The Northern Ireland experience of growth hormone therapy for short stature

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SUMMARY
In 1967 the first patient in Northern Ireland commenced growth hormone treatment for short stature. By the end of December 1988 a total of 89 patients had been treated. Thirty-two had idiopathic isolated growth hormone deficiency, an incidence of 1·5 new cases per year (in a population of 1·5 million with approximately 30,000 births per year). Since 1967 the mean age at starting treatment has fallen from 18 years to 10 years and the height standard deviation score has fallen from $-4·7 \pm 0·6$ to $-3·4 \pm 0·3$. The group with classical growth hormone deficiency (maximum $GH < 7mU/l$ during insulin-induced hypoglycaemia) had a greater increase in height velocity over the first year of treatment, $3·8 \pm 0·4$ cm, than those with a partial deficiency (maximum growth hormone $7·1—20 mU/l$), $1·9 \pm 0·4$ cm. All pre-pubertal children responded with a rise in the height velocity standard deviation score from $-1·8 \pm 0·3$ before treatment to $+3·5 \pm 0·4$ over the first year of treatment.

58% of the adult males and 25% of adult females have attained an adult height within the normal range (3rd centile or above). There have been three deaths, one each from Fanconi’s aplastic anaemia which predated growth hormone treatment, an accidental fire injury and a relapsing craniopharyngioma. There have been no deaths from Creutzfeldt-Jakob disease. Growth hormone therapy is safe and effective, but continues to be commenced late in terms both of age and height standard deviation score.

INTRODUCTION
The growth promoting activity of crude anterior pituitary extracts in hypophysectomized and intact laboratory animals was first demonstrated by Evans and Long in 1921. Isolation and characterization of a relatively pure growth promoting factor was achieved by Li and his associates in 1945. It was a further decade before a favourable response to human growth hormone (hGH) treatment was reported by Raben in a 19-year-old male with growth hormone deficiency. In 1967 the first patient in Northern Ireland commenced treatment with growth hormone for short stature. Over the next 18 years, all growth hormone used was of human cadaver origin but this was withdrawn in 1985 because of isolated reports from elsewhere of possible contamination with a slow...
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The virus causing Creutzfeldt-Jakob disease. Since then all patients in Northern Ireland have been treated with growth hormone manufactured by recombinant DNA technology. Although there are many reports on the improved growth rates in growth hormone deficient children, the ultimate success of treatment is the attainment of a normal adult height. Final heights achieved in patients treated within the last two decades have been disappointing, and may reflect the late onset of therapy or inadequate doses administered. We have examined the case records of the 89 patients treated in Northern Ireland from 1967 to 1988 and report on final height, response rates and practice trends over these 21 years.

METHODS

Laboratory diagnosis: The diagnosis of classical growth hormone deficiency was made if plasma GH concentration did not exceed 7 mU/l during insulin hypoglycaemia. Partial growth hormone deficiency was defined as a GH response of greater than 7 but less than 20 mU/l. 35 patients were diagnosed as growth hormone deficient after their bone age had reached 10 years. A small number of this group (13%) excluding those with hypopituitarism or precocious puberty were not reassessed by either a repeat sex hormone primed stimulation test or by retesting at cessation of therapy.

Anthropometric measurements: Height was measured according to the recommendations of Tanner and Whitehouse, using a Harpenden stadiometer. For analysis, the cross sectional standards of Tanner et al were used. Bone age was determined from X-rays of the left hand and wrist (Tanner et al). To compare growth data at different ages in both sexes, height (and height velocity in the pre-pubertal group) was expressed as the standard deviation score (SDS) calculated from the measured height (X), the mean height (X) and the height standard deviation at that age (SD) according to the formula:

\[ SDS = \frac{X - \bar{X}}{SD} \]

Height velocity was determined from the difference between two height measurements divided by the time interval between the measurements in decimal years. Only observed periods of six months or more were used for calculation. Adult height was predicted at the onset of therapy using the tables of Tanner et al and subsequently compared to the actual achieved adult height in those who had completed growth. Target heights were calculated using the mid-parental heights. Comparisons of actual heights with predicted and target heights were made using paired t-tests. Means ± SEM are reported.

PATIENTS

In the past 21 years, 89 patients have been treated with growth hormone for short stature in Northern Ireland. Thirty-two had idiopathic isolated growth hormone deficiency and one was secondary to cranial irradiation for acute lymphoblastic leukaemia. Sixteen had partial growth hormone deficiency. Twenty-seven had panhypopituitarism — 15 idiopathic (of which two presented in infancy with recurrent hypoglycaemia) and 12 due to known organic pituitary disease (cranio-pharyngioma, chromophobe adenoma or granulomatous disorders). Ten had Turner's syndrome, two normal short stature and one spondyloepiphyseal dysplasia. Of those patients with Turner's syndrome, one had in addition classical growth hormone deficiency, five had partial growth hormone deficiency, and four had normal growth hormone secretion.

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Fig 1. Number of patients on growth hormone treatment per year and the number of new cases diagnosed each year in Northern Ireland, 1967–1988.

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Fig 2. Mean age and height standard deviation score (SDS) when growth hormone treatment first commenced (1967–1988)

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The numbers of patients on treatment and the numbers of new patients commenced on treatment each year, including those with a diagnosis of classical idiopathic growth hormone deficiency has risen with time (Fig 1). The mean age at onset of therapy has fallen from 18 years in 1967 to 10 years in 1988 and the mean height SDS at commencement of therapy has also fallen with time (Fig 2). Five cases had a bone age in advance of their chronological age at the onset of therapy, of whom four had received cranial irradiation which has been reported to be associated with the premature onset of puberty. The mean delay in bone age in the rest of the group with growth hormone deficiency at commencement of therapy was $-2.8 \pm 0.2$ years.

