

ORIGINAL ARTICLES

Spontaneous growth in idiopathic short stature

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Abstract

Documenting the spontaneous growth pattern of children with idiopathic short stature (ISS) should be helpful in evaluating the effects of growth promoting treatments. Growth curves for children with ISS were constructed, based on 229 untreated children (145 boys and 84 girls) from nine European countries. The children were subdivided according to target range and onset of puberty, and the growth of these subgroups was evaluated from standard deviation scores (SDS). At birth, children with ISS were already shorter than normal (means; boys - 0.8 SDS, girls - 1.3 SDS). Height slowly decreased from - 1.7 SDS at the age of 2 years to - 2.7 SDS at the age of 16 years in boys and 13 years in girls. Final height was - 1.5 SDS in boys and - 1.6 SDS in girls (mean (SD): boys 164.8 (6.1) cm, girls 152.7 (5.3) cm), which was 5-6 cm below their target height. The onset of puberty was delayed (boys 13.8 (1.3) years, girls 12.9 (1.1) years). Subclassification resulted in similar growth curves. These specific growth data may be more suitable for evaluating the effects of growth promoting treatments than population based references.

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Keywords: growth, growth disorders, reference values.

Several disease specific growth charts have been constructed during the last decade (for a review, see Ranke¹). These charts are essential for following spontaneous growth and evaluating the effects of therapeutic intervention in children with particular growth disorders. In most children with short stature in whom no specific cause can be found, the term idiopathic short stature (ISS) is used.²⁻⁵ Despite the high prevalence of ISS, no specific growth charts have been constructed so far, and the spontaneous and stimulated growth of these children is usually compared to the growth of normal children.⁶⁻⁸

Children with ISS have usually been subclassified into those of normal height for their genetic background (termed familial short stature, FSS), those with delayed growth and

maturation (termed constitutional delay of growth and adolescence, CDGA), and those with a combination of familial short stature and constitutional delay.^{3-5,9} However, no generally accepted criteria for this subclassification are available. Recently an international consensus was achieved on the definition and classification of ISS.¹⁰ According to this consensus, children with ISS are classified before onset of puberty as familial short stature or non-familial short stature (non-FSS), depending on whether their height is within their target range or not. Both FSS and non-FSS can be associated with normal or delayed puberty.

Over the last 10 years, children with ISS have been subjected to growth promoting treatments in many clinical trials. So far, no long term controlled studies have been reported. To allow proper interpretation of the results of uncontrolled studies, we have investigated the growth pattern of a large series of untreated children with ISS. We have constructed growth charts and have compared these with the British references.¹¹ We have, in addition, evaluated the differences in growth and onset of puberty in children, who were classified on the basis of target range or pubertal onset.

Methods

From paediatric departments of nine European countries, 229 children (145 boys, 84 girls) with ISS were selected (the Netherlands, 126; United Kingdom, 23; France, 23; Germany, 21; Austria, 9; Israel, 8; Finland, 8; Spain, 7; and Greece, 4). Inclusion criteria were: at least four height measurements available, of which at least one was more than 2 standard deviations (SD) below the mean according to British references¹¹; birth weight > - 2 SD according to gestational age¹²; and growth hormone peak in at least one stimulation test of ≥ 20 mU/l. Children with an organic cause of growth failure or dysmorphic syndromes were excluded. All available height measurements of these children were collected, mainly retrospectively. The final height measurement was performed at the local paediatric department (n = 85) or at the patient's home following detailed written measuring instructions (n = 56). The total number of measurements was 3419, giving a

Table 1 Number, observed and smoothed mean and SD of the height measurements in cm, and the SDS of the smoothed measurements based on British reference of children with idiopathic short stature

