

Come to Rome! ESPE 2022

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Welcome

At last, we can look forward to gathering in person for the first time in 3 years, as ESPE holds its 60th Annual Meeting on 15–17 September in Rome, Italy. Make sure you register by 18 July, to benefit from the early bird delegate rates.

This issue of *ESPE News* focuses not only on the Meeting, but also on neuroendocrinology and the pituitary. The authors of three of our four feature articles are, in fact, speakers at ESPE 2022. You can get an impression of the depth and diversity of talks at the ESPE Meeting by looking at the sessions listed on **page 9** and, in greater detail, at www.espe2022.org.

On **page 5**, Hermann Müller explains how survivors of craniopharyngioma may suffer from severe, lasting effects caused by hypothalamic damage, as he discusses the pathophysiology and management of hypothalamic syndrome in patients with childhood-onset disease. He concludes that some novel therapeutic approaches provide future hope for hypothalamic dysfunction and obesity.

Paediatric Cushing's disease differs from the condition seen in adult patients in a number of ways, and Constantine Stratakis describes these differences on **page 6**. His article examines diagnosis, treatment and genetics, and gives a taste of what to expect in his Meet the Expert session in September at ESPE 2022.

Mirjam Christ-Crain will give a plenary lecture on 'Copeptin in vasopressin-dependent fluid disorders' at ESPE 2022. On **page 7**, she writes about copeptin's potential in the differential diagnosis of various disorders, as a prelude to further discussions at the Meeting.

On **page 8**, Jacques Young discusses the challenges in diagnosis and management of congenital hypogonadotropic hypogonadism, along with the underlying genetics and the implications for the increasing number of patients who proceed to have children, through assisted reproduction. You can also hear him speak at ESPE 2022.

As we all hope for peace in Ukraine, you can read about the positive action ESPE is taking to support those affected (**page 3**). Also, don't miss the opportunity to join with your colleagues in applying to hold next year's ESPE Science Symposium (see right). As always, there are numerous other events and activities to look forward to, with full diary dates on **page 10**.

Happy reading!

Sarah Ehtisham

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ESPE 2022

15–17 September 2022, Rome, Italy

Register before 18 July to benefit from the early bird registration rates for ESPE 2022.



www.espe2022.org

FIND OUT MORE
ON **PAGE 9**



ESPE 2022 ROME
The 60th Annual Meeting 15-17 September 2022

OPPORTUNITIES

Your chance to host the ESPE Science Symposium 2023

The ESPE Science Symposium disseminates new scientific knowledge in the paediatric endocrinology community. By promoting networking between clinicians and researchers, it reduces the gap between research and patient care.

It is run by a Local Organising Committee, led by an ESPE member. They can choose the symposium topic, which must be attractive to researchers in basic, translational and clinical research. One session will be dedicated to the patient perspective, organised with patient representatives or a patient advocacy group.

Applications from ESPE Working Groups, either individually or jointly, are welcomed.

Apply now to host the 2023 event. Full details, including the financial support provided by ESPE to organisers and delegates, are available at the web address below.



Apply to host by
24 June 2022



See www.eurospe.org/education/espe-science-symposium-apply-to-host

GRANTS

ESPE Clinical Fellowship

The ESPE Clinical Fellowship was heavily affected by the COVID-19 pandemic throughout 2020 and 2021, with members of the 2019–2020 intake unable to complete their Fellowships until 2022.

Thankfully, due to the hard work of the ESPE Clinical Fellowship Committee, the graciousness of the ESPE Clinical Fellowship hosts, and the patience and resilience of the Fellows themselves, 13 of the 15 recipients have now finished their valuable visits. The successes and impact of this intake are presented in a new executive report, which you can read to find out how the Fellowship can shape your career and your practice at your home institution.



See www.eurospe.org/media/2871/clinical-fellowship-executive-report-2019-20-intake-final.pdf

YOUR SOCIETY



ESPE stands with Ukraine

The ESPE Council has carefully considered how our Society should respond to the situation in Ukraine and how best to support the healthcare and welfare of Ukrainian children, as well as to assist our colleagues who care for them.

ESPE's action plan

- We have arranged a 6-month supply of endocrine medications for Ukrainian children with endocrine disorders, based on the list provided by the Ukrainian Association for Paediatric Endocrinologists.
- We are offering free ESPE membership for 2022 to practising Ukrainian paediatric endocrinologists, and free online access to ESPE 2022 for Ukrainian ESPE members.
- For as long as the war continues, we have decided not to hold ESPE events in Russia or Belarus, and not to accept grant applications from employees of Russian or Belarusian institutions, or to consider them for membership of ESPE committees.

