Growth in patients with isolated gonadotrophin deficiency

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Abstract

The growth pattern of 66 patients (50 males, 16 females) with isolated gonadotrophin deficiency (IGnD), who had reached their final height with epiphyseal closure, was evaluated. For the purpose of analysis the males were divided into two groups according to age at referral: group 1 <16 years (n=23) and group 2 ≥16 years (n=27). Sex hormone treatment was initiated at a mean (SD) chronological age of 15·8 (1·3) and 18·6 (1·2) years in groups 1 and 2 in the males and at 15·3 (1·3) years in the females. The duration of treatment (until epiphyseal closure) in the males was 3·9 (1·5) years in group 1 and 2·1 (1·0) years in group 2 and 2·8 (1·3) years in the females. There was no significant difference between the mean final height in groups 1 and 2, but it was significantly higher than the mean parental height (mean height SD score (HtSDS): 0·1 (1·1) *v* −0·8 (0·9)) and they were significantly correlated. For females the mean HtSDS compared with parental height was 0·4 (1·5) *v* −0·6 (1·2).

It is concluded that the timing of induction of puberty by sex hormones in males and females with IGnD has no significant effect on final height provided that moderate doses are used. Furthermore final height was significantly correlated to mid-parental height.

Patients with isolated gonadotrophin deficiency (IGnD) often present a diagnostic problem because of the difficulty in differentiating between it and idiopathic delayed puberty in the prepubertal period.[1 2] Referral for endocrine evaluation and treatment is thus often delayed. Although growth of IGnD patients is usually described as normal,[3 4] at the age of puberty there is a slowing of the growth rate. The effect of timing of the initiation of sex hormone replacement therapy is controversial.[5]

We carried out a retrospective analysis of the growth pattern of a large group of patients of both sexes with IGnD who have reached final height.

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Subjects and methods

We studied 66 patients (50 males, 16 females) with IGnD of idiopathic origin who were followed up from prepuberty to completion of puberty and achievement of final height. They were referred to our clinic for evaluation of delayed puberty, hypogenitalism, or slowing of growth. Anosmia was diagnosed in 13 males and three females; five of them (four males, one female) belonged to two families. Three males aged 2 months to 4 years were siblings of known patients with Kallmann's syndrome and during follow up for hypogonadism and hypogenitalism were eventually diagnosed as having Kallmann's syndrome. Patients with multiple pituitary hormone deficiencies, central nervous system tumours, or other hypothalamic pituitary disorders, adrenal or thyroid disease, or primary gonadal failure, were excluded. Patients with IGnD who had received previous hormonal treatment at other clinics were also excluded. The diagnosis of IGnD was confirmed in all patients at final height and epiphyseal closure by discontinuation of sex hormone treatment for 6–12 months and documenting the following: no spontaneous testicular growth and low plasma testosterone concentrations in the males, no spontaneous menstruation and a low plasma β oestradiol in the females, and absence or prepubertal response of luteinising hormone and follicle stimulating hormone to gonadotrophin releasing hormone stimulation in both sexes.

Height was measured by a trained nurse with a wall mounted Harpenden stadiometer. Pubertal rating of pubic hair and genitals for the males and of the breast for the females was performed according to Tanner's criteria.[6] Bone age was estimated from radiographs of the left hand and wrist using the atlas of Greulich and Pyle for carpal and phalangeal bones.[7]

Upon referral all patients underwent a comprehensive work up, including routine physical examination and determination of plasma concentrations of sex steroids, gonadotrophins, and prolactin (all assessed by routine radioimmunoassay methods). The diagnosis of IGnD was established by lack of response of plasma luteinising hormone and follicle stimulating hormone to single and repeated gonadotrophin releasing hormone stimulation.[8] In the males the response of testosterone to human chorionic gonadotrophin (1500 U given intramuscularly on three alternate days) and in the females the response of oestradiol to human menopausal gonadotrophin (75 U given intramuscularly on three alternative days) were also tested. Data were obtained on parental height. Sex corrected mid-parental height was calculated by adding or subtracting 6·5 cm from the mean parental height (cm) for males and females, respectively. Patients were seen for follow up at intervals of three to six months. Bone age was estimated upon referral and thereafter at intervals of six to 12 months until complete closure of epiphyses of the hand and wrist. Age at termination of puberty and achievement of final height was considered to be that at which growth velocity

was less than 1 cm/year and the epiphyses of the hand and wrist were fully ossified.

