Neonatal endocrinology

Providing the best start in life

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ESPE AWARDS  – make your nominations by 10 December  – www.eurospe.org/awards
On pages 4 and 5, you will find ESPE’s Award Winners for 2018, while page 11 features highlights from the meeting, including the very memorable Greek dancing! You can nominate your own choice of winners for the 2019 ESPE Awards until 10 December. See www.eurospe.org/grants-awards/awards for details.

The focus of this issue of ESPE News is neonatal endocrinology, and we welcome the contributions of colleagues working across a broad range of topics.

On page 7, Rod Mitchell (Edinburgh, UK) examines the potential effect of analgesic use in pregnancy on the fertility of the next generation. In response to the latest research, his message to expectant mothers is to take paracetamol only when necessary, and to obtain medical advice before using ibuprofen.

Hypophosphatasia is a thankfully rare but devastating bone disease in newborns and infants. Treatment with asfotase alfa offers considerable benefits and, on page 8, Raja Padidela (Manchester, UK) offers us his experience and advice in diagnosing and treating this disorder.

Also rare in neonates, Cushing’s syndrome presents particular challenges in this age group, and sadly has a poor prognosis. Christina Tatsi and Constantine Stratakis (the 2018 ESPE International Award Winner), both from Bethesda, MD, USA, examine the disorder’s genetic causes, diagnosis and treatment on page 9.

On page 10, Juliane Léger (Paris, France) considers Graves’ disease in the fetus and neonate. She provides us with a diagnostic algorithm for use in high risk pregnancies, and a protocol for management of neonatal autoimmune hyperthyroidism.

This wealth of information is complemented as usual by the latest news from ESPE and details of the many forthcoming events. Happy reading!

Sarah Ehtisham
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Your new Secretary General-Elect

At ESPE’s Annual Business Meeting in September, Anita Hokken-Koelega (Rotterdam, The Netherlands) was formally elected as the next Secretary General of ESPE, following an e-vote amongst Society members.

Professor Hokken-Koelega will take office as Secretary General in September 2019, when Peter Clayton steps down from the post after completing an extended term of 4 years.

Anita is Professor of Paediatric Endocrinology at Erasmus University Medical Center/Sophia Children's Hospital in Rotterdam. She has previously been ESPE's Treasurer and Chair of the Strategic & Finance Committee.

Talking about her vision for the Society in the coming years, Anita said, ‘ESPE has a great responsibility and an important role in improving healthcare for children and adolescents with endocrine disorders, in training paediatric endocrine fellows and in developing quality indicators and standards of care, as well as in prioritising research activities, across Europe and worldwide. It is important that ESPE remains a leading paediatric society, and that it collaborates with other paediatric and adult societies, for example by participating in the International Consortium of Pediatric Endocrinology (ICPE).’

In total, 365 members voted in the election, with Anita receiving 53.2% of the votes and candidate Gary Butler receiving 46.3%. Anita was welcomed to her new role by Peter Clayton.

Welcome

It was wonderful to see so many of you at ESPE 2018 in Athens. This highly successful ESPE Meeting brought together paediatric endocrinologists from across our discipline, to enjoy the very best science and clinical research.

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Editorial Board:
Assimina Gali-Tsinopoulou
Antje Garten
Abel López-Bermejo
María Salomón Estébanez

Peter Clayton to lead ICPE for another year

ESPE’s Secretary General, Peter Clayton, will remain as Chair of the International Consortium of Pediatric Endocrinology (ICPE) for another year, as agreed by ICPE members at the Consortium’s meeting in Athens in September. This 1-year extension of his leadership will align with his term of office as Secretary General of ESPE.

The Hague to host ESPE 2023

The 62nd Annual Meeting of ESPE in 2023 will be held in The Hague, the third largest city in The Netherlands and the seat of the Dutch government. This follows a successful bid by Paul Van Trotsenburg, Professor of Paediatric Endocrinology at the University of Amsterdam.
New ICPE website

The International Consortium of Pediatric Endocrinology (ICPE) has launched its own website to showcase the meetings, training events and clinical practice documents of all member societies globally.