Age (years)	Boys						Girls					
	No	Observed values		Smoothed values			No	Observed values		Smoothed values		
		Mean	SD	Mean	SD	SDS		Mean	SD	Mean	SD	SDS
0	112	49.9	2.4	49.9	2.9	-0.77*	56	48.8	2.2	48.8	2.4	-1.32*
1	39	69.5	3.0	69.5	2.9	-1.84	23	68.2	2.1	68.2	2.4	-1.69
2	44	79.9	3.7	79.9	3.0	-1.81	25	78.9	2.7	78.9	2.5	-1.74
3	42	88.0	3.4	88.0	3.0	-1.62	29	86.2	2.9	86.2	2.5	-1.79
4	54	94.0	3.3	94.0	3.1	-1.76	33	92.4	2.9	92.4	2.6	-1.86
5	53	99.0	3.0	99.5	3.1	-1.87	29	97.4	2.5	97.4	2.7	-2.09
6	60	105.0	3.3	105.0	3.2	-1.89	37	102.4	3.0	102.4	2.8	-2.15
7	57	109.9	2.8	109.9	3.2	-1.93	41	108.2	2.9	107.3	2.9	-2.18
8	49	114.4	3.1	114.4	3.3	-2.07	48	112.4	2.8	112.4	3.1	-2.17
9	58	118.9	3.2	118.9	3.4	-2.12	50	116.9	3.1	116.9	3.2	-2.28
10	68	123.6	3.5	123.6	3.5	-2.13	49	121.8	2.9	120.9	3.4	-2.42
11	72	127.5	4.0	127.5	3.7	-2.15	55	125.7	3.5	125.7	3.6	-2.43
12	73	131.4	3.8	131.4	3.9	-2.21	60	130.9	3.8	130.9	3.8	-2.42
13	82	135.7	3.6	135.7	4.0	-2.27	58	136.4	4.5	136.4	4.0	-2.77
14	83	141.1	4.1	141.1	4.2	-2.37	50	142.0	4.7	142.0	4.3	-2.75
15	78	147.3	4.5	147.3	4.4	-2.50	35	145.6	4.3	146.1	4.5	-2.51
16	47	152.1	5.2	153.1	4.6	-2.69	32	148.9	5.0	148.9	4.8	-2.21
17	35	158.2	5.4	158.2	4.8	-2.41	11	152.8	4.9	151.2	5.1	-1.83
18	21	160.7	4.3	161.0	5.1	-2.04	—	—	—	152.1	5.2	-1.68
19	—	—	—	162.5	5.3	-1.82	—	—	—	152.6	5.3	-1.60
20	—	—	—	163.8	5.6	-1.63	—	—	—	152.7	5.3	-1.58
21	—	—	—	164.7	5.8	-1.49	—	—	—	152.7	5.3	-1.58
Adult	88	164.8	6.1	164.8	6.1	-1.48	53	152.7	5.3	152.7	5.3	-1.58
Target height	142	171.1	4.8	—	—	-0.54	83	157.5	5.3	—	—	-0.78

* Based on Usher and McLean.²⁰

median of 15 measurements per individual (range 4-44).

The subclassification of the children with ISS was performed by two methods. The first was based on a recently achieved international consensus on the definition and classification of ISS.¹⁰ Non-FSS was defined if there were at least two height measurements during childhood below the target range for distinguishing from FSS. Bone age was not used as a criterion. Childhood was defined as the period between age of ≥ 3 years and the onset of puberty ($B < 2$ or $G < 2^{13, 14}$). If the onset of puberty was unknown, the upper limit of childhood was defined as age ≤ 10 years (F) or ≤ 11 years (M). Target range was calculated as: Target range = r midparental height SDS $\pm 2 \sqrt{(1-r^2)}$ where midparental height SDS = $(\text{height SDS}_{\text{father}} + \text{height SDS}_{\text{mother}}) / \sqrt{2(1+r_{\text{fm}})}$; r is the correlation between the child's height SDS and the midparental height SDS, which is 0.5 between the ages of 2 and 9 years¹⁵; and r_{fm} is the correlation between the parents' heights, which is 0.3.¹⁵

The second method was based on the criterion of pubertal onset. If the age at onset of puberty was > 2 SD above the mean, that is, > 13.8 years (M) or > 13.4 years (F),^{13, 14} the child was labelled as having delayed puberty.

The height measurements were linearly interpolated and extrapolated to the nearest integer age, resulting in at most one height measurement for a patient at an exact integer age. Interpolation was only performed when the interval between two subsequent measurements was shorter than three years. Extrapolation was only done at the first available visit after birth when the difference between the age of first measurement and the extrapolated integer age was less than 0.2 years. For both

sexes the mean and SD were calculated per integer age.

