

Differences in physical characteristics, perinatal histories, and social backgrounds between children with growth hormone deficiency and constitutional short stature

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SUMMARY Four hundred and forty-nine children with heights below -2.5 SD were identified by screening for height a total population of 48 221 in three Scottish cities. Children participating in the study could be classified into 5 groups: severe growth hormone deficiency ($n = 13$), partial growth hormone deficiency ($n = 25$), low birthweight short stature ($n = 34$), constitutional short stature ($n = 178$), and short stature associated with some underlying disease ($n = 106$). Children with growth hormone deficiency tended to be shorter, were more likely to be obese, were growing more slowly, more often were the products of an abnormal pregnancy, and were less socially disadvantaged than constitutionally short children. Their parents were also more likely to have sought medical advice about the short stature. These findings have important implications for improved case-finding of children suffering from growth-hormone deficiency, who in this study accounted for about 10% of all short but otherwise normal children who came from non-disadvantaged communities.

Previous reports^{1 2} of the differences in physical characteristics between children with growth-hormone (GH) deficiency and constitutional short stature have been based on very short children referred to hospital clinics and may have been unrepresentative of such children generally. Any differences may therefore have been affected by bias. The present report is based on a cohort of very short children identified by screening a defined population of schoolchildren for short stature. The primary objective of the study was to determine the cause of short stature in every child but this paper reports on differences in physical characteristics, perinatal histories, and social backgrounds that were noted between children with GH deficiency and those with constitutional short stature.

Materials and method

For the purposes of this study, children were defined as having short stature if their height standard deviation (SD) score, based on the standards of Tanner *et al.*,³ was ≤ -2.5 . Height SD scores were calculated as follows:

$$\text{SD score} = \frac{X - \bar{X}}{\text{SD}}$$

X = child's height (mm)

\bar{X} , SD = mean and standard deviation appropriate for age and sex.

The heights of all 2nd- and 3rd-year primary pupils attending education authority schools and some attending independent schools in Edinburgh, Glasgow, and Aberdeen were screened during 5 months in 1975-76. In Aberdeen 4th-year pupils too were screened. (An unknown (but small) amount of within-city migration took place during the screening, particularly in Glasgow, where measurements took 3 months to complete, which resulted in some children being measured twice and others not at all.)

With shoes removed, each child was measured while standing in the classroom, by one of the investigators (GVV) using a Harpenden portable anthropometer. Any child with severe physical handicap was measured lying down. The smallest children in each age group were then measured again by the same investigator, this time using the technique recommended by Tanner *et al.*¹ with a wall-mounted stadiometer transported in a purpose-built

mobile clinic. The accuracy of the stadiometer was checked at each school, and the reliability of the measurements was confirmed by finding that when 28 children from one school were measured on successive days, 95% of repeat heights were within 4.5 mm.

The numbers of children in each class and the numbers absent were obtained from the teacher who also was able to give personal details of the children measured with a stadiometer. Schools were visited again so as to measure any absentee thought by his teacher to be small.

Attempts were then made to get into contact with the parents of all children with short stature. The initial contact was by post, and any non-responder was followed up personally and told about the study and the possible benefits for the child. With parental consent, information about appreciable medical conditions was sought from general practitioners and paediatricians who had treated the child.

Later, generally at the child's school, details of any previous major illness or medical investigation on the child were obtained by interviewing one parent (often the mother) or both of them. This interview, carried out by one of three specially-trained interviewers, was based on a previously tested precoded interview schedule. It also sought to elicit information about the child's perinatal history and social background. Parents were asked if they had been concerned about their child's short stature and whether they had sought medical advice about it.

From information obtained at interview a 'social disadvantage score' was derived for each child based on indicators of social disadvantage previously described.¹⁹ One point was given for the presence of each of the following, resulting in a minimum score of 0 and a maximum score of 3: (a) only one parent, or five or more children in family; (b) low income family—that is family had at some stage been in receipt of Supplementary Benefit, or the child had been eligible for free school meals; (c) poor quality housing—that is more than 1.5 persons per room, or no exclusive use of hot water.

