Growth: from molecules to medicines

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**ESPE 2018: DON’T FORGET – SUBMIT YOUR ABSTRACTS BY 16 APRIL!**
As well as all-important ‘News’ items, you remarked that you particularly enjoy updates from the world of research. Our new, regular ‘Hot topics’ section therefore highlights discoveries of interest to paediatric endocrinologist colleagues. By expanding the ‘Events’ pages, we will better alert you to forthcoming ESPE activities.

Each issue will also include selected features on a theme. This time you will find insights into growth but, as well as medical topics, in future we will also address areas of general interest, such as career development or grants, and we will of course focus on our annual ESPE Meeting.

You can look forward to members’ news, interviews, opinions and much more besides in coming issues. As always, your own contributions and suggestions are central to the success of ESPE News. Please send them to espe@eurospe.org.

We hope you agree that growth is an appropriate first topic for a developing newsletter (see pages 5–9). We are honoured to start with Ron Rosenfeld’s summary of the history of growth hormone therapy, followed by exciting developments of a molecular nature from Jesús Argente and Ravi Savarirayan. Lastly, we welcome the recent guidelines on Silver-Russell and Turner syndromes.

ESPE’s first Science Symposium is another exciting development, addressing the topical subject of ‘The Science of Gender’ (page 10).

Finally, as we prepare for the 2018 ESPE Meeting in Athens, please remember to submit your abstracts by 16 April, and to register by 22 June to benefit from discounted rates!

Sarah Ehtisham
Editor, ESPE News
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Welcome
It is with great pleasure that I introduce the first issue of the newly redesigned ESPE News, which reflects ESPE’s mission to advance excellence in paediatric endocrinology, and your feedback from recent surveys.

Congratulations
We congratulate ESPE member Peter Hindmarsh (London), who recently won The Daily Mail’s Health Heroes award.

Peter is Professor of Paediatric Endocrinology at University College London and Consultant in Paediatric Endocrinology and Diabetes at University College London Hospitals and Great Ormond Street Hospital for Children. He specialises in adrenal disorders and diabetes mellitus, using pump technology in both conditions to improve patient well being. His research has established a way of deriving individualised rates to deliver hydrocortisone mimicking the circadian rhythm.

Peter was selected for the award on the basis of nominations by the general public. It was presented by the UK Prime Minister, Teresa May, at 10 Downing Street in London.

You can read more at: www.dailymail.co.uk/health/article-5192375/Britains-inspiring-health-worker.html.

ESPE’s e-Learning portal provides an interactive learning environment for up to date information in paediatric endocrinology.

The section on ‘Calcium and bone’ spans calcium–phosphate metabolism, bone dysplasia, growth plate maturation and hypophosphatasia. Five interactive case presentations have recently been added to this section, concerning children with convulsions, rickets, fractures and short stature.

You can register free of charge to use the portal.

Follow ESPE online...
Keep an eye on the latest ESPE news and activities at www.eurospe.org
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Peter with his daughter at 10 Downing Street.
ESPE Grants

Deadline day: 30 April

Don’t forget the forthcoming deadline for applications for the following ESPE Grants. 30 April is the closing date to secure your:
• Early Career Scientific Development Grant
• Scientific Career Development Grant
• Research Unit Smaller Grant, or
• Research Unit Larger Grant (final applications)

See www.eurospe.org/grants-awards/grants for more details.

ESPE Grants can support your career

Aneta Gawlik is a clinician and researcher at the Medical University of Silesia in Poland. Here she explains how ESPE Grants helped build her career.

“As a young doctor almost 20 years ago, ESPE Travel Grants enabled me to attend international conferences and keep abreast of trends in our discipline. In 2000, I took part in the ESPE Winter School in Prague, Czech Republic, and in 2007 I was accepted for the ESPE Summer School in Helsinki, Finland. More recently, I have participated in four ESPE Advanced Seminars. These all allowed me to meet and work with brilliant individuals, who greatly inspired me.

