Adult height after long term treatment with recombinant growth hormone for idiopathic isolated growth hormone deficiency: observational follow up study of the French population based registry

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Abstract

Objective To evaluate the efficacy of recombinant growth hormone for increasing adult height in children treated for idiopathic isolated growth hormone deficiency.
Design Observational follow up study.
Setting Population based registry.
Participants All 2852 French children diagnosed as having isolated idiopathic growth hormone deficiency whose treatment started between 1987 and 1992 and ended before 1996.
Main outcome measures Change in height between the start of treatment and adulthood; classification of patients according to whether treatment was completed as scheduled or stopped early.
Results Adult height was obtained for 2165 (76%) patients. The mean dose of growth hormone at start of treatment was 0.42 IU/kg/week. Height gain was 1.1 (SD 0.9) standard deviation (SD) scores, resulting in an adult height of –1.6 (0.9) SD score (girls, 154 (5) cm; boys, 167 (6) cm). Patients who completed the treatment gained 1.0 (0.7) SD score of height in 3.6 (1.4) years. Patients with treatments stopped early gained 0.6 (0.6) SD score in 2.7 (1.4) years while receiving treatment and a further 0.4 (0.9) SD score after the end of treatment. Most of the variation in height gain was explained by regression towards the mean, patients' characteristics, and delay in starting puberty. Severe growth hormone deficiency was associated with better outcome. Each year of treatment was associated with a gain of 0.2 SD score(1.3 cm).
Conclusion The effect of growth hormone is unclear in many patients treated for so called idiopathic isolated growth hormone deficiency. Most of the patients have pubertal delay and a spontaneous growth potential, which must be taken into account when measuring the effect and cost effectiveness of treatments. Growth hormone deficiency should be clearly distinguished from pubertal delay, and criteria should restrict the definition to patients with severely and permanently altered growth hormone secretion as our results support the use of growth hormone in such patients. Long term trials are required for most patients currently treated.

Introduction

Idiopathic growth hormone deficiency is the indication for treatment in 50% of children receiving growth hormone, as reported for 100 000 children worldwide in 1999.[1] Growth hormone treatments aim to normalise growth, correct health problems associated with growth hormone deficiency, and help patients achieve an adult height in the normal range for the general population and for familial genetic potential.[2–4]

Growth hormone has been used for four decades, initially as an extract and now in recombinant form, but we still know little about its long term effects on adult height.[1] No long term controlled trial has been performed, and evaluation of the effect of growth hormone is based on comparisons with historical controls or on changes in height.[5 6] Growth hormone deficiency is poorly defined and ranges from severe to borderline. The issue of diagnostic criteria for growth hormone deficiency has been widely considered,[7–11] but profiles of patients treated around the world do not always fit the strict definitions, with little change in profile over time. Long term follow up is needed to provide data on adult height. Adult heights are generally recorded for patients who have been followed over a long period, but not for patients who stop treatment prematurely, therefore results can be biased.[12]

Most published studies have reported the short term (1 to 2 years) effects of growth hormone. Most results from long term studies published in the 1990s concern small groups of patients.[1] Cooperative studies have reported results for a small proportion (<5%) of the patients enrolled; analyses are therefore prone to selection bias.[13–15]

From 1973 to 1997, every prescription of growth hormone in France had to be approved by a central agency (Association France-Hypophyse). This facilitated the collection of data from a population based cohort of patients.

In 1997, we presented data for height for 1700 patients, 55% of whom had received growth hormone

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of human origin.[12] We then collected data on adult height of patients treated solely with recombinant growth hormone for idiopathic isolated growth hormone deficiency.

Participants and methods

Participants

Our present study included all French children who were diagnosed with isolated idiopathic growth hormone deficiency whose treatments began between 1 July 1987 and 31 December 1992 and who had attained adult height by September 1999 (fig 1).