You can view the site at www.intpedendo.org

2019 IFCAH-ESPE Grants

The IFCAH-ESPE fund provides grants of up to €150,000 per project for research on congenital adrenal hyperplasia. To find out how to apply for a grant in 2019, see www.eurospe.org/grants-awards/grants/ifcah-espe-grant.

Letters of intent should be submitted by 14 January 2019.

Congratulations

We congratulate Franco Chiarelli (Chieti, Italy) who received the Japanese Society for Pediatric Endocrinology’s International Prize at their 52nd Annual Scientific Meeting in Tokyo.

Nominate your colleagues for an ESPE Award

If you’d like to see your colleagues celebrated for their work and achievements – clinical or scientific – please nominate them for a 2019 ESPE Award. Information about all ESPE Awards is available at www.eurospe.org/grants-awards/awards. You can find details of the 2018 winners on pages 4 and 5.

The deadline for nominations is 10 December 2018.

Neonatal endocrinology in e-Learning

In keeping with the theme of this issue of ESPE News, ESPE e-Learning includes many informative cases of newborns with endocrine problems, which you will find within ‘General Content’:

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Case(s)</th>
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<tr>
<td>Adrenal disorders</td>
<td>A newborn with ambiguous genitalia and skeletal malformations</td>
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| Calcium and bone | A 2-week-old baby  
| | A baby with convulsions |
| DSD | A newborn with DSD |
| Growth | John, a jittery baby |
| Hyperinsulinism | Elisa and Joe |
| Thyroid | Neonatal thyrotoxicosis – an agitated newborn case  
| | A 6-day-old boy with abnormal newborn screening |

Please visit www.espe-elearning.org. Remember, registration is free of charge.

ESPE Summer School 2019

The next ESPE Summer School will be held at the secluded medieval castle of Burg Feistritz am Wechsel, 1 hour south of Vienna, Austria, on 16–18 September 2019.

The school provides up to date, interactive teaching, case presentations and plenty of discussion between faculty and students. As one 2018 attendee put it, ‘This experience was really amazing, as everyone could debate hot topics with the other delegates and the faculty. I think that every aspiring paediatric endocrinologist should try to participate in the ESPE Summer School.’

There is no registration fee, and travel between Vienna and the venue, accommodation and meals are free of charge. The Summer School is supported by an educational grant from Ferring Pharmaceuticals.

You must apply by 8 February 2019. See www.eurospe.org/education/summer-school.
We congratulate the winners of the 2018 ESPE Awards, many of whom received their prizes at the ESPE Meeting in Athens, Greece, in September.

**ESPE Andrea Prader Prize** supported by Pfizer

Yves Le Bouc (Paris, France) received the ESPE Andrea Prader Prize, in recognition of his lifetime achievement in teaching and research, outstanding leadership and overall contribution to the field of paediatric endocrinology.

**ESPE Outstanding Clinician Award**

John Gregory (Cardiff, UK) was presented with the ESPE Outstanding Clinician Award, in recognition of his outstanding clinical contribution to the practice of paediatric endocrinology.

**ESPE International Award**

Constantine Stratakis (Bethesda, MD, USA) received the ESPE International Award. This is presented to an outstanding paediatric endocrinologist from a country outside Europe and the Mediterranean basin.

**ESPE International Outstanding Clinician Award**

Palany Raghupathy (Bangalore, India) received the ESPE International Outstanding Clinician Award, in recognition of his contribution and commitment to clinical paediatric endocrinology in a country outside Europe and the Mediterranean basin.

**ESPE Research Award** supported by Pfizer

Christa Flück (Bern, Switzerland) received the ESPE Research Award, in recognition of research achievements of outstanding quality in basic endocrine science or clinical paediatric endocrinology.