In 2010, thanks to an ESPE Visiting Scholarship (now the Early Career Scientific Development Grant), I was able to train at the Technion-Israel Institute of Technology, Haifa, Israel, under the supervision of Ze’ev Hochberg and Dov Tiosano.

Now, I am the principal investigator for our most recent multicentre study ‘Personalised approach to non-syndromic childhood obesity using multi-omics disease signature’, which was chosen to receive the 2017 ESPE Research Unit Larger Grant.

I try to contribute to ESPE, and am Treasurer of the Turner Syndrome Working Group and a member of the Clinical Practice Committee. ESPE has supported me throughout my career, and I couldn’t be more grateful for all of the opportunities it has given me.”

Remember that ESPE could help you in the same way!

Don’t miss ESPE 2018:
Key dates and deadlines

‘Narrative and Precision Medicine in Paediatric Endocrinology’
57th Annual ESPE Meeting
27–29 September 2018
Athens, Greece

ESPE 2018 abstract submissions 16 April
ESPE 2018 Travel Grant applications 16 April
ESPE 2018 early bird registration 22 June

Preliminary programme available online now!
Find out more at www.espe2018.org

Clarification

This list of founding members which accompanied the article entitled ‘Six decades of ESPE’ on page 7 of the last issue of ESPE News is the list of founding members of ESPE. It differs from the list of founding members of the earlier Paediatric Endocrinology Club. Both lists, and further information, can be found in ESPE – The First 50 Years edited by Wolfgang Sippell and published by Karger (www.karger.com/Book/Home/255429).
Mechanism of brain damage by Zika virus

Zika virus (ZIKV) is an emerging, mosquito-borne RNA virus. Its rapid spread in the Americas unveiled microcephaly (in newborns) and Guillain–Barré syndrome (in adults) as major ZIKV-associated neurological complications. ZIKV can also cause other neurological manifestations, including myelitis, meningoencephalitis and fatal encephalitis.

The immune system’s response to ZIKV, rather than the virus itself, may be responsible for the nerve-related complications, according to a study from Yale University (New Haven, CT, USA). Akiko Iwasaki’s team examined the spread of infection in mice models of human brain.

When mice were infected with ZIKV, the virus soon invaded astrocytes that help maintain the crucial blood:brain barrier. Once that barrier was compromised, CD8 T cells flooded the brain. These defensive immune cells blocked the spread of ZIKV, but also killed the infected neurones: ‘The immune cells generated by infection start attacking our own neurones. The damage is not occurring through the virus infection, but rather the immune response to the virus.’ Immune-mediated nerve damage also underlies Guillain–Barré syndrome, which affects some people infected with ZIKV.

The findings suggest that ZIKV-associated neurological complications might be treated by suppressing the immune response.

Read the full article: Jurado et al. 2018 Nature Microbiology 3 141–147

Blood test to diagnose localised cancer

CancerSEEK, a multi-analyte blood test developed by researchers at Johns Hopkins University (Baltimore, MD, USA), can detect the presence of eight tumour types (ovarian, liver, stomach, pancreatic, oesophageal, colorectal, lung and breast) at relatively early stages.

The test uses a PCR-based assay to identify circulating tumour DNA by assessing the presence of mutations in 16 genes, and measures levels of eight proteins characteristic of specific cancer types, to help determine the tumours’ organ of origin.

The test was trialled on 1005 patients with non-metastatic cancer (stage I–III) and on 812 healthy controls. The median sensitivity amongst the eight cancer types was 70% and ranged from 98% for ovarian cancer to 33% for breast cancer, with a specificity of >99%. Importantly, the sensitivity for stage I cancers was only 43%. It also helped identify the tumours’ location, narrowing the origin of the cancer to two possible sites in about 80% of patients. The estimated cost is $500, similar to a colonoscopy.

Although more research is needed, this work may represent a step towards creation of routine blood tests to screen for cancer.

