The Short Child with Subnormal Plasma Somatomedin C¹

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ABSTRACT. In 59 male and 59 female healthy children of average stature between 7 and 10 yr old, the normal range of plasma somatomedin C was investigated. The 95% tolerance limits narrowed progressively when the child's plasma somatomedin C status was described by the mean of one, two, three, or four determinations at 6-wk intervals. The 95% tolerance limits were therefore based on the mean of four determinations. In 97 children, age 7 to 10, below the 3.0 percentile in height, 44 had an average plasma somatomedin C below the 2.5 percentile. Among these hyposomatomedinemic short children, 19 were partially or totally deficient in growth hormone, 20 had normal immunoreactive growth hormone responses to dopa, glucagon, and sleep (nongrowth hormone deficient), and five had borderline provocative tests. Both growth hormone deficient and nongrowth hormone deficient children showed significant linear growth responses to 6-month courses of human growth hormone (0.16 to 0.70 unit/kg/wk). The responses of the latter group were 50 to 90% as great as those of the former. (*Pediatr Res* 19: 975-980, 1985)

Abbreviations

SmC, somatomedin C
GH, growth hormone
GHD, growth hormone deficient
Non-GHD, nongrowth hormone deficient
RIA, radioimmunoassay
hGH, human growth hormone
ACTH, adrenocorticotrophic hormone
TSH, thyroid-stimulating hormone

Until recently, identification of GHD children required measurement of the serum level of immunoreactive GH during provocative tests, after exercising or during sleep. In 1977, an alternative approach became possible with the introduction of the RIA for SmC (1). It soon became apparent that there were substantially more short children with low SmC levels than there were GHD children (2). Some of the hyposomatomedinemic boys and girls who had normal levels of immunoreactive GH responded with accelerated linear growth to treatment with hGH (3-5). It was suggested that these responsive, non-GHD short children might have a structurally abnormal form of endogenous GH (3-6).

The present study had these objectives. (a) To estimate toler-

ance limits for plasma SmC in children of normal height, 7 to 10 yr old. (b) To estimate the prevalence of subnormal SmC in the population of short (less than third percentile) children, age 7 to 10. (c) To estimate the prevalence of GHD in those children with low SmC. (d) To compare the linear growth responses to hGH treatment between hyposomatomedinemic, GHD short children and hyposomatomedinemic, non-GHD short children.

METHODS

The study proceeded in two phases. Phase 1: determination of the prediction limits of plasma SmC in healthy children, 7 to 10 yr old, of normal stature (5th to 95th percentile for chronologic age). Phase 2: measurement of plasma SmC in 97 children age 7 to 10, who were below the third percentile in height for chronological age. We selected those children whose SmC level was below the normal mean for chronologic age by at least 2 SD. These children were evaluated to classify them as GHD or non-GHD. Both groups of children then received hGH for 6 months at standard doses, to determine the linear growth responses to the hormone.

Methods: Phase 1. For each yearly interval between 7 and 10 yr, 14 or 15 healthy prepubertal children were referred by local pediatricians. They met these criteria: (a) height between the 5th and 95th percentile; (b) body weight between 95 and 115% of ideal; (c) no known chronic medical condition; (d) no drug treatment during the period of study; (e) normal history and physical examination within 6 months before the beginning of the study; (f) normal hemogram and urinalysis within 6 months before the beginning of the study.

In addition, seven prepubertal GHD children whose clinical data are given in Table 1, were studied. Criteria for diagnosing deficiency of GH and other pituitary hormones have been given before (4). These criteria included a mean peak immunoreactive GH level less than 4 ng/ml during four pharmacologic provocative tests (L-dopa or glucagon), as well as a plasma level of SmC less than 0.30 unit/ml. Deficiencies of ACTH, TSH, or antidiuretic hormone, when present, were treated as described elsewhere (4). Human GH had not been given for at least 3 months.

Blood for SmC was drawn in EDTA at 1300 to 1600. The blood was spun immediately at 25° C for 10 min; the plasma was then stored at -20° C and mailed in dry ice within 2 wk to Nichols Institute, Los Angeles, for analysis by RIA (1). Intra- and interassay coefficients of variation were 6 and 10%, respectively.

