ESPE NEWS

BRINGING THE LATEST IN PAEDIATRIC ENDOCRINOLOGY TO YOU

ESPE
European Society for Paediatric Endocrinology
Improving care of children with endocrine diseases by promoting knowledge and research

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Growth and overgrowth

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ESPE 2024 Liverpool, UK, 16–18 November – save the date!

Welcome

The start of a new year sees us already looking forward to our next ESPE Annual Meeting. This year's event will be in Liverpool, UK, a city of great historic and cultural significance, and home to the world-renowned Alder Hey Children's Hospital. Preparations for ESPE 2024 are well underway. Learn more on page 9 and save the date: Saturday 16–Monday 18 November!

In this issue of *ESPE News*, we take the opportunity to highlight various aspects of disease relating to growth and overgrowth.

On **page 5**, Guillaume Canaud describes his group's exciting work in the discovery of the first drug therapy for *PIK3CA*-related overgrowth spectrum (PROS) disorders. As well as developing the first successful mouse model of the human disease, they implemented treatment using an existing PIK3CA inhibitor, which has proved very effective in many cases.

Long-acting growth hormone is another novel, exciting opportunity to improve the care of our patients, but the formulations are not all the same. On **page 6**, Bradley S Miller examines the fundamental differences between them, including the mechanisms used to prolong their action, issues such as dosing, and considerations surrounding patient selection.

In her article on **page 7**, Éloïse Giabicani draws our attention to issues other than growth in children born small for gestational age (SGA). These can include metabolic effects and cardiovascular morbidity in adulthood. She suggests strategies for the management of patients born SGA, which should be adopted by the wider community of paediatricians, not just paediatric endocrinologists.

The ESPE Bone and Growth Plate Working Group supports members working in this area of our field. Find out more from Evelien Gevers on **page 8**.

Among the latest news, grant and event information, on **page 3**, you can learn how to submit your ideas for the Joint Congress of ESPE and the European Society of Endocrinology in 2025. You can also see the list of exciting ESPE Connect Webinars for 2024 on **page 9**; don't forget, these webinars are free for ESPE members.

Finally, please don't forget to complete the ***ESPE News* survey**.

I wish you a happy and fruitful 2024!

Antje Garten
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Complete the *ESPE News* survey

We want to know what you think about your newsletter. Complete a short survey to tell us what you would like to read in *ESPE News*, and **have the chance to win a €20 Amazon voucher**.

Please tell us what you think

View the survey

GRANTS

ESPE Research Unit

One large grant of up to €100 000 will be awarded to support collaborative research among members, ideally from at least three different countries, for a period of 2 years.

Preliminary applications by **11 March 2024**

Find out more at **www.eurospe.org/grants-awards/grants/espe-research-unit**

ESPE Visiting Professorship of Rare Diseases

These grants of up to €15 000 aim to develop long-lasting collaborations, by supporting multiple short visits or by hosting a visiting professor. The grants are for mid-career paediatric endocrinologists (not just professors).

Apply by **15 April 2024**

Find out more at **www.eurospe.org/visiting-professorship-of-rare-diseases**

ESPE Early Career Scientific Development Grant

Finance a short visit to an external institution to learn a technique or develop methodology, or fund a visit by an expert to your department. Three grants are available per year of up to €2500.

Apply by **31 May 2024**

Find out more at **www.eurospe.org/early-career-scientific-development-grant**


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YOUR SOCIETY

An update
ESPE for Armenia

The humanitarian crisis in Nagorno Karabakh (also known as Artsakh; see *ESPE News* 61) has become a refugee crisis, with more than 100 000 inhabitants fleeing from the enclave to Armenia. Elena Aghajanova, President of the Armenian Association of Pediatric Endocrinologists, has sent us the following report.

"Children who were previously registered at the local endocrine clinic in Artsakh have arrived in Armenia and have been registered at the Endocrinology Clinic of Muratcan University Hospital. Our hospital is the sole reference centre for paediatric endocrinology with access to life-saving endocrine treatment. However, under Armenia's current healthcare system, not all investigations and medications are covered by the state, and the needs of refugees, many with few or no personal possessions, have put significant strain on limited resources.

"Shoher Grigoryan, a former paediatric endocrinologist at Stepanakert Hospital in Artsakh, is herself a refugee with her own family. She is now providing endocrine care at Muratcan. Shoher confirms that the 10-month blockade of Artsakh by Azerbaijan has left children without life-saving medicines for months. Almost all refugee children have experienced decompensation and stress, and almost all present with signs of malnutrition and severe illness complications, which is heart-breaking."

In response, ESPE and the Armenian Association of Pediatric Endocrinologists have alerted different non-governmental organisations (NGOs) and industry partners to the urgent needs of these children with endocrine diseases.

You, too, can help by donating to the VIVA Foundation, a charitable NGO, which has a main mission to provide the hospitals and clinics of Armenia with facilities, medication, surgical materials and instruments.

