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Growth insulin
LGH ornithin

Transient Partial hGH Deficiency in Prepubertal Children with Delay of Growth

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Summary

The hGH response to an ornithin or an insulin test was measured in 105 children from 11–18 yr old with delay of growth more than 2 SD. Besides 74 subjects with normal values and 7 with complete lack of response, 24 subjects exhibited a partial rise of GH. Most of the latter had decreasing growth rate and no sign of puberty. Out of 15 assessed for GH function after onset of puberty, 14 showed a normal response accompanying a markedly increased growth velocity. Four other subjects with partial response who were receiving sexual hormones for 48 hr before the second test showed a normal response also. An exogenous hGH treatment administered in two of these patients resulted in a marked and sustained growth increase far before entering puberty.

Speculation

The findings that plasma GH responses to stimulation tests is reduced in some children with decreasing growth rate before puberty and return to normal after onset of sexual development, would suggest a transient and functional defect in growth hormone secretion and the physiologic role of sexual hormones on GH release mechanism at that period of life.

Among the children with short stature referred to our laboratory for somatotropic function investigation are a great number of boys with delayed puberty. Whereas most of these subjects show a normal response to the GH stimulation tests, a subnormal rise of GH has been observed in several cases.

The influence of gonadal hormones on GH levels has been investigated by several authors (8, 14). However, the precise role of pubertal development on GH secretion has not been clearly elucidated, as evidenced by the conflicting conclusions (1, 7, 12, 16). The present study was undertaken in order to assess hGH release in response to the ornithin test in prepubertal and pubertal subjects, and to study the relationship between sexual hormones and hGH secretion.

MATERIALS AND METHODS

MATERIALS

105 subjects were studied, 25 girls and 80 boys, from 11–18 yr old, who exhibited isolated short stature. In all cases, height was below 2 SD for age, and in 50 cases, below 4 SD. No endocrine or metabolic disease was present, and psychosocial conditions were deemed to be noncontributory. In most cases, the following parameters were available: growth velocity, bone age, parental height, and stage of pubertal development assessed using Tanner's classification (19). The 105 subjects were submitted to hGH stimulation tests; 14 were given ornithin and insulin and 104 only ornithin. An informed consent was obtained from the parents before the tests.

METHODS

hGH Stimulation Test. Ornithin test (4); 1 hr after insertion of an indwelling catheter, a 25 g/m^2 load of ornithin chlorhydrate (62.5 g/l) was infused over 30 min. Blood samples were drawn at the end of the infusion and 15 min later. In 22 cases, additional blood samples were drawn 1 hr before, at the onset, and 1 hr after the infusion.

Insulin tolerance test, (0.10 U/Kg) of insulin was administered iv. Blood samples for hGH and glucose determination were drawn at the following times: 0, 30, 60, 90, and 120 min after insulin.

hGH levels were determined by radioimmunoassay (3). Normal values in our laboratory are defined as a peak plasma hGH concentration above 11 ng/ml (17).

In 15 subjects, the GH stimulation test was performed both before and after the onset of puberty and, in 4 others, after treatment with sexual hormones. This treatment was 2.5 mg of conjugated estrogens (Equigyne, Merrel-Toraude Laboratory) for 2 days (2 girls) and 200 mg of testosterone propionate for 2 days (2 boys).

hGH Treatment. After two stimulation tests with lack of GH response, 3 of these 19 subjects received hGH therapy for their isolated GH deficiency (Table 1, patients 13, 14, 15). At the beginning of the treatment, their bone ages were 11, 11, and 11½ yr, respectively. The dose and duration of hGH treatment were 12 mg/m^2 weekly for 3 yr, 9 months; 11 mg/m^2 weekly for 3 yr, 4 months; and 9 mg/m^2 weekly for 3 yr, respectively. In each case, puberty occurred spontaneously under hGH treatment. The last ornithin test was performed 1 month after hGH treatment was discontinued.

Serum somatomedin and testosterone levels were measured in several cases. Serum somatomedin levels were determined by radioactive sulfate incorporation into chick embryo cartilage (18) and testosterone was measured by radioimmunoassay, after a chromatography of the plasma extract on LH 20 Sephadex column in heptane-chloroform system (50 v/50 v).

RESULTS

The subjects were divided into 3 groups according to the hGH responses to GH stimulation test (Fig. 1).

