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ACROMEGALOID CHANGES OF BODY PROPORTIONS DURING TWO YEARS OF GROWTH HORMONE (HGH) TREATMENT IN PATIENTS WITH ULLRICH-TURNER-SYNDROME (UTS).

The typical feature of acromegalic patients are large hands, feet, ears and wide noses. We have performed various anthropological measurements at yearly intervals in 23 children with UTS (aged 7 to 15.5 years). The patients received therapy with hGH (18 -24 U/m²/week) and Oxandrolone (0.1 mg/kg/day). Thus, we were able to investigate whether high doses of hGH may artificially cause changes of body proportions. During therapy, body height increased significantly, i.e. the differences of body height compared to normal decreased by 0.3 SDS. The length of hand and feet, however, increased markedly more, i.e. the difference towards normal decreased by 0.65 (hand) and 0.73 (foot). The same trend proceeded throughout the second year.

Resumee: More attention should be paid to changes of body proportions particularly of hands and feet during treatment with high doses of hGH.

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TWO YEAR AUXOLOGICAL RESULTS OF A GROWTH HORMONE (GH) DOSE-RESPONSE STUDY IN TURNER SYNDROME (TS).

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In a multicenter dose-response study, 68 girls with TS (Tanner stage B1), age 6.5 (2.3) yr (range 2.1-11.0 yr) were randomized into 3 groups according to CA and H-SDS_{CA}: A (n=23) 4 IU hGH/m² b.s. for 4 yr, B (n=23) 1st yr 4 IU and 2nd-4th yr 6 IU/m², C (n=22) 1st yr 4 IU, 2nd yr 6 IU, 3rd and 4th yr 8 IU/m² (Norditropin®) daily s.c. We report auxological data (n=67, drop out: 1xB) after 2 yr GH therapy, in which period B+C were evaluated as one group.

METHODS: Standing height (H) was measured by the same observer (AvT). SD scores for CA were calculated using combined data of an untreated Dutch-Swedish-Danish TS reference population. Bone age (BA) was determined according to TW2-RUS to assess the index of potential height (H-SDS_{BA}) and according to G&P for final height (FH) prediction according to Bayley-Pinneau. Values are expressed as mean (SD). *compared with preRx, $p \leq 0.001$; ° change from preRx between groups, $p \leq 0.02$; ' change from yr 1 between groups, $p = 0.03$.

RESULTS:	preRx A	preRxB+C	1st yr A	1st yr B+C	2nd yr A	2ndyrB+C
HV (cm/yr)	6.0 (1.7)	5.8 (2.1)	10.1 (1.6)*	10.1 (1.3)*	7.6 (0.9)*	8.6 (1.1)*°
H-SDS_{CA}	0.1 (1.0)	0.3 (1.1)	1.3 (1.1)*	1.5 (1.1)*	1.9 (1.1)*	2.3 (1.1)*°
ΔBA (yr/yr)			1.4 (0.4)	1.4 (0.6)	1.2 (0.4)	1.3 (0.6)
FH-pred	152.0 (8.2)	149.3 (5.9)	157.2 (8.6)*	155.3 (6.8)*	157.7 (7.6)*	157.7(7.6)*'
H-SDS_{BA}	1.0 (1.3)	1.1 (1.3)	1.8 (1.3)*	1.9 (1.4)*	2.1 (1.4)*	2.2 (1.2)*

In the 1st and 2nd yr HV and H-SDS_{CA} increased compared with preRx in both groups ($p \leq 0.001$). 2nd yr HV and ΔH-SDS_{CA} were higher for B+C than for A ($p \leq 0.002$). PreRx BA and ΔBA in yr 1 and 2 were not different between groups. In yr 2, a further increment of FH-pred occurred only in B+C ($p = 0.03$). ΔH-SDS_{BA} after 2 yr was different from preRx in both groups ($p < 0.001$), without difference between groups. Age at start of Rx was negatively correlated ($p = 0.01$) with ΔH-SDS_{CA} after 2 yr Rx in B+C ($r = -0.31$), but not with ΔBA.

CONCLUSIONS: A GH dose increment after the 1st yr of Rx from 4 to 6 IU/m² b.s./d results in a better growth response expressed as HV and H-SDS_{CA} as well as in a better FH-pred after the 2nd yr Rx. However, H-SDS_{BA} did not improve more with the higher dose. Bone age appears not to be influenced by the dosage increment. Start of GH Rx at a younger age might be favourable.