Donate to Viva and learn more at **www.viva.foundation**
To donate specifically for endocrine problems, include 'ESPEforArmenia'

EVENTS

Send your programme suggestions

Work on the scientific programme for the Joint Congress of ESPE and ESE 2025 has begun! We welcome suggestions for plenary lectures, symposia, Meet the Expert/Basic Scientist sessions, debates, and sessions on controversies and New Scientific Approaches.

Please send your suggestions by **12 February 2024**

Find out more at **www.espe-ese-congress2025.org**

RESOURCES

Test yourself with e-Learning

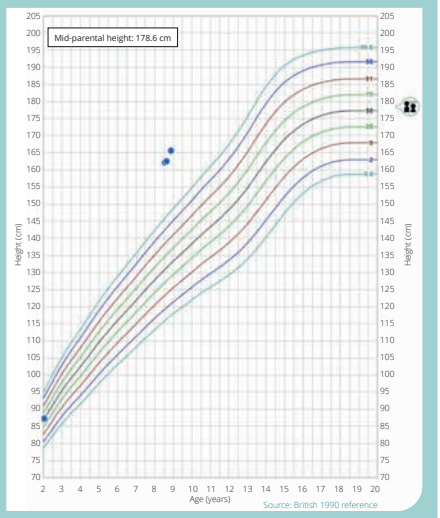
The ESPE–ISPAD (International Society for Adolescent and Pediatric Diabetes) e-Learning web portal is an interactive resource on paediatric endocrinology and diabetes mellitus. Use it, free of charge, to expand your knowledge of paediatric endocrinology.

For more details, see **www.eurospe.org/education/e-learning**

Register for free access at **www.espe-elearning.org**

This issue's clinical case highlight

How would you determine the cause?
An 8-year-old boy is referred for tall stature and recent-onset, early morning headaches. He has an 18-month history of intermittent headaches that wake him at night: no nausea, vomiting or visual disturbances. In the first 2 years of life, he grew along the 50th centile, then started to grow quickly at around the age of 5 years (see chart). He is taller than his classmates, has most of his adult teeth and requires adult-sized shoes. He has hypermetropia and amblyopia, a large head with a large jaw, asymmetric facial appearance, bulbous lips and a large tongue, widely spaced, large frontal teeth, large hands and feet, and is prepubertal. His height is 162.1cm and his weight is 43.5kg.



Which initial investigations would you order?

- ☐ Serum level of growth hormone
- ☐ Serum level of prolactin
- ☐ Serum levels of thyrotrophin and free thyroxine
- ☐ Serum levels of LH, FSH and testosterone
- ☐ Serum level of insulin-like growth factor-1

For the answer, see **page 10**.

New section in '*Children*'

The online, open access journal *Children* (**www.mdpi.com/journal/children**) has launched a new section devoted to paediatric endocrinology. The section's Editor-in-Chief is the highly regarded paediatric endocrinologist and long-standing ESPE member, Zvi Laron.

Learn more at **www.mdpi.com/journal/children/sections/pediatric_endocrinology**

Bringing you recent highlights from the world of research

Effects of localised T3 production in iPSC-derived hepatic organoids

Thyroid hormones are important for both function and development of the human liver. Thyroid hormone action in hepatocytes is controlled by deiodinase 2, which is responsible for local activation of thyroxine (T4) to the biologically active tri-iodothyronine (T3). Interestingly, deiodinase 2 expression is not found in adult liver in mammals. In mice, an acute surge in thyroid hormone signalling was observed shortly after birth, due to a transient peak of deiodinase 2 expression.

To find out whether deiodinase 2 plays a role during the development of human liver, Hidalgo-Álvarez *et al.* used human induced pluripotent stem cells (iPSCs) to generate hepatic organoids. They found that the organoids exhibited developmental stages similar to those observed in human hepatic organogenesis. Deionidase 2 expression was seen from the early stages of human hepatoblast formation through to the transition to more mature cells. The resulting pulse of locally produced T3 altered the expression of key transcription factors, as well as the transcriptome of the maturing hepatocytes.

Read the full article at Hidalgo-Álvarez *et al.* 2023 *Journal of Clinical Investigation Insight* https://doi.org/10.1172/jci.insight.173780

Teplizumab and B-cell function in newly diagnosed type 1 diabetes

Teplizumab is a monoclonal antibody to CD3 on T cells, and is approved for use in children aged 8 years or older who have preclinical type 1 diabetes, to delay the onset of clinical disease.

Ramos *et al.* conducted a randomised placebo-controlled trial to determine whether intravenous teplizumab could prevent disease progression in children and adolescents with newly diagnosed type 1 diabetes. Patients were randomised to receive either teplizumab (217 patients) or placebo (111 patients) for two 12-day courses. The primary endpoint was change from baseline in B-cell function, as measured by C-peptide levels at week 78.