We identified patients as having growth hormone deficiency according to the criteria used at the time, which included data on height, two growth hormone stimulation tests, or assessment of spontaneous growth hormone secretion.[12] Growth hormone assays were performed by the centres where children were receiving treatment. For analysis, patients were assigned to one of three categories according to the initial assessment of growth hormone secretion: classical growth hormone deficiency if the peak of the two growth hormone stimulation tests was below 10 µg/l, neurosecretory dysfunction if peak growth hormone concentration was >10 µg/l but spontaneous growth hormone secretion was low, and inadequate criteria if the patient had been considered growth hormone deficient but the criteria were not met. Sex steroid priming was used before growth hormone testing in 2% of patients.

Data collected

At baseline and follow up visits (every three to six months), paediatric endocrinologists recorded the height, weight, age, bone age,[16] and pubertal stage of the patients,[17 18] together with the dose of growth hormone they were taking, the frequency of injections, and any associated treatments. The Association France Hypophyse decided annually whether the treatment should be continued. Criteria for discontinuation of treatment (scored as completion) were growth velocity <3 cm/year, bone age ≥13 years (girls) or ≥15 years (boys), or height ≥160 cm (girls) or ≥170 cm (boys). The third criterion applied to 30 of the 2852 patients (1.1%).

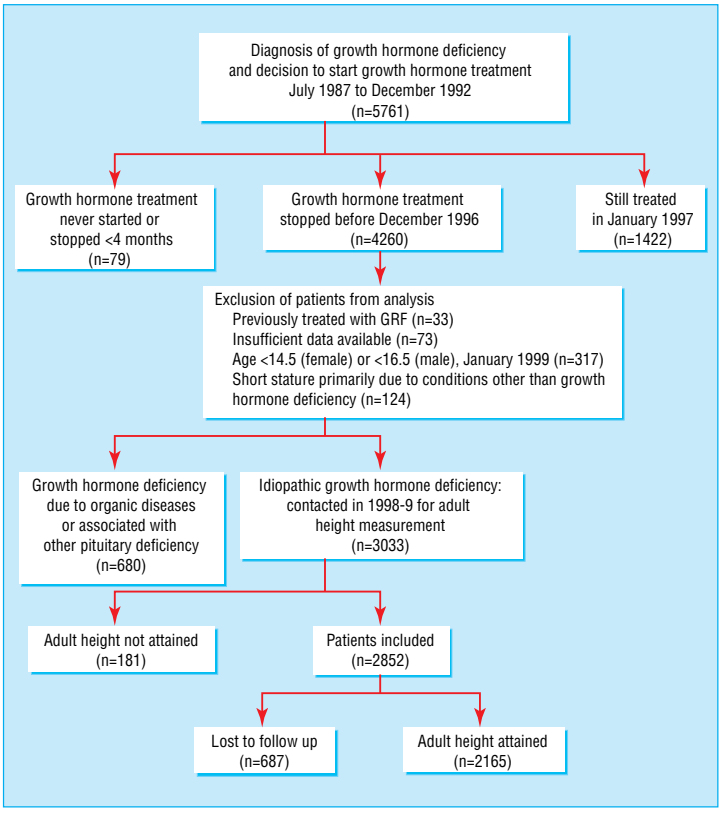

Fig 1 Description of cohort. GRF=growth hormone releasing factor

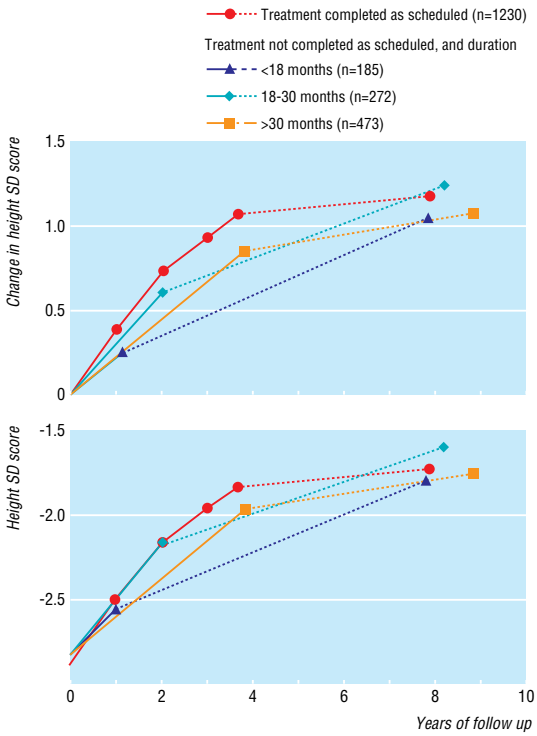

Fig 2 Changes in height in standard deviation (SD) score in patients treated with growth hormone, relative to beginning of treatment (top) and in absolute values. Solid line indicates treatment; broken line indicates end of treatment to attainment of adult height

We prospectively collected follow up data in 1998-9 from doctors or from patients who provided "self reported" values for height and weight. We considered that adult height had been attained if growth velocity was ≤1 cm/year or if bone age was ≥16 years (girls) or ≥18 years (boys) (99.6% of adult height).[19] If data on bone age were not available, bone age was estimated from previous measurement(s).[13] We obtained adult heights for 2165 patients (75.9% of 2852), 335 (15%) of which were self reported.