**ESPE Young Investigator Awards** supported by Pfizer

These awards are for paediatricians who are still in training or have been in a senior (principal investigator) role for no more than 5 years. They are made in recognition of their scientific publications, and were presented to:

- Valentina Chiavaroli (Chieti, Italy) whose award lecture was entitled ‘Early life events and postnatal effects from infancy to adolescence: findings from recent studies on Italian and New Zealand cohorts’
- Laetitia Martinerie (Paris, France) whose award lecture was entitled ‘Deciphering the mineralocorticoid signalling pathway in neonates: from physiology to pathology’

**Henning Andersen Prizes** supported by Novo Nordisk

These awards for the most highly rated abstracts were presented to:

- Daniel Rodríguez Gutiérrez (Fribourg, Switzerland) for ‘Generating a human gonadal cells model from terminal differentiated fibroblast-derived induced pluripotent stem cells’
- Alessandra Mancini (London, UK) for ‘EAP1 mutations cause an impaired transcriptional activity on GnRH promoter that leads to self-limited delayed puberty’

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Nominations for 2019 ESPE Awards  I  Deadline is 10 December 2018  I  See www.eurospe.org/awards for details
President’s Poster Awards

This year’s prizes for the best posters at the meeting were awarded for the abstracts listed on the right. The recipients are pictured below (L–R, in the same order as the listed abstracts) with the President of ESPE 2018 George Chrousos.

• Disease burden and systemic manifestations of HPP in children enrolled in the global HPP registry (P1–P038)
  Wolfgang Högl er et al. (UK, USA, France, Japan, Canada & Germany)
• Role of urinary NGAL and KIM-1 as early kidney injury biomarkers in obese prepubertal children (P1–P112)
  Cosimo Giannini et al. (Italy)
• Serum IGFBP-2 concentration in neonates with potential diagnosis of growth hormone deficiency (P1–P147)
  María Gabriela Ballerini et al. (Argentina)
• More than a gut feeling: preliminary evidence supporting a role for lifestyle habits in shaping the intestinal microbiota in childhood and adolescence (P1–108)
  Mél anie Henderson et al. (Canada)
• Prevalence of diabetes among children treated with growth hormone in Israel (P1–P155)
  Miri Lutski et al. (Israel, award collected by Zvi Laron)

ESPE Hormone Research in Paediatrics Prizes supported by Karger

These prizes for the best original papers published in Hormone Research in Paediatrics were presented to:

• Samim Özen et al. (Izmir, Turkey) for ‘Rapid molecular genetic diagnosis with next-generation sequencing in 46,XY disorders of sex development cases: efficiency and cost assessment’ (best original paper)
• Hana Sediva et al. (Prague, Czech Republic) for ‘Short stature in a boy with multiple early-onset autoimmune conditions due to a STAT3 activating mutation: could intracellular growth hormone signalling be compromised?’ (best ‘Novel Insights from Clinical Practice’ paper)

ESPE Research Unit Grant supported by Sandoz

Awards have been made to the following recipients to facilitate collaborative research in paediatric endocrinology:

• Lars Sävendahl, Colin Farquharson, Ondrej Soucek & Jarod Wong for ‘Potential of humanin to prevent bone growth impairment and osteoporosis in inflammatory bowel disease’ (£15 000)
• Irène Netchine, Mohamad Maghnıe, Justin Davies, Jovanna Dahlgren, Susan O’Connell, Anita Hokken-Koelega & Gerhard Binder for ‘Silver Russell syndrome and metabolic function: building the knowledge for transition and care into adulthood’ (£130 000)

ESPE Clinical Fellowship supported by Merck

These fellowships to promote patient care, clinical management and clinical research in paediatric endocrinology have been awarded to Ne ha Agarwai (Delhi, India), N abat Aghayeva (Baku, Azerbaijan), Beatriz Corredor Andrés (Madrid, Spain), R uma Deshpande (Pune, India), Hüseyin Anıl Korkmaz (Balıkesir, Turkey), María Cecilia Mallo (Mar del Plata, Argentina), Hari Mangtani (Pune, India), Mya Sandar Thein (Yangon, Myanmar), Marzhan Rakhimzhanova (Kazakhstan), Ebrhim Reham (Khartoum, Sudan), Nadira Rouabah (Setif, Algeria), Sonia Samvelyan (Armenia), Aashish Sethi (New Delhi, India), Ingrida Stankutė (Kaunas, Lithuania), Laman Sultanova (Baku, Azerbaijan) and Khurshid Urinov (Uzbekistan).

