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DECREASE OF INSULIN-LIKE GROWTH FACTOR I RECEPTOR IN PATIENTS WITH RING CHROMOSOME 15

The r(15) syndrome is characterized by mental retardation, microcephaly, peculiar facies and growth deficiency. The insulin-like growth factor I receptor (*IGF1R*) gene is known to be localized at 15q26-qter. To evaluate the causal relationship between the loss of *IGF1R* gene and growth deficiency, we studied DNA analysis of *IGF1R* gene and a receptor assay of *IGF1R* in two unrelated female patients with r(15). Karyotypes were 46,XX,r(15)(p12q26.3), and 46,XX,r(15)(p11q26.3), respectively. Except for clinical features consistent with the r(15) syndrome, both patients had severe short stature. Values of serum growth hormone by conventional stimulation tests and IGF1 were within the normal range. A density of the band of Southern blots for *IGF1R* gene was reduced in both patients. The signal for *IGF1R* gene in fluorescence in situ hybridization was seen only on a normal chromosome 15. The IGF1 receptor assay using fibroblastes (performed in one patient) showed decreased number of IGF1 receptor. These results suggested that decrease of *IGF1R* due to a loss of *IGF1R* gene is related to severe growth deficiency in r(15) patients.

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SPONTANEOUS GROWTH AND FINAL HEIGHT IN SGA INFANTS.

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Small for gestational age (SGA) infants are a high risk group in respect of postnatal mortality, morbidity and/or disturbed development, although little is known about the long term effects. The aim of this work was to define the risk for SGA infants of being short in higher ages and to compare this risk when using birth length and birth weight in the definition of SGA. The material consists of all children (n=4500) being in the last class in school, Göteborg, Sweden. Perinatal information was collected from the birth register and growth and health data from the child health care units and the schools. SGA infants, i.e. shorter than -2SDS at birth was found to represented 20 - 25% of the short children in higher ages. However, the risk of being short was much higher in SGA infants than in non-SGA infants; 9 times higher at 3 years and 5 times higher at 8 years of age. Birth length appeared to be twice as sensitive than birth weight in predicting postnatal shortness. Four different postnatal growth patterns were identified in SGA; catch-up growth (1) before 6 months of age in 40%, (2) before 3 years of age in 25%, (3) after 3 years of age in 20%, and (4) without any catch up growth in 15%. The mean final height SDS in the first two groups were close to the mean midparental height SDS, but not for group 3 and 4. This study is the first to describe the spontaneous postnatal growth patterns and final height in SGA infants. Catch-up growth was usually seen before 3 years of age. The SGA- children still being short at 3 years of age reached a final height below their genetic potential, independently of the existence of a slow catch-up growth after 3 years of age, or not.

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GROWTH HORMONE (GH) TREATMENT IMPROVES HEIGHT AND HEIGHT VELOCITY (HV) IN UREMIA AND CYSTINOSIS. N. Albers, L. Winkler, G. Offner, J. Brodehl, Department of Pediatrics, Medizinische Hochschule, Hannover 61, Germany

Uremia impairs growth in children. Pronounced short stature can be seen in nephropathic cystinosis (NC). We treated 25 patients (age 6-16) with rhGH for 1 to 3 years. Inclusion criteria were short stature (<2.5SD), growth velocity <50 percentile, short stature after transplantation (TX), GFR <35ml/m²/min and age >5 years. 13 patients had TX, 7 children had chronic renal insufficiency (CNI) and 5 were on dialysis. 10 patients had NC (3 TX, 5 CNI, 2 dialysis). Dosage was 4 mg/m²/day s.c. daily. Pre-treatment values were compared to values after 1 to 3 years by ANOVA.
Mean HV improved from 2.9±1.65 cm/year to 7.5±4.1 cm/year after 1 year and remained at 6.9±3.4 cm/year after 2 years ($p<0.001$ for all patients). Height-SDS increased from -4.1±3.3 SDS pre-treatment to -3.9±3.0 SDS after 1 year and -3.7±2.1 SDS after 2 years ($p<0.05$). For patients with NC, mean HV improved from 2.8±1.2 to 7.2±4.9 cm/year (after 1 year; $p<0.05$) and to 6.3±1.3 cm/year (2 years) ($p<0.01$). 3 patients did not respond to treatment (2 girls with NC, 1 girl with nephronophthisis and severe hyperparathyroidism). Treatment has been stopped in 12 patients after 2 to 36 months (non-response, non-compliance, TX, final height reached). Renal function declined steadily in most patients similarly to an age-matched control group, but we observed only 1 episode of acute TX loss due to transplant-glomerulopathy. No further significant side-effects were observed.

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DEMOGRAPHY OF CHILDREN ON GROWTH HORMONE (GH) TREATMENT ENROLLED 1987-1992 IN KIGS- Kabi Pharmacia International Growth Study. K. Albertsson-Wikland[1], P Wilton, A Wallström and L Karlsson, on behalf of the KIGS International Board. [1]Int Growth Research Centre, Dep of Paediatrics, University of Göteborg, Sweden.
In 1987, collection of efficacy and safety information of children on Growth Hormone (GH) treatment started within KIGS. Today, 8887 patients are enrolled from 28 countries. Parental, perinatal and pretreatment information are given for the major groups in the Table. During this 5 year period, the age at start of treatment has been maintained except for the reduction from 9.7 to 5.0 years in the congenital GHD children. The height at start of treatment has increased for all groups with an average of 0.4 SDS. The male dominance has been kept and the parental height has been below average for all patients but those with malignancies. This KIGS database will continue to provide us with important information about children on GH treatment in order to achieve earlier diagnoses, more optimal treatment for different etiology groups as well as collecting safety information.