Analysis of growth and statistical methods

We calculated standard deviation (SD) scores of height and weight for age, sex, or gestational age, and target height.[12] Age at onset of puberty was expressed in standard deviations.[17 18] We calculated growth hormone dose in IU/kg/week and used the data to construct regression equations: dose=initial dose+K time, where K is the slope of the change in dose.

We constructed, in several stages, a model for predicting adult height.[5 20] We grouped the potential predictors into those accounting for regression

towards the mean, those describing genetic growth potential, those describing the child at baseline, and those describing growth hormone and associated treatments (see table 3). We tested variables in each group as predictors of outcome after adjusting for variables identified at previous stages. These predictors were included in a final model (table 4). The main outcome response—the difference between adult and baseline heights (standard deviation scores)—was approximately normally distributed. Two potential predictors (initial dose of growth hormone and maximum stimulated peak level of growth hormone) were log transformed to yield normally distributed variables. As all models were adjusted for baseline height, they describe adult height gain — that is, the difference between adult and baseline height expressed in standard deviations — and adult height itself (in standard deviations).[5] We used the SAS statistical package for analysis.

Results

Characteristics of participants at baseline and treatments

At a mean age of 13.3 years (boys) and 11.6 years (girls), 1178/1836 (64%) boys and 677/1016 (66%) girls were prepubertal, indicating pubertal delay (table 1). These initially prepubertal patients entered puberty late, at 14.1 (SD 1.5) years (boys) and 12.5 (1.3) years (girls) (0.9 (1.3) SD score). The mean dose of growth hormone at start of treatment was 0.42 IU/kg/week (0.29 to 0.62 IU/kg/week in 90% of the patients). Puberty inhibitors were used in 237 (8.3%) patients. Sex steroids were used in 132 (4.6%) patients, at a mean age of 15.2 (2.2) years (boys) and 12.9 (2.1) years (girls).

Table 1 Baseline characteristics and details of growth hormone therapy for the children in the study. Values are mean (SD) unless otherwise specified