At the same time the child underwent a careful physical and anthropometric examination. The height of one parent, or if possible both, was measured to the nearest centimetre using the anthropometer. All anthropometry was done by one observer (GVV). Triceps and subscapular skinfold measurements were made with Harpenden skinfold calipers.⁴ Occipitofrontal head circumference and mid-upper arm circumference were measured with a flexible steel tape measure, and mid-upper arm muscle circumference was derived from the formula given by Jelliffe.⁵

Upper arm muscle = upper arm circumference (mm)

Circumference (mm) $-\pi \times$ triceps skinfold thickness (mm)

Most children were seen on several occasions during the course of the study enabling an annual height velocity to be calculated, but to lessen any seasonal effect on growth rate only those in whom the height velocity was derived from measurement intervals in excess of 0.875 years were included in the analysis.

All raw anthropometric data were converted to an SD or centile score by making use of established standards. For height, the cross-sectional standards of Tanner⁶ were used. Skinfold thickness was expressed as a centile ranking derived from the revised British standards of Tanner and Whitehouse.⁴ Upper arm muscle circumference was calculated as a percentage of the mean given by Jelliffe⁵ as no British standards are thought to exist. Because the distribution of height velocity is not gaussian over the whole age range of the cohort, each height velocity was accorded a centile ranking⁶ rather than an SD score.

In the absence of previous investigations or any evident organic basis for short stature, informed consent to carry out a battery of diagnostic tests was sought from the parents. These tests included post-exercise serum growth hormone,⁷ thyroxine, thyroid-stimulating hormone, urea, 25-hydroxycholecalciferol, calcium, phosphorous, white cell count, urine culture (girls), and chromosome analysis (girls). Unless the parents refused, any child with a post-exercise GH level of less than 10 mU/l or any child with a level less than 18 mU/l in whom the height velocity over 12 months was less than the 25th centile for chronological age was admitted to hospital for an insulin hypoglycaemia test. All GH investigations were done in the same laboratory to satisfy high quality control criteria.⁷ An x-ray film of the left wrist and hand was also taken for subsequent bone age estimation⁸ by a trained reader (AFV). Results pertaining to many of these investigations will be reported elsewhere.

If the mean and SD scores of variables in the diagnostic groups could be derived, between-group comparisons were made using Student's *t* test, unless small skewed samples were being compared in which case the Mann-Whitney U test was used.

If a child had been assigned to a centile ranking for a particular variable, a between-group comparison was made using a test for trend in proportions.¹⁸ The test statistic (*c*) is normally distributed and its significance can be read from tables of the normal distribution.

If binary variables were examined, between-group

comparisons were made using a χ^2 test for two independent samples (corrected for continuity if appropriate).

Results

Four hundred and forty-nine children with short stature aged between 6.03 and 9.36 years were identified in a total screened population of 48 221 (Table 1). Of these, 108 (24%) children had an organic basis (other than GH deficiency) for the short stature (Table 2). Only 26 of these children were investigated in the study, the underlying organic basis for the short stature being newly diagnosed in only two (a girl with hypothyroidism and one who was a Turner's mosaic). Another was a boy with acute lymphoblastic leukaemia who was only partially investigated by an exercise test (GH 4.8 mU/l) before he suffered an unrelated relapse and died. In the other 82 children the nature of the disease was thought sufficient to exclude the need for further investigations. The parents of a further

77 (17%) children with short stature refused to participate in the study, but the remaining 264 children had either been adequately investigated previously (n = 10) or underwent investigation in this study (n = 254).

Table 2 Short stature associated with organic disease excluding GH deficiency in 108 children (mean height; SD scores, and range in brackets)