A dedicated section of the ESPE website has been created to provide updates on the actions taken by ESPE, and useful information for professionals and affected patients and their parents. We hope for rapid resolution of the war in Ukraine and the restoration of peace.



See additional information at www.eurospe.org/about/espe-response-to-war-in-ukraine

Hypothalamic dysfunction in childhood

ESPE Science Symposium 2022

Princess Máxima Center, Utrecht,
The Netherlands, 7–8 October 2022

This 2-day event will discuss the aetiology of genetic and acquired hypothalamic dysfunction in childhood, its consequences and new ways of management to improve outcome.

We will also focus on building new networks and collaboration within ESPE and Europe, together with patient organisations and Endo-ERN.



Find out more at www.eurospe.org/education/espe-science-symposium-2022-hypothalamic-dysfunction-in-childhood



RESOURCES



Supporting this issue's theme

Within **Courses in paediatric endocrinology and diabetes:**

- the chapter **Pituitary** includes a section on **Hypopituitarism** and two cases: Nikola, an 8-year-old boy with early-onset obesity, and Ryan, a neonate with low blood sugar
- the chapter **Growth and growth regulation** contains data and cases regarding growth hormone deficiency.

Healthcare in resource limited settings and **ESPE Caucasus & Central Asia School** also contain resources on growth hormone deficiency.

News in e-Learning

The European Accreditation Council for Continuing Medical Education (CME) is currently reviewing our demonstration, offering 30 CME credit points of online learning.



See www.espe-elearning.org
Registration is free of charge

Patient leaflet translations

We thank all the individuals and societies who have helped translate ESPE's patient information leaflets. The leaflets are now available in Arabic, English, French, Spanish and Ukrainian.



You can download the leaflets from
www.eurospe.org/patients



To help with translation see
www.eurospe.org/news/item/15324



6th ESPE Connect Webinar

13 July 2022
16.00 CEST/15.00 BST

The next ESPE Connect Webinar will be on the subject of **congenital adrenal hyperplasia**. Further details will follow.



See www.eurospe.org/education/webinar-series

Bringing you recent highlights from the world of research

Kisspeptin receptor as a therapeutic target in steatohepatitis

Non-alcoholic fatty liver disease (NAFLD) currently affects approximately 25% of the global population. NAFLD is linked to obesity and type 2 diabetes and is characterised by increased accumulation of fat in the liver. In a proportion of patients, NAFLD can further progress to the inflammatory non-alcoholic steatohepatitis (NASH), which can lead to the development of fibrosis, cirrhosis and hepatocarcinoma. No approved pharmacological therapies are currently available for NAFLD and NASH.

Kisspeptins and the kisspeptin receptor are well known for their role in regulating reproduction, but have so far not been implicated in the pathogenesis of NAFLD. Guzman *et al.* show that a deletion of the kisspeptin receptor in a dietary mouse model of NAFLD worsened hepatic steatosis. Conversely, activation of the kisspeptin receptor protected against steatosis and counteracted fibrosis in a diet-induced mouse NASH model by activating AMP-activated kinase, a master regulator of energy metabolism. The kisspeptin receptor could therefore be a new therapeutic option for the treatment of NASH.



Read the full article at Guzman *et al.* 2022 *Journal of Clinical Investigation* e145889

Teamwork, targets, technology and tight control

Most children with type 1 diabetes mellitus (T1DM) do not meet the International Society for Pediatric and Adolescent Diabetes recommendations for glycated haemoglobin (HbA1c) of <7%. The Hvidoere study and SWEET registry have shown the value of target setting in lowering HbA1c. Continuous glucose monitoring (CGM) technology has also been demonstrated to lower HbA1c and improve diabetes control, and there is evidence that early good glycaemic control influences the HbA1c trajectory.

The 4T programme – teamwork, targets, technology and tight control – was developed to intensify diabetes management in the first year, to improve outcomes. Newly diagnosed children were offered CGM within 1 month of diagnosis, allowing their team to remotely monitor their glucose levels. Their HbA1c was significantly lower in the first year post-diagnosis compared with historical controls (–0.58% by 12 months) and use of remote monitoring lowered the HbA1c further (–0.14%). The increase in HbA1c seen between months 4 and 12 post-diagnosis was lower in the 4T cohort. By 12 months post-diagnosis, 53% of youth in the 4T programme achieved an HbA1c of <7% compared with only 28% in the historical cohort. This study emphasises the importance of precision medicine, teamwork, technology, intensified education and target setting in diabetes care.