Methods: Phase 2. The subjects in phase 2 were 97 prepubertal children, 7 to 10 yr old, referred to this clinic during 1978 to 1983 because of height less than third percentile for chronologic age (Table 2). They were referred by the same group of pediatricians as the controls in phase 1, and had not previously been evaluated for cause of short stature. Exclusion criteria were: birth weight < 5.5 lb; previously diagnosed gastrointestinal, pulmo-

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Table 1. Clinical data of the GHD subjects (phase 1)

Case	Cause of GHD	Age (yr)	Sex	Ht (cm)	Wt (kg)	Bone age (yr)	Hormone deficiency
1	Idiopathic	7	F	103	20	4	GH
2	Craniopharyngioma	10	M	125	27	7	GH, ACTH, TSH, ADH
3	Idiopathic	8	F	109	18	5	GH, ACTH
4	Idiopathic	7	F	100	21	4	GH
5	Idiopathic	7	M	106	22	4	GH, TSH
6	Idiopathic	8	F	112	24	5	GH, TSH
7	Craniopharyngioma	8	M	115	19	6	GH, ACTH, TSH, ADH

Table 2. Clinical data base summary of short children studied in phase 2 (values are mean $\pm$ SE)

		GHD (n = 12)	Partial GHD (n = 7)	Non-GHD (n = 20)
Chronologic age	yr	9.0 $\pm$ 1.0	8.0 $\pm$ 0.9	9.1 $\pm$ 0.6
Ht age/chronologic age		0.58 $\pm$ 0.15	0.59 $\pm$ 0.10	0.65 $\pm$ 0.09
Wt age/chronologic age		0.59 $\pm$ 0.30	0.57 $\pm$ 0.14	0.64 $\pm$ 0.13
Ht age/wt age		1.18 $\pm$ 0.58	1.06 $\pm$ 0.12	1.05 $\pm$ 0.30
Bone age/chronologic age		0.61 $\pm$ 0.04	0.66 $\pm$ 0.03	0.66 $\pm$ 0.04
1-3 percentile in ht		40%	43%	63%
< 1 percentile in ht		60%	57%	37%
Sex	Male/female	10/2	4/3	17/3
Birth wt	kg	3.1 $\pm$ 0.2	3.4 $\pm$ 0.2	3.0 $\pm$ 0.1
IQ		92 $\pm$ 5	92 $\pm$ 9	86 $\pm$ 8
Growth rate before hGH	cm/yr	3.1 $\pm$ 0.4	4.0 $\pm$ 1.1	4.0 $\pm$ 0.2
SmC (average of 4) before hGH	unit/ml	0.34 $\pm$ 0.03	0.21 $\pm$ 0.01	0.30 $\pm$ 0.03
Sleep tests, mean peak level*	ng/ml	2.5 $\pm$ 0.7	4.1 $\pm$ 1.2	13.8 $\pm$ 0.8
Provocative tests, mean peak level*				
L-dopa	ng/ml	1.6 $\pm$ 0.2	4.8 $\pm$ 1.4	16.3 $\pm$ 5.1
Glucagon	ng/ml	1.7 $\pm$ 0.3	7.5 $\pm$ 0.6	13.1 $\pm$ 1.5
TSH deficiency	+/-	7/5	0/7	0/20
ACTH deficiency	+/-	3/9	0/7	0/20
ADH deficiency	+/-	1/11	0/7	0/20
Sit/stand ht		0.55 $\pm$ 0.01	0.58 $\pm$ 0.01	0.56 $\pm$ 0.02
Mother's ht	Inches	64 $\pm$ 1	65 $\pm$ 2	62 $\pm$ 1
Father's ht	Inches	69 $\pm$ 2	70 $\pm$ 1	69 $\pm$ 1

* By polyclonal assay.

nary, renal, hepatic, endocrine, or metabolic disease; chronic treatment with steroids or ritalin; previously diagnosed Turner syndrome; clinical evidence of psychosocial deprivation; history of birth trauma. Mental retardation, seizures, and congenital heart disease not causing heart failure or cyanosis were not exclusions.