<i>Neurological abnormalities</i> (n = 39)		
Spina bifida (-3.7; -2.5 to -5.6)		14
Cerebral palsy (-3.2; -2.5 to -5.1)		13
Microcephaly (-3.0, -3.2, -4.0)		3
Arrested hydrocephalus (-2.6, -2.7)		2 (2*)
Epilepsy and severe mental retardation (-3.4, -4.6)		2
Hemiplegia (-2.5)		1 (1*)
Neurofibromatosis (-3.3)		1 (1*)
Meningitis and nerve deafness† (-2.7)		1 (1*)
Non-specific severe mental retardation (-3.0, -3.2)		2
<i>Skeletal abnormalities</i> (n = 17)		
Scoliosis (-2.8; -2.5 to -3.1)		5 (1*)
Achondroplasia (-4.8, -4.3, -5.5)		3
Achondroplasia and spina bifida occulta (-5.2)		1
Hypochondroplasia (-4.5)		1
Sacral tumour (-5.3, -4.8)		2
Perthes's disease (-3.2, -2.6)		2 (2*)
Klippel-Feil abnormality (-3.1)		1
Metaphyseal dysostosis (-3.3)		1 (1*)
Rickets‡ (-3.7)		1 (1*)
<i>Chromosomal abnormalities</i> (n = 17)		
Down's syndrome (-3.2; -2.5 to -4.2)		15
'Trisomy 18' (-4.0)		1
Turner's mosaic (45, XO/46, Xi(Xq))		1 (1*)
<i>Respiratory disorders</i>		
Asthma (-2.7; -2.5 to -3.4)		5 (2*)
Chronic bronchitis (-2.7, -3.3)		2 (2*)
Cystic fibrosis (-2.5)		1
<i>Cardiovascular disorders</i> (n = 6)		
Pulmonary stenosis (-3.1, -2.6, -2.8)		3 (2*)
Ventricular septal defect (-3.7)		1 (1*)
Patent ductus arteriosus (-3.2)		1
Intersex and chronic heart disease (-4.3)		1
<i>Gastrointestinal abnormalities</i> (n = 6)		
Celiac disease (-3.1, -3.2, -2.6)		3 (1*)
Hirschsprung's disease (-3.7)		1
Imperforate anus and mental retardation (-3.2)		1
Tracheo-oesophageal fistula (-6.3)		1 (1*)
<i>Metabolic and storage disorders</i> (n = 4)		
Glycogen storage disease (-2.9)		1 (1*)
Hurler's syndrome (-5.6)		1
Morquio's syndrome (-4.8)		1
Non-specific storage disorder (-3.2)		1
<i>Haematological disorders</i> (n = 2)		
Acute lymphoblastic leukemia (-2.9)		1 (1*)
Chronic idiopathic thrombocytopenic purpura (-2.2)†		1
<i>Renal disorders</i> (n = 2)		
Renal hypoplasia (-5.1)		1 (1*)
Severe recurrent urinary tract infections (-3.5)		1 (1*)
<i>Endocrine abnormalities</i> (n = 2)		
Hypothyroidism (-2.6)		1 (1*)
Gonadal hypoplasia (-3.2)		1
<i>Miscellaneous</i> (n = 5)		
Russell-Silver syndrome (-3.5, -4.0)		2 (1*)
Ataxia telangiectasia (-2.4)		1
Progeria (-4.7)		1
Smaller of discordant twins (-3.7)		1 (1*)

* Number of children investigated.
 † This height SD score was calculated at a time of examination and investigation, generally some months after the initial height screening, when all subjects were < -2.50.
 ‡ Past history

Table 1 Short stature—numbers and prevalence rates per 1000 by city, gender, and type of school

	Edinburgh	Glasgow	Aberdeen	Total
<i>Primary schools</i>				
Boys				
Number	26	159	13	198
%	4.47	12.03	2.91	8.42
Girls				
Number	30	119	24	173
%	5.30	9.48	5.66	7.71
Total				
Number	56	278	37	371
%	4.88	10.8	4.25	8.07
<i>Special schools</i>				
Boys				
Number	8	26	9	43
%	129	158.5	154.2	149.3
Girls				
Number	5	16	12	33
%	116.3	116.8	230.8	142.2
Total				
Number	13	42	21	76
%	123.8	139.5	184.2	146.2
<i>Independent schools</i>				
Boys				
Number	—	—	—	—
%	—	—	—	—
Girls				
Number	—	1	1	2
%	—	3.01	8.77	2.29
Total				
Number	—	1	1	2
%	—	1.95	5.08	1.14
<i>All schools</i>				
Boys				
Number	34	185	22	241
%	5.23	13.6	4.77	9.77
Girls				
Number	35	136	37	208
%	5.72	10.4	8.39	8.83
Grand total				
Number	69	321	59	449
%	5.47	12.08	6.54	9.31

On the basis of perinatal, auxological, and biochemical criteria it was possible to classify all but 14 of these 264 children into 4 groups. Each of the 14 children who could not be so classified had a post-exercise GH level of <18 mU/l and a height velocity of less than the 25th centile, but because of emigration (n = 1) or refusal by the parents, did not undergo an insulin hypoglycaemia test. Although GH deficiency could not be positively excluded it is possible that other influences—such as low birthweight, or genetic factors—might have been responsible for the short stature.

