Final height of short subjects of low birth weight with and without growth hormone treatment

S Zucchini, E Cacciari, A Balsamo, A Cicognani, D Tassinari, E Barbieri, S Gualandi

Abstract

Aim—To compare final height in two groups of low birth weight children examined for short stature: the first group untreated because of normal growth hormone (GH) secretion, the second treated with human growth hormone (hGH) because of abnormal secretion.

Methods—A total of 49 subjects born at term of birth weight below the 10th centile were consecutively examined for idiopathic short stature. The first group of subjects (n = 20) with normal GH peaks after pharmacological tests (>8 µg/l) spontaneously reached final height. The second group (n = 29) with abnormal secretion were treated with hGH (20 U/m²/week) for 36–84 months. At diagnosis the two groups were of similar height for chronological age and bone age, and had similar target height.

Results—In both groups final height was significantly lower than target height (−0.65 (SEM 0.20) in untreated cases, −0.61 (0.18) in treated cases). Fewer than one third of subjects had a final height above target height. Final height data of untreated and treated cases were not different. In the treated group the best results were obtained by those subjects who improved their height for bone age after three years of therapy.

Conclusions—Our subjects with birth weight below the 10th centile remained as short adults with final height below target height. Treatment with hGH 20 U/m²/week in those diagnosed as deficient was not effective, with final results overlapping those of untreated subjects.

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It is generally recognised that babies of low birth weight with persistent postnatal short stature do not have a favourable statural outcome.[1–3] Replacement treatment with human growth hormone (hGH) at the usual doses has led to equivocal results in those with low birth weight or length.[4–7] This evidence is from short term studies, in which, despite promising initial growth acceleration, excessive maturation of bone age (BA) led to a fall in height prediction.[4 5] Few studies have provided final height.[6 7] Furthermore, it is not clear whether the traditional diagnostic tests to define GH secretion, often described as unreliable in choosing which short subjects are most likely to be treated successfully,[8] are of use in low birth weight, short children.

We evaluated retrospectively the final height data of two groups of subjects with birth weight less than the 10th centile, who were referred to us for idiopathic short stature. The first group was diagnosed as normal after provocative tests and therefore untreated; children in the second group were treated as they were found to be GH deficient after the same tests.

Subjects and methods

SUBJECTS

The study included 49 subjects born at term with birth weight below the 10th centile according to Wilcox and others,[9] consecutively referred to us because of short stature in the period 1990–94. All subjects underwent two provocative tests and we chose a cut off of 8 µg/l to define pathological GH secretion: 20 cases had a peak ⩾8 µg/l and so were not treated, while 29 cases had a pathological secretion and were treated with hGH. Table 1 shows their clinical characteristics.

No subjects had a specific syndrome as a cause of low birth weight. We chose birth weight rather than length as our discriminator as it is the most reliable and reproducible parameter.[10] All subjects had short stature—that is, height below the 3rd centile (n = 34) according to Tanner *et al* or between the 3rd and the 10th centile but growth less than 3 cm/year and a predicted height lower than target height (n = 15). Puberty occurred and progressed spontaneously in all subjects.

Subjects with GH deficiency

This group of subjects had isolated and idiopathic GH deficiency and was treated with hGH at a constant dose of 20 U/m²/week with 6–7 injections/week for a median period of 55.7 months (range 36–84 months). hGH dose was adjusted every six months and treatment continued until final height (growth less than 0.5 cm in the last six months of treatment). At

Department of Pediatrics, University of Bologna, Bologna, Italy
S Zucchini
E Cacciari
A Balsamo
A Cicognani
D Tassinari
E Barbieri
S Gualandi

Correspondence to:
Prof. E Cacciari, Clinica Pediatrica, Via Massarenti 11, 40138 Bologna, Italy
Cacciari@alma.unibo.it

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Table 1   Clinical and auxological characteristics at diagnosis of the two groups of subjects studied

	M/F	Birth weight (g)	CA (y)	Height for CA SDS	Height for BA SDS	Predicted height SDS	Target height SDS	Prepubertal/ pubertal
Untreatred group (n = 20)	9/11	2558 (58)	10.7 (0.6)	−1.97 (0.12)	−0.95 (0.33)	−1.64 (0.25)	−1.22 (0.15)	13/7
Treated group (n = 29)	16/13	2420 (57)	10.9 (0.4)	−2.28 (0.09)	−0.97 (0.20)	−1.83 (0.19)	−1.17 (0.14)	19/10
Difference		138	0.2	0.31	0.02	0.19	0.05	

Data are expressed as mean (SEM).