Read the full article: Cohen et al. 2018 Science doi: 10.1126/science.aar3247

Skin-derived insulin-producing cells in diabetes

Researchers in Bergen, Norway, have transformed skin fibroblast cells from patients with HNF4α mutations (linked to maturity-onset diabetes of the young type 1; MODY1) into insulin-producing cells, using stem cell techniques. The aim is to transplant these cells under the skin of diabetic patients, replacing insulin injections and blood sugar measurements with insulin-secreting cells capable of automatically secreting insulin in response to the blood sugar level. This could be by implanting a capsule with tailor-made cells into each patient.

They reprogrammed skin fibroblasts from four donors from the same MODY1 family: a parental diabetic mutation carrier and three offspring (one diabetic mutation carrier, one non-diabetic mutation carrier and one non-diabetic non-mutation carrier (family control)). They used global proteomics and cellular biology techniques to investigate the differentiation capacity of insulin-producing cells, using a seven-step protocol to differentiate these reprogrammed stem cells into cells capable of producing insulin in vitro, despite their MODY1 mutation status.

Until now, stem cells generated this way have usually been immature ‘β-like’ cells, unable to perform accurate glucose-stimulated insulin secretion unless transplanted into mice and allowed to mature in vivo, as the full differentiation pathway was not fully elucidated. This proteomics approach now permits their differentiation in vitro.

Read the full article: Vethe et al. 2017 Scientific Reports 7 doi: 10.1038/s41598-017-04979-w
Growth hormone therapy: a history

Recombinant DNA-derived growth hormone (GH) has been available for over 30 years and is used in many clinical conditions. This, of course, was not always so. Ron Rosenfeld gives us a brief review of GH therapy's interesting past.

GH and the pituitary

By the late 19th century, the association between acromegaly and sella enlargement had been noted, although a causal relationship with the pituitary was not confirmed until the early 20th century, when pituitary surgery was undertaken to alleviate the symptoms of this condition. Studies in rats showed that growth was stunted by hypophysectomy, but stimulated by injections of beef pituitary extract.

In 1944, Li and Evans isolated bovine GH and eventually deduced the 191 amino acid structure. Neither it nor porcine GH, which was subsequently purified, had any growth-promoting or metabolic actions in humans, demonstrating its high species specificity.

Early treatment

With the purification of GH from human pituitary glands, therapy in GH-deficient children became possible. The US National Pituitary Agency was established in 1960, to co-ordinate GH extraction from human cadaver pituitaries and clinical research. It is estimated that, between 1963 and 1985, 8000 children in the USA and 27,000 children worldwide received human cadaveric GH.

In 1985, however, the report of four cases of Creutzfeldt–Jakob disease in GH recipients led to the termination of distribution of cadaveric GH. Fortunately, the human GH (hGH) gene had been cloned and sequenced in 1979, leading to development of synthetic, recombinant DNA-derived hGH in the early 1980s. With the non-availability of cadaveric hGH and demonstration that synthetic GH was effective and safe, the US Food and Drug Administration (FDA) approved synthetic methionyl hGH for use in GH-deficient children in 1985.

A changing definition of GHD

The availability of theoretically unlimited quantities of synthetic hGH allowed expansion of indications for GH therapy. Previously, therapy was restricted to children identified as having ‘severe’ GH deficiency (GHD). Initially defined as failure to raise serum GH above 5ng/ml following at least two pharmacological provocative tests, and eventually liberalised to a cut-off of <7ng/ml, the definition of GHD was changed to a failure to achieve a serum GH level >10ng/ml.

Notably, no experimental or clinical data supported this redefinition, but it has been estimated that this change at least doubled the number of children labelled as GH-deficient and so qualifying for GH treatment.

Additionally, the common practice of ‘priming’ prepubertal children with low-dose sex steroids to enhance responsiveness of normal children to stimulation testing was abandoned by many endocrinologists, further loosening criteria for a diagnosis of GHD. Accordingly, it has been estimated that as many as 70% of children labelled as GH-deficient are not truly so.

