

# ESPE

NEWS



ISSUE 53 / AUTUMN 2021  
ISSN 2045-5003 (ONLINE)

BRINGING THE LATEST IN PAEDIATRIC ENDOCRINOLOGY TO YOU

## Perspectives on puberty

Special issue  
P6-8 >

### Polycystic ovary syndrome

Lourdes Ibáñez and Francis de Zegher examine potential treatments P6 >

### MKRN3 and central precocious puberty

Genotype-phenotype correlations, described by Ana Claudia Latronico P7 >

### Rising to the challenge

Margaret Zacharin explores complicated issues in puberty management in the clinic P8 >

### ALSO INSIDE:

#### News

Annual Business Meeting, New Early Career Taskforce, Rare Disease Advisory Group and Grants P2 >

ESPE Connect webinars, European Training Requirements, Reports from ESPE schools, Patient leaflets plus e-Learning P3 >

#### COVID stories

A patient's perspective P4 >

#### Hot topics

The latest research P5 >

#### Events and diary

ESPE 2021 Online P9 >

Future meetings, dates and deadlines P10 >

ESPE 2021 Online – standard registration closes 7 September – see page 9

# Welcome

It is just a few weeks until ESPE 2021 Online. This year's ESPE Meeting is sure to bring you right up to date with the latest research. The online platform will also provide plenty of opportunities for you to connect both with your peers and with speakers worldwide. Register by 7 September to benefit from the standard registration rate. See page 9 for more details.

This issue of *ESPE News* takes a look at several aspects of puberty. Polycystic ovary syndrome is increasingly common among girls and young women, and is associated with a range of co-morbidities. Therapies have concentrated on alleviation of symptoms, but, on page 6, Lourdes Ibáñez and Francis de Zegher discuss a potential new approach to treatment that focuses on the underlying pathophysiology.

Loss-of-function mutations of the *MKRN3* gene are the most common cause of familial central precocious puberty. Ana Claudia Latronico's research has examined the correlation between genotypes and phenotypes associated with mutations of this gene. You can read about her findings on page 7.

Issues surrounding puberty can be complex and require a particularly sensitive clinical approach. The ability to consider wider family life is crucial, as Margaret Zacharin illustrates on page 8, in a poignant story of the relationship between clinician and parent.

As always, we are also pleased to bring you news of new ESPE initiatives. In the next column, you can learn about the new Early Career Paediatric Endocrinologists (ECPE) Taskforce, which has been set up to identify the best ways of supporting young paediatric endocrinologists, and now needs five keen ESPE members to get involved. The ESPE Rare Disease Advisory Group was also recently launched; it will advise Council on how ESPE can best sustain its activities in the field of rare disease.

News of the updated European Training Requirements follows on page 3, along with details of the next ESPE Connect webinar, on Noonan syndrome. New leaflets have also been published to advise patients on monogenic diabetes.

On page 4, we hear about life in the pandemic from a patient's perspective, as Arlene Smyth, Executive Officer of the UK-based Turner Syndrome Support Society, describes her own experience of supporting her daughter Kylie, as well as issues encountered by the wider endocrine patient community.

Other updates from ESPE span diverse topics such as grants and education, events and research. I wish you happy reading!

**Sarah Ehtisham**  
Editor, *ESPE News*

Sarah.Ehtisham@medclinic.ae



## Follow ESPE online...

Keep an eye on the latest ESPE news and activities at [www.eurospe.org](http://www.eurospe.org)

You can also follow ESPE on Facebook and Twitter



### Editorial Board:

Meghna Chawla  
Antje Garten  
Rakesh Kumar  
María Salomón  
Estébanez

Cover image: *lisegagne/Stock*

### YOUR SOCIETY

## Annual Business Meeting 2021

For the latest updates from ESPE, members are invited to join us for our Annual Business Meeting, which will be held virtually at 15.00 CEST on Monday 13 September 2021. Book your place via the link that was recently emailed to you.

## New Early Career Taskforce

The new Early Career Paediatric Endocrinologists (ECPE) Taskforce will develop ESPE's strategy for supporting younger colleagues. Five positions are available on the Taskforce. Apply now to get involved.



Apply by **15 September 2021**



See [www.eurospe.org/about/vacancies](http://www.eurospe.org/about/vacancies)

## Rare Disease Advisory Group

This new working group will advise ESPE Council on how best to sustain our activities in the field of rare diseases, alongside other organisations worldwide.



Find out more at [www.eurospe.org/about/committees/rare-disease-advisory-group](http://www.eurospe.org/about/committees/rare-disease-advisory-group)

### GRANTS

## ESPE Grants

There are deadlines in September for applications for two of our grants, offering funding opportunities for paediatric endocrinologists in either the early or mid-stage of their careers.

### Visiting Professorship of Rare Diseases



Apply by **15 September 2021**



See [www.eurospe.org/grants-awards/grants/visiting-professorship](http://www.eurospe.org/grants-awards/grants/visiting-professorship)

### Early Career Scientific Development Grant



Apply by **30 September 2021**



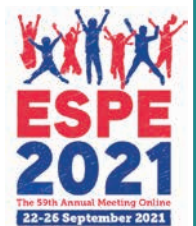
See [www.eurospe.org/grants-awards/grants/early-career-scientific-development-grant](http://www.eurospe.org/grants-awards/grants/early-career-scientific-development-grant)

## RECONNECT AT ESPE 2021 ONLINE

Expert clinicians and researchers will lead this year's ESPE Annual Meeting on 22–26 September. Our rich, educational programme, combined with a high-tech, virtual exhibition and poster area, will reconnect the paediatric endocrine community.