Puberty was induced as follows: the males received a testosterone depot preparation (Testovirone, Schering), 100 mg intramuscularly monthly and after stage 3 puberty at a dose of 250 mg/month. The females were given conjugated oestrogens (Premarin, Ayerst), 0·625 mg/day and after stage 4 puberty at a dose of 1·25 mg/day, with the addition of medroxyprogesterone acetate (Oragest, Teva), 10 mg/day for seven days each month, on day 21 of the cycle once vaginal bleeding had occurred. Treatment was maintained throughout the follow up period.

Duration of induced puberty in years and total pubertal growth in cm were calculated by subtracting the age and height respectively at initiation of sex hormone treatment from that at achievement of final height. Also calculated were the growth velocity during the year before initiation of treatment (GV_0) and that during the first year of treatment (GV_1). Standing height was expressed in actual measurements (cm) and in standard deviation score (HtSDS), using Tanner's SD tables.[9] Parental HtSDS was calculated from the sex corrected mid-parental height by the same method, using the highest age available in the SD tables. Bone maturation index was calculated from the pretreatment and treatment periods using the equation Δ bone age: Δ chronological age.

Statistical analysis of the results was performed using the paired or unpaired Student's *t* test with two tailed significance levels for comparison of differences between means of longitudinal or mixed groups respectively, and simple linear regression and correlation tests for evaluation of the relationships between various parameters. Outliers were not eliminated from the data sets. All data are presented as mean (SD) unless otherwise specified.

Table 1 Distribution of age at referral of males and females with IGnD

Age (years)	*No (%) of males (n=50)*	*No (%) of females (n=16)*
0–1·0	1 (2)	—
1·1–4·0	2 (4)	—
4·1–6·0	—	—
6·1–8·0	6 (12)	—
8·1–11·0	3 (6)	—
11·1–13·0	5 (10)	7 (44)
13·1–16·0	6 (12)	5 (31)
16·1–18·0	8 (12)	4 (25)
18·1–20·0	17 (34)	—
>20·0	2 (4)	—

Results

As can be seen from table 1 there was a considerable difference between the males and females. Whereas the range for the males was very wide, from birth to 22 years (23 were referred below age 16 and 27 at age 16 years or older), the range in the females was from age 12 to 18 years. As the age at which sex hormone treatment was initiated was significantly influenced by the age at referral the pertinent clinical and laboratory data at referral (table 2) and during follow up (table 3) are given separately for the two age groups for the males.

The mean basal plasma concentrations of sex hormones and prolactin were within the normal prepubertal range for both sexes (table 2). In the males the mean peak plasma testosterone response to human chorionic gonadotrophin was significantly lower than in normal prepubertal boys aged 10–14 years (8·1 (2·6) nmol/l; $p<0·002$). Treatment with sex hormones was initiated at a bone age of 11–15 years in the males and 10–14·5 years in the females, subject to the age at referral (table 3). At the onset of induction of puberty the males referred below the age of 16 years (group 1) had attained a mean (SD) of 91 (2)% of their final height whereas those referred at 16 or older and the female patients had attained 95 (2)% of their final height.

The mean growth velocity was similar in all patients in the year before initiation of treatment (GV_0) and increased significantly in the two male groups ($p<0·02$) during the first treatment year (GV_1). The mean GV_1 and mean changes in growth velocity over the first treatment year (GV_1-GV_0) were highest in the younger males (group 1) and lowest in the females (table 3). The mean maximal growth velocity (GV_{max}) achieved at a bone age corresponding to that of boys with normal puberty[10]

Table 2 Pertinent clinical and laboratory data of 66 isolated hypogonadotrophic patients at referral