	Boys	Girls
No of patients	1836	1016
Chronological age (years)	13.2 (2.2)	11.6 (1.9)
Bone age (years)	10.6 (2.3)	9.5 (2.0)
Height (SD score)	–2.6 (0.7)	–2.8 (0.8)
Growth velocity (cm/year)	4.5 (1.7)	4.7 (1.7)
Growth velocity (SD score)	–0.8 (1.4)	–0.9 (1.9)
Target height (SD score)	–1.2 (1.0)	–1.1 (1.0)
Weight (SD score)	–1.5 (0.8)	–1.5 (0.9)
Pubertal stage:		
No (%) prepubertal	1178 (64)	677 (66)
No (%) pubertal	658 (36)	339 (34)
Severity of the deficiency (%):		
Maximum peak GH concentration <3 μg/l	4	3
Maximum peak GH concentration ⩾3 μg/l and <7 μg/l	23	23
Maximum peak GH concentration ⩾7 μg/l and <10 μg/l	48	48
Neurosecretory dysfunction	9	10
Inadequate criteria for GH deficiency	16	16
Maximum GH stimulated peak concentration (μg/l)*	8.6 (3.6)	8.7 (3.5)
No (%) treatment completed as scheduled	851 (46)	673 (66)
Age on 1 January 1999	22.2 (2.4)	20.3 (2.2)
Treatment duration (year)	3.2 (1.5)	3.2 (1.4)
Year of treatment start (No (%)):		
1987-8	427 (23)	167 (16)
1989-90	877 (48)	481 (47)
1990-1	532 (29)	368 (36)
Growth hormone dose:		
Initial dose (IU/kg/week)	0.42 (0.11)	0.43 (0.11)
Slope of changes in dose (IU/kg/week/year)	–0.01 (0.05)	–0.01 (0.05)
Mean number of GH injections over the treatment period (No/week)	5.7 (0.9)	5.7 (0.8)
No (%) associated treatment:		
Sex steroids at the time of puberty	115 (6)	17 (2)
Puberty inhibitors†	128 (7)	109 (11)

SD=standard deviation.
*Median (interquartile range).
†When given for at least six months.

Changes in height

We classified patients according to whether treatment was completed (1524, 53.4%) or stopped early (table 2). When treatment was completed, the height gain was 1.0 (0.7) SD in a total of 3.6 (1.4) years; most of the height was gained during the first two years (fig 2). If treatment was stopped early, the height gain was significantly smaller (see fig 2 — for example, during the first year of treatment, 0.38 (0.39) SD *v* 0.31 (0.37) SD in the patients who completed or stopped the treatment, respectively; P=0.0003). Normal results in retests of growth hormone secretion were the reason for non-completion in 14%. Pubertal girls were the most likely to complete the treatment (272/339, 80%), prepubertal boys the least likely (485/1186, 41%).

Adult height was recorded in 81% and 70% (1232/1524 and 933/1328) of patients who completed treatment and patients who did not, respectively. After growth hormone treatment, patients who completed treatment gained 2.8 (2.8) cm, and those who did not complete treatment gained 12.3 (8.0) cm. Mean adult height was therefore similar (– 1.6 SD), 0.4 SD below target height.

Predictive models for adult height

The continued increase in height after early termination of growth hormone treatment indicated that changes in height standard deviation scores were not necessarily directly due to growth hormone. Growth is a multifactorial process and baseline differences between patients who completed treatment and those that did not may hinder comparison. Therefore, we constructed a multivariate model of factors explaining adult height (table 3). In the final model (table 4), target height and birth weight and regression towards the mean accounted for 33% of outcome variance. Variables determined at baseline that predicted a good outcome were age, bone age delay, and prepubertal status. Thus, older patients presenting no signs of puberty and with marked bone age delay had better outcomes. A negative association with male sex reflected sex dependent differences in pubertal age. Severe growth hormone deficiency was associated with better outcome. Whether or not treatment was completed, and length of treatment were independent predictors. Patients who did not complete the study grew 0.3 SD more than those who did; conversely, duration of treatment was positively associated with outcome (0.2 SD per year of treatment). Growth hormone dose did not predict adult height. Together, all variables associated with treatment accounted for 4.5% of outcome variance.

In a separate analysis (1048 prepubertal patients for whom the onset of puberty could be recorded), age at onset of puberty was positively associated with outcome and accounted for 5% of outcome variance. The proportion of patients entering puberty was higher for completers than for non-completers at an

equivalent time point (fig 3). Thus, response is related to treatment, its completion, and the onset of puberty.

Discussion

We found that children treated for idiopathic growth hormone deficiency had a mean adult height 8-10 cm below that of the general population and did not reach their target height. Children who stopped treatment early continued to grow and reached similar adult heights to patients who completed treatment. Pubertal delay accounted for a large proportion of the catch-up growth observed, and children with severe growth hormone deficiency had better outcomes than children with borderline diagnoses.