### Working Groups at ESPE 2021 Online

The 2021 Working Group symposia will include the Bone and Growth Plate Working Group's event on 26 September, featuring 'The osteocyte: translating biomechanics into endocrine signals' and 'Craniosynostosis – genes and bone biology'.

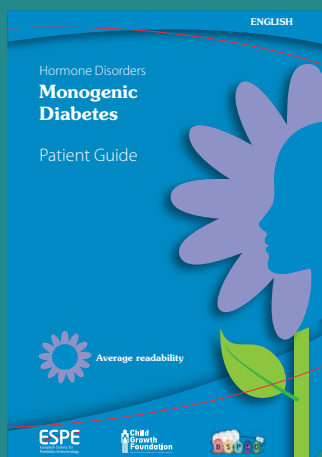


SEE PAGE 9 FOR DETAILS OF OUR EXCITING PROGRAMME



## RESOURCES

## New leaflet on monogenic diabetes



'Monogenic diabetes' is the topic of the latest ESPE patient information booklet. It is available in both easy and average readability versions.



You can find all the patient booklets at [www.eurospe.org/patients](http://www.eurospe.org/patients)

## ESPE e-Learning

## Supporting this issue's theme

The category **Puberty** under **General Content** includes five chapters:

- Puberty
- Delayed puberty
- Management of early and precocious puberty
- Polycystic ovary syndrome, and
- Breast disorders in adolescents.

Nine problem-solving cases are also described.

In addition, **Puberty** within **Resource Limited Countries** provides a chapter 'Precocious and delayed puberty' and three problem-solving cases, all in five languages (English, French, Spanish, Chinese and Swahili). The category **Puberty** in the Russian language has one chapter entitled 'Puberty' and a problem-solving case of precocious puberty.



See [www.espe-elearning.org](http://www.espe-elearning.org)  
Registration is free of charge



## EDUCATION

## ESPE Connect webinars

In response to your request for increased year-round educational content, we have launched ESPE Connect: a series of webinars taking place every 2 months. The webinars will maintain the high levels of scientific quality for which ESPE is renowned. ESPE Connect webinars are free for ESPE members to attend. Non-members can register for each webinar for just €25.

Our next ESPE Connect webinar is:

## A multidisciplinary approach to Noonan syndrome

**Convenor: Mehul Dattani (UK)**

Tuesday 12 October 2021 16.00–17.30 CEST

- **Introduction and welcome** – Mehul Dattani (UK)
- **Cardiac associations** – Juan Pablo Kaski (UK)
- **Genetics of Noonan syndrome** – Emma Burkitt Wright (UK)
- **Endocrine aspects** – Bradley Miller (USA)
- **Panel discussion**
- **Close discussion** – Mehul Dattani (UK)



Register at [www.eurospe.org/education/webinar-series](http://www.eurospe.org/education/webinar-series)



## European Training Requirements

The latest *European Training Requirements in Paediatric Endocrinology & Diabetes* document (ETR) was approved by the European Academy of Paediatrics, European Board of Paediatrics and Union of European Medical Specialists earlier this year.

The ETR was revised by Syllabus Taskforce members Kanetee Busiah (Switzerland), Aleksandr Peet (Estonia), Gianluca Tornese (Italy) and Naomi Weintrob (Israel) under the leadership of Leena Patel (UK). Many trainees, consultants, and members of the Education and Training Committee and of ESPE Council provided valuable contributions.

We recognise that each country must comply with its own professional regulatory requirements for postgraduate medical training. The ETR can be used to complement country-specific training programmes.

Please put us in contact with the lead for paediatric endocrinology and diabetes training in your country via [espe@eurospe.org](mailto:espe@eurospe.org) to help disseminate the ETR effectively in your region.

## ETR content/syllabus tracking tool

Trainees will shortly be able to download a tracking tool from the ESPE website, to help self-assess their level of competence regarding the items in the syllabus, to keep a record for their portfolio and to jointly review with their trainer/educational supervisor.



You can download the ETR at [www.eurospe.org/education/education-training-syllabus](http://www.eurospe.org/education/education-training-syllabus)

## Reports from ESPE schools

Both the ESPE Summer School and the ESPE Diabetes, Obesity & Metabolism (DOM) School took place in May. They were held virtually, due to the impact of COVID-19. Although those involved would have liked to have met in person, both schools were a great success and received very positive feedback.



Read the Summer School report at <https://bit.ly/SummerSchoolReport>



Read the DOM School report at <https://bit.ly/DOMReport>

## Patients during COVID

Our perspective on the pandemic in this issue comes from the family of a patient living with an endocrine condition in the UK. What impact did COVID-19 and its associated restrictions and effects on healthcare have on our patients?



Kylie and Arlene Smyth

“

We did Zoom mindfulness, coffee and chats, kids' parties... But it was not the same as meeting up face-to-face”

**Kylie Smyth** has Turner syndrome and lives in Scotland in the UK. Her mother, **Arlene**, tells us of their experience as a family. Arlene also runs the UK-based Turner Syndrome Support Society, and reflects upon the experience of others who have a family member with the condition.