Variable	*Males*		*Females (n=16)*
	Group 1 (n=23)	*Group 2 (n=27)*	
Mean (SD) chronological age	8·9 (5·2)	17·5 (1·0)	14·6 (1·5)
Median (range)	7·5 (0·2–15·5)	17·9 (16·1–22·2)	14·2 (12–18)
Mean (SD) bone age (years)	7·7 (4·3)	14·0 (1·0)	11·5 (1·5)
Median (range)	6·7 (0–12)	13·5 (10–15·5)	11·0 (9–14)
Mean (SD) height (cm)	122·0 (31·0)	164·0 (8·8)	150·4 (7·3)
Mean (SD) HtSDS	−0·8 (1·3)	−1·1 (1·2)	−1·3 (1·6)
Pubic hair (Tanner 1–5)	1–3	1–4	1–3
Testicular volume (ml)	0·5–2·5	1–3	—
Breast stage (Tanner 1–5)	—	—	1–2
Mean (SD) testosterone (nmol/l)*			
Basal	0·3 (0·1)	0·5 (0·2)	
Peak	3·3 (1·1)	4·7 (0·9)	
Mean (SD) 17 β oestradiol (pmol/l)†			
Basal	—	—	51·4 (14·7)
Peak			220·3 (132·2)

Group 1: age at referral <16 years and group 2: age at referral ≥16 years.
*Plasma testosterone (peak concentration after human chorionic gonadotrophin 1500 U on three alternate days.
†Plasma 17 β oestradiol (peak concentration after human menopausal gonadotrophin 75U on three alternate days.

Table 3 Effect of treatment on growth in isolated hypogonadotrophic patients

Variable	*Males*		*Females (n=16)*
	Group 1 (n=23)	*Group 2 (n=27)*	
Chronological age at initiation of treatment	15·8 (1·3)	18·6 (1·2)	15·3 (1·3)
Bone age at initiation of treatment	12·6 (1·2)	14·6 (1·0)	12·6 (0·8)
Height (cm)	157 (13·8)	169 (8·5)	156 (9·2)
HtSDS	−1·4 (1·1)	−0·8 (1·3)	−1·1 (1·5)
GV_0 1 year (cm/year)	4·0 (1·3)	4·5 (2·0)	4·0 (0·7)
GV_1 (cm/year)	5·7 (1·1)	5·3 (1·7)	4·4 (1·5)
$GV_1 - GV_0$ (cm/year)	1·8 (0·2)	1·1 (0·3)	0·9 (0·4)
Treatment period (years)*	3·9 (1·5)	2·1 (1·0)	2·8 (1·3)
GV_{max} (cm/year)	7·2 (1·3)	6·0 (1·5)	4·7 (1·0)
Chronological age at GV_{max} (years)	17·0 (0·9)	19·2 (0·5)	16·9 (1·0)
Bone age at GV_{max} (years)	14·0 (0·5)	15·2 (0·7)	13·0 (1·1)
Total pubertal growth (cm)†	15·8 (4·0)	7·5 (2·3)	10·0 (4·8)
Bone age maturation index pretreatment‡	0·7 (0·4)	0·9 (0·5)	0·7 (0·4)
Bone age maturation index during treatment	1·3 (0·4)	1·6 (0·5)	1·3 (0·5)
Final height (cm)	172·7 (6·9)	176·6 (7·8)	164·7 (9·3)
Final HtSDS	−0·3 (1·0)	0·3 (1·2)	0·4 (1·5)
Chronological age at final height (years)	19·7 (1·0)	20·7 (0·6)	18·2 (0·5)
Mid-parental height (cm)§	168·1 (5·8)	171·0 (5·6)	158·0 (7·0)
Mid-parental HtSDS	−1·0 (0·9)	−0·6 (0·8)	−0·6 (1·2)
Final height − mid-parental height (cm)	4·9 (0·9)	6·3 (1·8)	6·2 (3·0)

*Until epiphyseal closure.
†Total pubertal growth from initial treatment to epiphyseal closure.
‡Bone age maturation index Δ bone age: Δ chronological age.
§See subjects and methods.

was also higher in the males referred at a younger age than those referred beyond age 16 ($p<0·05$) and than in the females ($p<0·05$).

The duration of induced puberty was longest in the younger male group ($p<0·001$), similar to the normal pattern of puberty in males, and shortest in the females (table 3). The mean total pubertal growth was significantly greater in the younger males than in the older males and in the females ($p<0·0001$) and lowest in group 2 of the males. The bone maturation index increased significantly ($p<0·01$) in all patients during the treatment period as compared with their pretreatment values (table 3). The mean final HtSDS was close to the mean normal range in all groups (table 3) and significantly higher than at initiation of treatment ($p<0·001$). The mean final height was also higher than the mean mid-parental HtSDS in all groups ($p<0·05$). There was no significant difference in the mean final HtSDS between the younger and older male groups.