Strengths and weaknesses of the study

Studies generally assess change in height and assume that all improvement results directly from treatment. We did not select our sample according to outcome. Instead, we studied all children who started treatment; in this population, growth continued in children who stopped treatment before the end of growth. Multivariate analysis showed that patients who did not complete the treatment did better, and that length of treatment was positively associated with outcome. Patients who completed the treatment generally had more severe growth hormone deficiency and increased in height with longer treatments. Patients who do worse initially stop treatment and finally do as well. Our results are consistent with completion bias, analogous to indication bias, in which more severely affected patients receive heavier treatment.[21] Overall, treatment of a child for 3.2 years was associated with an estimated mean height gain of 4.2 cm.

We should also consider methodological aspects, such as whether the diagnosis of growth hormone deficiency was valid in our study population. The main criterion for a diagnosis of growth hormone deficiency in short children in the 1990s was a peak growth hormone value, measured in two stimulation tests, of < 10 μg/l.[11 22–24] However, this cut off has recently been questioned.[24] Sex steroid priming before growth hormone testing increases growth hormone secretion and may prevent the incorrect diagnosis of growth hormone deficiency, especially if puberty is delayed.[25] Only 2% of our patients were primed with sex steroids, and priming would have increased growth hormone secretion in many of the others. Growth velocity is an important diagnostic criterion[26–28] but was only slightly reduced in our patients compared with normative values for age and sex. However, these patients are typical of patients treated worldwide for growth hormone deficiency. All data were obtained from routine examination in daily practice and various growth hormone tests and assays were used, therefore their reliability may be questioned.

Finally, we selected a subgroup of the patients treated for growth hormone deficiency; patients with non-idiopathic growth hormone deficiency or abnormalities on pituitary magnetic resonance imaging were excluded, and patients with early onset growth hormone deficiency were excluded by the design of the study focusing on adult height. Therefore, our findings cannot be generalised to other patient populations.

Table 2 Changes in height in subgroups of patients receiving growth hormone treatment. Values are means (SD) unless otherwise specified

	Treatment completed as scheduled	Treatment stopped early
Baseline:		
No (% boys) of patients	1524 (56)**	1328 (74)
Age (years)	12.9 (2.1)**	12.3 (2.3)
No (% boys) prepubertal	881 (55)**	974 (72)
No pubertal boys	371	287
No pubertal girls	272	67
Bone age (years)	10.6 (2.2)**	9.8 (2.4)
Height (SD score)	–2.7 (0.8)	–2.7 (0.8)
Weight (SD score)	–1.4 (0.9)*	–1.6 (0.8)
Growth velocity (cm/year)	4.8 (1.8)**	4.4 (1.5)
Peak GH concentration (μg/l)†	8.5 (3.6)*	8.8 (3.5)
Target height (SD score)	–1.1 (1)	–1.2 (1)
End of treatment:		
No	1524	1328
Age (years)	16.6 (1.5)	15 (2.1)
Duration of treatment (years)	3.6 (1.4)	2.7 (1.4)
Height (SD score)	–1.7 (0.8)	–2.1 (0.9)
Height (cm) (boys/girls)	163 (6)/151 (5)	152 (11)/141 (10)
Change in height (SD score)	1.0 (0.7)	0.6 (0.6)
Adult height:		
No (% of patients at baseline)	1232 (81)	933 (70)
Age (years)	20.8 (2.9)	20.9 (2.6)
Total duration of follow up (years)	7.9 (2.2)	8.5 (1.7)
Height (SD score)	–1.6 (0.9)	–1.5 (1)
Height (cm, boys/girls)	167 (6)/154 (5)	167 (6)/154 (6)
Change in height from end of treatment (SD score)	0.1 (0.5)	0.4 (0.9)
Change in height from baseline (SD score)	1.1 (0.9)	1.1 (1)

SD=standard deviation.
Comparisons at baseline with patients who stopped treatment early (Student's *t* test and Kruskall-Wallis test for peak GH, P<0.01 considered to be significant, given the number of comparisons performed): *P<0.001; **P<0.0001.
†Median (interquartile range).