Read the full article at Prahald *et al.* 2022 *Journal of Clinical Endocrinology & Metabolism* 107 998–1008

Salt supplementation in CAH

International guidelines recommend salt supplementation in infants with classic congenital adrenal hyperplasia (CAH). Using the international CAH registry (i-CAH), the use of salt supplementation was investigated in 331 children with classic CAH from 13 countries.

Salt supplementation was given to 61% of patients. Children who were treated with salt had lower hydrocortisone dosages in the neonatal period and lower fludrocortisone dosages between 1.5 and 4.5 months of age. No differences in weight, length and blood pressure were observed between subgroups. However, all children showed an increase in body mass index during the first 3 years of life, nearly half of the cohort had hypertensive blood pressure readings within the first 1.5 years of life, and there was also a decrease in mean height and an increased difference between height and parental target height during the first 6–9 months after birth.

This study suggests that salt supplementation during the first 3–6 months of life may allow reduction of hydrocortisone and fludrocortisone dosage, which may help to reduce later life co-morbidities associated with glucocorticoid and mineralocorticoid treatment.



Read the full article at Neumann *et al.* 2022 *European Journal of Endocrinology* 186 587–596

Weekly versus daily GH

A multicentric, randomised, controlled, open-label phase 2 trial among prepubertal children with growth hormone deficiency (GHD) evaluated the efficacy, safety and tolerability of once-weekly somapacitan and once-daily GH over 3 years.

Children with GHD ($n=59$) were randomised to four groups who received somapacitan at 0.04mg/kg per week ($n=14$), 0.08mg/kg per week ($n=15$) or 0.16mg/kg per week ($n=14$) or daily GH (equivalent to 0.238mg/kg per week; $n=14$) subcutaneously during the first year, after which all subjects on somapacitan received 0.16mg/kg per week.

In the 53 subjects who completed 3 years of treatment, the change in height velocity standard deviation score from baseline to year 3 was comparable between the somapacitan 0.16/0.16mg/kg per week group, the pooled somapacitan groups, and daily GH. The mean insulin-like growth factor levels were similar in all groups during the study period, and there were no clinically significant adverse effects in any group.



Read the full article at Sävendahl *et al.* 2022 *Journal of Clinical Endocrinology & Metabolism* 107 1357–1367

Several other long-acting GH formulations are currently in development. For an overview, see Pampanini *et al.* 2022 *Hormone Research in Paediatrics* doi: 10.1159/000523791

Hypothalamic syndrome in craniopharyngioma

Hermann Müller examines the pathophysiology and management of hypothalamic syndrome in patients with childhood-onset craniopharyngioma.

Although craniopharyngiomas are of low grade histological dignity, survivors may suffer from devastating consequences caused by hypothalamic damage. This leads to a typical clinical manifestation called 'hypothalamic syndrome'. Disease- and/or treatment-related hypothalamic damage can lead to disturbed feelings of hunger-satiety and thirst, decreased energy expenditure, behavioural problems, disturbances of circadian rhythm, temperature dysregulation, and pituitary dysfunction.¹

Hypothalamic dysfunction

Hypothalamic function is regulated by a complex network. The ventromedial hypothalamus (VMH) and arcuate nucleus (AN) regulate hunger, satiety and energy balance. Insulin, ghrelin, glucagon-like peptide 1 (GLP-1) and leptin are key hormones in the regulation of energy balance and signalling to the VMH and AN. Oxytocin is a peptide hormone that is produced in the hypothalamus and secreted by the posterior lobe of the pituitary gland. Oxytocin is released in the brain and modulates social bonding, memory, cognition, social behaviour, appetite and metabolism.

Symptoms related to hypothalamic dysfunction, such as hypothalamic obesity, psychosocial disorders (obsessive compulsive disorders) and sleep disturbances, have been found at diagnosis in at least 35% of patients with childhood-onset craniopharyngioma. After treatment, the prevalence of hypothalamic dysfunction increases drastically, with some studies reporting levels of up to 65–80%.

The degree and extent of hypothalamic dysfunction are strongly correlated with the degree of obesity.² In 2011, Müller *et al.* reported a magnetic resonance imaging grading system for pre-surgical hypothalamic involvement and surgical hypothalamic dysfunction in childhood craniopharyngioma, to illustrate the relationship between surgical lesions of the anterior region plus the region behind the mammillary bodies and post-operative weight gain.³ Sterkenburg *et al.* illustrated that patients with hypothalamic involvement of their craniopharyngioma develop a significant increase in body mass index standard deviation score during the first year after diagnosis.⁴

As well as the severe obesity, hypothalamic dysfunction may be characterised by behavioural disturbances, rage outbursts and extensive daytime sleepiness.