The correlation regression analysis revealed that the most significant factor affecting the induced pubertal growth in both sexes was the bone age at initiation of sex hormone treatment (table 4). It did not, however, affect the final height. The height of patients, both at initiation of sex hormone treatment and upon achievement of final height, was found to be significantly correlated with the mid-parental height (all patients $r=0·62$, $p=0·03$ and males: $r=0·64$, $p=0·02$; females: $r=0·67$, $p=0·01$, respectively).

Discussion

Patients with IGnD provide a clinical model for the evaluation of the role of gonadotrophins in prepubertal growth and of sex hormones in achieving maximal final height. It has been well documented that a close relationship exists between puberty and growth, and that sexual development, whether spontaneous or induced, is associated with a rise in plasma growth hormone and insulin-like growth factor-1 (IGF-I).[11–14] The rise in IGF-I concentrations during puberty is mediated by the gradual increase in growth hormone secretion induced by the rising concentration of sex hormones. The relatively short stature of our IGnD patients upon referral before initiation of sex hormone treatment may reflect a low pituitary growth hormone output and a low plasma IGF-I concentration due to insufficient secretion of sex hormones during the pretreatment period.[15–17]

Our review of this large series of both sexes showed that IGnD tends to be diagnosed at an earlier age in boys than in girls. This is due to the fact that hypogonadism and hypogenitalism are more readily apparent in the male. This difference led to earlier initiation of sex hormone treatment in some of the boys (group 1).

Table 4 Correlation matrix of growth related variables in males and females with IGnD

	HtSDS at start of sex hormone treatment	*Duration of induced puberty*	*Total pubertal growth*	*GV_{max}*	*HtSDS at termination of induced puberty*
Bone age at start of sex hormone treatment					
Males					
r	0·78	−0·50	−0·80	−0·52	0·21
p	0·001	0·02	0·0001	0·008	0·10
Females					
r	0·65	−0·65	−0·90	−0·28	0·24
p	0·01	0·01	0·0001	0·09	0·20

This study confirms previous reports that IGnD patients of both sexes achieve a normal final height.[3 4] In the males institution of treatment with a low dose (100 mg/month) of a depot preparation of testosterone and progressively increasing the dose up to 250 mg/month resulted in a comparable final height whether treatment was initiated at an earlier or later age. However, the earlier initiation of treatment in the boys in group 1 resulted in a longer period until ossification of the epiphyses had been completed and in a greater height gain during the period of induced puberty, as compared with the boys in group 2. The latter were, however, taller upon initiation of treatment, which compensated for the lesser growth during the period of induced puberty and the result was a similar final height in both these groups. These results are in agreement with those of Bourguignon who compared the effect of sex hormone induced puberty on final height in hypopituitary patients with growth hormone and gonadotrophin deficiency with that in hypopituitary patients with spontaneous occurrence of puberty.[5 18]

The females with IGnD showed a growth pattern similar to that of the group 2 males. In both the females and the group 2 males chronological age and bone age at referral and initiation of treatment were relatively greater than in the males of group 1.

The importance of the genetic influence on growth is reflected in the significant positive correlation between the height of the patients, both pretreatment and final height, and the sex corrected mid-parental height. Most of the patients with IGnD, and particularly the females, achieved a significantly taller final height than the sex corrected mid-parental height. This can be explained partly by the effect of the secular trend of the general population. Pescovitz in a review of the endocrinology of the pubertal growth spurt, suggests that in IGnD the absence of gonadal sex steroids results in a delayed pubertal growth spurt and probably a small but significant increase in final adult height.[19] The fact that at initiation of sex hormone treatment the height of patients was relatively short in comparison with the mid-parental height and that there was a height gain of 1 SD during the period of treatment supports the suggestion that with low to moderate doses of sex hormones, such as used in the present study, there is initially more effect on linear growth than on bone maturation.[20 21]

Of interest among the findings in this study is the fact that plasma testosterone response to human chorionic gonadotrophin stimulation in the males with IGnD was significantly lower than in normal boys at comparable pubertal stages, indicating the usefulness of this test to distinguish between 'simple' delayed puberty and permanent IGnD states in males.

In conclusion, the results of this study indicate that IGnD patients achieve normal final height irrespective of the timing of initiation of sex hormone treatment. It is therefore suggested that the timing of sex hormone replacement treatment should be decided on the basis of psychosocial determinants.

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