Table 2   Final results in the two groups of subjects studied

	Final height	Target height − final height	Cases with final height > target height
Untreated group (n = 20)	−1.87 (0.21)	0.65 (0.20)	6/20 (30%)
Males (n = 9)	−1.81 (0.31)	0.56 (0.30)	3/9 (33%)
Females (n = 11)	−1.92 (0.30)	0.75* (−0.33 + 1.35)	3/11 (27%)
Treated group (n = 9)	−1.78 (0.18)	0.61 (0.18)	7/29 (24%)
Males (n = 16)	−1.77 (0.25)	0.63 (0.27)	4/16 (25%)
Females (n = 13)	−1.80 (0.25)	0.83* (0.07 + 1.20)	3/13 (23%)

In the first two columns data are expressed in SDS as mean (SEM) or median* (interquartile range).
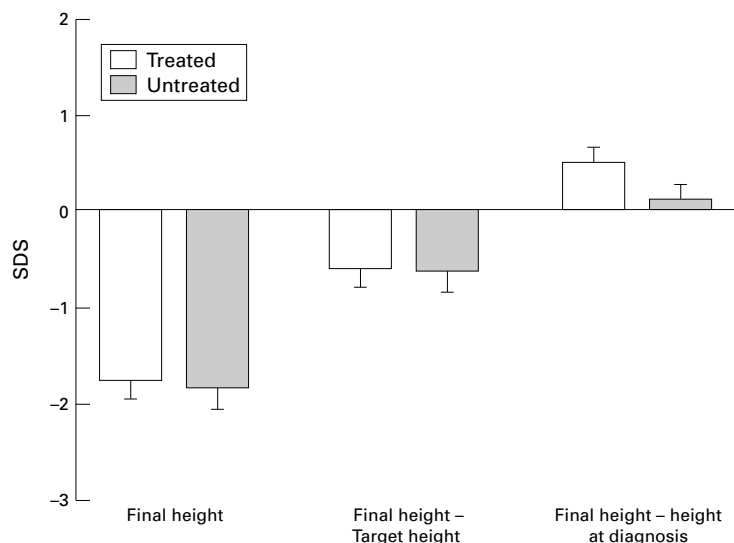

Figure 1   Final height, final height − target height, and final height − height for CA at diagnosis in untreated and treated subjects.

diagnosis no subject presented any disturbance apart from GH deficiency and they reached final height without other endocrinological problems.

METHODS

At initial diagnosis all subjects had two pharmacological tests (arginine and L-dopa) performed as previously described.[11] No patient had GH antibody titres which could have influenced the results of the tests. Birth weight and gestational age values were collected from the individual birth charts of the patients. Those treated with hGH had an auxological evaluation every six months and left hand x ray for bone age determination at least once a year. In the treated subjects final height was established when height velocity was less than 0.5 cm in the preceding six months. In the untreated subjects final height was measured at chronological age (CA) greater than 16 years in females and greater than 18 years in males. At recording of final height all subjects had completed pubertal development and females had been menarchal for at least three years.

We defined target height as sex corrected mid-parental height (father's height + mother's height/2 + 6.5 cm for males and −6.5 cm for females) and was expressed in standard deviation score (SDS) units. Mother's height was measured in all cases and father's height in 43 cases (87%), the remaining fathers' heights being obtained from their general practitioners. Height was measured in the morning with a Harpenden stadiometer. BA was evaluated

according to the methods of Greulich and Pyle,[12] and height was expressed as SDS for CA and BA.[13] [14]

Serum GH was measured by a commercial solid phase radioimmunoassay (Technogenetics, Milan, Italy).