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EFFECT OF GROWTH HORMONE (GH) TREATMENT ON LEFT VENTRICULAR (LV) CARDIAC DIMENSIONS IN TURNER SYNDROME (TS).

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Modest changes in bloodpressure (BP) and LV dimensions have been reported after only 1 yr GH-Rx in idiopathic short children (1). GH excess, as in acromegalic pts, may lead to (a)symmetrical cardiac hypertrophy and hypertension. We evaluated LV dimensions in TS before, after 1 and 2 yrs hGH-Rx in increasing dosages.

PATIENTS: In a multicenter dose-response study, 68 girls with TS (Tanner stage B1), age 6.5 (2.3) yr (range 2.1-11.0 yr) were randomized into 3 groups according to CA and H-SDS_{CA}: A (n=23) 4 IU hGH/m² b.s. for 4 yr, B (n=23) 1st yr 4 IU and 2nd-4th yr 6 IU/m², C (n=22) 1st yr 4 IU, 2nd yr 6 IU, 3rd and 4th yr 8 IU/m² (Norditropin®) daily s.c. During the 1st and 2nd yr B and C were evaluated as one group. Girls with a previous coarctation repair, but without a residual gradient (n=7) and girls with a non-stenotic abnormal aortic valve (n=2) were included; 2 girls (B+C) were excluded because of stenosis.

METHODS: All ecg and echocardiographic tracings were evaluated by the same investigator (AvT). On ecg LV activity (=RV6+SV1) was assessed and on M mode echocardiography end diastolic (ed) and end systolic (es) measurements of septal (IVS) and posterior wall (PW) thickness and LV internal dimensions (LVID) were used to calculate relative wall thickness (RWT=[(PW+IVS)/2]/ LVID) and shortening fraction (SF=(LVIDed-LVIDes)/LVIDed*100%). BP was determined with a Dinamap Critikon 1846SX in sitting position. Values are expressed as mean (SD).

RESULTS:	preRx A	preRxB+C	1st yr A	1st yr B+C	2nd yr A	2ndyrB+C
LV act (mV)	18 (6)	19 (8)	19 (6)	17 (7)	21 (6)*	19 (8)*
RWTes	0.38 (.07)	0.38 (.08)	0.40 (.09)	0.37 (.08)	0.38 (.07)	0.38 (.06)
RWTed	0.14 (.03)	0.15 (.03)	0.15 (.02)*	0.15 (.03)*	0.16 (.03)*	0.16 (.03)*
SF (%)	36.7 (3.8)	35.8 (4.8)	37.0 (6.4)	34.6 (5.7)	34.9 (4.2)	34.4 (5.0)
BPs (mmHg)	112 (16)	104 (12)	111 (11)	106 (13)	112 (11)	109 (13)*
BPd (mmHg)	69 (8)	67 (9)	69 (7)	65 (8)	70 (7)	68 (8)

* compared with preRx, $p < 0.05$.

After 1 and 2 yrs, changes from preRx were not significantly different between groups. LV act values after 2 yr and RWTed values after 1 and 2 yr differed from preRx ($p \leq 0.03$), but remained within the normal range. Systolic BP in B+C after 2 yrs was higher than preRx ($p = 0.02$).

CONCLUSIONS: In girls with TS prior to and during GH treatment, irrespective of the two dosages:
1 Tähere were no signs of LV hypertrophy, although a slight, but significant increase in RWTed was observed.
2 BP remained within normal age related limits and did not differ between groups.

REF (1): Barton et al 1992, Acta Paediatr Suppl 383: 35-8.

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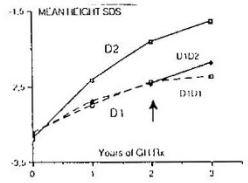
THREE YEARS RESULTS OF TWO DOSE-REGIMENS OF GROWTH HORMONE (GH) IN PREPUBERTAL CHILDREN WITH IDIOPATHIC INTRA-UTERINE GROWTH RETARDATION (IUGR). M. Colle, M. Maes, P. Chatelain, J.C. Job, M. Vanderschueren-Lodeweyck and B. Job. On behalf of the Belgian and French pediatric clinics involved in multicentric study with Sanofi Recherche 94256 Gentilly (FRANCE).