There have been three deaths in the group, one each from an accidental fire injury, Fanconi's aplastic anaemia which predated growth hormone therapy and from a relapse of a craniopharyngioma. There were no deaths from Creutzfeldt-Jakob disease.

RESULTS

In 22 patients (25%) assessment of the response to growth hormone treatment was not possible, as there was either no pre-treatment assessment of growth velocity (9 patients) due to the late age of diagnosis (15.2–18.9 years), or because the duration of therapy was less than six months (13 patients). In the remaining 67 patients, 41 (61%) responded with an acceleration in growth velocity of greater than 2.0 cm/year in the first year of treatment (range 2.0–10.6 cm/yr), 19 (29%) showed an acceleration of less than 2.0 cm/year, and 7 (10%) showed no response to treatment (3 panhypopituitarism, one idiopathic growth hormone deficiency, one normal short stature and two with Turner's syndrome). The group with classical growth hormone deficiency had a greater increase in height velocity than those with partial growth deficiency (3.8 ± 0.4 vs 1.9 ± 0.4 cm/yr). All patients with growth hormone deficiency in the pre-pubertal group responded with a rise in height velocity SDS, which was $-1.8 \pm 0.3$ before treatment and $+3.5 \pm 0.4$ after treatment. There was a significant negative correlation between the change in height velocity SDS after the first year of growth hormone treatment and the growth hormone response to insulin-induced hypoglycaemia in this pre-pubertal group ($r = -0.42$, $p < 0.05$; $n = 25$) (Fig 3). The ratio of change in bone age to chronological age ($\Delta BA/\Delta CA$) up to a bone age of 12 years in girls and 14 years in boys was $1.1 \pm 0.06$.

Twenty-nine patients had completed therapy and an adult height has been recorded in 19 males and 8 females. The mean adult height for males was 162.4 ± 0.9 cm and for females 147.4 ± 2.8 cm; these were not significantly different from the mean predicted adult height (actual height 159 ± 1.4 cm vs predicted height 158 ± 1.7 cm). However, they were significantly lower than the target height (males 162.4 ± 0.9 cm vs 170.8 ± 0.9 cm, $p < 0.001$; females 147.4 ± 2.2 cm vs 156.6 ± 2.0 cm, $p < 0.05$).

DISCUSSION

It has been postulated that growth becomes growth hormone dependent after birth. A highly significant correlation between height and spontaneous growth hormone secretion has been described in pre-pubertal children. Our findings of 100% response rates in the pre-pubertal group, and the significant negative correlation between the change in height velocity standard deviation score over

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the first year of treatment and growth hormone secretion in this group would be in accordance. A non-linear relationship between growth hormone secretion and height has been described in the pubertal ages. Sex hormones account for pubertal growth acceleration which can occur in the presence of very little growth hormone. Patients with Laron-type short stature, who have an end organ resistance to the action of growth hormone, can have a normal pubertal growth spurt.

A recent study comparing final heights of children treated before and after growth hormone became available found no significant difference between the final heights of those patients with multiple hormone deficiencies treated with growth hormone and androgens, and those treated with androgens alone. Growth hormone succeeded in achieving an adult height approximately 3·4 years earlier, suggesting that fusion of the epiphysis occurred earlier in the GH treated group. All but one of the patients in the growth hormone treated group had been pubertal at onset of therapy.

Our findings of final heights 2·0 SD below the normal population mean for males and 3·0 SD below for females are in accordance with others. The failure to reach target heights based on mid-parental heights suggests that the patients failed to reach their true genetic potential for growth. It has been postulated that
growth hormone therapy in growth hormone deficient children prevents further “loss” of height potential but may not succeed in regaining lost height. The disappointing final heights may reflect the late age of diagnoses and greater “lost” height at diagnoses. All of the patients who have reached adult height in Northern Ireland were treated with a standard dose regimen three times a week. Optimum doses are now being worked out based on body weight and given by daily subcutaneous injection with improved growth rates.

As growth has been shown to be growth hormone dependent in the pre-pubertal years, (when the ratio of bone age to chronological age does not advance at a figure greater than 1·0) treatment of the growth hormone deficient child early in this period of growth should allow greater potential for normal growth and improved final height. We would recommend that height measurements should be plotted on a height centile chart. A height falling three standard deviations below the mean for age on a single measurement, or a height velocity over a full year below the 25th centile, should be referred for further evaluation. A random sample of growth hormone is of little value; a serum sample greater than 20 mU/l following exercise or sleep excludes growth hormone deficiency. If the growth hormone level is below 20 mU/l, growth hormone deficiency is possible, and the child should be investigated further.

Endocrinological evaluation will vary depending on the child’s bone age; at a bone age of greater than 10 years, a sex hormone primed insulin-induced hypoglycaemic stimulation test should be carried out. A growth hormone response of less than 7 mU/l to insulin stimulation indicates classical growth hormone deficiency. A response of between 7·1 and 20 mU/l suggests partial growth hormone deficiency. However, the stimulation test should be repeated in such cases.

The trend in Northern Ireland over the last 21 years reflects an earlier age at diagnosis and a fall in the height deficit at onset of therapy. However, the mean age at diagnosis in 1988 was still at the end of the pre-pubertal growth phase, when a large height deficit has already occurred. If the final height prognosis is to improve, children with short stature should be identified earlier, ideally before school age. With the improved availability of treatment and the establishment of optimum treatment regimens, the height prognosis for children in the next two decades should improve.

We are grateful to many colleagues who have referred patients because of short stature over the years of this study. The Growth Clinics at the Royal Victoria Hospital and the Royal Belfast Hospital for Sick Children continue to assess and supervise the management of children and adults requiring growth hormone therapy.

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