Comparison with other studies

Our patients data are similar to patients in other studies in terms of age and height standard deviation scores at the start of treatment (tables 5 and 6).[23 29 30] The growth hormone doses used were 20% lower than those used in other European countries at the time but are unlikely to explain the differences found because growth hormone dose did not predict outcome.[29] We followed 76% of our target population, whereas other reports focused on a smaller proportion (1.9% to 3.5%) of the patient sample. Such selection may focus on patients who responded well to treatment, providing an overoptimistic view of the results (fig 2). This probably explains the 15% to 30% difference from other studies. Our study design also enabled us to take into account the potential for spontaneous catch up of patients treated.

Influence of pubertal delay

Overall, the onset of puberty was delayed considerably in our patients, as in the Pharmacia International Growth Database,[31] and variables linked to pubertal delay positively were associated with adult height. This strongly suggests that many had constitutional delay in growth and puberty, which should not be confused with growth hormone deficiency.[2 25 32]

Conclusion

Long term treatment with growth hormone has no clearcut benefit in a large proportion of patients treated for so called idiopathic isolated growth hormone deficiency. Most of the patients actually have pubertal delay and a potential for spontaneous catch

Table 3 Predictive factors for adult height gain in patients with growth hormone deficiency: step by step evaluation of the variables

Variable	Regression coefficient*	P value
Variables for regression towards the mean		
Height at baseline (SD score)†	–0.45	<0.0001
Duration of follow up from baseline to adult†	0.06	<0.0001
Interaction of height and duration†	0.01	0.21
Patients' characteristics tested individually with previous variables (†) as adjustment covariates		
Sex (male=1, female=0)†	0.14	0.0005
Birth weight (SD score)†	0.21	<0.0001
Target height (SD score)†	0.36	<0.0001
Birth height (SD score)	0.20	<0.0001
Baseline variables tested individually with previous variables (†) as adjustment covariates		
Baseline measurements:		
Age (years)†	0.16	<0.0001
Weight (SD score)†	–0.25	<0.0001
Pubertal (yes=1, no=0)†	0.12	0.0017
Bone age delay (years)†	0.23	<0.0001
Log peak growth hormone concentration (μg/l)†	–0.07	0.025
Growth velocity (SD score)	0.04	0.001
Interaction between age and sex	0.01	0.66
Interaction between growth velocity and log peak growth hormone concentration	0.07	0.0003
Interaction between target height and log peak growth hormone concentration	0.01	0.50
Treatment and follow up variables tested individually with previous variables (†) as adjustment covariates		
Duration of treatment (years)†	0.14	<0.0001
Completion of treatment as scheduled (yes=1, no=0)†	0.01	0.75
Log mean growth hormone dose (IU/kg/week)	0.14	0.067
Log initial growth hormone dose (IU/kg/week)	0.12	0.067
Change in growth hormone dose (IU/kg/week/year)	0.28	0.37
No of injections/week	0.03	0.11
Age at onset of puberty (SD score)‡	0.27	<0.0001
Sex steroid treatment (yes=1, no=0)	0.12	0.092
Treatment with GnRH agonists (yes=1, no=0)	–0.08	0.13
Peak GH concentration at re-evaluation (μg/l)	0.00	0.76
Adult height recorded by doctor (1) or self reported (0)	–0.04	0.32
Size of centre (in three groups, <50, 50-150 or ⩾150 patients per centre)	0.77	0.40
Interaction between ages at onset of puberty and completion of treatment	–0.04	0.10
Interaction between duration of treatment and completion of treatment	0.02	0.44
Interaction between completion of treatment and peak growth hormone concentration at re-evaluation	0.00	0.54
Interaction between completion of treatment and log mean growth hormone dose	0.26	0.013

GnRH=gonadotropin releasing hormone; SD=standard deviation.
*Regression coefficient represents the change in SD score per unit change in predictor.
†Variables retained in final model.
‡This variable could be recorded with precision only in patients entering puberty during the course of treatment (not in patients who had already entered puberty by the start of the treatment, nor in patients who stopped treatment early); therefore, it was not included in the final model.
Some of the variables that were individually associated with outcome during the construction of the model did not remain significant predictors after adjusting for important covariates introduced at the next steps.