Group	No	Birth weight SDS	Sex Ratio M/R	At start of therapy Age year	At start of therapy Height SDS	Target height SDS
Idiopathic GHD	**3956**	**-0.6**	**2.3**	**10.1**	**-2.7**	**-0.7**
Organic GHD	**1310**	**-0.3**	**1.6**	**10.2**	**-2.2**	**-0.2**
Congenital	253	-0.6	1.6	7.6	-3.0	-0.3
Pit/hypo tumors	399	-0.2	1.3	10.8	-1.6	-0.2
Cranial tumors	315	-0.1	1.6	9.8	-2.0	-0.1
Others	**3621**	**-1.2**	**2.1**	**10.7**	**-2.8**	**-0.7**
Turner	946	-1.2	-	11.4	-2.9	-0.1
Idiop. short	1244	-0.9	2.3	11.1	-2.6	-1.0
IUGR	535	-2.4	2.1	9.0	-3.0	-1.3
Total	**8887**	**-0.8**	**2.1**	**10.4**	**-2.7**	**-0.7**

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PREDICTION OF GROWTH RESPONSE IN GROWTH HORMONE (GH) TREATED SHORT PREPUBERTAL CHILDREN - INFLUENCE OF GROWTH IN EARLY LIFE.
B Kriström[1], J Karlberg[2], K Albertsson-Wikland[2] and the Swedish Pediatric Study Group for GH Treatment, Int Pediatric Growth Research Centre, Dep of Pediatrics, [1]University of Umeå and [2]University of Göteborg, Sweden.
There is a need for better criteria for initiation of growth hormone (GH) treatment in children. The aim of this study was therefore to identify possible predictors of the growth response to GH treatment in short children of different GH status, especially growth data from birth to two years of age.
Prepubertal children (n=206) treated for at least two years with GH (0.1 U/kg x day) were included. Their maximal GH response to provocation test ranged from 0-80 mU/L. At start of treatment the mean age was 8.4 years (range 2.6-15.4 years) and mean height -3.0 SDS. The individual 2 years growth response was correlated with the log GH_{max} at AITT (r=-0.40), the midparental height SDS (r=0.33), the age at start of treatment (r=-0.32), the height SDS at start of treatment (r=-0.21), delta SDS value (r=-0.21) and the difference between the height SDS at onset of GH treatment of an individual child and the midparental height SDS, (diff SDS; r = -0.42).
The growth response during the first two years of treatment could be predicted in a multiple regression model to 33% in terms of GH_{max} at AITT and the diff SDS. We also found that the GH_{max} at AITT and the diff SDS both were positively correlated to birth length and height velocity during the first and second year of life as well as to the pretreatment height velocity. The complex etiology of being short, involving genetic potential, growth disturbances in the past, and GH secretion may explain the relatively low prediction of the growth response using ordinary multivariable analysis. Another approach would be to subgroup the children in terms of background variables before applying some predictive models. For instance on two years of GH treatment the children with low GH_{max} increased 1.8 SDS independently of birthlenght, whereas the growth response in children with high GH_{max} was positively related to birthlenght; 1.2 SDS in normal birthlength children vs 0.8 SDS in low birthlength children.

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SUSPENSION OF SEASONALITY IN GROWTH VELOCITY DURING GROWTH HORMONE THERAPY IN SHORT CHILDREN. L. Gelander, J. Karlberg and K. Albertsson-Wikland, Int Pediatric Growth Research Center, Dep of Pediatrics, University of Göteborg, Sweden
We have previously shown a clear seasonality in growth velocity in prepubertal school children of normal height, both for height and lower leg length velocity (LLLV). The mechanisms behind seasonality is not known, thought previous studies have focused on seasonal changes of light as the synchronizing factor. It is not known if the hormones involved in the growth regulation are affected by the seasons. The aim of this study was to analyze seasonality in LLLV in children of short stature with spontaneous growth hormone (GH) secretion, before and during GH therapy. Twenty-seven short prepubertal children (19 boys and 8 girls; aged 4.9-12.6 years), with height SDS < -2 were followed one year prior to treatment, and during 18 months of GH therapy (0.1 U/kg·day). Lower leg length was measured using the Knemometer. The *results* show a clear seasonality in LLLV prior to GH treatment. The mean monthly LLLV before treatment was 1.81 cm/year (SD=0.25). During the spring-summer period the mean LLLV was 2.46 cm/year (SD=1.97) as compared to 1.88 cm/year (SD=0.63; $p<0.001$) during the autumn-winter. LLLV was 1.87 cm/year (SD=0.73) during the 3 months prior to GH-start and a significant increase ($p<0.0001$) was seen after the start of GH treatment giving a mean LLLV during the initial 3 months of 3.26 cm/year (SD=1.79). Seasonality in LLLV was not noted during the first 6 months of GH treatment. Further, between 6 and 18 months after start of GH treatment, still no such seasonality could be noted comparing the summer-spring period (2.70 cm/year; SD=1.32) with the autumn-winter (2.71 cm/year; SD=1.05). The annual LLLV was 2.32 cm/year (SD=0.42) during this year on GH treatment. Despite of no clear seasonality in LLLV, during GH treatment, a large individual variation could be noted in short term growth. *In conclusion*, seasonality in LLLV was found in short children, as previously also been found in prepubertal school children of normal height. The seasonality pattern was, however, suspended during GH therapy, during 18 months of follow up.