Final height was defined as height at an age ≥ 22 years (M) or ≥ 18 years (F), or height velocity ≤ 0.5 cm in the foregoing year, calculated over at least six months. Data on final height were available for 88 boys (61%) and 53 girls (63%). Final height has not yet been attained in 47 boys (32%) and 20 girls (24%), and was unknown in 10 boys (7%) and 11 girls (13%). The measurement was performed at a median age of 22 years (range 16 to 34 years) in boys and 21 years (range 16 to 31 years) in girls. In a sample of 30 subjects, the validity of the reported measurement at the patient's home was evaluated by comparing the reported height with a measurement made by an experienced person. The mean difference between reported and measured final height was 0.5 cm (range: -11.2 to 4.7 cm). To see whether the children with a final height measurement were representative of the total group, the growth curves of children with a final height measurement were compared to those of children without a final height measurement.

The observed overall growth curves were smoothed by eye. The smoothed growth curves are presented alongside the British growth standards and are expressed as SDS.¹¹

To evaluate whether a child tends to grow at the same SDS level, all heights were expressed as SDS according to the smoothed ISS growth curves. The difference between a child's final height SDS and the height SDS at a certain integer age in childhood (from 3 years to onset of puberty) was calculated. At each integer age, the mean and SD of these differences were determined.

Target height, according to Tanner *et al*,¹⁵ was calculated by the equation: $(\text{height}_{\text{father}} + \text{height}_{\text{mother}}) / 2 \pm 6.5$ cm and expressed in cm.