up, which must be taken into account when measuring the effect and cost effectiveness of growth hormone treatments. The diagnosis of idiopathic isolated growth hormone deficiency should be restricted to a small minority of patients with severely and permanently altered growth hormone secretion: our results support the use of growth hormone in such patients. We propose that peak growth hormone values should be below 2-4 μg/l, that sex steroid priming is used before growth hormone testing, and that more attention is paid to the causes of hypopituitarism.

Long term controlled trials to evaluate the effects of growth hormone treatment in patients who do not have growth hormone deficiency are needed, given the number of children treated worldwide. We should try to identify predictive markers for short stature in adults and focus intervention on patients at higher risk.

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Table 4 Predictive factors for adult height gain in patients with growth hormone deficiency: final model

Variable*	Regression coefficient† (95% CI)	P value
No of patients in final model‡ (r^2)	1885 (0.58)	
Patients' characteristics:		
Target height (SD score)	0.22 (0.19 to 0.25)	<0.0001
Birth weight (SD score)	0.11 (0.08 to 0.13)	<0.0001
Sex (male=1, female=0)	–0.54 (–0.62 to –0.47)	<0.0001
Baseline variables:		
Age (years)	0.31 (0.28 to 0.33)	<0.0001
Pubertal (yes=1, no=0)	–0.19 (–0.26 to –0.11)	<0.0001
Bone age delay (years)	0.18 (0.15 to 0.20)	<0.0001
Weight (SD score)	–0.19 (–0.23 to –0.14)	<0.0001
Log peak growth hormone concentration (μg/l)	–0.08 (–0.13 to –0.03)	0.002
Treatment variables:		
Completion of treatment as scheduled (yes=1, no=0)	–0.30 (–0.37 to –0.22)	<0.0001
Duration of treatment (years)	0.22 (0.19 to 0.25)	<0.0001

SD=standard deviation.
*The model includes baseline height SD score, time interval between baseline and adult height measurements, and the interaction between these two variables; therefore, the model similarly predicts the factors for adult height itself (in SD).
†The regression coefficient represents the change in SD score per unit change in predictor.
‡The number of subjects corresponds to those with no missing value for any predictor variable.

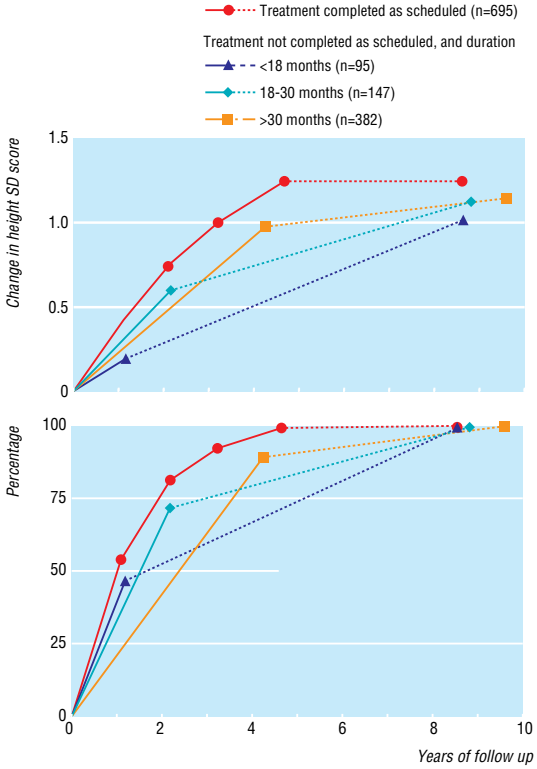

Fig 3 Changes in height in prepubertal patients treated with growth hormone (top) and proportion of patients who reached pubertal Tanner stage 2[17–18] (bottom). Solid line indicates treatment; broken line indicates end of treatment to attainment of adult height

What is already known on this topic

Large numbers of children are treated with recombinant growth hormone for so called idiopathic isolated growth hormone deficiency

The effect on adult height is unclear because of a lack of controlled trials and analysis, and that subgroups, rather than entire populations, are analysed.