Wider use of GH therapy

The demonstration of the effectiveness and safety of synthetic GH in childhood GHD opened the door for its use in many other conditions characterised by growth failure. In 1993, the FDA approved its use in children with chronic renal insufficiency. Growth failure in such patients occurs despite GH sufficiency and is undoubtedly multifactorial, including some degree of resistance to GH-dependent insulin-like growth factors (IGFs), perhaps related to disturbances in IGF-binding proteins.

The FDA approved GH treatment in Turner syndrome in 1997, following studies demonstrating that it resulted in short-term acceleration of growth and improvement in adult height. The short stature characteristic of Turner syndrome is probably explained by a skeletal dysplasia, which can be partially overcome by super-physiologic levels of GH and IGFs.

In 2000, GH was approved for growth failure in children with Prader–Willi syndrome, many of whom may have partial GHD, although studies suggest possible beneficial metabolic effects as well. Subsequent approval was obtained for small for gestational age infants who have not shown evidence of normalisation of growth by 2 years of age (2001), short stature homeobox-containing (SHOX) gene deficiency, causes including, but not restricted to, Turner syndrome (2006), Noonan syndrome (2007) and adult GHD (1996).

Perhaps most controversial has been GH therapy for idiopathic short stature: approved in the USA, but not in most other countries. Defined as stature below –2.25 SDs, with no obvious aetiology, this heterogeneous group includes children with partial GH and/or IGF resistance, mild skeletal dysplasias, and a variety of other subtle defects. Inevitably, it also includes otherwise normal children at the far end of the Gaussian distribution for height.

Ron Rosenfeld
Professor and Chair of Pediatrics (Emeritus), Oregon Health and Sciences University. and President, STAT5, LLC, Portland, OR, USA
Discovering the first mutation in PAPP-A2

In 2015, a 9-year-old girl visited our department for short stature. Her height was in centile 10, 1.68 SDs below her target height in centile 50–75.

Colleagues have asked why we studied a child whose height was above −2 SDs for her age and sex. However, not only was she far from her target centile, her parents were concerned, as they perceived her height to be progressively worsening compared with her peers.

This was later confirmed, as she and her affected brother had a continuous reduction in their growth velocity. Indeed, her younger brother, 6 years of age, exhibited a similar phenotype and auxological abnormalities. Two other siblings did not present these findings. She was quite thin and hormonal abnormalities were found in these patients. Two other siblings did not present these findings. She was quite thin and hormonal abnormalities were found in these patients.

The first biochemical analyses indicated that the growth hormone–insulin-like growth factor (GH–IGF) axis was affected. She had serum IGF-I, IGF-binding protein-3 (IGFBP-3) and acid-labile subunit (ALS) higher than any patient that I have ever seen (all were greater than +3 SDs). Spontaneous GH secretion over 8h was elevated, so this was obviously not a case of GH insensitivity. The high level of total IGF-I indicated that they lacked this protease which cleaves IGFBPs from the ternary complex. In addition to IGFBP-3, both IGFBP-4 and IGFBP-5 were elevated. The extremely low levels of free IGF-I, as well as the low bioactivity of the IGFs, concurred with the lack of proteolytic liberation of this growth factor from the ternary complex.

Jan Frystyk (Aarhus, Denmark) measured IGF bioactivity, using the KIRA (kinase receptor activation) assay.

Horacio Domené (Buenos Aires, Argentina) showed that the levels of IGFBP-3 in the ternary complex were markedly elevated in the affected subjects, indicating that, although total IGF-I was very high, it was sequestered in the ternary complex, again most probably due to the reduced proteolytic processing by PAPP-A2.

The excitement came when he called to say the most likely candidate was PAPP-A2, a protease involved in cleaving IGFBPs (pregnancy-associated plasma protein-A2).