IFCAH-ESPE Grants

Michel Polak (Paris, France), President of IFCAH’s Scientific Committee, presented these awards for research into congenital adrenal hyperplasia (CAH):

• Gérard Babot (Boston, MA, USA) for ‘Generation of human steroid-producing organoids: a new approach towards a treatment for CAH’ (£150 000 from AFM (the French Muscular Dystrophy Association) plus €50 000 from IFCAH)
• Claus Gravholt (Aarhus, Denmark) for ‘The epidemiology of congenital adrenal hyperplasia: a nationwide study’ (£100 000)
• Li Chan (London, UK) for ‘In vivo characterisation of ACTH receptor antagonists’ (£100 000)

ESPE Research Fellowship supported by Novo Nordisk

Emily Cottrell (London, UK) has been awarded this fellowship, which enables talented young scientists, investigators and paediatric endocrinologists to conduct research at leading institutions worldwide, for ‘Characterisation of novel genetic causes of growth failure’ (£125 000 for research training plus £15 000 for consumables).

Nominations for 2019 ESPE Awards

I   Deadline is 10 December 2018   I   See www.eurospe.org/awards for details
**Metabolic health and preconception paternal cold exposure**

Research by Sun et al. has indicated that people conceived in colder months (October–February) have more active brown adipose tissue (BAT). Using mice, they have proved their hypothesis that cold exposure (CE) before conception can cause changes in the BAT of offspring by epigenetic mechanisms. 

CE of male (but not female) mice before mating resulted in improved systemic metabolism and protection from diet-induced obesity in the offspring. The sperm from male mice revealed several differentially methylated regions and expressed genes associated with enhanced BAT neurogenesis and formation. CE induces epigenetic programming of the sperm such that the offspring harbour hyperactive BAT and have improved adaptation to over-nutrition.

Intergenerational memory of past CE may have helped improve survival during prolonged cold periods, such as the ice age 2.6 million years ago, and may be advantageous nowadays by protecting the offspring from metabolic derangements.

*Read the full article in Sun et al. 2018 Nature Medicine 24 1372–1383*

**Predicting neonatal hyperthyroidism**

Neonatal hyperthyroidism (NH) is related to transplacental passage of maternal anti-thyrotrophin receptor antibodies (TRAbs), mainly in the context of maternal Graves’ disease. Banigé et al. aimed to predict NH during the disease’s presymptomatic stage. In a retrospective multicentre 7-year study, they retrieved the medical records of 415 mothers with Graves’ disease who had positive TRAbs at least once during pregnancy. NH was defined as detection of goitre by ultrasound or of clinical signs of NH. Biochemical NH was defined as thyrotrophin (TSH) <2.5th percentile and free thyroxine (fT4) >97.5th percentile between days 3 and 7 of life.

Offspring fT4 levels could not predict NH. However, offspring TSH <0.90mIU/l (days 3–7 of life) predicted NH with 78% sensitivity, 99% specificity, 90% positive predictive value, 98% negative predictive value and area under the curve 0.99. 

TRAb levels (days 0–5 of life) and TSH levels (days 3–7 of life) constitute the proposed method of screening for NH in all asymptomatic but suspected newborns. Early therapeutic care is essential to avoid cardiac and neurologic complications.

*Read the full article in Banigé et al. 2018 Journal of Pediatrics 197 249–254*

**CRISPRa in human pluripotent reprogramming**

Induced pluripotent somatic cells (iPSCs) are increasingly used in research and are moving towards human clinical trials. It is therefore essential to be able to exactly replicate cellular phenotypes.

Weltner and colleagues report a method for reprogramming adult human cells into iPSCs using the CRISPRa (CRISPR-Cas9-based gene activation) system. A catalytically inactivated form of the Cas9 protein is recruited to genomic sequences defined by short guide RNA molecules. This results in transcriptional activation or silencing of endogenous genes. 

In addition to inducing transcription of conventional reprogramming transcription factors, a conserved Alu-motif was targeted which is enriched in the promoter areas of the first genes expressed during human embryo genome activation. This strategy resulted in the activation of a subset of endogenous genes that work as reprogramming factors.

