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EVALUATION OF GROWTH HORMONE (GH) SECRETION COMPARING THE RESPONSE TO 1-44 GROWTH HORMONE RELEASING FACTOR (1-44 GRF) WITH THE SLEEP SECRETION AND THE RESPONSES TO PHARMACOLOGIC STIMULI.

GH secretion was evaluated in 54 short patients with mean growth retardation of 3.3 ± 0.96 SD (32 M and 22 F aged 5 to 19 years), comparing their peak response to GRF 1-44 Sanofi 2 µg/kg IV (GRF P) and to 2 conventional pharmacologic stimuli (arginine, insulin, glucagon, ornithine) (PS P) with the peak value of their sleep secretion (SS P). GRF P was more significantly correlated with PS P($r = 0.53$, $p < 0.001$) than with SS P ($r = 0.33$, $p<0.02$).

The patients have been classified into 5 groups according as usually to the sleep and pharmacologic GH levels: group I = 26 endocrinologically normal with both PS and SS peaks > 10 ng/ml; group II = 5 completely GH deficient with both PS and SS peaks < 6 ng/ml; group III = 8 partially deficient with both PS and SS P 6 to 10 ng/ml; group IV = 9 with normal SS P and low PS P; group V = 6 with low SS P and normal PS P.

GRF P ($\bar{x}$ ± SEM) was 39 ± 5.6 ng/ml in group I, 12 ± 3.4 in group II, 24 ± 3.7 in group III, 12 ± 5.0 in group IV and 21 ±5.3 ng/ml in group V. It was significantly higher in group I than in all others (I vs II and vs IV $p < 0.001$, I vs III and vs V $p < 0.05$). However there was a large overlap of the GRF P between the 5 groups. It is concluded that the GRF test contributes to the evaluation of GH secretion but probably does not improve the definition of atypical deficiencies.

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GH SECRETION DURING SLEEP AND GRF-STIMULATION IN GH-DEFICIENT AND SHORT NORMAL CHILDREN

In 22 short-statured children GH was determined every 20 minutes from 20:00 to 8:00 with continous EEG registration to demonstrate stage 4 sleep. Peak and mean GH values were analyzed. At 8:00 a bolus of 1 µg/kg GRF 1-44 was given and GH measured every 15 minutes. Group A (n=12) had been previously diagnosed as GH-deficient (GHD)(peak GH < 6 ng/ml in 2 independent tests, height and growth rate < -2 SDS). These children had been treated with GH for 1.5-12 years and were off treatment for > 6 months when reexamined. Group B (n=2) had been diagnosed and treated as GHD but showed normal growth velocity after cessation of therapy. Both had reached Tanner III and might be classified as transient GHD. Group C consisted of 8 children in whom GH rose above 8 ng/ml in at least one conventional test.

Table 1 gives mean ± SEM for chronological age (CA), bone age (BA), height (SDS) and growth velocity (cm/year), peak (P) and mean (M) GH values during sleep and peak GH after GRF (ng/ml). Individual values in group B.

group	CA	BA	height	velocity	sleep-P	sleep-M	GRF
A (12)	14.9±0.9	11.6±0.8	-3.0±0.7	2.0±0.5	2.0±0.2	1.1±0.1	4.2±0.7
B (2)	14.9/14.6	13/13	-3.7/-3.4	7.8/9.4	9.4/7.7	5.5/3.0	10.5/11.7
C (8)	12.9±0.5	10.1±0.5	-3.2±0.4	4.7±0.6	16.1±3.0	5.4±0.9	12.8±3.2

Spontaneous growth correlated only with mean GH during sleep ($r=0.45$; $p < 0.05$).
Conclusion: 1)Nocturnal GH profiles with EEG monitoring of sleep provide a physiologic method to assess GH status. 2)Diagnosis of GH deficiency should be reevaluated when entering puberty - especially in children with isolated GH deficiency.

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GRF-INDUCED AND NOCTURNAL GH SECRETION IN THALASSEMIC CHILDREN

To test the hypothesis of an hypothalamic origin of the growth retardation observed in thalassemic children at the time of puberty, 18 males and 6 females, aged 9 to 20 years, have been studied under high-regimen blood transfusion and desferrioxamine therapy for the GH response to GRF (2ug/kg, 1-44 NH2, Sanofi), conventional tests and sleep. Pubertal stages according to Tanner were as follows: 6 M and 4 F at stage 1, 8 M at stage 2 and 4 M and 2 F at stage 3 or more. 13 M and 5 F showed evidences of hypogonadotropic hypogonadism. The conventional test responses were normal in 17 and low in 7 patients. A blunted response to GRF was seen in 2 patients which previously show normal pharmacological response. The GH nocturnal peak was above 20 uI/ml in 14 patients. 8 have a decreased nocturnal secretion in contrast to normal GRF response. The mean values of the nocturnal- and GRF-induced peaks were below normal for the age. There was no correlation between the conventional GH response and GRF or sleep response. The nocturnal response was correlated with the GRF-induced peak but not with either bone-age retardation, growth velocity or ferritin blood level. In conclusion thalassemic children show evidences of GH dysfunction suggesting a primary hypothalamic dysfunction and/or an secondary effect of hypogonadism on the GH secretion likely related to hemosiderosis.