GROUP 1

Subjects who failed to respond ($n = 7$); peak hGH values ranged from 0.5–3 ng/ml. Additional stimulation tests confirmed a complete GH deficiency.

GROUP 2

Subjects with normal hGH responses ($n = 74$); the peak GH concentrations ranged from 16–66 ng/ml with a mean of 28.7 ng/ml. When GH levels were correlated with various parameters, it could be seen that there were no significant differences when compared either to sex, chronological age, bone age, growth velocity, or sexual development of the subjects; and that both prepubertal and pubertal subjects elicited similar responses.

GROUP 3

Subjects with a partial GH response ($n = 24$); peak concentrations ranged from 3–8 ng/ml with a mean of 6.5 ng/ml. This

Table 1. *Subjects with transient partial hGH deficiency*

N	Sex	Age (yr, month)	Delay of growth (SD)	Bone age (yr, month)	Growth rate, cm/month	Puberty stage (according to Tanner's classifications (19))	Peak of hGH ng/ml ornithine test	Peak of hGH ng/ml insulin test
1	M	11,3	<−4	11	0.35	P_1		6.2
		12,2			1	P_3		17
2	F	12,6	−4	9,6	0.38	P_1	5.4	
		13,8		10,6	0.85	P_3		22
3	M	15,6	<−4	11,9	0.62	P_2	6.8	
		16			1.25	P_3		22
4	M	15,6	−4	13	0.5	P_2	5	
		15,9			1.3	P_3		24
5	M	12,6	−3.5	Unknown	0.31	P_1	8	
		13,6			0.37	P_2		14
6	F	11	−3.5	8,6	0.21	P_1	7.5	
		11,4			0.20			6.7
		13,8			0.43	P_2	19	
7	M	12,10	<−4	10	0.38	P_1	8	
		13,1			0.40			4
		16,5			Unknown	P_2	39	
8	M	14	<−4	10	0.31	P_1	7	
		14,4			0.36	P_1		2.8
		15,3			0.66	P_3	14	
9	M	13,10	−3	12,6	0.56	P_2	7	
		14,1			0.75	P_3		22
10	M	15,10	<−4	13,6	0.38	P_2	7	
		16,2			0.55	Unknown		11
11	M	12,9	−2	10	Unknown	P_1	8	
		14,3			0.17	P_2	33	
12	M	14,1	<−4	11	0.25	P_1	3	
		14,6		14,6	0.25	P_1	6.4	
		18,2			0.46	P_4	45	
13	M	14,2	<−4	10	0.21	P_1	4.5	
		14,4			0.21	P_1		4.5
		17,11			0.58	P_4	16	
14	M	14,9	−4	Unknown	0.44	P_1	3	
		15,2				P_1		6
		17			0.57	P_4	21	
15	M	12,6	−3	8,6	0.10	P_1	6	
					0.25	P_2		4.2
					0.48	P_3	8	
16	M	15	<−4	Unknown	Unknown	Unknown	8	
17	M	14	−4	11	0.33	P_1	7	
		14,7			0.33	P_1		9
18	F	11	−2.5	10	Unknown	P_1	8	
19	F	15,10	−2.5	13	0.10	P_1	7	
		16,2			0.40	P_2	8	
20	M	15,4	−2	12,6	Unknown	P_2	7	

Table 1. *Continued*

N	Sex	Age (yr, month)	Delay of growth (SD)	Bone age (yr, month)	Growth rate, cm/month	Puberty stage (according to Tanner's classifications (19))	Peak of hGH ng/ml ornithine test
21[1]	M	14,10	−3.5	13	0.38	P_1	6
		15,7			0.35	P_2	44
22[2]	F	10,10	−2	6,10	0.31	P_1	5
						P_1	23
23[2]	F	11,7	−2.5	10	0.10	P_1	5
						P_1	25
24[1]	M	12	−2	11	0.35	P_1	7
						P_1	49

[1] Androgen pretreatment.
[2] Estrogen pretreatment.