Intergenerational memory of past CE may have helped improve survival during prolonged cold periods, such as the ice age 2.6 million years ago, and may be advantageous nowadays by protecting the offspring from metabolic derangements.

*Read the full article in Weltner et al. 2018 Nature Communications 9 2643*

**Mortality in type 1 diabetes in relation to age at onset**

This worrying report by Rawshani and co-workers highlights excess cardiovascular risk in those diagnosed with type 1 diabetes (T1DM) at a young age.

Data from the Swedish National Diabetes Registry (which includes 27 195 individuals with T1DM) was compared with that from 135 178 age-matched controls. Glycated haemoglobin was higher in those diagnosed at a younger age. Those diagnosed before 10 years of age had a 30-fold increased risk of coronary heart disease and acute myocardial infarction compared with controls, and those risks were even higher in women. Development of T1DM before 10 years of age resulted in a loss of 17.7 life years for women and 14.2 life years for men, compared with a loss of 10 years if diagnosed later.

Age at onset of T1DM appears to be an important determinant of survival and of cardiovascular disease, and earlier consideration may need to be given to cardioprotective medications as well as improving glycaemic control in those diagnosed young.

*Read the full article in Rawshani et al. 2018 Lancet 392 477–486*
The impact of *in utero* analgesic exposure

The concept of environmental exposures acting as endocrine disruptors during fetal life and having an impact on subsequent male reproductive health is not new. The increasing incidence of male reproductive disorders over recent decades suggests environmental factors may have a role, as Rod Mitchell discusses.

Endocrine disruptors

Analgesics are used by most (55–80%) women at some point in pregnancy. This usually involves short term use of paracetamol (acetaminophen), with a smaller proportion using ibuprofen.

Whilst paracetamol use in pregnancy has been considered safe, a number of epidemiological studies have reported associations between maternal analgesic use and the development of cryptorchidism in male offspring.1,2 Cryptorchidism, in addition to other male reproductive disorders (hypospadias, testicular germ cell cancer and impaired spermatogenesis), is associated with suboptimal androgen production or action during fetal life.

In order to investigate the effect of analgesic exposure on testosterone production, we used a xenograft approach to show that prolonged (≥7 days) exposure to paracetamol leads to reduced fertility in male pups per litter.6,7

To conclude

Exposure of human fetal gonads to human-relevant concentrations of paracetamol and ibuprofen consistently decreases fetal germ cell number. These effects are robust and are conserved in the rat and human across different model systems, probably resulting from disruption of prostaglandin signalling.

Whilst translation of these results to human pregnancy must be considered with caution, the findings support recommendations that paracetamol should only be used in pregnancy if needed, and then only for the shortest period necessary to manage symptoms.8

**Paracetamol should only be used in pregnancy if needed, and then only for the shortest period necessary to manage symptoms**

Rod Mitchell

MRC Centre for Reproductive Health, Queen’s Medical Research Institute, Edinburgh, UK

**References**

5. Hurtado-Gonzalez et al. 2018 Environmental Health Perspectives 126 047006.
Hypophosphatasia (HPP) is a rare, inherited, metabolic bone disease caused by loss of function mutation(s) of the ALPL gene, which encodes the tissue-non-specific isoenzyme of alkaline phosphatase (TNSALP). Hypophosphatasia is a heterogeneous disease, with severe perinatal and infantile forms manifesting in utero and by 6 months of age respectively. Low TNSALP activity results in extracellular accumulation of inorganic pyrophosphate (PPi), which inhibits bone mineralisation by blocking growth of hydroxyapatite crystals, appearing as rickets in children and osteomalacia in adults. In addition, TNSALP dephosphorylates pyridoxal 5'-phosphate (PLP), the principal circulating form of vitamin B6, to pyridoxal, which allows it to cross cell membranes and be rephosphorylated intracellularly to PLP. Thus, vitamin B6-dependent seizures can occur in some severely affected infants.

Additional life-threatening complications in the severe perinatal and infantile forms of HPP may include respiratory failure from rachitic chest deformity and rib fractures, elevated intracranial pressure due to craniosynostosis, and nephrocalcinosis and renal compromise secondary to hypercalcaemia.