### Please tell us how Kylie's healthcare needs are normally met

Kylie sees an endocrinologist who specialises in Turner syndrome. As a child, she was seen every 4–6 months, and as an adult, once a year. We have been lucky and received excellent paediatric and adult care. Being seen at a specific Turner syndrome clinic is good, as it focuses the mind of the specialist. We also get to meet other families in the waiting area, which is helpful.

### During the pandemic, how have the restrictions affected you?

In the UK, we have had three lockdowns. In the first, we did not work unless we could do so from home, or leave the house except for medicine and food. Lockdown two was a little better, with more virtual sessions and being able to go back to work some of the time. We are just emerging from the third lockdown; we work from home if we can and go to work if we can't. It has been challenging, especially from a mental health point of view.

### Has Kylie been able to attend medical appointments during this time?

All appointments were moved to be phone calls or video links and were delayed. That is starting to improve now. Calls to the Turner Syndrome Support Society increased, due to people's anxiety at not having their usual appointments.

### How do you feel about the clinical care and appointments that Kylie has received?

I think appointments need to go back to being face-to-face as quickly as possible. It is especially important for obtaining accurate measurements, blood pressure, pubertal staging, etc.

### Do you think Kylie received the same level of care as usual?

No, but it was not the health professionals' fault. I believe they did their best in extreme circumstances.

### How do you feel about future appointments?

For the next few years, I think we will do part phone call or video and part face-to-face. However, it is important that the patient is consulted and allowed to do what works best for them and the doctor.

### What was the hardest thing to cope with during the restrictions?

For those who have Turner syndrome, it was anxiety, fear of catching COVID, not knowing when things will improve, and the change. We did our very best to support our families. We did Zoom mindfulness, coffee and chats, kids' parties, drawing, and all sorts of things. But, it was not the same as meeting up face-to-face.

### What else would you like to say?

I think it will take a long time to recover from this experience. Those with Turner syndrome and, indeed, many other endocrine patients will need a lot of support. I think this is where the patient support groups and endocrine doctors and nurses can work together, to support patients.

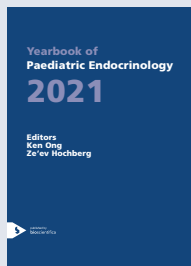
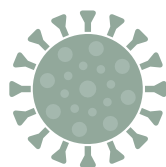
### Arlene Smyth

Executive Officer, Turner Syndrome Support Society



You can contact the Turner Syndrome Support Society at:

12 Simpson Court	Tel: +44 141 9528006
11 South Avenue	Helpline: +44 300 1117520
Clydebank Business Park	Mobile: +44 7947 554587
Clydebank G81 2NR, UK	Web: <a href="http://www.tss.org.uk">www.tss.org.uk</a>



## Yearbook of Paediatric Endocrinology 2021

This year's *Yearbook of Paediatric Endocrinology* will be available shortly. Here is a preview of some of the carefully selected articles you can look forward to seeing, on the subject of puberty.

**Trends in the incidence of central precocious puberty and normal variant puberty among children in Denmark, 1998–2017** Bräuner *et al.* 2020 *JAMA Network Open* doi: 10.1001/jamanetworkopen.2020.15665

**FSH-stimulated inhibin B: a novel marker for the accurate prediction of pubertal outcome in delayed puberty** Chaudhary *et al.* 2021 *Journal of Clinical Endocrinology & Metabolism* doi: 10.1210/clinem/dgab357

**Cranial MRI abnormalities and long term follow up of the lesions in 770 girls with central precocious puberty** Helvacioğlu *et al.* 2021 *Journal of Clinical Endocrinology & Metabolism* doi: 10.1210/clinem/dgab190

**Genotype–phenotype correlations in central precocious puberty caused by *MKRN3* mutations** Seraphim *et al.* 2021 *Journal of Clinical Endocrinology & Metabolism* doi: 10.1210/clinem/dgaa955



You will be able to find the new Yearbook at [www.espeyearbook.org](http://www.espeyearbook.org)

## Bringing you recent highlights from the world of research

### Changes to care delivery in COVID-19

This multicentre, questionnaire-based, online survey by Sarreau and colleagues assessed the changes to delivery of care to children with type 1 diabetes in nine centres across five countries (the USA, Australia, Sweden, China and India). The survey was conducted between May and August 2020, covering the immediate adaptation of these centres to the first peak of the COVID-19 pandemic.

This article makes an interesting read, as the responses of these centres were quite variable in four areas: 'clinic roles', 'care delivery', 'data collection and administrative platforms' and 'provider and patient concerns and challenges'. Healthcare provider concerns over increased frequency of diabetic ketoacidosis, widening disparities in resources, and challenges for patients associated with non-availability of internet/technology for telemedicine are emphasised.

The survey also highlights the unanticipated 'silver linings' in terms of the emergence of telemedicine as 'new best practice', improved data sharing between patient and clinic staff, improved efficiency of consultation and adherence to routine care.



Read the full article in *Pediatric Diabetes* 22 463–468

### How healthy is metabolically healthy obesity?

Obesity is the main cause of the current global epidemics of type 2 diabetes, hypertension, cardiovascular disease and many other disorders. A subgroup of patients with obesity shows preserved insulin sensitivity, normal blood pressure and a beneficial lipid profile. These individuals are often referred to as having 'metabolically healthy obesity' (MHO). MHO is controversially discussed as either a stable phenotype or a transitional state that progresses to metabolic dysfunction (metabolically unhealthy obesity).

