Original articles

Growth hormone state after completion of treatment with growth hormone

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SUMMARY After completion of treatment with growth hormone (GH) 19 patients with isolated 'idiopathic' GH deficiency and 15 with post-irradiation GH deficiency underwent retesting of GH secretion with an insulin tolerance test or an arginine stimulation test, or both. Patients with post-irradiation GH deficiency comprised 13 patients with central nervous system tumours distant from the hypothalamo-pituitary axis and two with acute lymphoblastic leukaemia, who had received cranial or craniospinal irradiation.

All 15 patients with post-irradiation GH deficiency remained GH deficient (peak GH response <7 mU/l ($n=10$) and $7-15$ mU/l ($n=5$)). Of the 19 retested patients with idiopathic GH deficiency, however, five (26%) had peak GH responses of >15 mU/l (regarded now as transient or false idiopathic GH deficiency) and were indistinguishable from the remainder (permanent or true idiopathic GH deficiency, peak GH responses <7 mU/l ($n=12$) and $7-15$ mU/l ($n=2$)), by pretreatment anthropometry and post-treatment height standard deviation score, but had a lower first year height velocity (mean (SD) velocity 5.6 (0.5) cm/year for false idiopathic deficiency v 8.7 (1.75) cm/year for true idiopathic deficiency, $p<0.01$) and height increment on treatment (mean (SD) increment 2.2 (1.5) cm/year for false idiopathic deficiency v 5.2 (2.3) cm/year for true idiopathic deficiency, $p<0.05$). By current practices two patients with false idiopathic deficiency may have been distinguished by sex steroid priming.

Thus post-irradiation GH deficiency seems to be permanent, but errors in diagnosis in idiopathic GH deficiency are common.

Growth hormone (GH) was first introduced for the treatment of GH deficiency in 1958,¹ and there is no doubt of its efficacy.² The question of who should receive treatment with GH, however,³⁻⁶ has been broadened, concurrent with the availability of biosynthetic GH. GH deficiency may no longer be a prerequisite for treatment, as it has been suggested that constitutionally short children⁷⁻⁹ or girls with Turner's syndrome¹⁰ may benefit from its use, though long term side effects in such groups have not yet been evaluated.¹¹

As the scope for treatment with GH widens it is of interest to evaluate those criteria that are used conventionally to confirm the diagnosis of GH deficiency.¹² These criteria will not encompass those patients who produce adequate GH to pharmacological stimuli but do not exhibit normal 24 hour GH production under basal circumstances¹³ nor those with a bio-inactive form of endogenous GH,¹⁴ whose growth accelerates with exogenous GH.

Errors in diagnosis have been recognised in patients with isolated 'idiopathic' GH deficiency, who may be indistinguishable auxologically and biochemically from the constitutionally short child with delayed development.¹⁵ There has also been argument about the need for treatment with GH in children with radiation induced GH deficiency, who, it has been suggested, may pass through a transient state of GH deficiency that is insufficient to affect long term growth.^{16 17} In an attempt to audit the success of current diagnostic criteria we have studied GH secretion in patients diagnosed as GH deficient initially and in whom treatment with GH has been completed.

Patients and methods

Since the inception of the north west regional growth clinic in 1972, 69 children (44 boys and 25 girls) have received and completed a course of treatment with GH. The categories of patients

Table 1 No of cases retested in each diagnostic category of patients with growth hormone deficiency and outcome of retesting

Diagnostic category	No of cases	On retesting		
		Diagnosis confirmed	Diagnosis refuted	Not retested
Craniopharyngioma	12	3	0	9
Other central nervous system tumours	24	15	0	9
Panhypopituitarism	5	3	0	2
Isolated growth hormone deficiency	28	14	5	9

reported and studied were craniopharyngioma (n=12), central nervous system (CNS) tumours (n=24), panhypopituitarism (n=5), where there is a deficiency of more than one anterior pituitary hormone, and isolated GH deficiency (n=28).