Classification

Group 1, severe GH deficiency (n = 13, 8 boys).
Short stature, maximum GH level after exercise and during insulin hypoglycaemia test ≤ 9.9 mU/l.

Group 2, partial GH deficiency (n = 25, 17 boys).
Short stature, maximum GH level after exercise and during insulin hypoglycaemia test ≤ 15.9 mU/l. All were from Glasgow.

Group 3, low birthweight short stature (n = 34, 24 boys).
Short stature, GH deficiency excluded, birthweight <5th centile for gestational age and maternal height,⁹ no other organic disease.

Group 4, constitutional short stature (n = 178, 90 boys).

Short stature, GH deficiency excluded, birthweight >5th centile for gestational age and maternal height, no other organic disease.

All but 11 met Tanner and Thomson's criteria for a diagnosis of short/delay.⁹ Most (75%) came from Glasgow.

Tables 3 and 4 show the auxological, perinatal, and social background characteristics of these 4 groups. It is clear that the children with GH deficiency were shorter, were growing more slowly, had thicker skinfolds, and had less muscle bulk than those with constitutional short stature. Although boys with GH deficiency were noticeably smaller than their constitutionally short counterparts, girls with GH deficiency were no shorter than those with constitutional short stature. The children with GH deficiency were more likely to have been born post-term, to mothers aged under 20, who had had a complicated pregnancy, and to have had a normal birthweight than those with constitutional short stature. They also tended to be members of numerically smaller families suffering less from overcrowding and social disadvantage than the constitutionally short group. Additionally their parents were more likely to have sought medical advice

Table 3 Auxological differences in children with severe or partial GH deficiency, low birthweight short stature, and constitutional short stature

Characteristic	Growth hormone deficiency		Low birthweight short stature Group 3 (n = 34)	Constitutional short stature Group 4 (n = 178)	Significance difference between groups 1 and 4
	Severe Group 1 (n = 13)	Partial Group 2 (n = 25)			
Mean height* (+ range)	-3.39(-2.50 → -4.84)	-2.95(-2.55 → -4.11)	-2.70(-2.07 → -3.63)	-2.77(-2.10 → -3.88)	t = 5.76 P < 0.01
Mean height* (+ range) (boys)	n = 8 -3.83(-2.72 → -4.84)	n = 17 -2.94(-2.55 → -3.50)	n = 24 -2.68(-2.07 → -3.88)	n = 24 -2.73(-2.21 → -3.88)	P < 0.01
Mean height SD score* (+ range) (girls)	n = 5 -2.69(-2.50 → -2.91)	n = 8 -2.96(-2.57 → -4.11)	n = 10 -2.77(-2.41 → -3.63)	n = 88 -2.81(-2.10 → -3.64)	NS
Percentage with height velocity <25th centile	n = 9† 89	n = 25 80	n = 27 59	n = 138 61	Test for trend c = 3.25 P = 0.001 NS
Bone age SD score	n = 10 -1.87(±0.95)	n = 25 -2.29(±1.06)	n = 34 -1.83(±1.11)	n = 173 -1.75(±1.00)	Test for trend c = 2.55 P = 0.01
Percentage with triceps skinfold thickness less than 25th centile	15	40	56	44	Test for trend c = 2.44 P = 0.015
Percentage with upper arm muscle circumference less than 90% of standard	69	40	29	30	
Head circumference SD score (mean ±SD)	n = 12 -0.6(±0.96)	n = 25 -1.21(±1.24)	n = 33 -1.29(±0.86)	n = 178 -1.17(±1.10)	t = 1.75 P = 0.1
Maternal height SD score (±SD)	n = 13 -1.44(±1.54)	n = 25 -1.75(±0.76)	n = 34 1.27(±1.06)	n = 169 -1.94(±0.76)	t = 2.08 P < 0.05

* This height SD score was calculated at time of examination and investigation, generally some months after the initial height screening, when all subjects were <-2.50.