We previously reported (ESPE 90) that GH treatment (SC, 6 d/w for 18 m) in 95 short IUGR non-GH-deficient prepubertal children (age 8.0 ± 0.2 yrs) increased height velocity in a dose dependent manner. We now report the results in 81 children GH-treated and measured during 3 years. They were at first randomized in 2 groups : D1 (n = 39) treated with 0.4 IU/kg/w of GH and D2 (n = 42) with 1.2 IU/kg/w. After 2 years, among D1 patients GH dose was increased to D2 in 24 (D1D2) and unchanged in 15 (D1D1). The mean height SDS for age are presented in the figure below. The total height gain significantly differs in D2 from D1D1 and D1D2 ($p \leq 0.0002$). Mean advances (± SEM) in bone age over 36 months were : 41.1 ± 3.6 (D1D1), 41.0 ± 2.8 (D1D2) and 46.4 ± 2.2 (D2). Pubertal stage 2 (Tanner) was reached in 15/50 M and 15/31 F during 1st yr (5 D1, 2 D2), 2nd yr (5 D1, 5 D2) or 3d yr (2 D1D1, 2 D1D2, 9 D2). Over the 3 years treatment, serious adverse events occurred in 5/95 children : 1 IC hypertension (related to brain germinoma, GH discontinued), 1 Grand Mal seizure (epilepsy history), 2 localized s. (1 neonatal anoxia, 1 related to brain cavernoma), 1 Petit Mal s. CONCLUSIONS : 1) the waning effect observed after the first year of GH treatment appears more pronounced for D1 than D2 ; 2) a slight catch up growth is possible in the 3rd year by increasing GH dose ; 3) the bone age increase in D2, although non significant versus D1, may reduce the dose-dependent benefit of GH treatment on final height.



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COPING AND SATISFACTION OF SHORT STATURE CHILDREN TREATED WITH GROWTH HORMONE

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This study deals with the coping ability and satisfaction with treatment of children whose stature was 2+ SD below the average for age and sex. The study included: 1) Children with normal response to growth hormone (GH) stimulation test without underlying disease (n=65); and 2) Children with underlying disease with normal or abnormal response to stimulation GH test (n=31). Patients were treated with daily injections of recombinant G.H. for 6-66 months. Self-administered questionnaires were completed on a regular visit to the outpatient clinic to assess coping and satisfaction with treatment. The average scores for coping and satisfaction were 3.2 and 3.0 respectively, on a scale ranging from 1 to 4 (low through high coping and satisfaction). No significant differences were found between the coping and satisfaction of patients of different genders, ages, length of treatment or the presence of underlying disease. In conclusion: although GH requires daily injections for several years, patients cope and are satisfied with the treatment.

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ENDOGENOUS NOCTURNAL GROWTH HORMONE (GH) RELEASE CONTINUES TO OCCUR IN PUBERTAL CHILDREN WITH IDIOPATHIC SHORT STATURE (ISS) DESPITE GH THERAPY. M. Almaguer, R. Wu, P. Saenger, B. Linder, J. DiMartino
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We have shown that the GH axis is resilient with a return of pulsatile GH release 48 hours after injection of GH in children with ISS (JCEM 70:1612, 1990). Pharmacokinetics of GH after a subcutaneous (SC) dose of GH has been performed in children with idiopathic GH deficiency (JCEM 72:1148, 1991). This study was performed to determine if daily GH therapy influences the endogenous nocturnal pulsatile GH release in prepubertal (PP) and pubertal (P) males. GH levels were obtained every 20 minutes over a 24 hour period from 9a.m.-9a.m. in 7 healthy children with ISS (height < 5%ile; and GH levels > 10ng/ml in response to provocative stimuli) on GH treatment for at least 3 months. GH (Protropin) 0.043mg/kg SC was given at 7 p.m. on the day of study. 5 pubertal males (Testes > 6 ml) and 2 prepubertal males with a Body mass index SD score < 2 SD of age- derived normal measures have been studied. GH parameters examined included 24 hour mean GH levels, mean peak frequency, and maximum GH peak amplitude (max GH-PA). GH peak analysis was performed using the Cluster Analysis Program.

	Pubertal	Prepubertal
24 hour mean GH (ng/ml) ± SD	9.8 ± 3.6	2.3, 3.5
mean peak frequency ± SD	2.8 ± 2.3	3.0, 6.0
Mean max GH-PA (ng/ml) ± SD	39.2 ± 17.9	10.4, 19.2

Pubertal boys achieved a higher 24 hour mean GH and a higher mean max GH-PA than the 2 prepubertal boys studied. Furthermore, the mean max GH-PA was higher than the levels of 14.16 ± 7.72 occurring in GH deficient boys reported previously (JCEM 72:1148, 1991). The presence of robust endogenous GH peaks in pubertal children with ISS indicates that endogenous GH release occurs despite regularly occurring evening injections of GH. GH therapy criteria in puberty may require revision.