STATISTICAL ANALYSIS

For normally distributed data the statistical significance was assessed using Student's *t* test, paired *t* test, Pearson's *r* correlation coefficient, and multiple regression analysis. For non-normally distributed data, the Mann–Whitney test and Pearson's *r* correlation coefficient computed on the ranks were used.

Results

As shown in table 1, both groups of subjects were clinically similar at evaluation. Height for CA had a tendency to be lower in the group diagnosed as GH deficient. Table 2 shows final height data in untreated and treated cases. There was no statistically significant difference between the two groups. Final height was significantly lower than target height in both groups (p = 0.005 in the untreated group; p = 0.003 in the treated group; paired *t* test); in both groups fewer than one third of subjects reached a final height above target height.

In the treated group, height gain SDS (final height SDS − height SDS at start) of the subjects starting treatment before puberty was not significantly greater than those treated at puberty (0.56 (SEM 0.18) *v* 0.37 (0.35); NS). Mean final height of those who increased their height for BA after three years of therapy (n = 10) was significantly higher than that of the remaining 19 subjects (−1.33 (SEM 0.30) *v* −2.07 (0.20); p < 0.05). Figure 1 shows the lack of difference in final outcome between treated and untreated subjects. The parameters considered were not statistically different between the two groups.

In both groups, final height was correlated with target height (untreated group: *r* = 0.34, p < 0.05; treated group: *r* = 0.41, p < 0.05), height for CA at diagnosis (untreated group: *r* = 0.38, p < 0.05; treated group: *r* = 0.78, p < 0.0001), and height for BA at diagnosis (untreated group: *r* = 0.39, p < 0.05; treated group: *r* = 0.42, p < 0.05). In the treated group no correlation was found between final height and GH peaks after pharmacological tests, height velocity after the first year of treatment, and duration of therapy. Multiple regression analysis confirmed the greater influence of height for CA SDS at diagnosis in the untreated group (r^2 = 0.61; p<0.0001), followed by CA at diagnosis (r^2 change = 0.10; p < 0.05) and in the treated group of height for BA SDS at diagnosis (r^2 = 0.15; p < 0.05), followed by height for CA SDS (r^2 change = 0.12; p < 0.05) and CA at diagnosis (r^2 change = 0.19; p < 0.01). Table 3 shows the correlations between the gap final height − target height SDSs. Collinearity between the various variables was excluded.

Table 3   Correlations between the gap target height − final height SDSs and various clinical and auxological parameters

	Untreated group (n = 20)	Treated group (n = 29)
Height for CA SDS	r = −0.44, p < 0.05	r = 0.39, p < 0.05
Height for BA SDS	NS	r = 0.38, p < 0.05
CA	r = −0.40, p < 0.05	NS
Target height SDS	NS	r = −0.43, p = 0.01
Multiple regression analysis	Height for CA SDS $r^2 = 0.20$, p = 0.05	Target height SDS $r^2 = 0.19$, p < 0.05
	Target height SDS r^2 change = 0.39, p = 0.0001	Height for CA SDS r^2 change = 0.12, p < 0.05
	CA r^2 change = 0.11, p < 0.05	CA r^2 change = 0.10, p < 0.05

Discussion

We have shown that children examined for short stature, born at term without any specific syndrome but with birth weight below the 10th centile, usually become short adults. Whether treated or untreated, our patients had a mean final height close to the 3rd centile and less than target height. This is not surprising, as it is known that children born small for gestational age, who do not catch up in the first years of life, are at risk of short stature. Thus, it seems that low birth weight (not necessarily below the 3rd centile), implies a negative prognosis for adult height when postnatal short stature persists.

The analysis of our untreated group confirms[6 15 16] that short subjects with low birth size, will not only remain well below their target height, but also do not reach their prediction, with final height close to height for CA at diagnosis. It was in fact the latter parameter, rather than height for BA at diagnosis, which had the strongest influence both on final height and on the gap between target height and final height (the greater the height for CA SDS at evaluation, the lower the gap). Therefore the theoretical advantage of bone age delay shown by our subjects at evaluation was probably nullified by pubertal progression.