† Three children previously diagnosed and on treatment (12-month height velocity not available in other case).

Table 4 *Perinatal and social background characteristics of children with severe or partial GH deficiency, low birthweight stature, and constitutional short stature*

Characteristic	Growth hormone deficiency		Low birthweight short stature, group 3	Constitutional short stature, group 4	Significance of differences between groups 1 and 4
	Severe group 1	Partial group 2			
Pregnancy order, percentage in which subject resulted from first pregnancy	38 (5/13)	8 (2/15)	12 (4/34)	17 (33/171)	Test for trend $c = 1.62$ $P = 0.1$
Percentage of mothers aged <20 at birth of first child	67 (8/12)	48 (/25)	65 (22/34)	55 (94/172)	NS
Percentage of mothers aged <20 at birth of subject	67 (8/12)	12 (3/25)	12 (4/34)	23 (39/172)	$\chi^2 = 9.22$ $P < 0.01$
Percentage with abnormal pregnancy history*	69 (9/13)	32 (8/25)	41 (14/34)	30 (51/168)	$\chi^2 = 6.57$ $P = 0.01$
Percentage with abnormal delivery	42 (5/12)	20 (5/25)	12 (4/34)	16 (28/170)	NS
Percentage born post-term (42 or more weeks' gestation)	31 (4/13)	28 (7/25)	12 (4/34)	10 (17/177)	$\chi^2 = -3.67$ $P = 0.06$
Percentage of mothers who smoked in pregnancy	42 (5/12)	68 (17/25)	79 (27/34)	57 (98/171)	$\chi^2 = 4.93\ddagger$ $P < 0.05$
Mean birthweight (g) \pm SD	n = 13 3238 \pm 613	n = 24 2865 \pm 482	n = 34 2334 \pm 339	n = 164 2970 \pm 480	$t = 1.90$ $P < 0.1$
Mean family size \pm SD	n = 13 3.23 \pm 1.48	n = 25 4.92 \pm 1.85	n = 34 4.64 \pm 2.14	n = 172 4.68 \pm 1.95	$t = 2.62$ $P < 0.01$
Percentage from families with 5 or more children	0 (0/13)	36 (9/25)	24 (8/34)	24 (49/172)	Test for trend $c = 2.63$ $P = 0.008$
Percentage from households living at density >1.5 persons per room	15 (2/13)	68 (17/25)	44 (15/34)	54 (93/172)	Test for trend $c = 3.32$ $P = 0.001$
Percentage from households in which father unemployed	23 (3/13)	32 (8/25)	44 (15/34)	29 (50/172)	NS
Percentage with social disadvantage score of 3	8 (1/13)	33 (8/24)	26 (9/34)	31 (53/170)	Test for trend $c = 1.99$ $P = 0.05$
Percentage of mothers concerned by subject's short stature	69 (9/13)	56 (14/25)	35 (12/34)	42 (71/171)	$\chi^2 = 2.73$ $P = 0.1$
Percentage who were thought to be smaller than siblings	82 (9/11)	76 (19/25)	65 (22/34)	69 (113/164)	NS
Percentage whose parents had sought medical advice	69 (9/13)	28 (7/25)	18 (6/34)	18 (31/170)	$\chi^2 = 15.52$ $P < 0.001$

* Specific questions about swelling/PET, vaginal blood loss, severe vomiting, or other complications.
 † Group 3 compared with group 4.

about the child's short stature than those of the constitutionally short children.

One-third of the constitutionally short children were severely socially disadvantaged by our criteria. Since this group comprised the bulk of the study population it was not surprising to find that this group was closely linked with the social and economic environment. For instance, short stature was twice as common in Glasgow as in Edinburgh or Aberdeen, and was 7 times more common in children attending education authority schools than in those attending independent schools. Moreover within Glasgow, where there was a 20-fold variation in the rate of short stature between different postal districts (Figure) a significant correlation ($R_s = 0.73$, $P < 0.01$) was found between the prevalence of short stature and the frequency of previously described census indicators of urban deprivation.¹⁰⁻¹² In Edinburgh (Figure) where organic causes of short stature were more common, the correlation was less pronounced and failed to reach statistical significance ($R_s = 0.41$, $P < 0.1$).