Zhou *et al.* examined data from 381 363 probands from the UK Biobank and determined the association of MHO, as well as its transition, with all-cause mortality, diabetes, atherosclerotic cardiovascular disease, heart failure and respiratory diseases.

They found that people with MHO had higher incidents of heart failure and respiratory disease, but not higher rates of atherosclerotic cardiovascular disease, compared with people who were not obese. The authors conclude that weight management should be recommended to all people with obesity, irrespective of their metabolic status.



Read the full article in *Diabetologia*  
doi: 10.1007/s00125-021-05484-6

### Grey and white matter differences with impaired awareness of hypoglycemia

Type 1 diabetes is associated with a degree of cognitive decline and smaller cortical volume. Hypoglycaemia is thought to play a role, especially severe hypoglycaemic episodes. Stantonoyong and coworkers investigated the effects of impaired hypoglycaemia awareness (IHA) amongst a cohort of 40 patients with type 1 diabetes, half of whom had IHA. The subjects underwent magnetic resonance imaging (MRI) studies for grey and white matter changes.

The patients with IHA had significantly reduced grey matter volumes and cortical surface areas, particularly in the frontal and parietal regions and in the white matter tracts. The differences seen correlated with severity of IHA and with the frequency of severe hypoglycaemia.

Whilst further studies are needed to establish causality, the MRI data are concerning. The implication is that IHA increases the risk of severe hypoglycaemia and further increases the risk of grey and white matter changes in the brain.



Read the full article in *Journal of Clinical Endocrinology & Metabolism* 106 450–458

### Predictive enrichment markers for LUM-201 in GH deficiency

LUM-201 is an oral growth hormone (GH) secretagogue that acts by stimulating the GHSR1 receptor in the hypothalamus and pituitary. Bright *et al.* conducted a randomised, placebo-controlled, multicentre study in 68 prepubertal children with an established diagnosis of GH deficiency, who had never been treated before. The aim was to determine predictive enrichment markers (PEMs) for subjects who would respond to LUM-201.

LUM-201 (ibutamoren) was administered in single daily oral doses of 0.4mg/kg ( $n=22$ ) or 0.8mg/kg ( $n=24$ ). Sensitivity, specificity and accuracy of potential markers to predict 6-month growth responses to LUM-201 and recombinant human GH were analysed. The PEMs identified for a favourable growth response to LUM-201 were a baseline insulin-like growth factor-1 concentration  $>30\text{ng/dl}$  and a peak GH response  $\geq 5\text{ng/ml}$  upon administration of a single dose of LUM-201.

Further studies to determine if the predictive accuracy is maintained for a longer duration of treatment are required.



Read the full article in *Journal of the Endocrine Society*  
5 1–10

# Recent advances in polycystic ovary syndrome

Lourdes Ibáñez and Francis de Zegher describe the latest potential treatments for this increasingly common disorder.



Lourdes Ibáñez



Francis de Zegher

Polycystic ovary syndrome (PCOS) is the most frequent cause of hirsutism and menstrual irregularity in adolescent girls and young women, and its prevalence is rising worldwide.<sup>1,2</sup> The condition is accompanied by long term co-morbidities (including subfertility and diabetes) that affect lifetime well-being, and result in a burden on healthcare systems.

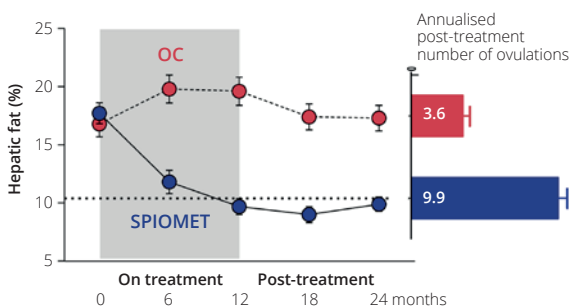
### The outcome of a mismatch

PCOS in adolescent girls is commonly driven by ectopic lipid accumulation (mainly in the liver and viscera) resulting from a mismatch between (reduced) prenatal weight gain and (augmented) postnatal weight gain: in other words, between early adipogenesis and later lipogenesis, or between the capacity for lipid storage and the subsequent demand for it.<sup>1,3</sup> PCOS is thus the outcome of a chronic need to store more fat than is safely feasible in subcutaneous white adipose tissue (WAT).

Genetic variants that control appetite may contribute to such a mismatch, along with an unhealthy lifestyle and a low activity of brown adipose tissue (BAT).<sup>1,3</sup> Ectopic fat accumulation is accompanied by insulin resistance, luteinising hormone hypersecretion, and low concentrations of circulating high molecular weight (HMW) adiponectin, an adipokine with insulin-sensitising and anti-inflammatory properties.<sup>1,3</sup>

### Treatment: let's reduce ectopic fat

There is no approved therapy for PCOS in adolescent girls and young women. The traditional approach is to focus on obvious symptoms such as hirsutism, acne/seborrhoea and



**Figure.** Changes in hepatic fat fraction (by magnetic resonance imaging) during and after treatment in adolescent girls with PCOS randomised to receive an oestro-progestogen OC (n=31) or SPIOMET (n=31). The dotted line shows the average percentage of hepatic fat in healthy control girls. Both treatments reduced the androgen excess towards normal within 12 months without changing body weight. OC failed to reduce the hepatic fat excess and was followed by a rebound of androgen excess. In contrast, SPIOMET normalised hepatic adiposity and insulin resistance and these effects extended beyond active treatment. The annualised number of ovulations after treatment was nearly threefold higher after SPIOMET than after OC. Results are means±SEM. P<0.001 for between group differences in on-treatment changes of hepatic fat, hepatic fat fractions after treatment, and ovulation rates after treatment.<sup>6,7</sup> Reproduced by permission from de Zegher & Ibáñez 2021 (John Wiley and Sons).<sup>7</sup> ©The American Association for the Study of Liver Diseases.

irregular menses. Accordingly, oral contraceptives (OCs) are prescribed to the vast majority of young PCOS patients, including to girls who are not sexually active.<sup>1</sup> OCs mask the problem, but do not solve it. They attenuate key symptoms, but do not revert the underlying pathophysiology, so that young patients with PCOS remain at risk for co-morbidities and for post-treatment rebounds.