To provide further confirmation that this was the cause of the growth retardation, we wanted to try and find at least one other family with a mutation in this gene. After conversations with Ron Rosenfeld (Portland, OR, USA), a second mutation was detected several months later in three patients of Palestinian ancestry with short stature, whose parents were first cousins, through liaison with Vindhini Desikan (New York, NY, USA), Radhika Muzumdar (Pittsburgh, PA, USA), and Andrew Dauber and Vivian Hwa (Cincinnati, OH, USA). These patients showed a missense variant in PAPP-A2 (c.3098C>T, p.Ala1033Val), PAPP-A2 levels in serum were diminished, but detectable. Similar hormonal abnormalities were found in these patients. Our research on the two unrelated families was published together.

Finding a further mutation

This discovery has not only increased our understanding of human postnatal growth, but also of the regulation of the GH–IGF axis.”
Bone analyses

Since pappa2 knockout mice show bone abnormalities, radiological surveys were performed. They did not show signs of dysplasia. However, thin long bones, most prominent in the fibulae, tibiae and femurs, were found. Bone mineral density was decreased at the lumbar spine in DXA (dual-energy X-ray absorptiometry) scans, in studies performed by Federico Hawkins (Madrid, Spain).

Both patients started recombinant human IGF-I therapy and over the past 2 years have shown a good response in growth velocity, bone mineral density and trabecular bone structure. This discovery of the first mutations in the metalloproteinase PAPP-A2 has not only increased our understanding of human postnatal growth, but also our comprehension of the regulation of the GH–IGF axis. Whether variants of PAPP-A, or of stanniocalcins (STC1 or SCT2) which modulate the activity of PAPP-A and PAPP-A2, can be implicated in pathological human growth remains to be demonstrated.

We thank all who have participated in our studies.

Jesús Argente
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References

Achondroplasia: a potential new treatment?

Achondroplasia is the most common form of human dwarfism. It is associated with gain-of-function mutations in the fibroblast growth factor receptor 3 gene (FGFR3), which is a negative regulator of bone growth.

At the cellular level, FGFR3 mutations induce increased phosphorylation of the tyrosine kinase receptor FGFR3, which correlates with an enhanced activation of its downstream signalling pathways. The skeletal phenotype involves defective proliferation and differentiation of the chondrocytes in the growth plate cartilage. Both endochondral and membranous ossification processes are disrupted.

Mechanisms of growth

C-type natriuretic peptide (CNP) and its receptor (NPR-B) are important regulators of longitudinal growth. In experiments in transgenic and knockout mice, CNP has been shown to be a potent stimulator of endochondral bone growth. In humans, biallelic loss-of-function mutations in the gene coding for NPR-B cause acromesomelic dysplasia, type Maroteaux, with extreme short stature.

Polymorphisms in two genes related to the CNP pathway have been implicated in height variability in healthy individuals. Heterozygous mutations in NPR2 are responsible for non-syndromic familial short stature. Conversely, heterozygous gain-of-function mutations in NPR2 cause tall stature, with a variable phenotype.

Steps towards therapy

A number of preclinical studies have been conducted to investigate potential treatments for achondroplasia, such as a CNP analogue (BMN-111 or vosoritide), intermittent parathyroid hormone (PTH) injections, soluble FGFR3 therapy, and meclozine and statin treatments.

In mice models of achondroplasia, targeted overexpression of CNP in cartilage or the systemic administration of CNP reverses the impaired skeletal growth, and this has led to interest in the potential therapeutic application of CNP analogues as a treatment for human skeletal dysplasia patients.

Among the putative approaches to antagonise FGFR3 signalling, vosoritide is one of the most promising strategies. Vosoritide acts as a key regulator of longitudinal bone growth by down regulating the mitogen-activated protein kinase pathway, which is activated as a result of a FGFR3 gain-of-function mutation.