Patients treated with teplizumab had significantly higher stimulated C-peptide levels (least-squares mean difference 0.13pmol/ml, 95% CI 0.09–0.17, $P<0.001$). There was no significant difference between the two groups with regards to secondary endpoints, which included insulin doses, glycated haemoglobin, time in target glucose range and clinically important hypoglycaemic events. Associated adverse events included headache, gastrointestinal symptoms, rash and lymphopenia.

The authors concluded that paediatric patients newly diagnosed with type 1 diabetes showed benefit with respect to preservation of B-cell function following two 12-day courses of teplizumab.

Read the full article at Ramos *et al.* 2023 *New England Journal of Medicine* https://doi.org/10.1056/NEJMoa2308743

Dasiglucagon for congenital hyperinsulinism in infants and children

Congenital hyperinsulinism (CHI) is a rare condition, resulting in severe and persistent hypoglycaemia with a high risk of brain injury. Causes of both transient and genetic CHI are increasingly well understood, but approved medical treatment remains limited to diazoxide, which is ineffective in a large proportion of patients.

Dasiglucagon is a novel glucagon analogue under development for patients with CHI. Thornton and colleagues recruited 32 patients with CHI aged 3 months to 12 years, who were randomised to standard of care (SoC) or SoC plus dasiglucagon via subcutaneous pump for 4 weeks. All patients were monitored by blinded Dexcom G4 continuous glucose monitoring (CGM) and via three or more fingerprick glucose checks per day.

There was no statistically significant difference in fingerprick-detected hypoglycaemia (<3.9mmol/l) between groups. However, CGM revealed a 43% reduction in hypoglycaemia (<3.9mmol/l) and severe hypoglycaemia (<3.0mmol/l) for those receiving dasiglucagon, supporting the use of dasiglucagon as a treatment for CHI.

Read the full article at Thornton *et al.* 2023 *Journal of Clinical Endocrinology & Metabolism* https://doi.org/10.1210/clinem/dgad648

Extracellular MIF contributes to obesity

Metabolic disorders are associated with chronic adipose tissue inflammation. Previous studies have shown that classic inflammatory factors, such as tumour necrosis factor-α, regulate lipolysis by activating hormone-sensitive lipase (HSL) in adipose tissue. HSL mediates fatty acid release from adipose tissue by catalysing hydrolysis of triglycerides and diacylglycerides. However, the precise cellular mechanisms underlying the regulation of HSL in obesity are largely unknown.

Chen *et al.* have examined the link between the proinflammatory cytokine macrophage migration inhibitory factor (MIF) and regulation of HSL activity in a mouse adipocyte model and different mouse models with high MIF expression. They found that extracellular MIF reduces HSL and subsequent lipolysis in adipocytes by activating the energy sensor AMP-activated kinase and c-Jun N-terminal kinase. Neutralising antibodies against MIF and blocking the MIF receptor CD74 exerted beneficial effects in reducing adipocyte hypertrophy and body weight gain in mice during feeding with a high-fat diet. This might indicate the possibility of developing a treatment option for metabolic dysfunction in people with high circulating MIF levels.

Read the full article at Chen *et al.* 2024 *Molecular Metabolism* https://doi.org/10.1016/j.molmet.2023.101834

Finding a therapy for PROS

Guillaume Canaud describes his group's work in the discovery of the first drug therapy for *PIK3CA*-related overgrowth spectrum (PROS) disorders.

Our research group is focused on genetic mosaic disorders associated with overgrowth syndromes and vascular anomalies. Overgrowth syndromes are rare genetic disorders characterised by abnormal tissue growth, which can be localised or generalised.[1] These mutations are not inherited, but occur during embryonic development, resulting in somatic mosaicism.

The genes involved in overgrowth syndromes are not yet fully understood, but many appear to be part of the RAS/PIK3CA/AKT/mTOR pathway, a significant player in cell growth and proliferation, with gain-of-function mutations in *PIK3CA* playing a prominent role.[2] Patients typically exhibit complex tissue malformations, including abnormal blood vessels, disordered adipose tissue, muscle hypertrophy and bone deformities.

Indeed, patients carrying somatic *PIK3CA* mutation have an extremely variable clinical presentation, ranging from benign malformation to a severe form of the disease when large parts of the body or vital organs are affected. While these disorders have always existed, somatic *PIK3CA* gene mutation was identified only in 2012.[3,4] Following a conference report in 2014, patients with *PIK3CA* mutation are now referred to as having *PIK3CA*-related overgrowth spectrum (PROS).[5]

Having trained as an adult nephrologist, I did not expect to see any patient with a PROS condition. In September 2015, my life changed, thanks to an encounter with a young adult patient who had a severe form of PROS and kidney dysfunction. His situation was dire and life-threatening, and we decided to do our best to improve his health.

