

## Pediatric Endocrinology

### PEDIATRIC ENDOCRINOLOGY: ADRENAL, THYROID, AND GENETIC DISORDERS

#### *Growth Hormone Therapy for Children With Duchenne Muscular Dystrophy and Glucocorticoid Induced Short Stature*

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**Background:** Duchenne Muscular Dystrophy (DMD) is the most common form of inherited muscle disease in childhood. DMD patients have severe growth retardation due to several reasons including chronic treatment with glucocorticoid (GC). Data regarding the efficacy and safety of Recombinant Growth Hormone (rGH) treatment in DMD patients is very limited. The aim of this study is to evaluate efficacy and safety of growth hormone treatment in 4 DMD boys with glucocorticoid induced growth failure. **Methods and Results:** 4 prepubertal patients with DMD on high dose of GC (Deflazacort or Prednisone) at an age range between 12-13.6 years and significantly delayed bone age (8.5-11 years) were studied. rhGH was subcutaneously administered at a dose of 0.033 mg/kg/d for a duration of 12-18 months. Pretreatment annual growth rate of the 4 patients (0, 3, 2.5, 1.5 cm/yr) improved during treatment (3.8, 7.8, 7.2, 3.3 cm/yr respectively). While height SD improved in 2 patients: -2.74 and -2.96 height SD to -2.52 and -2.64 height SD on rGH therapy, In the other two patients pretreatment continuous decline in height SD was arrested. Motor function decline was similar pre-growth hormone and during treatment. Cardiopulmonary function measured by ejection fraction and forced vital capacity was unchanged during the treatment period. **Conclusions:** This report of growth hormone therapy in DMD patients revealed an improved prepubertal growth velocity without detrimental effects observed on neuromuscular and cardiopulmonary function. Larger randomized control studies are required to prove safety and efficacy of this treatment in DMD patients.

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#### *Growth Patterns in Children With Multiple Endocrine Neoplasia Type 2B: Small Stature in Childhood*

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**Background:** Multiple Endocrine Neoplasia 2B (MEN2B) is characterized by medullary thyroid carcinoma (MTC) before the age of one, pheochromocytoma and

several non-endocrine manifestations. Marfanoid habitus is considered to be an important related feature, leading to the assumption that children with MEN2B have a tall stature. However, very little is known about actual growth patterns in children with MEN2B and its implication for final height.

**Aim:** To describe the growth patterns during childhood and adolescence and relate final height to target height (TH) in MEN2B patients.

**Methods:** Growth during childhood was investigated in eight patients with MEN2B under care in a Dutch MEN expertise center. Growth charts were assessed in relation to parental height, age at diagnosis and at thyroidectomy, body mass index (BMI), pubertal development and extensiveness of disease manifestations.

**Results:** Four out of eight patients showed longitudinal growth below their TH range. Three others showed prepubertal growth in the lowest margin of their TH range. Small stature was accompanied by delayed bone maturation. Arm span to height ratio was not increased in any of the (six) patients studied. All four patients who reached adulthood attained final height within their TH range, despite small stature during childhood. Small stature in childhood was not associated with age at diagnosis, age at thyroidectomy, extensiveness of MTC, BMI or endocrine deficiencies.

**Conclusions:** Children with MEN2B did not present with marfanoid features regarding height or arm span. In contrary, short stature may be prevalent, with longitudinal growth beneath the individual TH range. Nevertheless, a normal final height within the TH range may well be reached. Growth patterns seem to be independent of both age at diagnosis and thyroidectomy as well as disease severity.

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#### *Growth-Related Characteristics of Patients <18 Years of Age with Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency (21OHD): Real World Evidence from the I-CAH Registry*

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**Background:** Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is a rare, autosomal recessive disease of the adrenal cortex leading to a lack of cortisol production and compensatory ACTH secretion, which drives excess androgen production. The chronic exposure to excess androgen, coupled with suprphysiologic glucocorticoid doses, can lead to advanced skeletal maturation with reduced growth in puberty, premature epiphyseal