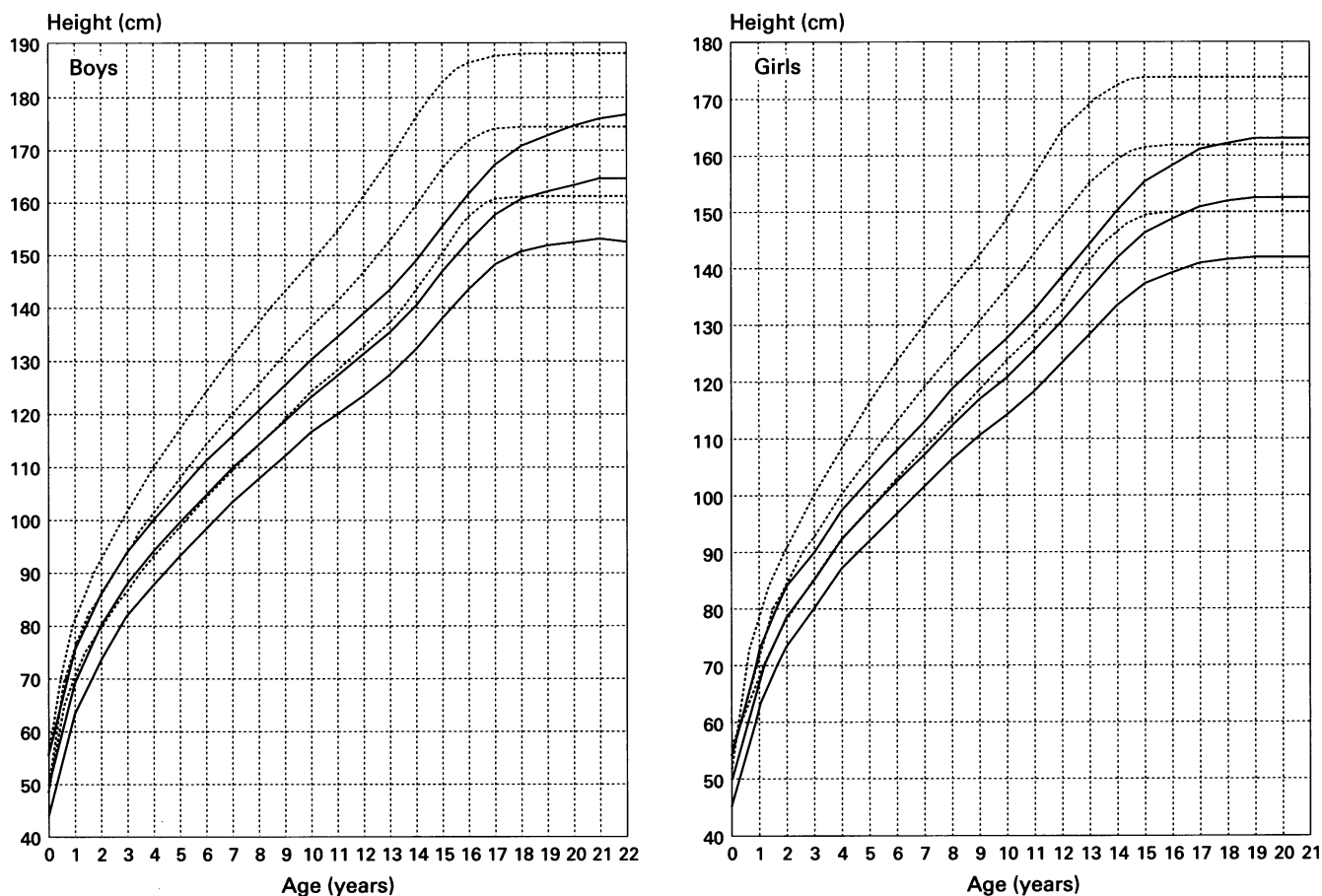


Figure 1 Smoothed growth curves for boys (left panel) and girls (right panel) with ISS, together with those of British reference. The means with 2SD limits are presented. Solid line = smoothed curve; interrupted line = British reference.

Student's *t* tests (paired and unpaired) were used to compare the means of the diagnostic subgroups with significance level $\alpha = 0.05$. Results are expressed as mean (SD). The difference of means of the subgroups and its 95% confidence interval are presented.

Results

The observed and smoothed mean of the height measurements of all children are given in table 1. The smoothed growth curves and the British reference curves are shown in fig 1. Although children with a birth weight -2 SD were excluded from the analysis, the growth pattern of children with ISS was already different at birth from the reference: mean birth length was -0.8 SDS in boys and -1.3 SDS in girls. Thereafter, height growth declined gradually to a mean value of about -2.7 SDS at the age of 16 years in boys and 13 years in girls, then increasing to mean final values of -1.5 SDS (164.8 cm) in boys and -1.6 SDS (152.7 cm) in girls. The mean value of final height in boys was 5.6 (5.2) cm and in girls 4.9 (5.5) cm below target height. The average age at onset of puberty was delayed, at 13.8 (1.3) years in boys and 12.9 (1.1) years in girls, compared to 11.6 (1.1) and 11.2 (1.1) years in the British reference, respectively (M: 2.1 years, confidence interval (CI) 1.8 to 2.4; F: 1.7 years, CI 1.3 to 2.1). The growth curves of children with a final height measurement were not different from those of children without a final height measurement (data not shown).

A child's tendency to grow at the same SDS level was evaluated for the childhood period. The overall mean of the differences between final height SDS and height SDS in childhood was 0.11. The SD of these differences decreased from 1.22 SDS at 3 years to 0.60 SDS at 14 years of age.

ANALYSIS OF SUBGROUPS

The growth curves of children with non-FSS were almost parallel to the curves of children with FSS (fig 2). Birth length did not differ between the two subgroups. The pubertal growth spurt was also not clearly different. The curve of boys with non-FSS was about 3-4 cm beneath that of boys with FSS, increasing to a difference of about 5 cm at the ages of 16 and 17 years. The curve of non-FSS girls was about 2-3 cm beneath that of FSS girls, increasing to about 4 cm at the ages of 12 and 13 years.

In table 2 the age at onset of puberty, final height, and target height are presented for all subgroups. The onset of puberty in children with non-FSS was more delayed than in children with FSS: M: 0.5 years (CI 0.02 to 1.1); F: 1.0 years (CI 0.4 to 1.6). The percentage of children entering puberty later than normal was 63% in non-FSS boys, 41% in FSS boys, 44% in non-FSS girls, and 13% in FSS girls. Boys labelled as non-FSS attained a final height 3.8 cm lower than boys labelled as FSS (CI 1.2 to 6.5 cm) and 8.3 cm beneath their target height (CI 7.1 to 9.5 cm). The difference between target height and final height of boys