Identifying a therapy

In a short period of time, starting in January 2016, we developed the first mouse model of PROS that successfully replicates the patient phenotype. We identified BYL719/alpelisib (Novartis), a PIK3CA inhibitor initially developed for oncology, as a potential therapy for PROS.[6] This drug was coming to the end of a phase 1 trial in women with breast cancer. Our subsequent testing in the mouse model demonstrated the drug's efficacy.

Based on these promising results, we received authorisation from both the French regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé) and Novartis to treat this first patient through a specific national compassionate programme. The overall clinical response went beyond our expectations, prompting us to ask for additional authorisation to treat both adults and children (a total of 19 patients aged 4–50 years) with severe forms of PROS.

The clinical outcomes following drug introduction were remarkable: previously untreatable vascular tumours reduced in size, congestive heart failure improved, and hemihypertrophy was reduced.[6] Notably, the treatment exhibited acceptable side effects.

We published this work in June 2018,[6] but were not prepared for the consequences of this study. After publication, we received thousands of emails from patients and physicians around the globe, requesting appointments and to learn more about this drug. This opened my eyes to the number of patients living with these diseases. Novartis was also contacted by an increasing number of physicians who wanted access to the drug through the Novartis Managed Access Program.

Guillaume Canaud

> *"We received thousands of emails from patients and physicians around the globe, requesting appointments and to learn more about this drug"*

Obtaining drug approval

Interestingly, in parallel to our activities, Novartis pursued the development of alpelisib for women with breast cancer, conducting both phase 2 and phase 3 clinical trials. The favourable outcome of these trials in oncology led the US Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) to approve alpelisib for women with breast cancer. This was good news, as it meant that drug development would not be halted.

Early in 2019, we sat down with Novartis and decided to launch a clinical trial based on evidence from real-world data, in order not to waste too much time for patients. In this clinical trial (NCT04285723), we enrolled the first 57 patients treated worldwide, including 44 at my institution.

All the data collected were analysed by an independent contract research organisation which confirmed, in a larger number of patients, our initial findings in terms of efficacy and safety.[7] These data were then reviewed by the oncology section of the US FDA in autumn 2021, which was followed in February 2022 by 2 weeks(!) of inspection at our site to verify their accuracy and reliability.

This led, in April 2022, to the US FDA's accelerated approval of alpelisib for patients with PROS over 2 years of age, making it the first and only approved treatment for these disorders.[8] We now must confirm these data in a randomised control trial (NCT04589650) which is currently ongoing, to satisfy US FDA and EMA requests.

In conclusion

From a research perspective, while the drug is generally beneficial, the response to treatment varies from good to exceptional. We are now exploring the role of each tissue in disease development, as our findings suggest that the physiopathology is more convoluted than originally thought, with complex endocrine anomalies.[9–12]

Finally, this example allowed us to demonstrate that drug repositioning is feasible in the context of rare diseases. Using a similar approach, we have now identified other promising drugs for other diseases not involving the phosphoinositide 3-kinase pathway, which will be published soon.

Guillaume Canaud

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References

1. Canaud *et al.* 2021 *Orphanet Journal of Rare Diseases* https://doi.org/10.1186/s13023-021-01929-8.
2. Morin & Canaud 2021 *British Medical Bulletin* https://doi.org/10.1093/bmb/ldab023.
3. Kurek *et al.* 2012 *American Journal of Human Genetics* https://doi.org/10.1016/j.ajhg.2012.05.006.
4. Lindhurst *et al.* 2012 *Nature Genetics* https://doi.org/10.1038/ng.2332.
5. Keppler-Noreuil *et al.* 2014 *American Journal of Medical Genetics A* https://doi.org/10.1002/ajmg.a.36552.
6. Venot *et al.* 2018 *Nature* https://doi.org/10.1038/s41586-018-0217-9.
7. Canaud *et al.* 2023 *Genetics in Medicine* https://doi.org/10.1016/j.gim.2023.100969.
8. US FDA 2022 www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-alpelisib-pik3ca-related-overgrowth-spectrum.
9. Delestre *et al.* 2021 *Science Translational Medicine* https://doi.org/10.1126/scitranslmed.abg0809.
10. Morin *et al.* 2022 *Journal of Experimental Medicine* https://doi.org/10.1084/jem.20212148.
11. Ladraa *et al.* 2022 *Science Advances* https://doi.org/10.1126/sciadv.ade7823.
12. Bayard *et al.* 2023 *Journal of Experimental Medicine* https://doi.org/10.1084/jem.20230926.

The era of long-acting growth hormone has arrived

Bradley S Miller gives an overview of the new long-acting GH formulations that are set to transform patient care.

Bradley S Miller

"With fewer injections required, adherence should improve and lead to better outcomes and reduced treatment burden"

The era of long-acting growth hormone (LAGH) has fully arrived, with three once-weekly growth hormone formulations available for children with growth hormone deficiency (GHD). Paediatric endocrinologists need to understand the similarities and differences between these molecules to guide their use in patients.

