

range from 74% to 84% and are comparable to those reported in previous series. Most reports of incontinence surgery give no information on non-attenders or the handling of missing data. They have by default assumed that non-attenders are equivalent to attenders. We have considered non-attenders or patients with missing data as treatment failures.

Long term follow up is needed to assess the continuing success of the two procedures and to provide further data on the development of prolapse and tape erosion; follow up to five years is planned.

We thank the patients and technical, secretarial, nursing, and medical staff of the participating hospitals, the monitoring staff of Ethicon, James Browning as the sponsor medical advisor to June 2000, Marjory Willins (trial manager), Jane Gibson (trial administration), Ailie Smith (quality assurance), and Peter Wilkinson (statistical advice and analysis).

Contributors: See [bmj.com](http://bmj.com)

Competing interests: KW was supported by a grant from Ethicon, which also provided materials and additional support to collaborating centres. PH and KW have been reimbursed by Ethicon for expenses associated with attending conferences where this, and related work, has been presented.

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(Accepted 15 May 2002)



The full version of this article appears on [bmj.com](http://bmj.com)

Editorial by Saenger

Groupe hospitalier Cochin-Saint Vincent de Paul and Faculté

Cochin-Université Paris V, 75014 Paris, France

Department of Paediatric Endocrinology and INSERM U561

Jean-Claude Carel  
professor of paediatrics

Jean-Louis Chaussain  
professor of paediatrics

Irène Bastié-Sigeac  
clinical research associate

Department of Biostatistics  
Emmanuel Ecosse  
statistician

Joël Coste  
associate professor of biostatistics

continued over

*BMJ* 2002;325:70-3

## 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

Jean-Claude Carel, Emmanuel Ecosse, Marc Nicolino, Maité Tauber, Juliane Leger, Sylvie Cabrol, Irène Bastié-Sigeac, Jean-Louis Chaussain, Joël Coste

### 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.<sup>1</sup> 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.<sup>2-4</sup>

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.<sup>1</sup>

We presented here data for 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.

## Participants and methods

### Participants

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.<sup>5</sup> Sex steroid priming was used before growth hormone testing in 2% of patients.

### Data collected

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  $\geq$  13 years (girls) or  $\geq$  15 years (boys), or height  $\geq$  160 cm (girls) or  $\geq$  170 cm (boys). The third criterion applied to 30 of the 2852 patients (1.1%).

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  $\leq$  1 cm/year or if bone age was  $\geq$  16 years (girls) or  $\geq$  18 years (boys). We obtained adult heights for 2165 patients (76% of 2852).

### 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.<sup>5</sup> Age at onset of puberty was expressed in standard deviations.<sup>6,7</sup>

We constructed, in several stages, a model for predicting adult height (for details see [bmj.com](http://bmj.com)).<sup>8,9</sup> The model was adjusted for baseline height, and describes adult height gain — that is, the difference between adult and baseline height expressed in standard deviation — and adult height itself (in standard deviations).<sup>8</sup>

## 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. 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).

### Changes in height

We classified patients according to whether treatment was completed (1524, 53.4%) or stopped early (table 1). 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 (figure). If treatment was stopped early, the height gain was significantly smaller ( $P=0.0003$ ). Normal results in retests of growth hormone secretion were the reason for non-completion in 14%.

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.

Department of Paediatric Endocrinology, Hôpital Robert Debré, 75019 Paris

Juliane Leger  
associate professor of paediatrics

Paediatric Endocrinology Unit, Hôpital Trousseau, 75571 Paris

Sylvie Cabrol  
associate professor of paediatrics

Department of Paediatric Endocrinology, Hôpital Debrousse, Lyon, 69322 France

Marc Nicolino  
associate professor of paediatrics

Department of Paediatric Endocrinology, Hôpital des Enfants, 31026 Toulouse, France

Mait Tauber  
professor of paediatrics

Correspondence to: J-C Carel  
carel@cochin.inserm.fr

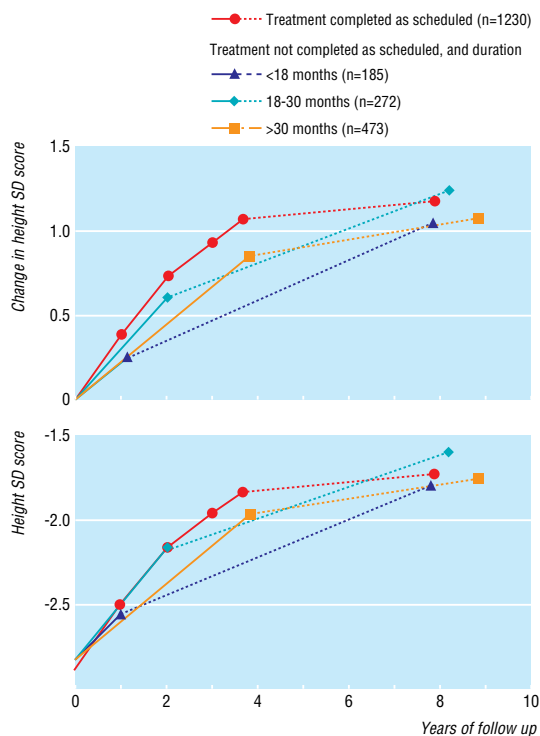
**Table 1** Changes in height in subgroups of patients receiving growth hormone treatment. Values are means (SD) unless otherwise specified

	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 ( $\mu\text{g/l}$ )†	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 Kruskal-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).



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

**Predictive models for adult height**

We constructed a multivariate model of factors explaining adult height. In the final model, target height and birth weight and regression towards the mean accounted for 33% of outcome variance (table 2). 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

**Table 2** 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 <sup>2</sup> )	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.

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.

**Discussion**

**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. Patients who completed treatment generally had more severe growth hormone deficiency and seemed to benefit from growth hormone in a time dependent fashion. Our results are consistent with completion bias, analogous to indication bias, in which more severely affected patients receive heavier treatment.<sup>10</sup>

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.<sup>11-14</sup> However, this cut off has recently been questioned.<sup>14</sup> 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.<sup>15</sup> 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<sup>16-18</sup> 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.

**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. 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.<sup>19</sup> We followed

## 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

76% of our target population, whereas other reports focused on a smaller proportion (1.9% to 3.5%) of the patient sample.<sup>20 21</sup> Such selection may focus on patients who responded well to treatment, providing an overoptimistic view of the results (figure). This probably explains the 15% to 30% difference from other studies.

### Influence of pubertal delay

Overall, the onset of puberty was delayed considerably in our patients, as in the Pharmacia International Growth Database,<sup>22</sup> 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.<sup>2 15 23</sup>

### 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 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.

We thank Vean Eng Ly, Sabine Ximenes, and Dr Elisabeth Kind for their invaluable contributions. Drs Noel Cabet, Valérie Porra, Stéphane Chen, and Francine Mallet also participated in data collection. We also thank all the physicians involved in the follow up of patients and in the review process at Association France-Hypophyse. See [bmj.com](http://bmj.com) for the clinicians who were involved in the follow up of a large number of children in the study.

Contributors: see [bmj.com](http://bmj.com)

Funding: The study was supported by a grant from Programme Hospitalier de Recherche Clinique AOM96016.

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.

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(Accepted 11 December 2001)