A full reassessment of GH secretion was performed in 40 children (26 boys and 14 girls) six months after they had completed their treatment with GH (Table 1). The group with CNS tumours consisted of 13 patients with cerebral tumours distant from the hypothalamo-pituitary axis and two cases of acute lymphoblastic leukaemia, all of whom received cranial or craniospinal irradiation as part of their treatment.

The initial biochemical confirmation of GH deficiency was based on the following provocative and physiological tests of GH secretion (placed in order of frequency of usage): insulin tolerance test, arginine, Bovril, sleep, glucagon, and clonidine stimulation. At least two tests of GH secretion were carried out on each patient, and both results had to concur to support a diagnosis. Total GH deficiency was diagnosed if the peak GH concentration was <7 mU/l, partial deficiency if the concentration was 7–15 mU/l, and normal GH secretion if the concentration was >15 mU/l. In 1981 sex steroid priming was introduced for patients whose bone ages were greater than 10 years. GH was assayed by double antibody radioimmunoassay in a single laboratory, which had participated in the United Kingdom external quality assurance scheme since 1976.

Auxological criteria for a diagnosis of GH deficiency were growth velocity, measured at the growth clinic over one year, below the 25th centile, a standing height more than 2.5 standard deviations below the mean for age and sex, and satisfactory general, auxological, and endocrine evidence to exclude or define any complicating factors.¹²

A diagnosis of GH deficiency was made on these grounds and the data presented to the health services human growth hormone committee, which authorised the release of pituitary extracted GH for treatment. At the end of the first year of treatment

an increase of 2 cm on the pretreatment height velocity was considered an acceptable response and worthy of continuing treatment.

In most of the 40 patients in whom GH state was reassessed an insulin intolerance test or arginine test, or both, was performed. Peak GH concentrations, as defined above, were used to confirm or refute the original diagnosis.

For those patients in the group with idiopathic GH deficiency, auxological variables before, during, and after treatment were compared between those in whom the diagnosis of GH deficiency was confirmed or refuted. Statistical methods consisted of Student's *t* test (two tailed) for those values distributed normally and Mann-Whitney U test for those that were not. Predicted heights at the start of treatment with GH were evaluated using the formulas of Tanner and Whitehouse.¹⁸

Results

Tumour groups. All patients whose GH deficiency resulted from craniopharyngioma or its treatment

Figure Growth hormone (GH) peaks after an insulin tolerance test or arginine provocation at initial testing and on retesting after stopping of treatment with GH in the group with post-irradiation GH deficiency. Mean (SD) GH peak at diagnosis was 7.2 (3.5) mU/l and at retesting was 4.8 (4.0) mU/l.

($n=3$) or from radiation induced damage to the hypothalamo-pituitary axis after treatment for acute lymphoblastic leukaemia ($n=2$) or a cerebral tumour distant from the hypothalamo-pituitary axis ($n=13$) were still GH deficient on retesting. At diagnosis and on retesting the three patients with GH deficiency due to craniopharyngioma had peak GH concentrations <7 mU/l. At diagnosis, six of the patients with post-irradiation GH deficiency had peak GH concentrations <7 mU/l, and nine fell in the partial range (7–15 mU/l). On retesting, however, 10 were totally and five partially GH deficient (Figure). Thus four patients initially diagnosed as partial had become totally deficient on retesting. The mean (SD) interval between diagnosis of tumour and start of treatment with GH for these patients with post-irradiation GH deficiency was 5.5 (3.2) years (range 1.3 to 10.9 years) and from diagnosis to retesting was 10.5 (3.6) years.

Panhypopituitarism. All three patients were totally GH deficient (peak <7 mU/l) both before and after treatment with GH.

Idiopathic GH deficiency. Of the 19 patients with idiopathic GH deficiency who were retested, 14 were confirmed as GH deficient (two partial and 12 total), with a mean (SD) interval from diagnosis to retesting of 7.4 (2.9) years. Of these, one who was initially diagnosed as totally GH deficient had a GH peak on retesting that was in the partial range.