Mechanism of prolongation of GH availability[1]

Each of these new drugs has a different mechanism for prolonging the half-life of GH, allowing once-weekly administration:

- Lonapegsomatropin (Skytrofa™) is a prodrug with GH covalently bound to polyethylene glycol (PEG) by a transient linker. Unmodified GH is released from the PEG carrier after injection at body pH and temperature.[2]
- Somapacitan (Sogroya™) is a modified GH with an albumin-binding linker similar to that used in long-acting insulins and glucagon-like peptide-1 agonists. Following injection, binding of somapacitan to albumin slows its clearance.[3]
- Somatrogon (NGENLA™) is a modified GH with three C-terminal peptide segments from human chorionic gonadotrophin added to the ends of the molecule, resulting in delayed clearance.[4]

Efficacy

Each LAGH product has been demonstrated to produce a non-inferior height velocity over 1 year, compared with a common dose of daily GH in children with GHD.[2–4] The approved doses of the drugs differ. In extension studies, continued growth has been shown for each drug, comparable with historical data for daily GH.

Safety

No new side effects have been reported for LAGH compared with daily GH. Anti-drug antibodies have been seen with each LAGH molecule. Neutralising anti-drug antibodies, when present, did not cause decreased growth velocity.[2–4]

Patient selection[1]

The choice to use an LAGH product in a child with GHD should be guided by that patient's particular circumstances, with GH-naïve and non-adherent patients being the most likely candidates. The LAGH drugs are approved for use in children with GHD and open epiphyses. There is variation in the lowest age approved for each product. Children with hypoglycaemia associated with severe GHD may not be good LAGH candidates, since the metabolic actions of GH may not last the whole week between injections.

Dosing[2–4]

The recommended dose of each LAGH is different, based upon differences in the molecules and their pharmacokinetics: lonapegstomatropin 0.24mg/kg/week, somapacitan 0.16mg/kg/week, somatrogon 0.66mg/kg/week.

In the clinical trials, the LAGH dose was adjusted primarily based upon weight gain.[2–4] There are few data regarding individualisation of the LAGH dose based upon the severity of GHD, insulin-like growth factor-1 (IGF-1) levels, height velocity or other parameters. The clinical trials of LAGH focused mostly on prepubertal children. Therefore, more data are needed to guide dosing in pubertal children. In patients switching from daily GH to LAGH, the LAGH can start the day after (or at least 8 hours after) the last daily GH injection.

Monitoring[5]

The pharmacodynamics of IGF-1 during treatment with each LAGH molecule are different. Following administration of LAGH, IGF-1 levels peak between 2 and 3 days and return to predose levels at day 7. The day 4 IGF-1 level is generally the best estimate of the weekly average.

Tables are available for estimating average IGF-1 from random blood draws, using the timing of the dose and the draw. The average IGF-1 level correlates best with height velocity and, in addition to height velocity and weight gain, may help guide dose adjustment. If the average IGF-1 level is elevated (more than +2 SDS), a dose reduction should be considered.

Long term follow up[1]

Due to the change in the pharmacokinetics of GH action with LAGH, and the modifications of GH to prolong its action, there may be long term effects that differ from daily GH. In order to capture this information, product registries have been developed by the manufacturers. In addition, there is an independent registry, GloBE-Reg (**www.GloBE-Reg.net**), developed through collaboration between paediatric endocrine societies, industry and patient advocacy groups to capture long term safety and efficacy data in children who have received LAGH and daily GH.

Other indications

Clinical trials are underway to determine if LAGH therapy is safe and efficacious in children with Turner syndrome, Noonan syndrome or idiopathic short stature, and in children born small for gestational age without adequate catch-up growth.

Summary[1]

Three new LAGH drugs are now approved and available in many countries for treatment of children with GHD. With fewer injections required, adherence should improve and lead to better outcomes and reduced treatment burden. No new safety issues with LAGH have been identified in clinical trials.

Real-world evidence is needed to document the benefits of LAGH and monitor the drugs' long term safety. If long term safety and efficacy are confirmed then, as paediatric endocrinologists gain experience with LAGH, these new drugs may replace daily GH in children with GHD and, possibly, other growth disorders.

Bradley S Miller

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*The disclosures and references for this article are at the foot of **page 7**.*

Fetal growth restriction: a long-lasting imprint in life

Paediatric endocrinologists should be aware of issues beyond growth in children born small for gestational age, as Éloïse Giabicani explains.

Éloïse Giabicani

> *"The underlying pathophysiological mechanisms extending from fetal growth restriction to long term metabolic disorders are largely unknown"*

Fetal growth is a dynamic process, regulated by interrelated factors such as (epi)genetics, hormonal systems and the environment.

Children born small for gestational age (SGA) have a higher morbidity and mortality and hypoglycaemia risk during the neonatal period, enhanced by prematurity.[1,2] Even if most children born SGA will demonstrate catch-up growth, around 10% will stay below the normal ranges of growth charts.

