P2-d1-630 GH and IGF Treatment 1

Accurate long-term prediction of height development during growth hormone (GH) treatment in prepubertal children with growth hormone deficiency (GHD) and Turner syndrome (TS)

Michael B. Ranke[1]; Anders Lindberg[2]; Mathias Brosz[3]; Stefan Kaspers[4]; Jane Loftus[5]; Hartmut Wollmann[4]; Maria Koltowska-Haggstrom[2]; Mathieu Roelants[6]

[1]University Children's Hospital, Paediatric Endocrinology, Tuebingen, Germany; [2]Pfizer Health AB, KIGS/KIMS/ACROSTUDY Medical Outcomes, Stockholm, Sweden; [3]StatConsult, Gesellschaft für klinische und Versorgungsforschung mbH, Magdeburg, Germany; [4]Pfizer Ltd, European Medicines Development Group, Tadworth, United Kingdom; [5]Pfizer Ltd, Outcomes Research, Tadworth, United Kingdom; [6]Free University Brussels, Laboratory of Anthropogenetics, Brussels, Belgium

Background: Treatment with GH during the pre-pubertal years is essential for improvement of the height outcome of short children. Optimizing and individualizing GH therapy requires the accurate simulation of height development based on empirical growth prediction models early during the course of treatment.
Methods: Pre-pubertal children with idiopathic GHD or TS documented within KIGS (Pfizer International Growth Database) were analysed. In a first step, cohorts which had previously been used to develop models for the prediction of height velocity (HV) during the first four pre-pubertal years of GH treatment were analyzed and a prediction algorithm for the annual gain in weight for an observed gain in height was developed. In a second step, the height simulations were validated in a separate population (validation cohort: 664 GHD and 607 TS patients from GH start up to 4 prepubertal years). The most likely height development was simulated prospectively by sequential application of the newly developed algorithms for gain in weight and the existing yearly prediction algorithms for HV.
Results: When height was simulated from GH start in GHD, the predicted mean (SD) gain after 4 years was 30.4 (3.4) cm when the first year model included GHmax, and 30.5 (2.9) cm when not, while the observed gain in height was 30.0 (5.0) cm. In TS the corresponding predicted and observed mean gains were 27.2 (2.2) cm and 26.5 (3.8) cm respectively. The simulation model was predictive in all but 22 (3.3%) of the 664 cases of the GHD validation cohort from GH start. This proportion was below 2% for all of the TS cohort or when simulation started after the first year of treatment (GHD and TS), using 98% confidence intervals.
Conclusion: Sequential application of annual prediction models permits accurate simulation of height development during the first four years of GH treatment in GHD and TS. The system is applicable for groups from GH start and for individuals after experiencing the 1st year growth response.

P2-d1-631 GH and IGF Treatment 1

Growth hormone treatment in a family with Léri Weill syndrome due to contiguous gene syndrome

Felix Reschke[1]; Gabriele Hahn[2]; Werner Walter[3]; Angela Huebner[1]

[1]Technical University Dresden, Division of Paediatric Endocrinology and Diabetology, Children`s Hospital, Dresden, Germany; [2]Technical University Dresden, Division of Paediatric Radiology, Dresden, Germany; [3]Technical University Dresden, Institute of Clinical Genetics, Dresden, Germany

Background: Léri Weill syndrome (LWS) is a pseudoautosomal inherited skeletal dysplasia being associated with *SHOX* haploinsufficiency (short stature homeobox-containing gene). It is located at the pseudoautosomal region (PAR) of the sex chromosomes. Clinical findings in LWS include mesomelic short stature and a characteristic dysostosis of the wrist (Madelung deformity). It was shown that the effect of growth hormone on final height of LWS patients is comparable to that of patients with Turner syndrome.
Objective and hypotheses: We present a family with SHOX deficiency due to a X/Y translocation and contiguous gene syndrome with lack of the SHOX, ARSE, MRX1 and STS genes. The male index patient presented 10.5 years with a height of 122.9 cm (- 3.3 SDS), facial dysmorphism, mental retardation and ichthyosis. Chromosomal analysis revealed a deletion of Xp including the PAR with translocation of the duplicated Yq to the X chromosome. After growth hormone (GH) treatment for 3.2 years the patient reached a final height of 145.9 (-3.8 SDS). Two adult sisters of the patient had the same chromosomal aberration and presenting with short stature (-2.6 and -2.0 SDS), but lacking ichthyosis and mental retardation. Altogether they have 3 affected sons, which are treated with GH starting at Tanner stage 1.
Results: In boy 1 treatment started at age 5.7 years (height -2.7 SDS). After 2.2 years height SDS gain was 0.7. Boy 2 was treated from age 4.5 years (height -2.2 SDS) for two years when a gain in height SDS of 0.8 was noted. In boy 3 treatment started at age 2.3 years (height -3.5 SDS). After 1.1 years on GH height SDS gain was 0.5.
Conclusions: The improvement of height SDS by GH substitution in these reported cases of familiar LWS depended on the age of initiation of GH therapy. Follow up examinations will show whether the effectiveness of GH for final height in these young patients will be comparable to those shown in a former study of 14 patients with SHOX deficiency, in which a height benefit of 1.1 SDS was demonstrated.

P2-d1-632 GH and IGF Treatment 1

Growth hormone treatment in a patient with Langer mesomelic dysplasia

Maria Cristina Maggio[1]; Andrea Liotta[2]; Silvano Bertelloni[3]; Giovanni Corsello[2]

[1]University of Palermo, University Department "Materno-Infantile, of Andrology and Urology", Palermo, Italy; [2]University of Palermo, University Department, Palermo, Italy; [3]University of Pisa, Pediatric Endocrinology, Division of Paediatrics, Department of Reproductive Medicine and Paediatrics, Pisa, Italy

Background: Homozygous mutation of the short stature homeobox-containing gene, SHOX, results in Langer mesomelic dysplasia (LMD). The expression of the SHOX gene in growing skeletal tissue of distal femur and tibia, ulna and radius has been detected.
Objective and hypotheses: Patients with homozygous SHOX gene deficiency have a final adult height of 130 cm, with severe short stature and skeletal deformities.
Methods: He was surgically treated for the scoliosis and at the age of 4 years, on the basis of genetic diagnosis of SHOX gene homozygous mutation, he started the treatment with GH for the poor growth, at the mean dose of 0,045 mg/kg/die.
Results: The growth velocity of the patient evidenced an improvement in the first years of GH treatment (4 cm/year), with progressive reduction of SDS of height velocity in the following years. At the age of 12 years his pubertal stage is PH2G2, his testicular volume 4 ml, his growth velocity is < 1 cm/year. The stature is 130 cm; the weight 30 kg. For the failure to achieve growth improvement, he stopped GH treatment. During the follow up however there was no worsening of the skeletal deformities.
Conclusions: Only a few cases of patients with homozygous mutation of SHOX gene treated with GH are described in the international literature. In a case with combined Turner syndrome and a deletion in the normal X chromosome authors concluded that GH treatment was not beneficial in the patient. Our patient reached a stature near the final stature reported in similar cases of homozygous mutation of the SHOX gene, even if not treated with GH. Hence these patients may not improve their linear growth with GH treatment.