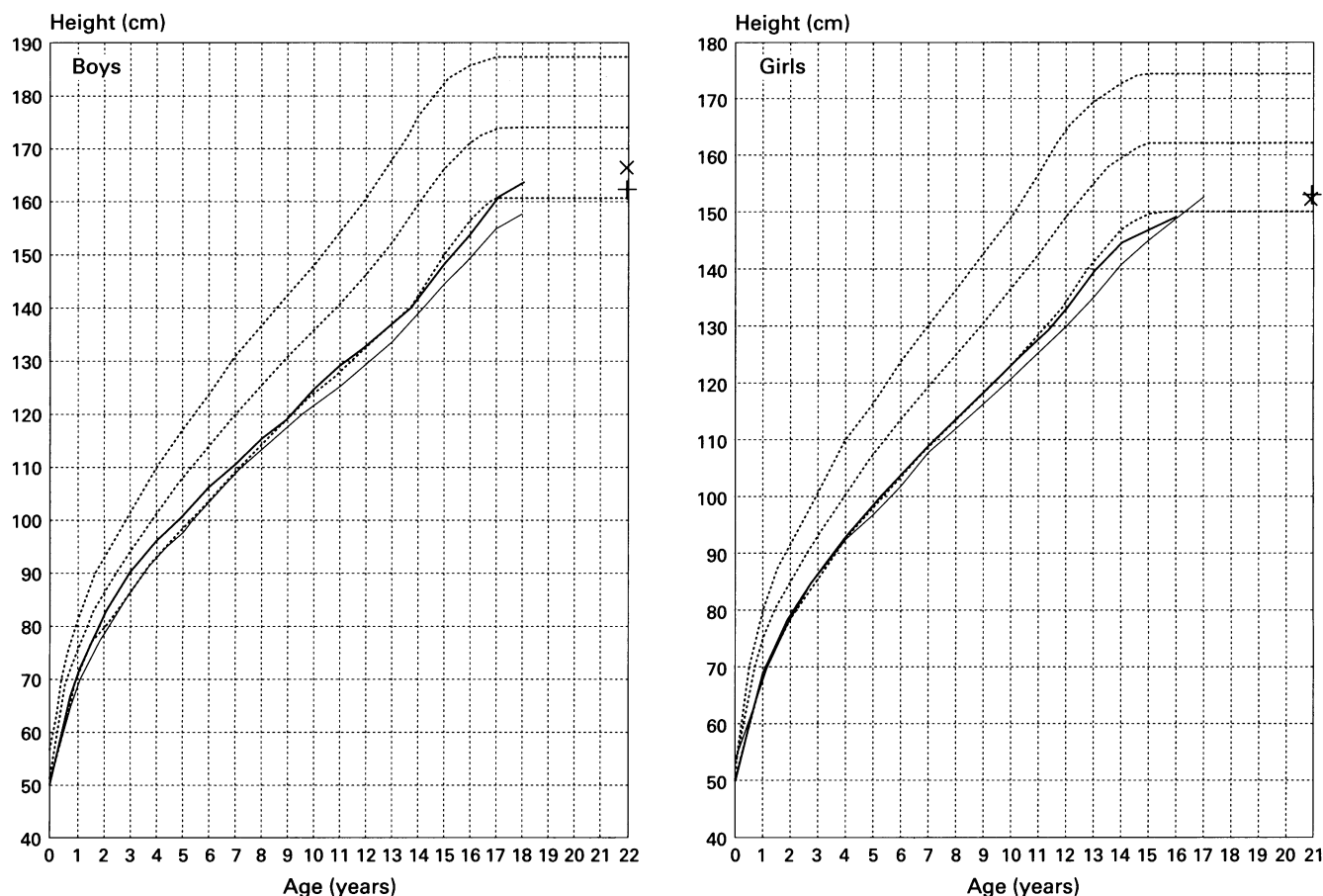


Figure 2 Unsmoothed growth curves with mean final height of FSS and non-FSS boys (left panel) and girls (right panel), together with the British reference. The means with 2SD limits are presented of the British reference. Thick solid line = FSS; thin solid line = non-FSS; interrupted lines = British references. \times = final height of FSS children; $+$ = final height of non-FSS children.

Table 2 Age at onset of puberty, final height and target height for subgroups of children with idiopathic short stature. Values are means (SD) (n)