Treating our subjects diagnosed as GH deficient led to the same result as that of the non-deficient untreated group. Our findings were even more disappointing than those obtained by Coutant and colleagues,[6] who also compared the results of two groups of small for gestational age subjects using lower GH doses (0.4 U/kg/week). Comparison of their data and ours, which were obtained with almost twice as much hGH, does not support the use of higher hGH doses in this group of short subjects. However, recently published short term data,[17] obtained with higher hGH doses (1–2 U/kg/week), have suggested the opposite. Since the reliability of GH stimulation tests is debated,[8 18 19] we cannot be sure of having treated those subjects likely to have the best response to therapy. Furthermore, small for gestational age short subjects usually show a blunted response to GH when compared to short subjects of appropriate birth weight. This has been shown in both short term studies,[4 5 20] and some of the few studies providing final height.[21 22]

In general the correlations calculated in our treated group suggested that treatment had little influence in modifyng statural destiny when examined at a mean age of 10.7 years. In fact variables such as first year response to treatment, therapy duration, and GH peaks after tests did not seem important, while final height was more dependent on height for BA and height for CA at diagnosis. Furthermore an earlier start of therapy, as in the treatment of our prepubertal subjects versus the pubertal ones, proved of little value. This partly conflicts with the findings of other studies,[17 21] which used higher doses, in which younger subjects seemed to benefit mostly from therapy. As a further confirmation, the analysis of the factors influencing the entity of the gap between target height and final height in the treated group (table 3) showed only that those starting treatment from a greater height for CA and BA and shorter parents had a greater chance of becoming taller than their parents. The latter result could be also a "regression towards the mean" effect.

We confirm[22] that careful auxological evaluation of patients during treatment is a reliable indicator of the final result: in fact our treated subjects who improved their height for BA for three years (10/29 cases) obtained a more significant effect with a mean final height of −1.33 SDS.

We conclude that our subjects, of birth weight below the 10th centile, referred with short stature, remain on average short adults with final height below target and predicted height. Treatment with hGH at standard doses for a mean of nearly five years in those diagnosed as deficient had no effect, with final results overlapping in the two groups.

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Children in Tibet

"They are small but otherwise healthy". "We need local growth charts because American and European charts are not relevant to these children". These are things that are said about stunted children in developing countries. But they are wrong. There is good evidence that well nourished children, wherever they live, grow in accord with international growth standards. A report from Tibet (Nancy S Harris and colleagues. *New England Journal of Medicine* 2001;**344**:341–7) has shown that stunted children there are not healthy.

Over 2000 Tibetan children aged up to 7 years were examined in 1994–95. It was estimated that 13.2% of the children born to the mothers in the survey had died. Half of the children (1067 out of 2078) had a z score for height of −2.0 or lower. Mean z score was −0.5 in the first 6 months of life, −1.6 by 12 months, and around −2.0 to −2.4 at later ages. Fifty six per cent of children aged over 24 months were stunted (z score −2.0 or lower) and 24% were severely stunted (z score −3.0 or lower). Stunting was found in 35% of urban and 60% of non-urban children. Two thirds of all the children examined had clinical rickets and 85% of 130 children tested had low serum concentrations of 25-hydroxyvitamin D. Fifty five per cent had abdominal distention, 43% hair depigmentation, and 40% dental caries. Three per cent had a goitre. Children living outside towns were less healthy than urban children.

Although many of the children had stunted growth, they were not wasted, their weight-for-height scores being normal. Nevertheless, 14% of those less than 24 months old had a mid-upper-arm circumference of less than 11.5 cm (a value previously shown to be associated with increased mortality) and 75 % of those in their second year had a chest-to-head circumference ratio of less than 1.0, indicative of undernutrition. There was evidence that the average height of 3 year olds had decreased between 1986 and 1995. There was no consistent relationship between the height of these children and the altitude at which they lived.

Many children in Tibet are small for their age and this stunting is due to malnutrition and is associated with considerable morbidity. The writers of an accompanying editorial (*Ibid*: 373–4) refer to "a silent calamity" and call for "the political and economic commitment to say that enough is enough; it is time to make things better".

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