The remaining five patients produced normal GH peaks (>15 mU/l) to provocation tests at a mean (SD) interval of 7.6 (3.8) years from diagnosis (auxological details, Tables 2 and 3). Of these five patients, case 1 was thought to have familial short stature clinically, and though the first year increment on treatment was unsatisfactory he started to show a pubertal growth spurt at the end of this period, and this development combined with paren-

Table 3 Mean (SD) values of various auxological variables before, during, and after treatment with growth hormone (GH) in patients with false or true idiopathic GH deficiency

Growth variables	Idiopathic GH deficiency group		p Value
	True	False	
Pretreatment:			
Age (years)	12.9 (3.3)	11.8 (3.7)	NS
Height SDS for chronological age	-4.7 (1.0)	-4.0 (1.2)	NS
Height SDS for bone age	-1.9 (1.4)	-1.4 (1.9)	NS
Bone age SDS	-3.5 (2.0)	-3.2 (1.7)	NS
Sitting height SDS	-5.2 (1.0)	-3.9 (1.5)	NS
Pretreatment velocity (cm/yr)	3.5 (1.8)	3.4 (1.6)	NS
First year velocity (cm/yr)	8.7 (1.8)	5.6 (0.5)	<0.01
First year increment (cm/yr)	5.2 (2.3)	2.2 (1.5)	<0.05
Post-treatment:			
Height SDS for chronological age	-2.6 (1.0)	-2.6 (1.0)	NS
Height SDS for bone age	-2.4 (0.9)	-2.6 (1.0)	NS
Time on treatment	5.7 (3.0)	5.7 (3.5)	NS
Final minus predicted height (cm)	+8.4 (6.4)	+4.2 (5.4)	NS

SDS=Standard deviation score; NS=Not significant.

tal pressure led to treatment continuing until growth had ceased. Case 3 also grew an unacceptable amount in the first year but further annual velocities were enhanced with an increased dose of GH and later with puberty. Treatment with GH was thus continued. Cases 2 and 5 would have received sex steroid priming during their diagnostic studies if they had presented after 1981, but both had acceptable first year responses to GH. Case 4 was a Turner's mosaic who was on a six month trial with GH, during which time her response was favourable. GH was continued for 1.76 years until growth ceased. Using Turner's growth curve data,¹⁹ her pretreatment height standard deviation score (SDS)

Table 2 Auxological data, peak growth hormone (GH) responses at diagnosis and retesting, ages before and after treatment, and year of onset of treatment in patients with false idiopathic growth hormone deficiency

Case No	Sex	Mid-parental height SDS	Onset of treatment					First year increment on treatment	Stopping of treatment		
			Age (years)	Year of onset of treatment	Height SDS for chronological age	Bone age SDS	Peak GH responses (mU/l)		Age (years)	Height SDS for chronological age	Peak GH responses (mU/l)
1	M	-2.4	9.9	1975	-4.5	-2.9	2.0	1.7	16.3	-4.1	45
2*	M	-0.7	13.4	1979	-3.7	-3.8	4.5	2.2	18.5	-2.0	40
3	M	-0.7	6.3	1972	-2.8	-5.1	10.0	0.7	17.5	-1.5	25
4†	F	+0.7	14.2	1981	-3.0	-0.5	8.3	1.8	16.0	-2.2	27
5*	F	-1	15.1	1980	-5.7	-3.5	3.4	4.8	19.2	-3.1	44

SDS=Standard deviation score.

*Primed tests would now be appropriate.

†Primed tests carried out at diagnosis.

was +1.33, final height SDS +1.94, and predicted final height SDS +1.74.