	Age at onset of puberty (years)	Final height (cm)	Target height (cm)
Boys			
FSS (n=52)*	13.4 (1.1) (n=37)	166.9 (5.7) (n=32)§	169.0 (4.0) (n=32)
FSS, normal puberty (n=22)‡	12.7 (0.8) (n=22)	165.1 (5.8) (n=12)	166.9 (3.7) (n=12)
FSS, delayed puberty (n=15)‡	14.5 (0.5) (n=15)	167.6 (4.8) (n=13)§	169.8 (3.9) (n=13)
Non-FSS (n=82)*	14.0 (1.3) (n=56)	163.1 (6.1) (n=48)¶	171.4 (4.7) (n=48)
Non-FSS, normal puberty (n=21)‡	12.7 (1.0) (n=21)	160.1 (7.2) (n=12)¶	170.4 (5.7) (n=12)
Non-FSS, delayed puberty (n=35)‡	14.8 (0.8) (n=35)	164.2 (5.5) (n=28)¶	171.7 (4.7) (n=28)
Normal puberty (n=44)†	12.7 (0.9) (n=44)	162.6 (6.9) (n=24)¶	168.6 (5.0) (n=24)
Delayed puberty (n=52)†	14.7 (0.7) (n=52)	165.3 (5.4) (n=42)¶	171.1 (4.5) (n=42)
Girls			
FSS (n=31)*	12.1 (1.0) (n=14)	152.3 (4.5) (n=18)	153.9 (4.0) (n=18)
FSS, normal puberty (n=14)‡	11.9 (0.9) (n=14)	151.3 (4.3) (n=13)	153.2 (4.2) (n=13)
FSS, delayed puberty (n=2)‡	13.4, 13.5	160.2	152.0
Non-FSS (n=51)*	13.2 (1.0) (n=41)	153.0 (5.8) (n=34)¶	159.8 (5.1) (n=34)
Non-FSS, normal puberty (n=23)‡	12.4 (0.6) (n=23)	151.8 (6.2) (n=17)¶	159.0 (5.5) (n=17)
Non-FSS, delayed puberty (n=18)‡	14.1 (0.6) (n=18)	154.0 (5.4) (n=15)¶	160.9 (5.0) (n=15)
Normal puberty (n=39)†	12.3 (0.8) (n=39)	151.5 (5.3) (n=31)¶	156.2 (5.8) (n=31)
Delayed puberty (n=20)†	14.0 (0.6) (n=20)	154.4 (5.4) (n=16)¶	160.4 (5.3) (n=16)

* 13 children (11 M, 2 F) could not be classified as FSS or non-FSS due to missing data on parental height or childhood heights.

† 72 children (49 M, 23 F) could not be classified as delayed or normal puberty due to missing data on pubertal onset.

‡ 66 children (FSS: 15 M, 15 F; non-FSS: 26 M, 10 F) could not be classified as FSS or non-FSS with delayed or normal puberty due to missing data on pubertal onset.

Differences between final height and target height: § $p \leq 0.01$; ¶ $p \leq 0.001$.

with FSS was 2.0 cm (CI 0.6 to 3.4 cm). In girls final height did not differ between the non-FSS and FSS group. Girls with non-FSS did not attain their target height (6.8 cm, CI 5.1 to 8.6), in contrast to girls with FSS (1.6 cm, CI -0.7 to 3.9). Boys with FSS and normal puberty did not differ from boys with FSS and delayed puberty with respect to final height, target height, and the difference between target height and final height. This was

also observed in boys and girls with non-FSS and delayed or normal puberty. The number of girls with FSS and delayed puberty (2) was too restricted for these comparisons.

The growth of children classified as having delayed puberty was similar to children classified as having normal puberty from birth to 13 years in boys and from 8 to 12 years in girls. In girls before the age of 8 years, the limited number of observations did not allow compari-

Table 3 Final height and difference between final height and target height of boys and girls with CDGA. The mean (SD) are presented in cm

Authors, year, country	Boys			Girls		
	No	Final height	Δ Target height – final height	No	Final height	Δ Target height – final height
Volta <i>et al</i> , 1988, Italy ²²	27	168.7 (4.9)	– 0.3	14	158.0 (5.6)	0.3
Ranke <i>et al</i> , 1989, Germany ²¹	20	167.4	4.0	5	147.8	9.0
Brämwig <i>et al</i> , 1990, Germany ²⁰	37	170.4 (5.4)	1.7 (5.7)	32	157.8 (4.2)	0.7 (4.3)
Willig <i>et al</i> , 1990, Germany ²³	77	168.9 (6.1)	7.7	—	—	—
Crowne <i>et al</i> , 1990, 1991, UK ^{25, 26}	43	164.1 (6.0)	6.5 (6.0)	15	153.0 (4.9)	4.9 (4.1)
Kalckreuth <i>et al</i> , 1991, Germany ²⁴	14	171.3 (5.3)	2.6	6	155.9 (2.2)	0.2
Albanese <i>et al</i> , 1995, UK ²⁸	78	160.5 (6.7)	10.9	—	—	—
Sperlich <i>et al</i> , 1995, Germany ²⁷	49	171.3 (4.9)	1.7	—	—	—

son of subgroups. During puberty the curves of both boys and girls with delayed puberty was at most 4 cm below the curves of children with normal puberty. Neither final height nor target height differed between children with delayed puberty and normal puberty (table 2). The deviation of target height from final height was also not different between these subgroups (M, 6 cm; F, 5 cm).