### Diagnosing HPP

Diagnosis of HPP in infants is established by typical skeletal manifestation of severe rickets: characteristic ‘tongues’ of lucency extending from the growth plate to the metaphysis of long bones, with reduced mineralisation and the absence of ossification centres of bones. Biochemical manifestations are low serum alkaline phosphatase concentrations and elevated substrates of TNSALP, PLP and PPI.

Confirmation of diagnosis is by genetic testing for mutations in the ALPL gene. Severe perinatal and infantile forms are autosomal recessive, while milder childhood, adult and odonto forms are either autosomal dominant or recessive.

### Treating HPP

If untreated, the perinatal form of HPP is fatal, and in infantile HPP there is ~50% mortality during the first year of life. A phase 2 open label study recruited 11 patients, of whom 10 completed 6 months of therapy and 9 completed 1 year. All patients showed biochemical improvements, with reduction in the concentrations of PLP and PPI.

In keeping with this, there was healing of rickets and improvement in developmental milestones and pulmonary function. There were no serious drug-related adverse events. Asfotase alfa was associated with improved survival in treated patients versus historical controls: 95% vs 42% at age 1 year and 84% vs 27% at age 5 years respectively (P<0.0001, Kaplan–Meier log-rank test).

Asfotase alfa is administered as subcutaneous injections, three times a week at 2mg/kg per dose. Higher doses may initially be required in infants with severe forms of perinatal HPP. However, asfotase alfa treatment does not prevent craniosynostosis and some of the infants require craniofacial surgery. Besides treatment with asfotase alfa, patients with perinatal and infantile HPP also require high quality supportive care from a team of medical, surgical and allied healthcare professionals. Care of such infants should therefore be ideally provided in specialist paediatric tertiary hospitals, where multidisciplinary care can be co-ordinated.

Even though no drug-related serious adverse events have been reported, caution must be exercised, as suppression of PPI with prolonged asfotase alfa treatment can potentially cause ectopic calcifications. Long term monitoring of safety and efficacy of prolonged treatment with asfotase alfa into adulthood is therefore required, which can be addressed through ongoing registry of HPP.

**Raja Padidela**

Royal Manchester Children’s Hospital, Manchester, UK

References

Given its rarity in neonates, the symptoms of CS are often misdiagnosed, leading to prolonged, detrimental exposure to high cortisol levels.

Common manifestations include deceleration of growth in length with unabated weight gain, round facies with plethora, increased fat deposition with central obesity, easy bruising and signs of virilisation (when associated with an androgen co-secreting adrenocortical lesion). Certain findings traditionally associated with CS, such as violaceous striae, are infrequent in infants.

Classification

The most common aetiology of CS in infants is an adrenal disorder (adrenocorticotrophin (ACTH)-independent CS), usually caused by unilateral tumours (adrenocortical tumours, ACTs). More rarely, bilateral adrenocortical hyperplasia, involving micronodular (<1cm) or macronodular (>1cm) disease, may lead to autonomous hypercortisolaemia.

ACTH-dependent CS is rarer in infants than in older children and adults, and is often associated with pituitary blastomas. Ectopic ACTH/corticotrophin-releasing hormone (CRH) production is uncommon but, when present, is often from an embryonic tumour, neuroblastoma or similar neuroendocrine lesions, rather than from bronchial carcinoids.

We reviewed all published CS cases in patients <3 years old not related to ACTs. Of the 95 identified non-carcinoma cases, 19 (20%) had a pituitary source; 11 were confirmed to be pituitary blastomas. Nine of the identified cases (9%) were caused by ectopic ACTH/CRH production, most commonly from neuroblastomas (67%) of ectopic cases. The remainder (71%) were associated with adrenocortical hyperplasia or of unclear aetiology.

Genetic causes

TP53 gene mutations are found in almost 70% of all cases of ACTs. If they occur in the germline they are associated with Li–Fraumeni syndrome, an autosomal dominant inherited disease predisposing to cancer. Screening is recommended for all children for germline TP53 mutations upon diagnosis of an ACT.