Clinical trials

Vosoritide is the only targeted pharmacological therapy for achondroplasia that has proceeded to human clinical trial. The phase 1 trial showed that vosoritide is well tolerated in healthy adult males. The phase 2 trial was an open-label, sequential cohort dose-escalation study involving children aged 5–14 years with a molecularly confirmed diagnosis of achondroplasia. Patients were randomised for 2.5, 7.5 or 15μg vosoritide/kg per day, by subcutaneous injection for 6 months (you can find details at www.clinicaltrials.gov). The results showed a favourable safety profile and efficacy at higher dosage, with a 50% increase in growth velocity over individual baseline in the 15μg/kg cohort. The trial has now proceeded to an 18-month extension study, and all participating patients have been switched to the 15μg/kg dose. These first clinical trials mark the first big step towards real treatment for skeletal dysplasia patients.

Sarah Ehtisham
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University of Melbourne, Australia

Further reading

Silver–Russell syndrome (SRS) is an imprinting disorder that causes prenatal and postnatal growth retardation with no catch up, severe feeding difficulties, recurrent hypoglycaemia, premature adrenarche, fairly early and rapid central puberty, insulin resistance and body asymmetry.

Although described in 1953, it is still difficult to diagnose, and requires complex multidisciplinary care. Because it is a rare disorder, evidence from controlled trials is limited.

An international consensus meeting was consequently organised to develop guidelines for diagnosis and management of patients with SRS. It took place in Poblet, Spain, just after ESPE 2015 in Barcelona. It was a joint venture involving the COST Action (European Network for Human Congenital Imprinting Disorders; www.imprinting-disorders.eu), ESPE, PES (Pediatric Endocrine Society), APPES (Asian Pacific Pediatric Endocrine Society) and SLEP (Sociedad Latino-Americana de Endocrinología Pediátrica), each nominating official representatives.

During the 3-day meeting, 36 experts from 16 countries (clinical and molecular geneticists, paediatric endocrinologists and a gastroenterologist), chosen for their publication record and expertise in SRS, collaborated with five non-voting parent support group representatives from different countries. A Delphi-like consensus methodology was adopted. A comprehensive review of over 600 articles formed the basis of discussion by three working groups (clinical diagnosis, molecular diagnosis, and treatment). Each presented a summary of their findings and proposed recommendations. The entire group then discussed, revised and then voted on these recommendations.

The resulting first-ever SRS consensus was subsequently published, containing 72 recommendations.1

In summary

The conclusions were that SRS is primarily a clinical diagnosis, based on a clinical scoring system. However, molecular testing enables confirmation of the diagnosis and defines the subtype. An early emphasis on adequate nutritional status is important, with awareness that rapid postnatal weight gain might lead to subsequent increased risk of metabolic disorders.

The benefits of treating patients with SRS with growth hormone include improved body composition, motor development and appetite, reduced risk of hypoglycaemia and increased height. Clinicians should be aware of possible premature adrenarche, fairly early and rapid central puberty and insulin resistance. Treatment with gonadotrophin-releasing hormone analogues can delay progression of central puberty and preserve adult height potential. Long term follow up is essential to determine the natural history and optimal management in adulthood.

This consensus has now been disseminated internationally, and a ‘patient friendly’ version is being translated into different languages with the support of the SRS global alliance (www.silverrussellsyndrome.org). The outcomes of this consensus will be presented in a symposium at ESPE 2018 in Athens.

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Emma L Wakeling
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Reference


‘Growth’ in e-Learning

If your interests include growth, remember that the ESPE e-Learning portal (www.espe-elearning.org) includes a section entitled ‘Growth and growth regulation’. This contains 4 chapters on the anatomy, (patho)physiology, genetics, diagnostic approaches and therapeutic interventions concerning short and tall stature. Alongside these chapters, 17 interactive cases discuss various disorders related to growth. The separate ‘Courses’ section also features a ‘Growth and puberty’ course, specifically intended for medical students.