Given the key role of ectopic fat excess in the development of PCOS, the prime aim of the treatment should be a preferential loss of ectopic or central fat. This can be achieved with sustained lifestyle measures that combine regular exercise with a healthy diet and with respect for biorhythm and sleep.<sup>4</sup>

### Pharmacological options

If these lifestyle measures fail, then a pharmacological addition can be helpful. In young PCOS patients with obesity, future studies with glucagon-like peptide-1 agonists will disclose their potential to elicit a loss of body weight and, in particular, a loss of central fat. In young PCOS patients without obesity, limited data suggest that combinations of time-honoured generics (acting through different pathways) can reduce ectopic fat without necessarily lowering body weight.

So far, the most promising results may be those obtained with SPIOMET, which is a low dose combination of:

- spironolactone (50mg/day), to antagonise androgen and mineralocorticoid effects, and to activate BAT
- pioglitazone (7.5mg/day), to increase WAT adipogenesis and to raise HMW adiponectinaemia, without increasing body weight, and
- metformin (850mg/day), to augment insulin sensitivity and to reduce appetite and liver fat, possibly via growth and differentiation factor 15 (GDF15),<sup>5</sup> which acts through a specific receptor in the brainstem.

The effects of SPIOMET versus those of an OC (containing ethinylloestradiol-levonorgestrel) have been investigated in two randomised, open-label, single-centre pilot studies performed in non-obese adolescents with PCOS who did not need contraception. The pooled results showed that SPIOMET had more normalising effects than the OC, notably on hepatic and visceral fat, on insulin sensitivity, and on post-treatment ovulation rate (Figure).<sup>6,7</sup>

In the coming years, the efficacy and safety of SPIOMET (in a single tablet) on top of lifestyle intervention will be investigated. This large, double-blind, multicentre, EU-funded trial is part of a paediatric investigation plan approved by the European Medicines Agency. Stay tuned!

**Lourdes Ibáñez**

University of Barcelona, Spain

**Francis de Zegher**

University of Leuven, Belgium

### References

1. Ibáñez et al. 2017 *Hormone Research in Paediatrics* **88** 371–395.
2. Ibáñez & de Zegher 2020 *Pediatric Obesity* **15** e12586.
3. de Zegher et al. 2018 *Trends in Endocrinology & Metabolism* **29** 815–818.
4. Lass et al. 2011 *Journal of Clinical Endocrinology & Metabolism* **96** 3533–3540.
5. de Zegher et al. 2021 *Scientific Reports* **11** 7018.
6. Ibáñez et al. 2020 *Journal of the Endocrine Society* **4** bvaa032.
7. de Zegher & Ibáñez 2021 *Hepatology* **73** 1623–1624.

“ Given the key role of ectopic fat excess in the development of PCOS, the prime aim of the treatment should be a preferential loss of ectopic or central fat ”



## MKRN3 mutations and central precocious puberty

Ana Claudia Latronico's research has examined genotype-phenotype correlations in central precocious puberty caused by *MKRN3* mutations.



Ana Claudia Latronico

“

*A shorter time to presentation and higher FSH levels were found in the patients with CPP due to MKRN3 mutations. Notably, severe MKRN3 defects can have a greater impact on phenotype when compared with pathogenic missense variants”*

Makorin RING finger 3 (*MKRN3*) is an intronless gene located inside a region containing an imprinted gene cluster at chromosome 15q11-q13. *MKRN3* loss-of-function mutations represent the most common genetic cause of familial central precocious puberty (CPP).<sup>1,2</sup> Different types of mutations (frameshift, stop gain, missense) affecting the *MKRN3* protein or the gene promoter region have been described in recent years.<sup>1</sup>

Recently, my research group at São Paulo University, in collaboration with international paediatric groups, described the genotypic and phenotypic features of a large cohort (Latin American, North American, European, Israeli and Turkish subjects) of patients with CPP due to deleterious defects of *MKRN3*.<sup>2</sup> This multiethnic cohort comprised 71 patients (from 36 unrelated families) with CPP caused by 18 *MKRN3*-inactivating mutations.

### Clinical characteristics

Both female and male patients carrying *MKRN3* mutations exhibited typical clinical and biochemical features of premature reactivation of the reproductive axis. Girls started pubertal development at a mean age of  $6.2 \pm 1.2$  years, whereas in boys it was at  $7.1 \pm 1.5$  years. We demonstrated higher levels of basal follicle-stimulating hormone (FSH) and an earlier age at diagnosis in girls with CPP associated with *MKRN3* defects when compared with an idiopathic CPP group. The shorter interval between initial manifestations and diagnosis of CPP in patients with *MKRN3* mutations was probably related to the fact that 51% of them had a familial history of precocious puberty, increasing the awareness of parents and doctors for premature sexual development in a second case in the same family.

