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When are we diagnosing growth hormone deficiency?

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SUMMARY The height and age at presentation of 458 children beginning treatment with growth hormone between January 1980 and June 1984 were retrospectively analysed. Three hundred and nine children with isolated growth hormone deficiency had a mean (SD) age of 10 (4·1) years on beginning treatment and a mean (SD) height standard deviation score (SDS) of −3·73 (0·93). One hundred and nine patients with hypothalamopituitary tumours began treatment with growth hormone on average 3·3 years after diagnosis of the tumour and at a mean (SD) height SDS of −2·42 (1·49). In both of these categories the height SDS showed a considerable improvement compared with previous reports. Forty two patients with growth hormone deficiency secondary to cranial irradiation started treatment with growth hormone on average 6·1 years after treatment for their tumours and had a height SDS of −2·45 (1·02) compared with that of −2·45 (0·98) seen in nine similar patients from the United Kingdom starting treatment with growth hormone between 1975 and 1978. Although closer surveillance of short children in the community is leading to earlier diagnosis of growth hormone deficiency, this could possibly be diagnosed earlier if routine screening of height was to be carried out at school entry. In addition, patients who have received cranial irradiation should be regularly measured and investigated when their height velocity becomes subnormal.

The success of growth hormone in treating short stature in cases of growth hormone deficiency is well documented.[1] Although growth hormone is currently only available for selected cases, this is likely to be a temporary state of affairs, and it is therefore important that the possibility of growth hormone deficiency is borne in mind by physicians dealing with children. As it is generally believed that the earlier replacement therapy is begun in such patients the better the prognosis for final stature,[2] a retrospective analysis was made of the heights and ages of children recently accepted for treatment with growth hormone in the United Kingdom.

Methods

The patients studied were those successfully submitted by 18 of the 19 regional growth centres for treatment with growth hormone to the Health Services Human Growth Hormone Committee from January 1980 to June 1984. Criteria for acceptance were usually a subnormal height velocity coupled with biochemical evidence of defective secretion of growth hormone in response to certain pharmacological stimuli and exclusion of other causes of these phenomena such as hypothyroidism. The patients were subdivided according to whether they suffered from idiopathic isolated growth hormone deficiency or a tumour involving the hypothalamopituitary tract or had developed an endocrinopathy as a result of cranial irradiation for other malignant disease. Patients with idiopathic multiple pituitary hormone deficiencies were not studied as they included a number of very young children with congenital hypopituitarism. The heights of patients at submission were expressed as standard deviation scores (SDS) from the mean, calculated as follows:

$$SDS = \frac{x - \bar{x}}{SD}$$

where x is the patient's height and $\bar{x}$ and SD the population mean height and standard deviation, respectively, at that age. The population standards used were those of Tanner and Whitehouse.[3] Patients were also subdivided according to year of

submission to assess whether a trend existed toward earlier diagnosis. Statistical analysis was by unpaired *t* test and linear regression.

Results

Isolated growth hormone deficiency. Three hundred and seven patients, comprising 199 boys and 108 girls, were accepted for treatment during the study period. The overall mean (SD) height SDS for these patients was −3·73 (0·93), with a mean (SD) age of submissions of 10·0 (4·1) years. Boys were on average one year older than girls at submission (10·37 (4·04) years and 9·32 (4·2) years, respectively) but had a significantly less deviant height SDS of −3·56 (0·86) compared with −4·05 (0·98) ($p<0·001$). Parental heights were available for 301 of the patients: the mean (SD) height SDS of their fathers was −0·33 (1·14) and of their mothers was −0·4± (1·18). Only nine parents had a height SDS of −3·0 or less.

Hypothalamopituitary tumours. One hundred and nine patients with this diagnosis were accepted for treatment, of whom 57 were boys and 52 were girls. Table 1 summarises details of these patients. The interval between diagnosis of their tumour and submission for treatment with growth hormone ranged from 0·27 to 13·15 years (mean 3·27 years). No significant difference was noted beween the sexes with regard to height SDS at submission for treatment with growth hormone or the time required for this. Thirty two patients had isolated growth hormone deficiency, and although they required roughly two years longer to be submitted for treatment with growth hormone, there was no significant difference between their height SDS (−2·63 (SD 1·51)) and that of the rest of the patients (−2·34 (1·48)). No correlation existed between the duration of time from diagnosis of the tumour to submission for treatment with growth hormone and the height SDS when accepted for treatment.

Radiation induced growth hormone deficiency. Forty two patients, of whom 25 were boys and 17 were girls, were submitted with this diagnosis. Details are summarised in Table 1. The interval between cranial irradiation and submission for treatment with growth hormone ranged from 1·4 to 11·86 years (mean 6·10 years). Boys had a significantly less deviant height SDS than girls at submission ($p<0·02$). Nine patients had additional endocrinopathies, and there was no significant difference between these and the remaining patients with regard to height SDS or duration of time required for submission. A highly significant negative correlation existed between the height SDS at submission and the duration of time from diagnosis of the tumour to submission for treatment with growth hormone ($p<0·001$).