Neonatal ACTH-independent CS may also develop in the context of a genetic syndrome. McCune–Albright syndrome (MAS) may present with CS in the first year of life. Additionally, Beckwith–Wiedemann syndrome has been reported in rare cases of cortisol-producing ACTs. Finally, pituitary blastomas present almost exclusively in the context of DICER1 gene mutations.

Other genetic syndromes known to lead to CS, such as multiple endocrine neoplasia type 1 or familial isolated pituitary adenomas, have not been reported in the infantile period. Carney complex may be diagnosed in infancy but, typically, the first tumour after birth in these patients is heart myxoma.

Diagnosis

The diagnosis of neonatal and infantile CS follows criteria established for the identification of CS at other ages. However, the hypothalamo-pituitary-adrenal axis is immature at birth, and it often takes 3–6 months for the circadian rhythm to be fully established, so investigation of the diurnal variation of cortisol is often not valid in infants. Additionally, measurement of free cortisol in a 24-h urine collection might require an indwelling catheter, which might be uncomfortable. Consequently, diagnosis often requires clinical judgement and the correlation of clinical, biochemical and imaging findings.

Treatment

Unfortunately, the prognosis of neonatal CS is poor. Surgical resection of the underlying cause is often recommended, involving either adenectomy or transcranial resection of pituitary lesions. Adjuvant chemotherapy with mitotane is often administered in cases with ACTs. The exception is in MAS, where CS is often noted to be transient. In such cases, if the infant survives the initial period of hypercortisolaemia with medical therapy, resolution of CS and further normal adrenal function may occur.

Even after successful treatment, it is not clear whether the exposure to glucocorticoids may lead to future persistent abnormalities.

Christina Tatsi and Constantine A Stratakis

Eunice Kennedy Shriver NICHD, NIH, Bethesda, MD, USA

This study was supported by the Intramural Research Program, Eunice Kennedy Shriver NICHD (to CAS).

References

Managing fetal and neonatal Graves’ disease

Fetal and neonatal autoimmune hyperthyroidism is a rare, serious, but transient disorder. Juliane Léger discusses early diagnosis and treatment to achieve an optimal prognosis.

The Figure below shows a diagnostic algorithm for high risk pregnancies in mothers with current or past hyperthyroidism related to Graves’ disease. This involves repeated fetal thyroid gland assessments from 20 weeks of gestation onwards, and maternal serum thyrotrophin receptor antibody (TRab) determination. Close monitoring is required if TRab levels exceed two to three times the upper limit of the normal range.

In fetuses with goitre, the main clinical issue is determining the cause. This could be maternal anti-thyroid drug (ATD) treatment that is appropriate for achieving normal maternal thyroid function but excessive for the fetus, resulting in hypothyroidism. This necessitates a decreased dose during pregnancy.

Alternatively, the presence of TRAbs may result in fetal thyroid stimulation and hyperthyroidism, requiring an increased maternal dose of ATD. Methimazole/ carbimazole should be initiated as soon as possible during the neonatal period, carefully managed over 1–3 months, and stopped when serum TRAbs are no longer detectable.

The Table on the right is a suggested approach for the management of neonates with autoimmune hyperthyroidism. Management of the mother, fetus and neonate requires an experienced multidisciplinary team of adult and paediatric endocrinologists, obstetricians, biologists and fetal radiologists.

Juliane Léger
Robert Debré University Hospital, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

“Management of the mother, fetus and neonate requires an experienced multidisciplinary team”

Table.

<table>
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<tr>
<th>Management of neonates with autoimmune hyperthyroidism. CMZ, carbimazole; FT4, free thyroxine; MMI, methimazole; TRAb, thyrotrophin receptor antibody; TSH, thyrotrophin.</th>
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Figure.

Management algorithm for at-risk pregnancies in mothers with current or past hyperthyroidism, mostly due to Graves’ disease (GD). ATD, anti-thyroid drug; CMZ, carbimazole; MMI, methimazole; PTU, propyliouracil; TRAb, thyrotrophin receptor antibody; TSH-R, thyrotrophin receptor.
ESPE welcomed more than 3600 attendees from well over 100 countries to its 57th Annual Meeting. We thank all of you who attended and made ESPE 2018 such a great success. Particular thanks are due to the Programme Organising Committee, led by Mehul Dattani.