The characteristics of these retested patients, defined as persistent or true and transient or false idiopathic GH deficiency, are shown in Table 3. There were significant differences between the respective first year height velocities (mean (SD) 8.7 (1.8) cm/year for true idiopathic deficiency *v* 5.6 (0.5) cm/year for false idiopathic deficiency, $p < 0.01$) and first year height increments (5.2 (2.3) cm/year *v* 2.2 (1.5) cm/year, respectively, $p < 0.05$). The two groups could not be distinguished by auxological criteria at the time of diagnosis nor at the end of treatment.

Discussion

It is not unexpected that GH deficiency seems to be permanent in distinct pathological conditions, such as craniopharyngioma or idiopathic panhypopituitarism. There has been contention, however, about the reversibility of irradiation induced GH deficiency. Griffin and Wadsworth reviewed the growth of children with malignant disease (leukaemia and solid tumours) who received cranial or craniospinal irradiation.¹⁷ Over the three to four years of study, they found a small decrement in eventual height and no suggestion of long term impaired GH secretion and concurred with the reports of Dacou-Voutetakis *et al*¹⁶ that the poor growth velocity in patients with leukaemia during the first year after irradiation could be due to transient GH deficiency. Shalet *et al* agreed that few children receiving CNS irradiation for leukaemia were clinically GH deficient and that their initial post-irradiation growth velocity after irradiation was poor, but they attributed this to chemotherapy, poor nutrition, and the disease itself rather than transient GH deficiency.^{20 21} Our results do not support the concept of transient GH deficiency: when radiation induced hypophyseal-pituitary damage has resulted in GH deficiency this remains and, in addition, GH secretion continues to decline for many years after the damage is inflicted.

We also suggest that the diagnosis of idiopathic GH deficiency was incorrect in 25% of patients treated in one major growth clinic over the last 14 years. This finding may seem surprising but compares favourably with other reports.²² (Burns EC, Preece MA. Personal communication. May 1986.) Such errors of categorisation are not attributable to nor avoided by baseline auxological data, which can be similar in constitutionally short children with delay in development and patients with true idiopathic GH deficiency.^{15 23} It is worth while repeating that the inconsistency of GH responses to

pharmacological tests is an unsatisfactory diagnostic criterion. The most commonly used test, the insulin tolerance test, has a reported failure rate of 25%, where a negative response is compared with a further GH provocation test that produces normal GH concentrations;²⁴ thus two or more tests are routinely performed to minimise error. An additional source of error, which may have occurred in two of our patients with false idiopathic GH deficiency, is the omission of sex steroid priming before testing children in the preadolescent years. Our findings further suggest that failure to increase height velocity by 3.5 cm/year or more in the first year of treatment should lead to close scrutiny of the original diagnosis.

At a time when a widening of diagnostic categories for treatment with GH is suggested,⁶ is this clinical audit of present treatment groups instructive? There seem to be three objectives of treatment with GH in the short child—namely, greater adult height, faster immediate growth, and no harmful side effects. Patients with true idiopathic GH deficiency have shown an appreciable increment in height velocity in the first year of treatment (with a mean of 5.2 cm/year) and an achieved adult height that exceeds the predicted height by a mean of +8.4 cm. Treatment of those truly deficient in GH is of benefit and we consider that this should be extrapolated to those with GH deficiency secondary to radiation damage. Assessment of the value of treatment in patients with false idiopathic GH deficiency is more difficult: there was a poorer increment of height velocity in the first year, with a mean of 2.2 cm/year, but achieved adult height exceeded that predicted by a mean of +4.2 cm. It is impossible to delineate any benefit from GH in such patients, but it is reassuring that no apparent impairment of adult height was seen. We suggest that a controlled trial of treatment with GH up to adulthood in the constitutionally short with delayed development is necessary to determine whether ultimate height is increased by additional GH.

PEC is supported by a grant from the Child Growth Foundation. We are grateful to those patients who agreed to be retested after treatment, Withington radioimmunoassay laboratory for GH estimations, and Mrs K Cordwell for secretarial help.

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Received 9 October 1986