Notably, 87.5% of all male patients with *MKRN3* mutations from this latest study were diagnosed through familial screening; only a few boys were index cases (5 out of 36 index cases). Some of these affected boys were under-diagnosed in childhood and the CPP history was only recognised retrospectively in adult life, while others were siblings of index patients and had an earlier diagnosis that might have been undetected otherwise. Therefore, we believe that male CPP caused by *MKRN3* mutations can be clinically subtle.

### Genetic analysis

To date, all described patients with *MKRN3* loss-of-function mutations have a paternal origin when familial segregation analysis was possible. A documented *de novo* *MKRN3* mutation has not been described to date, indicating that true sporadic cases are very uncommon.

Among the 18 rare inactivating mutations in the *MKRN3* gene, one was nonsense, six were frameshifts, and 10 were missense mutations, along with a promoter region deletion. A recurrent frameshift mutation (p.Pro161Argfs\*) was



© Shutterstock

identified in 46% of the patients with CPP, confirming this site as a hotspot region. Severe *MKRN3* mutations, such as stop gain and frameshift mutations, were associated with greater bone age advancement and higher basal luteinising hormone (LH) levels, suggesting that these mutations could lead to a prolonged or greater impact of oestradiol levels on bone maturation or more rapid advancement of puberty.

### Disease mechanisms

Based on *in silico* protein analysis and *in vitro* studies, we demonstrated that missense variants affecting *MKRN3* could lead to precocious puberty by at least two hypothetical mechanisms: (1) destabilising the protein and generating reduced inhibition of genes that promote puberty, and (2) affecting critical regions (i.e. RING fingers) that are relevant to ubiquitination and overall *MKRN3* repressor activity.<sup>3,4</sup> Other rarer mechanisms are deletions in the 5' untranslated regulatory region or even of the entire gene.<sup>4</sup>

A high prevalence of overweight and obesity was observed in CPP patients with or without *MKRN3* mutations (47.3% and 50% respectively), followed by a significant reduction after gonadotrophin-releasing hormone (GnRH) analogue treatment.<sup>2,5</sup> Mean final height was similar in CPP groups with or without *MKRN3* mutations when treated with GnRH analogues, indicating adequate response to this treatment in both groups.<sup>5</sup>

### In conclusion

Our study demonstrated that the premature sexual development phenotype caused by *MKRN3* loss-of-function mutations is indistinct from idiopathic CPP. However, collectively, a shorter time to presentation and higher FSH levels were found in the patients with CPP due to *MKRN3* mutations. Notably, severe *MKRN3* defects can have a greater impact on phenotype (greater bone age and high basal LH levels) when compared with pathogenic missense variants.

### Ana Claudia Latronico

São Paulo University, São Paulo, Brazil

### References

1. Soriano-Guillén et al. 2021 *Journal of Neuroendocrinology* doi: 10.1111/jne.12979.
2. Seraphim et al. 2021 *Journal of Clinical Endocrinology & Metabolism* **106** 1041–1050.
3. Abreu et al. 2020 *Journal of Clinical Investigation* **130** 4486–4500.
4. Macedo et al. 2018 *Neuroendocrinology* **107** 127–132.
5. Ramos et al. 2020 *Neuroendocrinology* **110** 705–713.

## Monday's challenge

Margaret Zacharin explores the issues and sensitivity involved in supporting families with additional needs, in the context of puberty.



Margaret Zacharin

“

*Clearly, advice and management will require complex interdisciplinary care, but much will devolve to you, to formulate a plan to make this family's life tolerable”*

So, it's Monday morning. You're on the way to outpatients, looking forward to a few TSH 7.5mU/l's, maybe a constitutional delay and, if you're lucky, a well-controlled CAH.

The first family appears: an exhausted mother, wheeling a double pram with a clearly developmentally delayed 8-year-old girl with a long leg plaster, plus her brother, thrashing around irritably next to her. They are accompanied by a 14-year-old agitated young woman, clasping her mother's arm. This morning's clinic is not looking to be as simple as you might have imagined!

A brief history ascertains that the older girl has severe autism, and is currently under the care of developmental paediatrics and psychiatry. She achieved menarche 3 months ago.

Enormous family and social difficulties become apparent in your history-taking: the girl having escalating anxiety at the sight of menstrual blood, demonstrating grossly disinhibited behaviours and tantrums, throwing away her menstrual pads in public. The other children are twins, born at 24 weeks gestation, with the unfortunate consequences of extremely preterm birth, both with cerebral palsy. The little boy is agitated but more mobile than his sister. He is intermittently quite aggressive, recently having sat on his severely disabled sister, breaking her femur.

Further history-taking ascertains that this is a single parent family, father having departed, struggling financially and socially, with major issues with school and carers. To make matters worse, the 8-year-old is showing distinct signs of breast development over 9 months, with increased irritable episodic screaming for no apparent reason. Mother has major fears that she will follow her sister's pattern after menarche.



© Shutterstock

How on earth are you going to manage this family? Being an endocrinologist, you haven't thought a lot about developmental problems and their consequences for quite some time and your gynaecology was always a bit scratchy. After taking a deep breath, you remember to ascertain that the little girl is non-verbal, gastrostomy fed, with difficult epilepsy, requiring four anticonvulsants. Pubic hair has been present from age four. Mother's concerns relate to puberty and whether she will manage!