Treatment of hypothalamic obesity

Hypothalamic obesity is one of the most serious manifestations of hypothalamic syndrome. As there is currently no effective treatment, survivors may develop morbid obesity and its consequences, such as sleep apnoea, cardiac problems and immobility, in combination with severe behavioural problems.^{5,6} The morbid obesity in these patients is the result of impairment in satiety regulation and energy expenditure.^{1,6} In combination with a distorted sympathetic activity, patients have an over-activated parasympathetic system, which results in

temperature regulation disturbances, reduced heart rate and excessive daytime sleepiness.^{1,6}

The obesity itself is usually unresponsive to conventional treatment efforts, such as lifestyle modifications, and may, therefore, require pharmacological intervention. Currently, there remains no consensus regarding the optimal pharmacotherapy. Reported pharmacotherapeutic interventions for hypothalamic obesity can be divided into four categories: (a) stimulants, (b) antidiabetic agents, (c) hypothalamic-pituitary substitution therapy and (d) others, such as oxytocin or octreotide.

Considering each of these, amphetamines, such as dextroamphetamine and methylphenidate, seem to be effective by increasing physical activity, but previous studies only reported on short term effects.⁶ Long term (side) effects have not yet been evaluated. The second group, antidiabetic agents (such as GLP-1 analogues) are given to modulate insulin sensitivity. Thirdly, hypopituitarism should be treated according to the clinical expertise of an endocrinologist, with the use of guidelines. To optimise weight control, glucocorticoid over-replacement should be avoided, and levothyroxine should be substituted to achieve free thyroxine levels in the middle to upper half of the reference range.

However, thus far, none of these pharmacotherapeutic interventions has proved to be effective in a controlled randomised trial setting in patients with childhood-onset craniopharyngioma and hypothalamic obesity over a prolonged follow-up period.⁷

Surgical bariatric intervention studies are scarce in children and adults after craniopharyngioma.^{5,6} Roux-en-Y gastric bypass showed the best results, including a total of six studies and fourteen patients, of whom all showed improvement in their body mass index.⁶ All of these studies had a small sample size. Post-operative complications, such as vomiting, diarrhoea, dumping syndrome and band readjustment, are frequently reported.^{5,6} Bariatric treatment is invasive, and treatment with irreversible bariatric interventions, such as Roux-en-Y gastric bypass, remains controversial in the paediatric population.

Conclusion

The late sequelae of craniopharyngioma can be severe, mainly caused by the consequences of hypothalamic dysfunction, and may lead to decreased quality of life. Prevention of hypothalamic obesity is most effective, thus hypothalamus-sparing therapeutic approaches should be the main focus in these patients.

When hypothalamic dysfunction has already occurred due to the tumour itself, and hypothalamic obesity cannot be prevented, some novel therapeutic approaches provide promising perspectives for hypothalamic dysfunction and obesity, although none of these studies has been proven to be effective, based on randomised controlled trials.

Hermann L Müller

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Hermann Müller



Prevention of hypothalamic obesity is most effective, thus hypothalamus-sparing therapeutic approaches should be the main focus in these patients"

Paediatric Cushing's disease

Cushing's syndrome in childhood differs in a number of ways from the condition seen in adult patients, as Constantine Stratakis describes.



Constantine Stratakis



Symptoms that are less commonly seen in children include sleep disruption, mental changes and muscle weakness"

By far the most common type of Cushing's syndrome has an exogenous cause, such as medication.¹ Endogenous causes are rare; they are all associated with a tumour of one form or another. For pre-pubertal children, and certainly for toddlers, the adrenals are more commonly the cause of endogenous Cushing's syndrome, whereas pituitary tumours are more often to blame in older children. Ectopic sources of Cushing's syndrome (a site other than the pituitary or adrenal) are extremely rare in children. Overall, there is a female to male predominance, which decreases with younger age. Cushing's disease refers to disease caused by pituitary adenomas only.

Presentation of Cushing's disease

The single most important symptom, shared by almost every patient with Cushing's disease, is weight gain. Fat accumulation leads to glucose intolerance and, depending on the body's individual predisposition, diabetes, which further exacerbates the vicious cycle of fat accumulation, increased insulin levels and insulin resistance, and (due to the rise in insulin but also due to excess cortisol directly) increased appetite.

