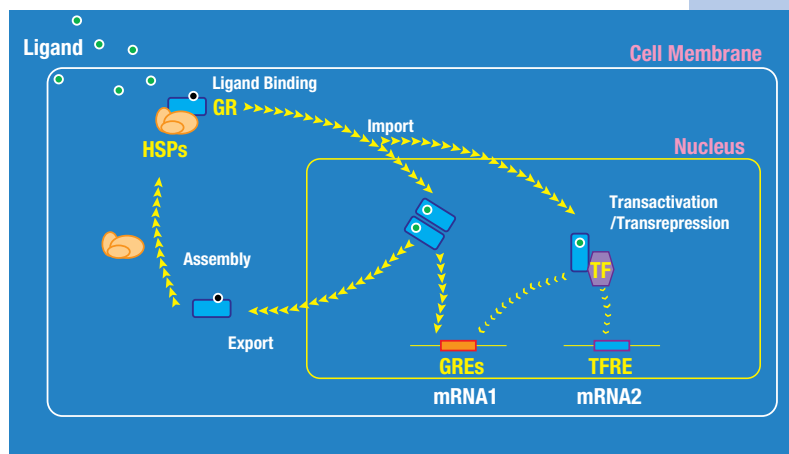
For adrenal insufficiency, the daily glucocorticoid dose is 10–15 mg hydrocortisone equivalent per m² per day. For minor stress, e.g. tooth extraction or febrile illness, doubling the dose is sufficient. At times of major stress, e.g. a major operation, Professor Chrousos recommends giving ten times the dose. If a high dose is required over a longer period of time methylprednisolone or dexamethasone should be given rather than hydrocortisone to avoid salt retention manifestations.

With regard to safety, few adverse effects have been seen with chronically administered inhaled glucocorticoid compounds when given within the dose ranges recommended by the manufacturers. Extremely rarely, idiosyncratic cases are seen, with fully fledged Cushing manifestations and clinically significant HPA axis suppression. In fact, asthma itself, before treatment with inhaled compounds, has been associated with mild suppression of the HPA axis, which in some patients corrects after inhaled steroid therapy is initiated.² Professor Chrousos stressed that it is vital to stay within the recommended doses, as the compounds available (some more than others) may have significant side effects if they are absorbed into the blood. When such effects are observed, testing of the HPA axis with a standard ACTH stimulation test may provide information about the presence of clinically significant adrenal insufficiency.

Despite the fact that inhaled steroids given correctly are extremely safe, patients require careful monitoring via physical examination (height and weight, blood pressure), and assessment of metabolic status and bone mineral density. Patients should also undergo testing for HPA axis suppression and be prescribed glucocorticoid coverage in times of stress, if necessary. A healthy diet is also important

Identification of patients with abnormalities of the HPA axis is mandatory to avoid life-threatening events in stressful conditions.

(low fat, high protein, high calcium) and patients should receive vitamin supplementation with appropriate doses of Vitamin D and calcium. They should also be prescribed an exercise regimen to protect their muscle and bone from atrophy and osteoporosis, respectively.



The glucocorticoid system is present in every cell in the body. In humans the ligand cortisol crosses the plasma membrane and binds to the glucocorticoid receptor, which is associated with other proteins (mainly heat shock proteins – HSPs) as a hetero-oligomer within the cytoplasm. Once the steroid binds to the receptor, the ligand-bound complex enters the nucleus via an energy-dependent process through the nuclear pore. In the nucleus it can act in two ways: either by forming dimers and binding to the glucocorticoid response elements (GREs) in the regulatory areas of glucocorticoid-responsive genes, or by acting as a monomer and interacting with other transcription factors such as NF- κ B, STAT5 or AP1, to then influence the complex of these other transcription factors and their own transcription factor response elements (TFREs). Once the action is exerted the receptor is exported to the cytoplasm and is recycled. From Charmandari et al.¹

Assessing adrenal function in children

Adrenal insufficiency is a severe disease with significant morbidity and increased mortality, defined by the impaired synthesis and release of adrenocortical hormones and classified based upon whether the aetiology is primary or secondary (or tertiary). Professor Helmuth Dörr (University Clinic Erlangen, Germany) explained that primary adrenal insufficiency is caused by disease of the adrenal cortex whereas secondary and tertiary adrenal insufficiency are caused by impaired release of ACTH from the pituitary gland or CRH from the hypothalamus, respectively.

Primary adrenal insufficiency is diagnosed if ACTH levels are high (usually > 100 pg/ml) in the setting of low cortisol, or with an abnormal ACTH stimulation test.³ If initial static ACTH tests are low, a variety of dynamic tests are used to further evaluate whether the adrenal insufficiency is secondary or tertiary.³ There is often evidence of mineralocorticoid deficiency, including a low fasting glucose value, hyponatraemia, and hyperkalaemia. Usually, PRA or renin concentration is elevated.