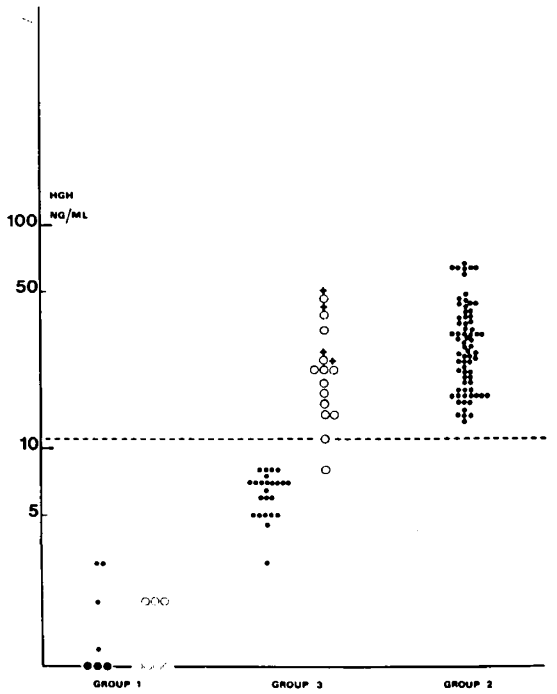

Fig. 1. HGH responses to stimulation tests: ● = first test; ○ = second test. Group 1, total hGH deficiency; group 2, normal subjects; group 3, partial hGH deficiency: ● = before puberty; ○ = after puberty; + = after sexual hormones × 48 hr.

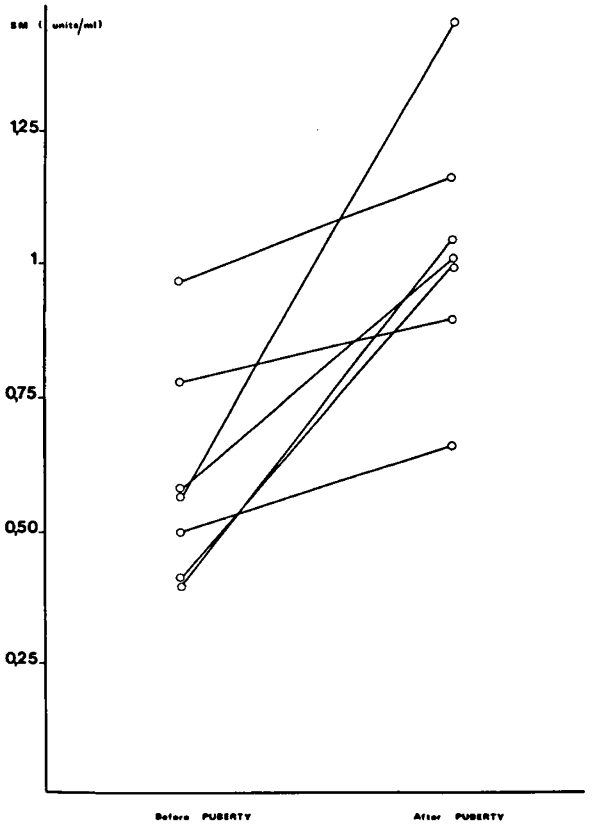

Fig. 2. Somatomedin level measured before and after puberty in six male subjects with a partial transient hGH deficiency.

group included 18 boys and 6 girls from 11 yr–15 yr, 10 months, who exhibited a marked growth retardation. Seventeen of them were below the third SD for height and 21 had a decreased growth velocity as compared to their own previous rate. Except for six who had sparse pubic hair development, none of these children showed any other characteristic sign of puberty. Most children in this group were born of parents with short stature. The mean of parental height was 161.8 ± 0.9 cm (SEM).

In all the 24 cases, the ornithin test (n : 23) or insulin (n : 1) elicited a subnormal GH response, and in seven cases where an insulin test was performed shortly afterwards, before onset of puberty, this subnormal response was confirmed (Table 1).

However, when the stimulation tests (insulin, $n = 7$ or ornithin, $n = 8$) were repeated after the onset of puberty, a normal GH response was elicited in 14 of 15 of these subjects (Fig. 1) with a mean hGH level of 23 ng/ml which was significantly different from the previous response ($P < 0.001$). An accelerated rate of linear growth was present in all the 14 cases.

Four other subjects, treated with sexual steroids for 2 days before the second test, showed normal GH responses after treatment: 23, 49, 44, and 25 ng/ml.

SOMATOMEDIN LEVEL (FIG. 2)

For the seven boys studied both before and after puberty, a constant rise of somatomedin level was observed; by pairing the results, the difference was significant ($P < 0.02$).