Her brother is smaller, as second twin, his birth weight 550 grams at 24 weeks. Fortunately, despite chronic lung problems, his epilepsy is less severe. Behavioural disturbance has significantly worsened since father departed, throwing household items and recently injuring his sister. Looking after these children, the mother is distraught, particularly with the older girl reacting so badly, with increased behavioural disturbance preceding and during menstruation. School has reported worrying, risky, sexualised interactions with boys at special school.

By this time you're feeling as desperate as the mother. Clearly, advice and management will require complex interdisciplinary care, but much will devolve to you, to formulate a plan to make this family's life tolerable.

To first deal with the older girl seems sensible, then perhaps a staff member can help while you discuss options for the twins. She reacts wildly when she sees blood, a common issue with autism. Stopping periods with a continuous contraceptive pill seems an option, but occasional respite care, visiting her father, risks erratic medication delivery, consequent withdrawal bleeds and exacerbated problems! The implantable progestogen rod is clearly inappropriate, with 10% likelihood of amenorrhoea and requiring general anaesthesia for insertion.

A progesterone-bearing IUD might solve the dilemma, being low dose without hypothalamic-pituitary-gonadal (HPG) axis inhibition, whilst providing 4–5 years of amenorrhoea and complete contraception. Mother was unaware of this possibility for a young teenager and is absolutely delighted to hear that gynaecologic referral may significantly alter the burden of care for her daughter. You breathe a sigh of relief as you appear to have gained the mother's trust.

You cautiously move to the 8-year-old, with a minimal trauma long bone fracture, at risk for more. When you examine her, she is 145cm with stage 3 breast and stage 4 pubic hair. A long explanation of various management options will confuse mother. You start with a GnRH agonist, but mother is worried; she just wants periods prevented and is not at all interested in maximised height. Two similar menstrual disasters would be impossible!

Repeated specialist visits would create a further burden, so you suggest depot progestogen to effectively prevent menstruation and slow pubertal progress. This sounds better, as the local doctor can administer 3-monthly injections. You remember to say that, whilst this treatment is good at age eight, under no circumstances can it continue beyond age 12 without addition of oestrogen, because it inhibits the HPG axis with failure of bone mass accrual. Eventually, an IUD like her sister will be possible, after completion of uterine growth.

Mother interrupts to ask about possible further fractures. The conversation is complicated. You explain that whilst anticonvulsants and immobility reduce bone quality, sex hormone accumulates cortical thickness, with

*Continued on page 9*



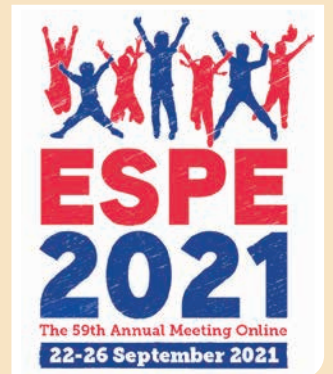
## Register for ESPE 2021 Online

22–26 September 2021

**ESPE 2021 Online is ESPE's virtual Annual Meeting, providing you with the latest developments in paediatric endocrinology.**

The theme of 'Lifelong endocrine care through collaboration, discovery and innovation' lays the perfect foundation for the inspiring scientific programme. Our online platform will allow you to plan and schedule the sessions that interest you most, whilst offering plenty of opportunities for you to connect with peers and speakers around the world to discuss the rich and stimulating content.

Sessions led by world-renowned speakers will be available on demand following their initial broadcast, allowing you to access more information than ever before!



### Register today and save!

Register today to save up to 30% on registration fees for **ESPE 2021 Online**. The standard registration fees are only available until Tuesday 7 September (23.59 BST), after which increased fees apply.



Standard registration deadline  
**7 September 2021**  
(23.59 BST)



For further information see  
[www.eurospe.org/espe2021online/registration](http://www.eurospe.org/espe2021online/registration)

### Programme highlights

#### Plenary sessions

- **A kiss before sex** Waljit Dhillon (UK)
- **New drugs for treatment of youths with type 2 diabetes** William Tamborlane (USA)
- **Iodine deficiency: a public health issue** Michael Zimmermann (Switzerland)
- **Development of novel therapies for obesity** Matthias Tschöp (Germany)
- **The transgender dilemma** Stephen Rosenthal (USA)
- **The current state of epigenetic research in humans: promise and reality** John Grealley (USA)
- **Novel insights into weight regulation** Sadaf Farooqi (UK)
- **The long term effects of adolescent obesity** Thomas Reinehr (Germany)

#### Meet the Expert sessions

- **Thyroid hormone resistance syndromes** Krishna Chatterjee (UK)
- **Diagnosis and management of a child with pituitary adenoma** Marianne Andersen (Denmark)
- **Cystic fibrosis-related diabetes** Andrea Kelly (USA)
- **Management of MEN1 in children and adolescents** Maria Luisa Brandi (Italy)
- **Autoimmune endocrinopathy** Eystein Husebye (Norway)
- **Endocrine and osteoporosis management of boys with DMD** Leanne Ward (Canada)
- **Real-life diabetes management during exercise** Andrea Scaramuzza (Italy)

#### You'll also enjoy:

- How do I ... ? sessions
- Controversy sessions
- Young Investigator Lectures and Awards
- 2020 and 2021 Awards sessions
- Symposia talks
- *Yearbook of Paediatric Endocrinology* updates

**We look forward to connecting with you this September.**

## FEATURE

'Monday's challenge' *continued from page 8*

“

*You are the first doctor to actually bother to listen to her and to understand the extremity of the burden under which she lives”*

trabecular mineralisation, thus reducing long term fracture risk. Switching off puberty might not be optimal for bone health! A couple of intravenous bisphosphonate infusions 6 months apart would protect her until puberty is complete.