See www.espe-elearning.org. Remember, registration is free of charge.
New guidelines for growth-related disorders: Turner syndrome

Turner syndrome (TS) is a condition requiring the involvement of many different medical specialists from intra-uterine life until old age. Patient care also necessitates close collaboration of those specialists at different time-points.

When we began the process of developing these new guidelines, we therefore established a set of criteria. We wished to involve as many different scientific societies as necessary, covering all aspects of TS care. Our aim was to include international specialists and young and upcoming individuals. We wanted the guidelines to be evidence-based as far as possible, and so we used GRADE (Grading of Recommendations, Assessment, Development and Evaluations) to analyse the knowledge base. The process had to be transparent and to have all 60+ experts genuinely involved in the work. Many different countries were to be represented, preferably from all continents.

Experts were involved from the ESE (European Society of Endocrinology), PES (Pediatric Endocrine Society), Endocrine Society, ESPE, ESHRE (European Society of Human Reproduction and Embryology), American Heart Association, Society for Endocrinology, and European Society of Cardiology. Specialists from further professional societies participated in work groups that developed the guidelines consensus statement. We also included patient advocate groups in all the working groups.

The resulting recent guidelines are 70 pages long. They are extensive, but very operational and useful in the clinical setting.

An overview

The recommendations cover many areas. Within the section on diagnosis and genetics, we define what should and should not be called TS. We also focus on delayed diagnosis and the frequent occurrence of non-diagnosis, suggesting new avenues. The inclusion of TS in newborn screening programmes is discussed, to avoid long diagnostic odysseys and non-diagnosis.

Growth and puberty are key issues of concern, and the guidelines cover optimal growth-promoting treatment and induction of puberty, especially given that 11–12 years is now the recommended age for pubertal induction.

Adults with TS judge fertility as the most important determinant of quality of life, and so several new recommendations concern this. Many women with TS are now able to achieve pregnancy and the birth of a healthy child after oocyte donation, if such a pregnancy is well-planned and preceded by a thorough cardiovascular work-up. We present detailed cardiovascular recommendations based on a wealth of new data coming from several centres worldwide.

Our review elucidated the frequent occurrence of congenital cardiac malformations, including some previously described (bicuspid valves and coarctation of the aorta), but now broadened to include, for example, elongated aortic arch, aortic dilation and dilation of the branching arteries. We emphasise that magnetic resonance imaging or other techniques should be used much more liberally. We also discuss rigorous treatment of the frequently encountered hypertension, especially in pregnancy.

Proposals to strengthen the transition process from paediatric to adult care are featured (see Figure). We present recommendations for appropriate care during adulthood, while covering all known comorbidities that affect people with TS. Neurocognitive impairment frequently affects individuals with TS, and we present new operational recommendations for neuropsychological care. Finally, we stress that care of patients with TS should take place in multidisciplinary clinics around the globe.

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Philippe Backeljauw
Cincinnati Children’s Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH, USA

Reference
The Science of Gender
1st ESPE Science Symposium
London, UK, 18–19 October 2018

Aimed at paediatricians and basic researchers, ESPE’s new Science Symposia will take place every 2 years, to promote the interactive dissemination of new scientific knowledge within the paediatric endocrinology community, closing the gap between research and patient care.

The first event takes place in London, UK, on 18–19 October 2018. On ‘The Science of Gender’, it will look at evidence for what shapes gender development and gender dysphoria, and the influences of nature and nurture. We will discuss the potential psychological–psychosocial impacts of endocrine treatment for gender dysphoria and the science behind this.

Organised by the ESPE Gender Dysphoria Working Group alongside the host organisation, the Gender Identity Development Service (GIDS, www.gids.nhs.uk), it will be held at the Tavistock Centre in London, UK, near the home of Sigmund and Anna Freud. It is organised with an educational grant from Pfizer.

The 1.5-day programme is for those with an interest in gender development, disorders/differences of sex development (DSD), neurocognition and hormones, and social factors.