Discussion

This is the first study describing in detail the growth pattern of children with idiopathic short stature from birth to adult height. Although children with intrauterine growth retardation, defined as having a birth weight less than -2 SD for gestational age,¹² were excluded from our study, our data show that most children diagnosed as ISS later in life were already relatively short at birth. This suggests a prenatal origin of the growth delay. At the age of 2 years, when the individual growth channel has been achieved,¹⁶ the height of a child with ISS was about 1.7 SD below the mean of their age mates. During childhood they gradually lost another 1.0 SD, resulting in a height SDS of -2.7 at the age of 16 years in boys and 13 years in girls. The onset of puberty was delayed. During puberty some catch up occurred, but final height was still about 1.5 SDS below the reference mean.

A child's tendency to grow at the same SDS level was evaluated for the childhood period in which growth is expected to be linear.¹⁷ There was a good validity and a moderate precision of prediction of final height SDS by means of height SDS during childhood. This suggests that in general the growth of children with ISS is well canalised, but the individual variation is rather large.

Few published data are available on the spontaneous growth of children with ISS. Holl *et al*¹⁸ reported on 88 short normal boys and observed a mean final height of 168.4 (5.4) cm, 2.8 cm beneath their target height. Compared to our study, final height was higher and the difference from target height less. In children with ISS in the Kabi Pharmacia International Growth Study database the median height at birth was -0.6 SDS, at 3 years of age it was -2.5 SDS, and it remained constant until start of treatment at a median age of 9 years.⁷ In our study the observed decline in height SDS from birth to puberty was more gradual. In the study of Ranke *et al*¹⁹ in boys, a height of -2.2 SDS was found at 13 years and

final height was -0.7 SDS; in girls height was -2.2 SDS at 11 years and final height was -0.8 SDS. An explanation for the difference between the study of Ranke *et al* and our study could be that they selected patients with a height below the 10th centile of the British reference, instead of -2 SD below the mean (that is, about the third centile) in our study.

Subclassification of children with ISS using the criterion of target range before onset of puberty, as proposed by the international consensus meeting, results in two groups with almost parallel growth curves: the curve of children with non-FSS was about 3 cm below that of children with FSS, with a small increase in the difference during puberty. A difference in adult height was only observed in boys. Children with non-FSS did not attain their genetic potential, in contrast to children with FSS. The percentage of children entering puberty later than normal was considerable for both FSS and non-FSS children. No difference was observed in final height or target height between FSS children with delayed versus normal puberty, or non-FSS children with delayed versus non-delayed puberty. The definition of non-FSS with delayed puberty corresponds to the commonly used definition of constitutional delay of growth and adolescence (CDGA). In our study the mean final height of boys and girls with non-FSS and delayed puberty was 164 cm and 154 cm, respectively. This was about 7 cm beneath their target height, which is in line with other studies. In table 3, the final height and difference between target height and final height from nine European studies on children with CDGA are presented. A wide range of mean final height was observed: 161 to 171 cm in boys and 148 to 158 cm in girls.^{20–28} Adult height was usually beneath the target height. The difference between target height and adult height ranged from -0.3 to 10.9 cm in boys and from 0.2 to 9 cm in girls.

If children with ISS were subdivided according to the age at onset of puberty, the growth curves of children with delayed puberty and normal puberty were similar before puberty. During puberty the difference was at most 4 cm. Adult height was similar for the two subgroups. Neither group reached their target height. Thus, timing of puberty does not seem to be relevant to final height.

Knowledge of the spontaneous growth pattern in children with ISS is important in evaluating the effect of growth promoting treatment in these children. For example, the effect of treatment

with recombinant human growth hormone can be masked if height is expressed as SDS based on the normal population, because from birth up to puberty there is a spontaneous decrease in height SDS in these children to about -2.7 . Thereafter height SDS increases to about -1.5 in adulthood. Our data can be used to calculate ISS-specific SDS scores, revealing more sensitively the effect of growth promoting treatment in these children.

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