Our first role, as paediatric endocrinologists, is frequently to manage this issue of growth retardation, but we are now aware that such patients can have other problems. Indeed, in childhood, precocious adrenarche and puberty are additional growth-threatening factors that should be monitored and sometimes delayed with personalised treatments.[1] Later in life, adults born SGA are also more susceptible to metabolic issues and cardiovascular morbidity, as demonstrated by numerous strong epidemiological data.[3,4]

Considering the bigger picture

The negative impact of rapid weight gain postnatally must be avoided and taught in general paediatric training, since it has now been well demonstrated that it will trigger cardiometabolic risk. Nevertheless, the underlying pathophysiological mechanisms extending from fetal growth restriction to long term metabolic disorders are largely unknown. The strategies employed to address this question are multiple, from observational or interventional cohort studies to animal model development.

It can also be of great interest to study some rare disorders with extreme fetal growth restriction, in order to better understand these mechanisms and, ultimately, to optimise the management of children born SGA. As an example, patients with Silver–Russell syndrome who are born extremely SGA with poor catch-up growth are inclined to develop insulin insensitivity, abnormal body composition, overweight or obesity as teenagers or young adults.[5,6]

An approach to management

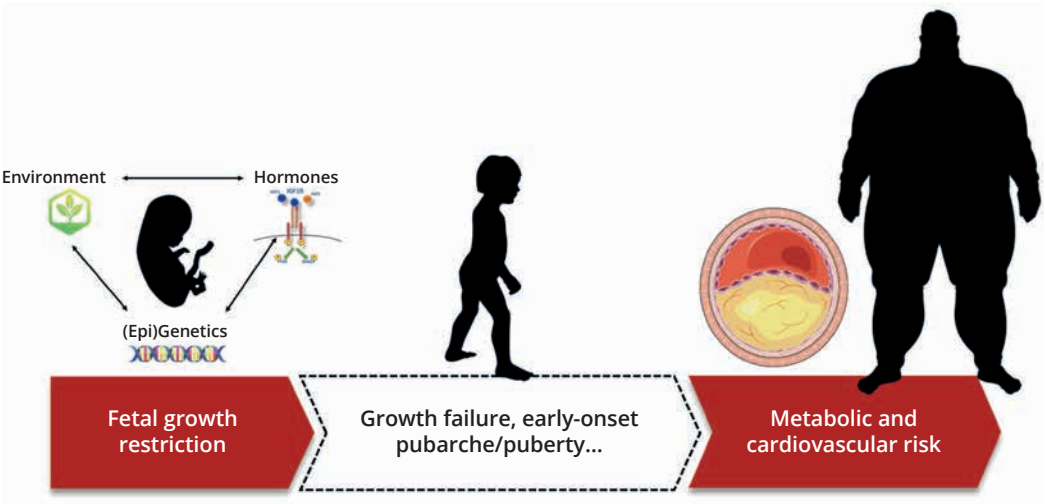
A pragmatic proposal for the management of these children born SGA, who cannot all be followed in paediatric endocrinology units, is probably:

(a) first to inform families and perinatal healthcare professionals of the increased long term metabolic risk and

(b) secondly to guide them in adopting a healthy lifestyle through their whole life.[2]

It is important that all paediatricians are aware of the need for early screening for neurocognitive impairment, which is particularly indicated in SGA children born preterm, as well as the need for careful follow up during the pubertal period.[1]

Patients born SGA with no catch-up growth, who can benefit from recombinant growth hormone treatment and the subsequent specialised follow up, will be more easily monitored for metabolic disorders. For this group of patients, after growth-related treatment cessation, the challenge is to change the focus towards metabolic risk monitoring and lifestyle guidance, without increasing the burden of medicalisation.



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References
1. Giabicani *et al.* 2018 *Best Practice & Research Clinical Endocrinology & Metabolism* https://doi.org/10.1016/j.beem.2018.03.013.
2. Hokken-Koelega *et al.* 2023 *Endocrine Reviews* https://doi.org/10.1210/endrev/bnad002.
3. Mericq *et al.* 2017 *Nature Reviews Endocrinology* https://doi.org/10.1038/nrendo.2016.127.
4. Amadou *et al.* 2023 *Diabetes & Metabolism* https://doi.org/10.1016/j.diabet.2022.101414.
5. Wakeling *et al.* 2017 *Nature Reviews Endocrinology* https://doi.org/10.1038/nrendo.2016.138.
6. Eggermann *et al.* 2023 *Nature Reviews Disease Primers* https://doi.org/10.1038/s41572-023-00443-4.

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Disclosures: Dr Miller is a consultant for Abbvie, Ascendis Pharma, BioMarin, Bristol-Myers Squibb, ENDO Pharmaceuticals, Eton Pharmaceuticals, GenSci, Novo Nordisk, Pfizer, Provention Bio, Sanofi and Tolmar and has received research support from Abbvie, Aeterna Zentaris, Alexion, Amicus Therapeutics, Foresee Pharmaceuticals, JCR Pharmaceuticals, Lumos Pharma, Novo Nordisk, OPKO Health, Pfizer, Prevail Therapeutics and Sangamo.