What this study adds

Half the patients treated for idiopathic isolated growth hormone deficiency stop treatment before reaching adult height and achieve adult heights similar to those of patients who complete their treatment

Many patients diagnosed as having growth hormone deficiency actually have pubertal delay

A small proportion of patients with severe growth hormone deficiency respond better to treatment than patients with less severe growth hormone deficiency

Hypophyse. The following clinicians were involved in the follow up of a large number of children in the study: Jacques Battin, Pascale Berlier, Michel Bost, Jean-Jacques Bouquier, Raja Brauner, Jacques Bringer, Jean-Pierre Charvet, Pierre Chatelain, Michel Colle, Paul Czernichow, Michel David, Francois Despert, Pierre-Andre Doyard, Herve Dubourg, Robert Dumas, Blandine Esteva, Christine Fedou, Anne Fjellestad-Paulsen, Patrick Garandeau, Philippe Garnier, Christine Gendrel, François Girard, Micheline Gourmelen, Muriel Houang, Roger Jean, Monique Jesuran, Jean-Claude Job, Jean-Georges Juif, Yves Lebouc, Marcel Lecornu, Bruno Leheup, Anne Lienhardt, Jean-Marie Limal, Eric Mallet, Georges Malpuech, Roger Mariani, Catherine Naud-Saudreau, Isabelle Oliver, André Orsetti, Christian Pauwels, Marc Petrus, Catherine Pienkowski, Theresa Pierret, Michel Pierson, Graziella Pinto, Olivier Puel, Raphael Rappaport, Marie-Charles Raux-Demay, Denis Reiss, Pierre Rochiccioli, Bernard Sablayrolles, Charles Saab, Gilbert Simonin, Sylvie Soskin, Charles Sultan, Jean-Edmond Toublanc, and Jacques Weill.

Contributors: JCC and JC had the original idea for the study and organised it; MN, MT, JL, SC, IBS, and JLC participated in the design of the study or provided advice in presentation and interpretation of the results. EE was responsible for data analysis and model construction. All authors commented on earlier drafts and helped to interpret the findings. JCC and JC are the guarantors.

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Competing interests: Competing interests involving growth hormone manufacturers: J-CC, MN, MT, JL, SC, J-LC, and JC have been reimbursed for attending conferences; J-CC, MT, and J-LC have received fees for speaking; MT has received funds for research; J-LC has received fees for organising education; J-CC, MN, MT, JL, SC, and J-LC have been investigators in clinical trials sponsored by manufacturers. EE and IBS: no competing interests declared.

Table 5 Comparison of baseline data from patients with idiopathic growth hormone deficiency from the present study with other published series

Inclusion period	No	Median age (years)	Median height (SD score)	Max growth hormone peak (µg/l)
Pharmacia International Growth Database				
1987-98[23,29]	1 2151	10.3	–2.7	5.6
1996-9[30]:				
United States	1378	10.9	–2.4	6.3
Elsewhere	2459	10.6	–2.4	6.5
This study* 1987-92	5761	10.7	–2.7	8.6

SD=standard deviation.
*For comparison with other series, we have indicated the age at start of treatment for the entire group of 5761 patients (fig 1) and not for the subgroup evaluated to adult height.

Table 6 Comparison of adult height data from patients with idiopathic growth hormone deficency in the present study with other published series

	No of patients enrolled	Age at enrolment (years)	No of adult heights reported (% of enrolled)	Adult (or near adult) height (SD score)	Change in height (SD score)
National Cooperative Growth Study[15]	13 876	11.5	258 (1.9)	–1.4	1.3
Pharmacia International Growth Database[14]	10 657	9.8	369 (3.5)	–1.5	1.6
This study	2852	12.6	2165 (76)	–1.6	1.1

SD=standard deviation.

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