And now for that difficult little boy. He is small and thin, so early puberty seems unlikely. Mother is only partly reassured. He is already boisterous and difficult. What will happen with puberty? Looking somewhat horrified and ashamed, mother whispers that he constantly plays with his penis, often in public, so she lives in fear of what will happen when he is older.

Fortunately you can allay her fears, knowing that this exaggerated but normal auto-stimulatory behaviour usually settles. Most boys with significant disability don't exhibit highly sexualised behaviours after puberty. You emphasise that preventing puberty is always totally inappropriate and mention that progestogen is a very helpful stratagem if future issues arise. Currently, linking with a developmental paediatrician will ensure good epilepsy control plus

sufficient nutrition and vitamin D to grow, without compromising bone health.

This has been a totally exhausting interview! Before escaping for long overdue morning coffee, you remember to give mother a booklet explaining the problems of puberty in children with disabilities, hoping that it will help her formulate questions for your next interview in 3 weeks.

You are happy to hear that her sister has messaged to say she will help escort the family home and will stay, so that together they may discuss today's consultation. You are thanked profusely as mother tells you, somewhat emotionally, that you are the first doctor to actually bother to listen to her and to understand the extremity of the burden under which she lives.

#### Margaret Zacharin

*Department of Endocrinology,  
Royal Children's Hospital, Parkville,  
Victoria, Australia*

## Future meetings

See [www.eurospe.org/meetings](http://www.eurospe.org/meetings) for details of all future meetings



### ESPE 2021 Online

22–26 September 2021

[www.eurospe.org/espe2021online](http://www.eurospe.org/espe2021online)



### 11th International Meeting of Paediatric Endocrinology

19–22 March 2022

Buenos Aires, Argentina



### 60th Annual ESPE Meeting

15–17 September 2022

Rome, Italy



### 61st Annual ESPE Meeting

September 2023

The Hague, The Netherlands



### 62nd Annual ESPE Meeting

September 2024

Marseille, France



## OTHER EVENTS

### OCTOBER 2021

#### ESPE Connect Webinar 2: Noonan Syndrome

12 October 2021

Online

#### ESPE Science Symposium

29–30 October 2021

Nijmegen, The Netherlands

### 2022

#### ESPE Caucasus & Central Asia School

Tbilisi, Georgia

#### ESPE Maghreb School

Casablanca, Morocco

#### ASPED-ESPE Endocrine Academy

Location to be confirmed

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

## DEADLINES

### SEPTEMBER

Early Career Paediatric Endocrinologists Taskforce vacancies – 15 September 2021

Visiting Professorship of Rare Diseases applications – 15 September 2021

Early Career Scientific Development Grant applications – 30 September 2021

ESPE Connect Webinar Series Assistant Convenor applications – 30 September 2021

For more information about vacancies on ESPE Committees and how to apply, see [www.eurospe.org/about/vacancies](http://www.eurospe.org/about/vacancies)

# ESPE

European Society for Paediatric Endocrinology

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

### Secretary General

Professor Anita Hokken-Koelega  
p.a. Stichting Kind en Groei  
PO Box 23068  
3001 KB Rotterdam  
The Netherlands

### ESPE Newsletter

© 2021 The European Society for Paediatric Endocrinology

*The views expressed by the contributors are not necessarily those of ESPE*

### Editor:

Dr Sarah Ehtisham  
Department of Paediatric Endocrinology  
Mediclinic City Hospital  
Dubai, UAE  
E: Sarah.Ehtisham@mediclinic.ae

### Editorial Board:

Dr Meghna Chawla  
(Pune, India)  
Dr Antje Garten  
(Leipzig, Germany)  
Dr Rakesh Kumar  
(Chandigarh, India)  
Dr María Salomón Estébanez  
(Manchester, UK)

### Sub-Editor:

Caroline Brewer

### Designed by:

[www.corbiculadesign.co.uk](http://www.corbiculadesign.co.uk)

### Published by:

Bioscientifica Ltd  
Starling House  
1600 Bristol Parkway North  
Bristol BS34 8YU, UK  
W: [www.bioscientifica.com](http://www.bioscientifica.com)  
*Bioscientifica is a subsidiary of the Society for Endocrinology*

### ESPE Office

Bioscientifica Ltd (address above) manages the ESPE Office. It is also the Professional Congress Organiser (PCO) for ESPE's Annual Meetings.

### ESPE Senior Operating Officers:

Joanne Fox-Evans and Hannah Bonnell

For ESPE enquiries, including membership:

T: +44 (0)1454 642246

F: +44 (0)1454 642222

E: [espe@eurospe.org](mailto:espe@eurospe.org)

W: [www.eurospe.org](http://www.eurospe.org)



[www.facebook.com/EuroSPE](https://www.facebook.com/EuroSPE)



[www.twitter.com/EuroSPE](https://www.twitter.com/EuroSPE)

### ESPE News archive

You will find previous newsletters in the archive at [www.eurospe.org/news/newsletters](http://www.eurospe.org/news/newsletters)