In none of the three groups was there any significant trend towards earlier diagnosis when the figures were subdivided on an annual basis.

Discussion

In this study children with idiopathic isolated growth hormone deficiency were below the first centile for height at diagnosis. A greater cause for concern is that their short stature seems to have been ignored until mid-childhood. Treatment with growth hormone is currently thought to be necessary for normal growth from birth onwards, and therefore these patients were probably always smaller than their peer group. In most cases the parents were of normal height and the patients' short stature could not therefore be explained on a genetic basis. No information was available as to how long the parents had been concerned about the child's growth, creating uncertainty as to what extent the late diagnosis was due to parental complacency. Reports of the final stature of children with growth hormone deficiency who have been treated have noted that they rarely fulfil their genetic potential for height,[2 4] and this has been attributed to delay in beginning

Table 1 *Mean (SD) height SDS, age at diagnosis of tumours, and interval between tumour diagnosis and submission for treatment with growth hormone of patients with intracranial tumours*

	Height SDS	*SD*	*Age at diagnosis*	*Interval between diagnosis and submission (yrs)*
Patients with hypothalamopituitary tumours				
All	−2·42	(1·49)	8·91 (4·84)	3·23 (2·97)
Boys	−2·53	(1·70)	8·83 (5·71)	3·11 (2·92)
Girls	−2·31	(1·22)	8·99 (3·78)	3·33 (3·02)
Patients with other central nervous system tumours				
All	−2·45	(1·02)	5·23 (3·33)	6·10 (2·78)
Boys	−2·13	(1·07)	5·58 (3·43)	6·27 (2·91)
Girls	−2·89	(0·77)	4·71 (3·21)	5·84 (2·65)

Table 2 *Comparison of current height SDS (mean (SD)) with previous publications*

	Patients with isolated growth hormone deficiency		*Patients with hypothalamopituitary tumours*	
	No	*Height SDS*	*No*	*Height SDS*
United Kingdom 1971[1]	35	−4·7 (1·1)	18	−3·8 (1·6)
Switzerland 1980[7]	30	−4·2 (1·2)	10	−2·9 (1·2)
Finland[6]	41	−4·8 (1·7)	15	−3·1 (1·6)
United Kingdom 1980–4	307	−3·7 (0·9)	109	−2·4 (1·5)

replacement therapy. It is tempting to speculate that if routine screening for short stature was to be carried out at school entry examination using simple devices such as the Oxford growth chart[5] this delay in diagnosis might be overcome. The irreversible height loss suffered by these patients, however, possibly occurs even earlier than this. If so, this would lay an extra responsibility on general practitioners and infant welfare clinics. Nevertheless, the current figures show a considerable improvement over earlier published work[2 6 7] (Table 2) in that the diagnosis of growth hormone deficiency is being made when the patients' height SDS is less deviant from the mean. It must be mentioned, however, that the data on these patients do not take into account patients who were too old at presentation to benefit from treatment with growth hormone and were on this basis either never submitted to the committee for treatment or rejected on these grounds. Inclusion of these patients would almost certainly make the results poorer than they seem at present.

The height SDS of patients with hypothalamopituitary tumours also show a considerable improvement over previous reports (Table 2). It is also noteworthy that those patients with isolated growth hormone deficiency in this group, who may initially have not been under endocrinological supervision, showed no significant difference in their height SDS compared with those with additional endocrinopathies. The current situation regarding patients with radiation induced growth hormone deficiency, however, shows more cause for concern. Unlike patients with hypothalamopituitary tumours, which are often slow growing and may affect hormone secretion long before diagnosis, patients with radiation induced growth hormone deficiency are likely to have been of normal or near normal stature at original diagnosis. The low height SDS at submission for treatment with growth hormone of these patients, however, implies that their height measurements had been crossing the centile lines for some time before appropriate investigation was begun. This is supported by the strong negative correlation between the height SDS of these patients and the interval between initial treatment and submission for treatment with growth hormone. Cranial irradiation was not clearly identified as a cause of growth hormone deficiency until the mid-1970s,[8] but it is of concern that the mean (SD) height SDS of nine UK patients submitted for treatment with growth hormone shortly after this was −2·45 (0·98), which is almost identical to the current figure. One problem facing clinicians is that the height velocity of cranially irradiated patients is often subnormal during the first year after treatment, regardless of whether any endocrinopathy is present;[9] after this, however, the height velocity of these patients should be regularly monitored and investigation begun if it remains subnormal.

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