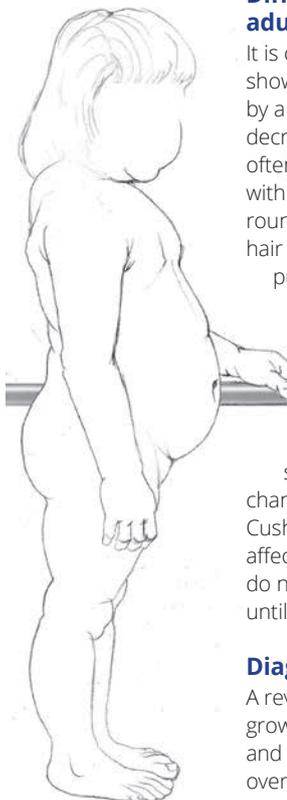
Differences between children and adults

It is common for children with Cushing's disease to show an increase in rate of weight gain accompanied by a decrease in growth rate (linear height), due to decreased growth hormone (GH) secretion. This is often easily detected in the growth charts of children with Cushing's syndrome. Other symptoms include rounded face, reddened cheeks, acne, headache, excess hair growth (fine downy hair on cheeks, arms and legs), purplish-pink stretch marks (more common in older children), darkened skin around neck and armpit areas, easy bruising, development of pubic hair at a younger age than usual, irregular or absent menstrual periods and high blood pressure.

Compared with adults with Cushing's syndrome, symptoms that are less commonly seen in children include sleep disruption, mental changes and muscle weakness. Although many adults with Cushing's syndrome report a change in mental status that affects their job performance, children with the syndrome do not usually report problems in school performance, until, interestingly, after surgery.

Diagnosing Cushing's disease in children

A review of the child's growth chart is essential. If the growth chart shows an increase in the rate of weight gain and a decrease in the rate of linear growth (height velocity) over the same time period, then further evaluation and monitoring are needed to determine the cause. Other diagnostic testing in children with Cushing's disease is similar to that in adults.



Typical body shape of a paediatric patient with Cushing's syndrome.

Treating Cushing's disease

Pituitary adenomas are usually removed by transsphenoidal surgery. Due to the highly specialised nature of this surgery, referral to a neurosurgeon who is experienced in this procedure is recommended.² In some patients, treatment with one or more medications that control or block cortisol production may be given on a short term basis. In patients where surgery has failed (or if they were not good candidates for surgery, which is very rare in children but more frequent in adults), radiation therapy is indicated.

Various studies report that, a year after surgical cure of paediatric Cushing's syndrome, most children had lost weight and body mass and their height and growth velocity had increased.³ However, final adult height is often impaired (by at least an inch (25mm)).

Many children and adolescents recovering from Cushing's disease experience changes in cognitive performance that can be stressful for both the child and the parents.⁴ The brain is affected by prolonged exposure to abnormally high cortisol levels and, once the cortisol levels are normalised, there is a period of readjustment. Symptoms reported by some children and adolescents include difficulty concentrating and problems with memory that may affect their academic performance for an indeterminate period. It is important to provide appropriate educational and psychological resources for the child or adolescent during this period. Adult patients, especially young adults, experience mood changes too, and their overall sense of well-being is affected, even years after treatment and cure.

Genetics of Cushing's disease

We have identified several hereditary diseases associated with genetic predisposition to the development of Cushing's disease (multiple endocrine neoplasia types 1 and 4, McCune-Albright syndrome, Carney complex, succinate dehydrogenase mutations and others). It is expected that more genes or other genetic factors will be identified, which may lead to better and targeted medical treatments.⁵

Conclusion

There have been significant improvements in both testing and imaging over the last 20 years in the diagnosis of Cushing's disease. These include better magnetic resonance imaging and higher specificity cortisol assays. Our understanding of effects on immunity and other systems has also increased.⁶ But more needs to be done, especially in detecting small tumours of the pituitary gland.

Constantine A Stratakis

Director, Human Genetics & Precision Medicine, IMBB, FORTH, Heraklion, Crete; Chief Scientific Officer, ELPEN Inc. and Director, ELPEN Research Institute, Athens, Greece; and Senior Investigator (retired), NICHD, NIH, Bethesda, MD, USA

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Constantine Stratakis will talk on 'Paediatric Cushing's disease' at ESPE 2022 (see [page 9](#)).

Copeptin in vasopressin-dependent fluid disorders

Mirjam Christ-Crain discusses copeptin's value in the diagnosis of vasopressin-dependent fluid disorders: diabetes insipidus and the syndrome of inappropriate antidiuresis (SIAD).