closure, and shorter final adult height. The I-CAH Registry, launched in 2007, currently has >1500 cases of CAH from 26 countries. Aim of the current study was to identify growth-related characteristics of children and adolescents with 21OHD CAH registered in the I-CAH registry and who were based in Europe. **Methods:** The I-CAH registry was queried on 8-Oct-2019 using the following criteria: CYP21A enzyme deficiency; European site, male or female, age <18 years; and  $\geq 1$  growth-related assessment. Descriptive analyses were conducted using data from all patient visits, with age subgroups defined as follows: 0 to <2 years (0-2yr), 2 to 11 years (2-11yr), and 12 to 17 years (12-17yr). Since I-CAH data are longitudinal, patients who aged during registry enrollment may be included in >1 subgroup. Analyses included standard deviation scores (SDS) for patients' height for chronological age (CA), weight for CA, and height for bone age (BA) using World Health Organization growth chart data for reference values. **Results:** Of 232 patients in 10 European countries, 126 (54%) were female and most were from Germany (25%), United Kingdom (23%), Netherlands (14%), and Italy (11%). The 232 patients had a total of 2042 visits, with 44% (900 visits) in the 0-2yr group, 42% (860 visits) in the 2-11yr group, and 14% (282 visits) in the 12-17yr group. No discernible pattern by age group was found for height for CA based on mean/median SDS scores. For weight for CA, mean/median SDS scores showed an increasing trend in older patients: 0-2yr (0.22/-0.06 [896 visits]); 2-11yr (0.47/0.55 [855 visits]); and 12-17yr (0.55/0.66 [278 visits]). Mean/median SDS scores for height for BA decreased with age: 0-2yr (0.31/0.05 [36 visits]); 2-11yr (-0.32/-0.23 [172 visits]); and 12-17yr (-0.49/-0.26 [44 visits]). Paired BA and CA values from 259 patient visits showed a trend towards bone age being greater than CA, starting at approximately 48 months of age and leveling out around 120-130 months. Mean BA was advanced by 9.7 months compared to CA (SD: 21.2 months, 95%; CI: 7.1 to 12.3 months, [p<0.0001]). **Conclusions:** As previous research has indicated, I-CAH registry data suggest that children and adolescents with classic 21OHD CAH in Europe have advanced BA relative to CA, with height relative to BA tending to decrease with older age. The I-CAH registry offers the opportunity to study a variety of growth determinants and measurements with an option for subgroup analysis.

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#### *Gut Microbiota Assessment in Obese Children and Adolescents by Machine Learning Algorithms*

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Gut microbiota has been recently established to play a contributory role in the development and progression of obesity, a multifactorial disease predisposing to several comorbidities. Our aim was to evaluate the gut microbiota composition by machine learning algorithms in 33 Italian obese children and adolescents. Patients were divided in 3 groups: simple obesity (n=10, mean age 11.6 +3.0, median 10.8), metabolic syndrome (n=16, mean age 13.3+3.0, median 13.5) or Prader Willi syndrome (n=7, mean age 8.3+5.3, median 8.7). Inclusion criteria were living in Northern Italy, born singleton birth, personal history negative for acute or chronic gastrointestinal diseases and/or antibiotic or probiotics administration in the previous month. As controls 17 healthy control (mean age 12.0+2.4 median 10.6) were analyzed using the same approach. Statistical analysis for sparse high-throughput sequencing data algorithm (metagenomeSeq) using cumulative sum scaling for data normalization was performed. False discovery rate adjusted p-value using zero-inflated Gaussian fit statistical model (indicated with q). Over all analyses *Parasutterella* resulted with a q=0.014424, the comparison between obese patients and controls was q=0.021194. In the overall analysis *Acidaminococcus intestini* showed q=0.039528 while the comparison in pairs of two between metabolic syndrome and controls was q=0.03979. Using the EdgeR algorithm *Clostridium bartlettii* abundance between Prader Willi patients and controls resulted in q=0.02189. In overall analysis *Ruminococcus flavefaciens* resulted q=6.1528E-17 (using the DESeq2 algorithm); in pairs analysis *Ruminococcus flavefaciens* showed significant difference in Prader Willi patients as compared to obese (q=0.013755) and metabolic syndrome ones (q=0.021898). In overall analysis *Veillonellaceae* showed a FDR q=0.029303. while its richness resulted more than 150 times higher in metabolic syndrome patients than in controls (q=0.039793 evaluated with DESeq2 algorithm). Among *Veillonellaceae* descendants, the *Veillonella rogosae* showed, on the contrary, the lowest abundance in metabolic syndrome patients as compared to other groups. In detail, *Veillonella rogosae* abundances were 13 (FDR q=0.014566), around 20 times (FDR q=0.010646) and >20 (FDR q=0.0025008) less abundant in metabolic syndrome patients than obese, Prader Willi patients and controls, respectively. Significant differences in gut microbiota composition was found among patients with different degrees of obesity and controls. Further, Prader Willi patients showed a peculiar microbiota assessment.