There were 1330 submitted abstracts, showcasing leading research across paediatric endocrinology, as well as eight plenary lectures, ten symposia, eight ‘meet the expert’ sessions and two brand new ‘How do I...’ sessions. It was possible to see ESPE’s work in action, as recipients of ESPE grants reported on their activities.

The Local Organising Committee, chaired by Bessie Spiliotis, arranged many networking opportunities, providing a chance to meet up with colleagues old and new, and enjoy many aspects of Greek culture. The works of renowned Greek composer Mikis Theodorakis featured in a concert on the opening day, before welcome drinks, including Greek wine, and hors d’oeuvres. Even the rain could not dampen proceedings at the ESPE evening, held at the impressive Zappeion Megaron near the Acropolis. Attendees enthusiastically participated in traditional Greek dancing, using skills taught by Bessie earlier in the meeting!

The ESPE Team enjoyed seeing so many of you, whether at the ESPE Connect stand, in busy committee meetings, at awards ceremonies or during the exciting meeting.

All the abstracts and handouts from ‘meet the expert’ sessions can be found via the Meeting Resources link at www.espe2018.org. You will also find a link at www.espe2018.org to view videos of the extremely well received plenary lectures.

Thank you once again for enthusiastically supporting ESPE 2018. We look forward to seeing you next year in Vienna, Austria.

George Chrousos
Bessie Spiliotis
President and Vice-President, ESPE 2018

ESPE’s 1st Science Symposium attracted 100 participants from 22 countries.

They gathered to discuss unmet scientific needs for evidence-based healthcare of transgender children and teenagers. Genes, hormones and social factors play a pivotal role for physical, emotional, social, sexual and cognitive development. The symposium focused on how to improve understanding of the impact of current treatment regimens in these areas. Evidence from disorders of sex development may or may not be helpful in this respect. Given the high prevalence of neurodevelopmental disorders (particularly autism spectrum diseases) in this group of adolescents, further exploration of the neurobiology of gender dysphoria may reveal novel aspects in its clinical care and understanding of its origin.

The current trend of commencing hormonal treatment at a younger age (potentially Tanner stage 2) calls for intensified collaborative research into the life-long impact of pubertal suppression and cross-sex puberty induction on physical health, growth, neurocognitive aspects, mental health and sexuality.

Save the date: ESPE 2019
‘Variety and variation in paediatric endocrinology’
19–21 September 2019, Austria Centre, Vienna, Austria
Registration and abstract submission will open soon

Dancing to the ESPE beat!
27–29 September 2018, Athens, Greece

Learning Greek dance with Bessie Spiliotis

The Science of Gender
18–19 October 2018, London, UK

ESPE NEWSLETTER / ISSUE 42 / WINTER 2018
Future meetings
See www.eurospe.org/meetings for details of all future meetings

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

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

60th Annual ESPE Meeting
May/June 2021
Copenhagen, Denmark

11th International Meeting of Pediatric Endocrinology
September 2021
Buenos Aires, Argentina

OTHER EVENTS

NOVEMBER
ESPE Maghreb School
Algeria
19–24 November 2018

Postgraduate Education Course: Type 1 Diabetes
Prague, Czech Republic
22–24 November 2018

FEBRUARY
ESPE Winter School
Azerbaijan
22–28 February 2019

ESPE Summer School
Burg Feistritz am Wechsel, Austria
16–18 September 2019

DEADLINES

DECEMBER
Maghreb School Steering Committee member applications
3 December 2018

ESPE 2019 Award nominations
10 December 2018

JANUARY
IFCAH-ESPE Grant
letter of intention submissions
14 January 2019

ESPE 2024 Host Country applications
31 January 2019

FEBRUARY
ESPE Summer School applications
8 February 2019

HELP RUN YOUR SOCIETY
There are many opportunities to get involved with ESPE’s Committees. To see which roles are currently available, check www.eurospe.org/about/vacancies.