Constitutional short stature was often associated with mental retardation as has been found by others.¹³ For instance, in Glasgow, schools for the

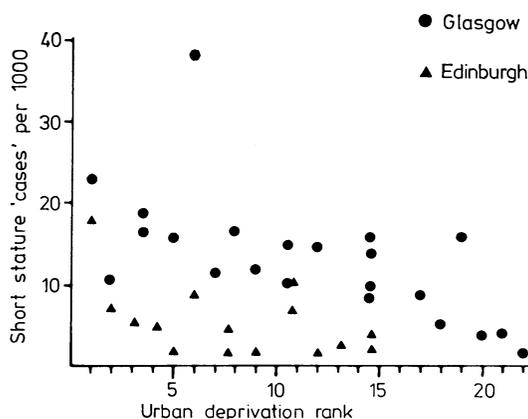


Figure *Relationship between short stature and deprivation in Glasgow and Edinburgh.*

educationally subnormal were attended by only 0.58% of the population but accounted for 4.4% of all short children. Furthermore, in Glasgow a further 14 children with short stature were transferred to schools for the educationally subnormal because of their inability to cope with normal learning.

In this study children with low birthweight short stature were only slightly different from those with constitutional short stature. Indeed the only statistically significant difference between the groups in any of these parameters was the fact that a higher proportion of mothers of children of low birthweight had smoked cigarettes during the relevant pregnancy.

The range of height and height velocity in the 77 non-participating children was similar for those with constitutional short stature. Only 14% had heights $\leq -3SD$ scores; only one girl (with a normal height velocity) was $< -4SD$ score.

Discussion

The results of this study show some of the auxological, perinatal, and social background factors which tend to distinguish children with GH deficiency from those with constitutional short stature. A chubby, normally intelligent, short child of normal birthweight, more often the product of a pregnancy marked by complications, who comes from a comfortable home is more likely to be GH deficient than a lean, sometimes dull, underweight child from poor circumstances. The perinatal differences noted here are consistent with those reported earlier by Rona and Tanner¹⁴ who noted an increased risk of GH deficiency in first-born children, those born after a breech delivery, or in those born after vaginal bleeding during pregnancy.

While we noted that there were some appreciable differences between groups of children with GH deficiency and constitutional short stature with respect to auxological and other characteristics, prediction of the correct diagnosis in each case on the basis of these is not always possible; this confirms the observation of Joss² who noted that parameters such as height and height velocity did not invariably distinguish between children with GH deficiency and those with constitutional short stature.

Unlike those with severe GH deficiency, children with partial deficiency are virtually indistinguishable from those with constitutional short stature in terms of perinatal and social background characteristics. This finding raises serious questions about the significance and aetiology of such children below normal GH responses. Is it valid to consider them as a separate diagnostic group? Probably only a

randomised, controlled therapeutic trial can answer that question. It is worth noting that 6 had other conditions which might have contributed to the short stature—such as coeliac disease, which has previously been reported to be associated with depressed GH responses,¹⁵ and one each had asthma, probable fetal alcohol syndrome, and Russell-Silver syndrome. Could it also be that social deprivation¹⁶ is an additional trigger to those described by Rona and Tanner¹⁴ and capable of producing depressed GH levels in those with a genetic susceptibility to GH deficiency?

Although previous estimates of the prevalence of GH deficiency have ranged from 1 in 30 000 to 1 in 10 000^{13 14 17} we found the prevalence to be about 1 in 4000. Our results clearly indicate that professional inactivity rather than a lack of parental concern was responsible for many of the missed diagnoses in this series. For instance the parents of children with GH deficiency were more likely to seek medical advice than the parents of constitutionally short children, but fewer than half (4 out of 9) had appropriate diagnostic investigations initiated. If all 9 had been investigated case-finding by practitioners independent of this study would have been doubled. These findings bear out the adage 'If parents suspect something is wrong, it probably is'. GH deficiency is one of the most common organic causes of short stature. In a non-disadvantaged community (for example Aberdeen or Edinburgh) it may account for 5% of all cases of short stature ($\leq -2.5 SD$ score), or 10% of cases if those with a known organic basis for their short stature are excluded.

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