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GROWTH HORMONE (GH) RELEASE AFTER GROWTH HORMONE RELEASING HORMONE(GRH) CORRELATES TO ENDOGENOUS 24-H-GH SECRETION IN 38 SHORT CHILDREN

In 38 short children we followed the endogenous GH-secretion for 24 h (sampling intervals of 20 min).This was immediately followed by an i v inj. of 1ug/kg of GRH 1-29. GH was estimated every 15min the following two hours. The aim was to study if the spontaneous GH-secretion, measured during the 24-h-period, had any relation to or influenced on the GH-release induced by GRH.
Patients: The chron. age of the children ranged 3-13y. 32 were prepubertal and 7 showed signs of early puberty. 6 children had a GH-response to insulin-arginine test below 14mU/l (classically GH-def). All children were otherwise considered healthy.
Results: In 32 children the 24-h-GH-secretion varied between 54-1588 mU AUC(Area Under the Curve) over basal and with a mean of 4.1-26mU/l. The GH-def. children showed a diminshed 24-h-GH-secretion. An increased GH-secretion after GRH was found in all but one of the 38 children. Max.level of 107 ±14mU/l, range 17-296mU/l. A high endogenous 24-h-GH secretion after GRH when estimated either as AUC over basal($r=0.47$;$p<0.01$) or as mean of the 24-h-period($r=0.48$;$p<0.01$). The endogenous GH-secretion measured during 3h before GRH inj. did not influence on the GH-response to GRH. However, very few of the children had endogenous secretion during these morning h.
Conclusions: The correlation between a high endogenous 24-h-GH-secretion and a high GH-response to GRH, indicates that the GRH test may be a useful tool to estimate the ability to release GH in short children.

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DISCORDANCES IN RELEASING TESTS IN DETECTING THE SITE OF THE DEFICIENCY IN PITUITARY PATIENTS.

The GHRF test is thought to be able to differentiate pitutary from hypothalamic defects in GH-deficient patients. Our purpose was to verify if the information obtained via GHRF test was in agreement with that of by the TRH and LHRH tests performed in pituitary subjects followed from 2 to 12 yrs. Subjects: 36 pituitary patients subdivided into 3 groups: I) 11 with normal puberty; II) 9 with pharmacologically induced puberty; III) 16 prepubertal with bone age < 12 yrs. GRF test (3 ug/Kg iv): a peak > 4 ng/ml was present in 10 subjects in group I (91% hypothalamic defect), 3 in group II (33% hypothalamic), 9 in group III (56% hypothalamic). TRH test (100 ug iv): group I normal response, no subject neeced replacement therapy; group II only one with a normal hypothalamo-pituitary-thyroidal axis, and 8 with hypothyroidism and a delayed and prolonged TSH response (hypothalamic deficiency 100%); group III: 4 with hypothyroidism (100% hypothalamic). LHRH test (50 ug iv): LH and FSH were significantly different in the 3 groups only after the start of puberty or when bone age was > 12 yrs. Conclusions: a) almost all patients with isolated GH deficit seem to be hypothalamic, b) patients with hypothyroidism all seem to be hypothalamic considering TSH response; GHRF test results are however concordant only in 50% of cases, c) the LHRH test is unable to detect hypogonadism in prepubertal pituitary patients and the level of the defect in hypogonadic subjects.

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GH RESPONSE TO hGRF AS A SENSITIVE INDEX OF GH NEUROSECRETORY DYSFUNCTION AFTER CRANIAL IRRADIATION.

After cranial irradiation for acute lymphoblastic leukemia(ALL) low GH response to pharmacological stimulation and/or during sleep has been considered as evidence of neurosecretory dysfunction.In order to further evaluate this condition, the GH response to hpGRF 1-44 (2 µg/kg IV) was studied in 19 prepubertal children irradiated at a mean CA of 4 10/12 ± 8/12 yr (m ± sem) with 2400 rad (12x200 rad/16 days). They were evaluated after a mean interval time of 4 8/12 ± 3/12 yr and compared to an age matched group with constitutional short stature (CSS).

	(n)	GH-AITT peak(ng/ml)	GH-GRF peak(ng/ml)	SmC/IGF$_I$(U/ml)
Irradiated	(19)	7.6 ± 1.7	16.6 ± 2.5	0.53 ± 0.1
CSS	(14)	17.1 ± 1.7	52.6 ± 8.5	0.70 ± 0.1
		(p< 0.001)	(p< 0.001)	(NS)

After irradiation the individual GH responses to GRF, although not correlated with the GH-AITT peak or SmC levels, were decreased in 17/19 cases. Furthermore in 4 cases with normal growth rates and GH-AITT peaks (9-22 ng/ml) a decreased response to GRF (12-19 ng/ml) was observed. These results suggest that an impaired GH response to GRF : 1) is a frequent finding after cranial irradiation in ALL ; 2) and may be the only sign of GH neurosecretory dysfunction.