Registration details
The event is limited to 100 attendees, including faculty. 25 fully sponsored places will be available for trainees, young clinicians and scientists (individuals within 8 years (FTE) of completion of doctorate training). The application deadline for free places is 1 July 2018. After this date, registration will be open to all, at a cost of €60.

For details or to register see www.eurospe.org/education/espe-science-symposium.

Topics for 2018

Science of sex and gender development
A range of perspectives: genetic, endocrine, cognitive, emotional and social
The effect of societal changes

Science of neurodevelopment
Brain maturation, emotional and cognitive development, endogenous hormones and maturation, exogenous hormones on brain function

Science of endocrine therapy
Pubertal blockade and cognitive/emotional development, efficacy of cross sex hormone treatment, effect of pubertal manipulation and cross gender hormone treatments, risks for bone and cardiovascular health and cancer

ESPE Schools
Our schools offer an interactive learning environment, providing up to date teaching in paediatric endocrinology for those who have entirely or partially completed their basic training. As well as our flagship Summer School, which takes place just before the annual ESPE Meeting, we also offer regional and specialist schools. Three of these are currently accepting applications:

- Diabetes, Obesity & Metabolism School
  Delphi, Greece, 30 September–2 October
  Application deadline 4 June

- Caucasus & Central Asia School
  (in Russian & English) Bishkek, Kyrgyzstan, 22–25 October
  Application deadline 30 April

- Maghreb School (in French)
  Algeria, 19–24 November
  Application deadline 30 April

For more on ESPE schools see www.eurospe.org/education

ESPE 2018: Athens, Greece
We look forward to welcoming you to Athens for the 57th Annual Meeting of ESPE on 27–29 September 2018. The meeting’s theme is ‘Narrative and precision medicine in paediatric endocrinology’. Plenary sessions, symposia and Meet the Expert sessions will encourage the exchange of high quality clinical information and basic science with international experts. The venue is in central Athens, so you will also be able to explore over 3000 years of history, philosophy, culture and art.

- Abstract submissions by 16 April
- Discounted early bird registration by 22 June
- Find the preliminary programme now at www.espe2018.org
Future meetings
See www.eurospe.org/meetings for details of all future meetings

57th Annual ESPE Meeting
27–29 September 2018
Athens, Greece

58th Annual ESPE Meeting
19–21 September 2019
Vienna, Austria

59th Annual ESPE Meeting
10–12 September 2020
Liverpool, UK

OTHER EVENTS

SEPTEMBER
ESPE Summer School
Delphi, Greece
24–26 September 2018
ESPE Diabetes, Obesity & Metabolism School
Delphi, Greece
30 September–2 October 2018

OCTOBER
1st ESPE Science Symposium
London, UK
18–19 October 2018
ESPE Caucasus & Central Asia School
Bishkek, Kyrgyzstan
22–25 October 2018

NOVEMBER
ESPE Maghreb School
Algeria
19–24 November 2018

DEADLINES

MARCH
Communications Committee Vacancy applications
31 March 2018

APRIL
ESPE 2018 abstract submissions
16 April 2018
ESPE 2018 Travel Grant applications
16 April 2018
Caucasus & Central Asia School applications
30 April 2018
Maghreb School applications
30 April 2018
Early Career Scientific Development Grant applications
30 April 2018
Scientific Career Development Grant applications
30 April 2018
Research Unit Smaller Grant applications
30 April 2018
Research Unit Larger Grant final applications
30 April 2018

MAY
Clinical Fellowship applications
31 May 2018

JUNE
Diabetes, Obesity & Metabolism School applications
4 June 2018
ESPE 2018 early bird registration
22 June 2018

JULY
ESPE Science Symposium applications for free places
1 July 2018

HELP RUN YOUR SOCIETY

Vacancies arise regularly on ESPE Committees. To see which opportunities are currently available, check www.eurospe.org/about/vacancies.