Clinical findings in children with secondary adrenal insufficiency are similar, except that signs of mineralocorticoid deficiency are not seen. Identification of patients with abnormalities of the hypothalamo-pituitary-adrenal (HPA) axis is mandatory to avoid life-threatening events in stressful conditions. Subnormal corticosteroid production during critical illness has been termed functional adrenal insufficiency or relative adrenal insufficiency. However in Professor Dörr's view, testing of the HPA axis during critical illness is a great challenge since there is currently no consensus on the diagnostic criteria.

Premature adrenarche has been connected to adverse metabolic features and increased risk of ovarian hyperandrogenism later in life.

The mystery of adrenarche

Adrenarche can be defined as an event of postnatal sexual maturation in which there is an increase in the secretion of adrenal androgens, mainly dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEA-S), not accompanied by an increase in cortisol secretion, explained Professor Järmo Jääskeläinen (University of Kuopio, Finland). He went on to outline that the weak androgens (or their precursors) produced by the adrenal cortex vary during the lifespan. Adrenarche begins before central puberty and is distinctly regulated from it. Premature adrenarche is defined as increased levels of adrenal androgens before the age of eight years in girls and the age of nine years in boys, which lead to androgenic signs. These range from increased height and androgenic (pubic and axillary) hair growth, to oily skin and adult type body odour. Premature adrenarche has been connected to adverse metabolic features and increased risk of ovarian hyperandrogenism later in life.

The pathogenesis of premature adrenarche is regarded as polygenic but the underlying genetic factors remain largely unknown.

Adrenarche is a gradual process beginning with maturing of the zona reticularis,⁴ and this process seems to start earlier than previously thought. Both human and higher primate studies have revealed certain changes in steroidogenesis in adrenarche: 17,20-lyase activity of CYP17 is increased, 3-beta-hydroxysteroid dehydrogenase activity is decreased, and the expression of cytochrome b5 and sulfotransferase are decreased during adrenarche.

Professor Jääskeläinen noted that insulin and insulin-like growth factor 1 have been associated with premature adrenarche and that children with premature adrenarche have a distinct pattern of growth from early life. However the association of premature adrenarche with small birth size is not consistent in all studies. Also, polymorphic and epigenetic variation within the androgen receptor seem to modify the clinical expression of adrenarche.

Talking points

Responding to a question from Professor Ghizzoni regarding the maximum safe dose of inhaled glucocorticoids in children, Professor Chrousos confirmed that patients should have no problems with the doses recommended by the manufacturers. Idiosyncratic problems can occur however, mostly with fluorinated inhaled steroids, more of which is absorbed into the systemic circulation at high doses and which remain in the plasma for a long periods, causing glucocorticoid excess problems. The third-generation inhaled steroids have very few side effects, even given at doses higher than recommended. Bone age is slightly delayed but the majority children reach their expected adult height, which is a good index of safety in Professor Chrousos' view.

Noting that Professor Chrousos recommended increasing glucocorticoid dose ten-fold to cover severe stress, Professor Dörr emphasised that this is not the recommendation in Germany. He recommends increasing the dose up to 3–5 times, and added that steroid cover for stress must be decided on an individual basis. A visit to the dentist is more stressful than a soccer game for example, and a surgical operation would count as severe stress. Professor Dörr gives hydrocortisone 100 mg/m² intravenously during surgery (a five-fold increase over the standard dose) or a synthetic glucocorticoid such as prednisone 10–20 mg intravenously. However Professor Chrousos noted that 100 mg/m² is ten times the daily unstressed production rate and that nobody has ever suffered any problems receiving higher doses of hydrocortisone in this situation, whereas too little hydrocortisone can be associated with cardiovascular instability.

On the topic premature adrenarche Professor Jääskeläinen noted that in these children bone mineral density tends to be normal for their relative weight, so they just achieve their peak bone mass earlier than controls.

References

1. Charmandari E, Kino T, Ichijo T, Chrousos GP. Generalised glucocorticoid resistance: Clinical aspects, molecular mechanisms, and implications of a rare genetic disorder. *J Endocrinol Metab* 2008; 93: 1563–72.
2. Priftis KN, Papadimitriou A, Anthracopoulos MB et al. Endocrine-immune interactions in adrenal function of asthmatic children on inhaled corticosteroids. *Neuroimmunomodulation* 2009; 16: 333–9.
3. Shulman DI, Palmert MR, Kemp SF et al. Adrenal insufficiency: still a cause of morbidity and death in childhood. *Pediatrics* 2007; 119: e484–94.
4. Nakamura Y, Gang HX, Suzuki T et al. Adrenal changes associated with adrenarche. *Rev Endocr Metab Disord* 2009; 10: 19–26.