References
1. Miller 2022 *Frontiers in Endocrinology* https://doi.org/10.3389/fendo.2022.980979.
2. Thornton *et al.* 2021 *Journal of Clinical Endocrinology & Metabolism* https://doi.org/10.1210/clinem/dgab529.
3. Miller *et al.* 2022 *Journal of Clinical Endocrinology & Metabolism* https://doi.org/10.1210/clinem/dgac513.
4. Deal *et al.* 2022 *Journal of Clinical Endocrinology & Metabolism* https://doi.org/10.1210/clinem/dgac220.
5. Bidlingmaier & Schilbach 2021 *Journal of Clinical Endocrinology & Metabolism* https://doi.org/10.1210/clinem/dgab016.

ESPE's focus on bone and growth plate

We talked to Evelien Gevers, Co-ordinator of the ESPE Working Group on Bone and Growth Plate, to find out about the Group's work and how you can get involved.

Evelien Gevers

> *"I am excited to say that we are going to develop a Bone Academy for ESPE. It will seek to educate participants in bone and growth plate diseases"*

Please tell us about the Working Group

The ESPE Working Group on Bone and Growth Plate represents ESPE from the perspective of bone health initiatives.

We are keen to maintain connections between the physiology of bone and growth plate, the clinical outcomes of disease, and innovative therapeutics for intervention, as well as underlying important links with basic science.

The Working Group supports the community of bone specialists within ESPE by:

- providing a dedicated forum for updates on basic and clinical research in our subject area
- setting up collaborative research projects and encouraging presentation of findings at the ESPE Meetings
- establishing the Working Group as a source of expert opinion regarding paediatric bone health throughout Europe, for the purpose of advocacy, commentary or recommendations.

At our meeting at ESPE 2023, we also added education to our aims, for example, through clinical case presentations.

We meet at other times to discuss future activity and the programme for our symposium at the ESPE Meeting. Following recent updates to the Working Group, we are planning new activities.

Who leads the Working Group?

I lead the Group as Co-ordinator, but there are three of us on the Steering Committee:

- **Evelien Gevers** (London, UK), with an interest in growth plate, short and tall stature, and autosomal dominant hypocalcaemia
- **Corinna Grasemann** (Bochum, Germany), with a focus on rare bone diseases
- **Adalbert Raimann** (Vienna, Austria), working on growth plate, and X-linked hypophosphataemic rickets.

What are the Group's latest projects and activities?

We recently performed a survey on the use of long-acting growth hormone, and we have focused on the role of radiologists and geneticists in the diagnosis of difficult cases.

I am excited to say that we are going to develop a Bone Academy for ESPE. It will seek to educate participants in bone and growth plate diseases, and Working Group members will soon be asked for their input.

What was the focus of your session at ESPE 2023?

Our symposium during ESPE 2023 in The Hague, The Netherlands, last September focused on radiology and genetics in skeletal dysplasia. Lecturers were selected from experts in the field:

- **Alistair Calder** (London, UK) discussed 'Radiology of rare and less rare skeletal dysplasia'
- **Giedre Grigelioniene** (Stockholm, Sweden) spoke on 'Genetics of rare skeletal dysplasia'.

Working Group members had been invited to submit difficult cases. Of these, three were selected for presentation by the members and discussion by Dr Calder and Professor Grigelioniene.

What exciting research is happening in your field?

Encaleret is a calcilytic, inhibiting calcium-sensing receptor activity. Its successful use in autosomal dominant hypocalcaemia to maintain normocalcaemia is very promising.[1]

The development of new therapeutics for achondroplasia is exciting and, more recently, the use of anti-sclerostin to increase bone mineral density in osteogenesis imperfecta.

Trials for the treatment of ENPP deficiency, which causes generalised arterial calcification and autosomal recessive hypophosphataemic rickets type 2, are on the way too.

Why should ESPE members join the Working Group?

We give members the opportunity to submit cases for discussion at our symposium, and we also hope to do this more often in the year. Members can take part in educational activities, and will receive updates when opportunities for clinical trials or other projects arise.

How can people get involved in the Group?

We are currently updating the membership details of all who attended the Working Group symposium at ESPE 2023 and indicated they wanted to be a Working Group member.

If you would like to become a member, you can contact me at **evelien.gevers@nhs.net**.

Evelien Gevers

Co-ordinator, ESPE Working Group on Bone and Growth Plate

Reference

1. Gafni *et al.* 2023 *New England Journal of Medicine* https://doi.org/10.1056/NEJMc2302708.

ESPE Connect Webinars 2024

14 February 2024
Congenital hyperinsulinism

18 April 2024
Pituitary

12 June 2024
Fertility and endocrine disruptors

17 October 2024
Rare thyroid conditions

All take place at 16.00-17.30 CET (15.00-16.30 GMT)

Free of charge to ESPE members (non-members €25)

Watch past webinars and find out more at **www.eurospe.org/education/espe-connect-webinar-series**

Come to ESPE 2024!