Mirjam Christ-Crain



Copeptin has been found to be a stable, sensitive and simple-to-measure surrogate marker of AVP release. As such, it has great potential in the differential diagnosis of various conditions"

Arginine vasopressin (AVP) is a peptide composed of nine amino acids that is synthesised in magnocellular neurones located in two discrete areas of the hypothalamus: the supraoptic and paraventricular nuclei. The physiological function of AVP is homeostasis of fluid balance, vascular tonus and regulation of the endocrine stress response.

AVP is difficult to measure, due to complex pre-analytical requirements and for technical reasons. Therefore, despite a great expectation that AVP would become a routine clinical marker in the differentiation of fluid disorders, measurement of AVP has never entered everyday practice.

Copeptin is the C-terminal part of the vasopressin precursor (see Figure), and has been shown to mirror AVP concentrations in blood. In contrast to vasopressin, it can be easily measured with a sandwich immunoassay and is stable *ex vivo*. In recent years, copeptin has therefore been found to be a stable, sensitive and simple-to-measure surrogate marker of AVP release. As such, it has great potential in the differential diagnosis of various conditions.

Polyuria polydipsia syndrome

The polyuria polydipsia syndrome describes a spectrum of disorders characterised by insufficient AVP synthesis or efficacy, ultimately resulting in inadequate urine concentration and increased urine output (hypotonic polyuria), usually accompanied by a compensatory increase in fluid intake (polydipsia), to preserve body fluid homeostasis.

We need to differentiate between three entities:

- central diabetes insipidus due to inadequate secretion, and usually deficient synthesis of, AVP in the hypothalamic neurohypophyseal system in response to osmotic stimulation
- nephrogenic diabetes insipidus due to renal insensitivity or inappropriate response to normal pituitary AVP secretion
- excessive fluid intake, which can, per se, also cause polyuria despite intact AVP secretion and renal response – referred to as primary polydipsia; this can result from either an abnormality in the thirst mechanism, or from psychiatric disorders, in which case it is often referred to as psychogenic polydipsia.

Differentiation of these disorders is important, since treatment strategies vary and wrong treatment can have deleterious consequences. However, the differential diagnosis is challenging. For decades, the water deprivation test was the diagnostic gold standard, but its interpretation



The cleavage of pre-provasopressin generates copeptin as well as vasopressin.

is often misleading and the test is cumbersome for patients due to the long thirsting period.

New osmotic and non-osmotic stimulation tests measuring copeptin will be shown and discussed in my forthcoming presentation at ESPE 2022. First, we have recently shown that osmotic stimulation with hypertonic saline raises copeptin levels in patients with primary polydipsia, but not in patients with central diabetes insipidus.¹ This new test has a superior diagnostic accuracy to the water deprivation test in differentiating between central diabetes insipidus and primary polydipsia.

Secondly, we have shown that a non-osmotic test using arginine infusion also has a high diagnostic accuracy, with a better tolerability than the hypertonic saline test.² The arginine would be especially attractive for the differential diagnosis of polyuria and polydipsia in children.

Hyponatraemia, particularly SIAD

Hyponatraemia, defined as a serum sodium concentration <135mmol/l, is the most common electrolyte disorder encountered in hospitalised patients, with a prevalence as great as 15–30%. In as many as two thirds of cases, SIAD appears to be the underlying cause of hyponatraemia.

The differential diagnosis of hyponatraemia is, again, challenging. My presentation will also discuss copeptin's potential, in patients with SIAD, to be a new marker in the differential diagnosis of hyponatremia and its possible value in predicting neoplastic SIAD.

Mirjam Christ-Crain

Professor of Endocrinology, Diabetes and Metabolism, University of Basel, and Deputy Head of the Endocrine Clinic and Head of the Department of Clinical Research, University Hospital of Basel, Switzerland

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Mirjam Christ-Crain will talk on 'Copeptin in vasopressin-dependent fluid disorders' at ESPE 2022 (see [page 9](#)).

Congenital hypogonadotrophic hypogonadism

Jacques Young discusses the diagnosis, management and genetics of the various forms of this condition.



Jacques Young



The genetic architecture is now known to be far more complex than previously thought. Classic Mendelian transmission was initially proposed as the main model, yet this is not the case in a significant number of familial and sporadic cases"

Congenital (or isolated) hypogonadotrophic hypogonadism (CHH/IHH) and Kallmann syndrome (KS) are rare diseases that prevent normal pubertal development and cause infertility in affected men and women.¹ In CHH/IHH, the gonadotrophin deficiency and gonadal impairment exist from the time of fetal development and, in the majority of cases, persist throughout life.²

Diagnosis

In females, CHH/IHH/KS is usually diagnosed in the teenage years, because of primary amenorrhoea, with absent or partial pubic hair and breast development, depending on the severity of the deficit in gonadotrophins and, thus, in ovarian steroids.^{1,3}

In boys, diagnosing CHH/IHH is sometimes challenging, particularly when differentiating from common causes of delayed puberty with impaired gonadotrophin secretion, such as constitutional delay of growth and puberty (CDGP).⁴ Differentiating CHH/IHH from CDGP is easier in cases when the clinical presentation of CHH is complex (hypopituitarism) and/or syndromic (CHH/IHH with associated non-reproductive phenotypes), as in KS where CHH/IHH is associated with anosmia. A history of cryptorchidism and/or micropenis also provides significant clues to a CHH diagnosis, as these clinical signs are rare in boys with CDGP.