TESTOSTERONE LEVEL

Before puberty, testosterone values were in the normal range for the bone age. After puberty, a rise in plasma testosterone was present in most of the 15 subjects submitted to the last GH stimulation test.

DISCUSSION

Our results suggest that some prepubertal children with decreased growth velocity have a temporary partial growth hormone deficiency.

The possibility that an ornithin screening test may be inadequate seems to be ruled out because, in normal subjects submitted to this procedure, GH levels are uniformly elevated, reaching a maximum at 30–45 min after the amino acid infusion, as previously reported (10). In addition, in 10 of the 24 patients with a subnormal response to the ornithin test, the growth hormone levels were measured on five different samples throughout the test. Moreover, the partial GH response to the ornithin test was confirmed by a partial response to an insulin tolerance test in seven of seven of the cases.

Some indirect data support the hypothesis of a partial defect in GH secretion: most of the subjects with a partial response to the ornithin test had shown a progressively decreasing growth velocity for months or years before the test, similar to that of hypopituitary dwarfs. Also, whereas prepubertal somatomedin levels were low simultaneously with a poor hGH response, that was observed in 5 cases, a postpubertal rise in their serum somatomedin levels paralleled a normal hGH response.

Finally, the growth rate of the two subjects treated with hGH must be considered with attention; in both, the pretreatment growth velocity was very slow, their gain of height was 13 cm in 4 yr 3 months and 18 cm in 6 yr, 10 months, respectively. At the beginning of hGH administration, both had a bone age of 11 yr. Once hGH was started at a dose schedule similar to that for hypopituitary dwarfs, they exhibited a markedly increased growth rate, that rose to 0.52 and 0.53 cm/month during the 1st yr of treatment. The children were examined every 2 months and the first signs of puberty were observed 12 and 17 months after hGH therapy had bgun.

All of these findings are consistent with a temporary failure of a sufficient amount of hGH to be released for a normal growth. Penny and Blizzard (15) have observed very low values, < 3 ng/ml, after insulin or arginin tests in three prepubertal boys with short stature with significantly higher response after entering stage IV of sexual development. Illig and Prader (11) and Martin *et al.* (13) have reported similar observations in males with delayed growth and puberty. This transient defect appears to be more common in boys ($n = 14$) than in girls ($n = 4$) in our observations. Eastman *et al.* (5) describe eight boys with delayed growth and puberty with a transitory somatotropic deficiency.

This phenomenon may be more usual than it appears; among the prepubertal children with a normal GH response to the ornithin test, 18 had an obviously decreasing growth rate. It is possible that a more physiologic stimulus would have induced a subnormal response in these subjects. Wise *et al.* (22) have recently reported a growth response to hGH administration in subjects who had normal hGH levels in response to pharmacologic stimuli, but subnormal responses after exercise.

The delayed secretion of sexual hormones presumably would play a role in the impaired GH release in these subjects. In our experience, partial response to ornithin test is twice as frequent in subjects in the 11–18 yr range as in those from 6 months–11 yr. Frasier *et al.* (9) have reported a quantitatively greater GH release in response to hypoglycemia in pubertal than in prepubertal children; and Finkelstein *et al.* (7) found GH secretion rates much higher in adolescents as compared to prepubertal subjects. On the other hand, no difference in the integrated concentrations of hGH as related to puberty was found neither by Plotnick *et al.* (16) in girls nor by Thompson *et al.* (20) or Butenandt *et al.* (1) in males. Enhancement of the GH response to stimulation testing that we have observed in 18 subjects, either after spontaneous puberty or exogenous sexual hormone therapy, is in agreement with a direct influence of gonadal hormones on the hGH releasing mechanism, as previously postulated either for androgens (11, 13) or estrogens (6, 8, 14, 21). The exact mechanism by which sexual hormones interact with GH secretion remains unclear.

From a practical point of view, it appears necessary to establish a distinction between a transient functional deficiency of somatotropic hormone, such as we have described above, and a definitive reduction of secretion. Both the clinical and biologic pictures of these two situations are quite similar, thus it seems worthwhile to repeat the GH stimulation test after a brief administration of sexual hormones, to help distinguish between these two cases (2).

However, the therapeutic use of sexual hormones cannot be proposed because of the increase in bone age which they induce. Growth hormone appears to be better suited to correct a temporary deficit in somatotropic function, but, unfortunately, the amount of available material is a limiting factor for this treatment.

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