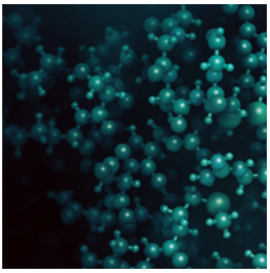
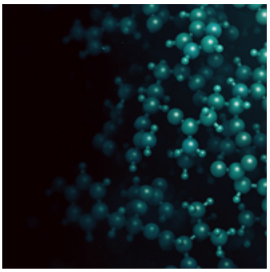
CONGRESS REPORT

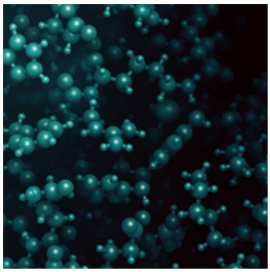
The 59th Annual Meeting of European Society for Paediatric Endocrinology



ESPE 2021

22-26 September 2021





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BIOGRAPHY

Claudio Giacomozzi

Claudio Giacomozzi has worked in the Pediatric Endocrinology Service of Carlo Poma Hospital in Mantua, Italy since 2015. His career and research interests have centred around pediatric endocrinology and growth disorders, including children born small for gestational age and children with growth hormone deficiency, and has included periods of employment in hospitals in Italy (Bambino Gesù Children's Hospital, Rome) and in the UK (Royal Hospital for Sick Children, Glasgow). He has written original papers published in peer-reviewed journals on growth disorders, IGF1, growth hormone, and children born small for gestational age. It is his personal conviction, and the driving force of his professional passion, that clinical research should start from the careful clinical observation of patients.

CONGRESS REPORT

The 59th Annual Meeting of the European Society for Paediatric Endocrinology was held virtually this year, due to the ongoing SARS-COV-2 pandemic. This change to an online format allowed the meeting organizers to arrange the program over more days than is usual for on-site events. Many vital topics were covered from both clinical practice and basic research over plenary sessions, symposia, meet-the-expert sessions, free communications and poster showings. As always, it was a valuable chance to connect scientists, physicians, nurses and all healthcare professionals involved in the care of pediatric patients with endocrine disorders, promoting collaboration, discovery and innovation.

Some very interesting sessions were focused on the advances in knowledge of growth disorders.

Nathalia Andrade (University of San Paulo, Brazil) presented the results of a retrospective analysis on a cohort of 44 patients with idiopathic short stature (ISS), evaluating the diagnostic yield of a targeted gene panel in children with ISS. Multigene sequencing analysis was carried out on each patient using a panel of 90 genes related to growth disorders. Andrade et al were able to identify a genetic cause of ISS in 9 out of 44 patients (20.5%). Among the pathogenetic variants detected, 5 were located in genes related to the growth plate (IHH, ACAN, FGFR3, COL2A1), 1 in a gene associated with the GH-IGF1 axis (GHSR), and 3 were in genes related to the Ras-MAPK pathway (RASopathies; CBL, NF1, PTPN11). Additionally, Andrade et al identified heterozygous pathogenic Copy Number Variations (CNVs) involving the SHOX and ACAN genes. This work is remarkable in highlighting that in a significant proportion of cases, the short stature defined as “idiopathic” is actually underlined by well-known genetic causes. The main challenges in correctly and promptly recognizing these cases are due to an extremely heterozygous phenotype-genotype correlation, especially in the milder forms. Analyzing a single gene in these cases has a very high diagnostic failure rate. The authors concluded that the multigene sequencing analysis approach to ISS is useful to determine the cause of short stature and can provide additional perspective for guiding treatment and clinical follow-up.

Xin Li (Shanghai Children’s Medical Center, China) presented data from diagnostic genetic tests based on next-generation sequencing (NGS) in 814 patients with short stature and at least one other clinical feature. The aim was to define the diagnostic efficiency of associated risk factors and their exome sequences for

screening. Pathogenic and likely pathogenic variants were found in 114 genes, and, again, RASopathies comprised the most important etiology. Furthermore, the diagnostic yield of NGS for short stature combined with intellectual disability or developmental delay was up to 70.71%, and 70.97% when patients had facial dysmorphisms. These data highlight the importance of a multidisciplinary approach to the diagnostic work-up of patients, involving clinical geneticists and child neuropsychiatrists.

Jan-Maarten Wit (Child Health Division, Leiden, The Netherlands) and Sandro Loche (Microcitemico Hospital, Cagliari, Italy) sparked a very interesting debate over whether children with isolated idiopathic growth hormone deficiency should be retested for growth hormone in early/mid puberty, rather than waiting until they achieve adult height. Among the reasons for supporting earlier retesting were:

- The high rate of normal provocative tests observed at the end of growth
- Evidence of high intra-individual variability in growth hormone peak values after a few months of treatment discontinuation
- Evidence of normal growth in those patients who have stopped growth hormone treatment at mid-pubertal stage.

The rationale for limiting early retesting were:

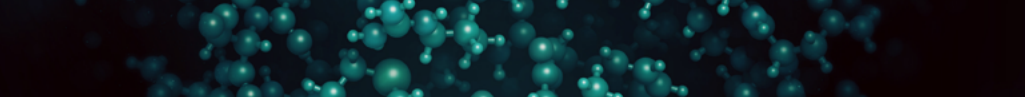
- The interval time without treatment to allow retesting could negatively impact patients' growth
- There is greater pressure and stress for those patients who might undergo a further test over a relatively short period of time between mid-puberty and end of growth
- Earlier retesting might be affected by the same rate of false pathological results observed at the end of growth.

Consensus was reached that patients should not be retested before achieving a testicular volume greater than 10 ml for males, and a Tanner breast stage equal or greater than B3 for girls. Further evidence is needed on the issue of retesting for growth hormone.

Carles Gaston-Massuet (Queen Mary University of London, UK) provided participants with new insights into the role of the MAPK pathway in hypothalamo-pituitary axis development and disease. He reported the association of Septo-Optic Dysplasia, including hypopituitarism, and Cardio-Facio-Cutaneous syndrome in patients harboring mutations in the BRAF gene, which is among the components of the MAPK pathway associated RASopathies.

With his collaborators, Gaston-Massuet demonstrated that BRAF mutations with gain of function led to abnormal cell lineage determination and terminal differentiation of hormone-producing cells, causing hypopituitarism, both in mice and humans. The critical role of BRAF in hypothalamo-pituitary-axis development implicates mutations found in RASopathies as a cause of endocrine deficiencies in humans (growth hormone, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone). Patients with Cardio-Facio-Cutaneous syndrome and other RASopathies should be tested for endocrinopathies early after diagnosis.

Last, but not least, Ravi Savariraya (Murdoch Children's Research Institute, Melbourne, Australia) presented a new therapeutic approach for short stature in patients with achondroplasia. Not only is stature severely affected in achondroplasia, patients also experience severe respiratory complications during early life and chronic pain later in life due to spinal cord complications. Achondroplasia is caused by pathogenic variants in the fibroblast growth factor receptor 3 gene, leading to impaired endochondral ossification. A new molecule, vosoritide, is in development for the treatment of achondroplasia. Vosoritide is an analog of C-type natriuretic peptide, and stimulates endochondral bone growth. In a double-blind, placebo-controlled study, children randomized to vosoritide showed an increased annualized growth velocity compared with controls and an improvement in height/sitting height ratio. The same gains were observed in children who crossed from placebo to vosoritide treatment in the extension study. No new adverse effects of vosoritide were detected. Further data are needed, especially results from treatment for longer than 2 years, but data are definitely encouraging.



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