For decades, investigators and clinicians have sought dynamic tests (gonadotrophin-releasing hormone (GnRH) or human chorionic gonadotrophin) or biomarkers (inhibin B) to distinguish CHH from CDGP in boys.⁴ However, GnRH-stimulated luteinising hormone (peak) and basal inhibin B levels are variable in both CHH and CDGP, with significant overlap. Both parameters therefore lack specificity and sensitivity to efficiently discriminate CHH/IHH from CDGP. This reflects the varying degree of gonadotrophin deficiency inherent to CHH/IHH.

These two diagnostic procedures may thus misdiagnose partial forms of isolated (non-syndromic) CHH, allowing them to be erroneously considered as CDGP.⁴ We therefore consider that the search for an inhibin B threshold should give way to a more probabilistic approach, where the clinician is aware of the diagnostic uncertainty.

Management

With appropriate hormonal therapy, male and female patients with CHH/IHH can develop secondary sexual characteristics, maintain normal sex hormone levels and a healthy sexual life, and achieve fertility.¹ Different regimens of treatment with several administrative routes exist and have been reviewed.¹ The choice of treatment depends on the therapeutic goal, the timing of treatment, and the preference of each patient. It must be emphasised that randomised controlled trials of hormonal treatment in CHH are scarce, and data on clinical observational studies

are also limited. Dogmatic attitudes should therefore be avoided.

Paediatric endocrinologists need to be aware that CHH/IHH/KS does not negatively affect stature in adulthood regardless of sex, clinical form (normosmic CHH versus KS) or genetic aetiology.⁵ Men and women with CHH/KS are, on average, taller than the general population, exceed their mid-parental target height, and males with CHH/KS have greater adult stature than unaffected brothers. Earlier replacement therapy does not negatively impact adult stature but solely makes it closer to mid-parental target height. Late treatment could produce a taller than predicted adult stature.

The modest increase in adult stature associated with late treatment is often obtained at the expense of a detriment in quality of life, lack of masculinisation or feminisation of CHH/IHH/KS adolescents, and suboptimal bone mass peak acquisition.⁶

Genetic aspects

A large number of loci (more than 30 genes) underlying CHH/IHH/KS have been discovered in the past 30 years.^{1,7} These genes account for roughly 50% of identified cases.^{1,7} The genetic architecture is now known to be far more complex than previously thought. Classic Mendelian transmission was initially proposed as the main model, yet this is not the case in a significant number of familial and sporadic cases.

Over the past nearly 10 years, genetic assessment of patients with CHH/IHH/KS has increasingly used massively parallel next-generation sequencing, allowing simultaneous analysis of tens to thousands of genes, depending on whether targeted exome or whole exome sequencing is used.^{1,7} Consequently, detecting more than one rare but potentially deleterious variant in a given patient (oligogenism/potential oligogenism) is becoming increasingly common.

In male and female patients with CHH/IHH/KS, the infertility carries a good prognosis, and increasing numbers of patients are now able to have children, through medically assisted procreation.^{1,3} Because these are genetic diseases, they can be transmitted to patients' offspring, and patients and their families should be informed of this risk and given genetic counselling.

CHH/IHH/KS are phenotypically and genetically heterogeneous, and the risk of transmission depends on the gene or combination of genes responsible. Inheritance which is classically Mendelian with variable penetrance or oligogenic is more complex and renders genetic counselling more difficult.⁷ Evaluation of newborns from parents with CHH/KS is systematically performed in our centre, as part of a transgenerational management.

Jacques Young

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Jacques Young will talk on 'Diagnosis and management of congenital hypogonadotrophic hypogonadism' at ESPE 2022 (see [page 9](#)).



ESPE 2022

15–17 September 2022
Rome, Italy

Personalised medicine in paediatric endocrinology

Join us in Rome, Italy, this September for the **60th Annual ESPE Meeting**. The ESPE Programme Committee has created an exciting and robust programme, covering basic science, translational research and clinical care, offering you the very best update in the field of paediatric endocrinology.