The 62nd Annual ESPE Meeting takes place in Liverpool, UK, on Saturday 16–Monday 18 November 2024.

'Lifelong endocrine care through collaboration, discovery and innovation' is the theme of the exciting programme, featuring plenary lectures and symposia delivered by outstanding international speakers.

You can also enjoy:

- Meet the Expert and How Do I sessions by world-leading clinicians
- Controversy and Novel Advances sessions to make us all re-evaluate how we think and work
- Free Communications, enabling experienced colleagues and trainees to present their work orally, and through physical and electronic poster sessions.

ACC Liverpool is an exceptional venue on the city's iconic waterfront. One of the great cities of the world, Liverpool has the attractions and infrastructure to cater for all, and is full of culture and heritage.

Meeting Host Mehul Dattani and Vice-Meeting Host Poonam Dharmaraj look forward to warmly welcoming you, to actively participate in an ESPE Meeting rich in both basic and clinical science, where delegates from around the world can present and discuss their latest findings.

Registration and abstract submission will open soon!
Submit your abstracts by **20 May 2024**

Register your interest at **www.surveymonkey.com/r/ESPE2024**
Look out for further details at **www.eurospe.org**

European Society of Endocrinology

ECE 2024

26th European Congress of Endocrinology

11-14 MAY 2024

Stockholm, Sweden

The European Society of Endocrinology (ESE) welcomes ESPE members to their annual Congress, which is taking place in Sweden in 2024.

Register by **25 March 2024** for Super Early Bird rates

Find out more at **www.ese-hormones.org/ece2024**

11th I-DSD Symposium

26–28 June 2024
Stockholm, Sweden

This event provides an update on conditions affecting sex development and maturation for healthcare staff, clinicians, researchers, parents and patient support groups, as well as providing networking opportunities and promoting crucial research in the field. In addition, there is a separate I-DSD Training Workshop on 26 June.

Submit your abstracts by **15 March 2024**
Register by **30 April 2024** for Early Bird rates

Find out more at **www.sdmregistries.org/11th-i-dsd-symposium-2024**

Future meetings

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

62nd Annual ESPE Meeting
16–18 November 2024
Liverpool, UK

Joint Congress of ESPE and ESE 2025
10–13 May 2025
Copenhagen, Denmark

64th Annual ESPE Meeting
8–10 September 2026
Marseilles, France

OTHER EVENTS

ESPE Connect Webinar: Congenital hyperinsulinism
14 February 2024

ESPE Winter School
24–28 February 2024
Cairo, Egypt

10th Copenhagen Workshop on Endocrine Disruptors
11–14 March 202
Copenhagen, Denmark

ESPE Caucasus & Central Asia School
4–7 April 2024
Samarkand, Uzbekistan

ESPE Connect Webinar: Pituitary
18 April 2024

26th European Congress of Endocrinology
11–14 May 2024
Stockholm, Sweden

ESPE Connect Webinar: Fertility and endocrine disruptors
12 June 2024

11th I-DSD Symposium
26–28 June 2024
Stockholm, Sweden

To stay up to date, follow ESPE on social media (see right) and read the ESPE News Alerts.

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

DEADLINES

FEBRUARY

Joint Congress of ESPE and ESE 2025 programme suggestions – 12 February 2024

MARCH

ESPE Research Unit preliminary applications – 11 March 2024

APRIL

ESPE Visiting Professorship of Rare Diseases applications – 15 April 2024

ESPE Research Unit final applications – 20 April 2024

MAY

ESPE 2024 abstract submissions – 20 May 2024

ESPE Early Career Scientific Development Grant applications – 31 May 2024

European Society for Paediatric Endocrinology

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

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ESPE e-Learning

Answer to the case query on **page 3**

Initial investigations to order

- ☑ Serum level of growth hormone
- ☑ Serum level of prolactin
- ☑ Serum levels of thyrotrophin and free thyroxine
- ☑ Serum levels of LH, FSH and testosterone
- ☑ Serum level of insulin-like growth factor-1

Thyroid function (thyrotrophin and free thyroxine) should be measured to look for possible hyperthyroidism. Insulin-like growth factor-1 levels should be determined to check for possible growth hormone (GH) overproduction. Random GH levels (although rarely useful in other indications, due to the pulsatile release of GH from the pituitary gland) are often found to be elevated in GH overproduction, because of disruption of the pulsatile release pattern.

Prolactin levels should be ascertained to help point towards a pituitary cause of the tall stature. Serum levels of LH, FSH and testosterone should be measured to look for possible sex steroid excess, although this is less likely in this case, where there are no other signs of sex steroid excess.