The meeting's theme, **'Personalised medicine in paediatric endocrinology'**, reflects a new dawn in our discipline, as innovative approaches become available to investigate diseases in childhood. We welcome all our speakers, who will engage with and stimulate us in exciting plenary lectures, symposia, Meet the Expert and 'How do I...?' sessions: we will learn from the most experienced international colleagues in their fields. Controversy and Novel Advances sessions will challenge our ways of thinking. Oral communications and physical and electronic posters will bring topical diversity and insight from senior and junior voices in the field alike.

The deadline for early bird registration is 18 July, so sign up today, to benefit from these discounted rates, and make sure that you reserve your place at ESPE 2022.

Avoid fraudulent websites

Fraudulent websites have been in operation, selling fake registration to ESPE 2022. The ESPE website (at www.eurospe.org or www.espe2022.org) is the only official website where you can register to attend ESPE 2022.

Early bird registration deadline

18 July 2022 (23.59 BST)

www.espe2022.org

Plenary lectures

- **Potentialities of gene therapy in paediatric endocrinology** Alessandro Aiuti (Italy)
- **Prevention of type 1 diabetes in children** Ezio Bonifacio (Germany)
- **Copeptin in vasopressin-dependent fluid disorders** Mirjam Christ-Crain (Switzerland)
- **Precision medicine in diabetes** Anna L Gloyn (USA)
- **Growth: genetic determinates of height** Joel N Hirschhorn (USA)
- **How science can benefit from philosophy** Lucie Laplane (France)
- **Nutritional control of growth and puberty** Stephen O'Rahilly (UK)
- **Novel advances in obesity** Uberto Pagotto (Italy)

Meet the Expert

- **Initial evaluation of a suspected difference or disorder of sex development** Faisal Ahmed (UK)
- **Management of NAFLD and treatment of NASH** Bertrand Cariou
- **Challenges in the care of transgender and gender-diverse youth** Daniel Klink (The Netherlands)
- **Endocrine consequences and management of anorexia nervosa** Karen Miller (USA)
- **Using androgens during infancy, childhood and adolescence** Alan Rogol (USA)
- **Paediatric Cushing's disease** Constantine Stratakis (USA)
- **The key role of physical activity against cardiometabolic risk in childhood obesity** Giuliana Valerio (Italy)
- **Diagnostics and management of hyperandrogenism in childhood and adolescence** Raimo Voutilainen (Finland)

How do I...

- **Manage a child with severe obesity?** Erica Akker (The Netherlands)
- **Diagnose and manage primary adrenal insufficiency?** Donatella Capalbo (Italy)
- **Manage a child with hypoparathyroidism?** Rachel Gafni (USA)
- **Manage communication with families after onset of type 1 diabetes?** Karin Lange (Germany)
- **Manage a child with disproportionate short stature?** Štěpánka Průhová (Czech Republic)
- **Replace oestrogens in Turner syndrome?** Theo Sas (The Netherlands)

See the full programme at www.espe2022.org

Future meetings

See www.eurospe.org/meetings for details of all future meetings



60th Annual ESPE Meeting

15–17 September 2022
Rome, Italy



11th International Meeting of Paediatric Endocrinology

4–7 March 2023
Buenos Aires, Argentina



61st Annual ESPE Meeting

21–23 September 2023
The Hague, The Netherlands



62nd Annual ESPE Meeting

November 2024
Liverpool, UK



63rd Annual ESPE Meeting

May 2025
Copenhagen, Denmark



OTHER EVENTS

6th ESPE Connect Webinar

13 July 2022
Online

ESPE Summer School

12–14 September 2022
Torgiano, Italy

ESPE Diabetes, Obesity & Metabolism School

18–20 September 2022
Torgiano, Italy

ESPE Caucasus & Central Asia School

21–24 September 2022
Tbilisi, Georgia

ESPE Science Symposium: Hypothalamic dysfunction

7–8 October 2022
Utrecht, The Netherlands

DEADLINES

JUNE

Host for ESPE Science Symposium 2023
application deadline – **24 June 2022**

JULY

ESPE 2022 early bird registration –
18 July 2022

SEPTEMBER

Early Career Scientific Development Grant
application deadline – **30 September 2022**

All dates, deadlines and plans are being constantly reviewed in light of COVID-19

For more information about vacancies on ESPE Committees and how to apply, see www.eurospe.org/about/vacancies

ESPE

European Society for
Paediatric Endocrinology

Improving care of children with
endocrine diseases by promoting
knowledge and research

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ESPE Newsletter

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