At entry we began to measure the child every 2 wk on a wall-mounted stadiometer. This continued as long as the child remained in the study. All children had four plasma SmC determinations at 6-wk intervals. Those with average SmC below the lower 2.5 percentile tolerance limit for chronologic age ("hyposomatomedinemic children") as defined during phase 1, then received the clinical evaluation for growth retardation described previously (4). Two or more provocative tests were done with dopa or glucagon (7) (if the peak value in the first two provocative tests averaged >12 ng/ml,² no more tests were done; if the first two peaks averaged <12 ng/ml, two further tests were done).

The hyposomatomedinemic children then entered 6-month alternating periods of treatment with hGH. During each period, one of four logarithmically equally spaced doses was administered: 0.16, 0.26, 0.43, and 0.70 unit/kg/wk, given in equally divided doses Monday, Wednesday, and Friday at 2200. The order of doses was randomized. The number of children who completed three, two, or only one period of hGH treatment were 25, 18, and 3, respectively.

² The conventional, commercially available RIA with polyclonal rabbit anti-serum was used to measure immunoreactive GH in the provocative tests. Our technique for carrying out this assay is described under "Methods" in the accompanying report (8).

RESULTS

Phase 1.

Variability studies. In three normal prepubertal 10-yr-old girls, we estimated four sources of variability associated with the measurement of plasma SmC samples. A single plasma sample for each girl was split into three aliquots and sent to Nichols Institute in a single blind fashion. Plasma samples also were collected on 3 consecutive days and at 6-wk intervals over 4 consecutive months. This allowed us to estimate intra-assay, day-to-day, and month-to-month variability.

The data, which are filed with the National Auxiliary Publication Service as document 04318, showed the following: intra-assay variability = 0.0015, estimated coefficient of variation = 4.3%; day to day variability = 0.0115, estimated coefficient of variation = 11.9%; month to month variability = 0.0627, estimated coefficient of variation = 30.1%. The substantial amount of month to month variability in plasma SmC samples suggested that single determinations would be of limited value in estimating tolerance limits for normal children.

Estimating tolerance intervals (normal values). The lower limit of the 95% tolerance limits based on single plasma SmC samples always was below the sensitivity of the assay (<0.10 unit/ml) (Table 3). Therefore we investigated the feasibility of estimating tolerance limits for normal children based on the average of several monthly plasma SmC samples.

Separate tolerance limits were estimated for each sex and age group based on the average of one, two, three, or four determinations of plasma SmC samples obtained at 6-wk intervals. The tolerance limits for each sex and age group are summarized in

Table 3. Means, SDs, and tolerance intervals by age and sex based on 1, 2, 3, and 4 determinations of plasma SmC levels (phase 1)*

		No. of determinations																
		1				2				3				4				
				95% tolerance interval		Mean $\pm$ SD		95% tolerance interval		Mean $\pm$ SD		95% tolerance interval		Mean $\pm$ SD		Tolerance intervals		
		# of children	Mean $\pm$ SD	95% tolerance interval	Mean $\pm$ SD	95% tolerance interval	Mean $\pm$ SD	95% tolerance interval	Mean $\pm$ SD	95% tolerance interval	Mean $\pm$ SD	95% tolerance interval	Mean $\pm$ SD	95% tolerance interval	50%	80%	95%	98%
Boys (yr)																		
6.5-7.4	15	0.451 $\pm$ 0.218	(0, 0.934)	0.494 $\pm$ 0.200	(0.051, 0.937)	0.491 $\pm$ 0.161	(0.134, 0.848)	0.495 $\pm$ 0.125	(0.406, 0.584)	(0.321, 0.669)	(0.218, 0.772)	(0.156, 0.834)						
7.5-8.4	15	0.565 $\pm$ 0.300	(0, 1.230)	0.544 $\pm$ 0.241	(0.010, 1.078)	0.577 $\pm$ 0.184	(0.149, 0.965)	0.536 $\pm$ 0.124	(0.447, 0.625)	(0.364, 0.708)	(0.259, 0.813)	(0.200, 0.872)						
8.5-9.4	14	0.583 $\pm$ 0.272	(0, 1.191)	0.578 $\pm$ 0.199	(0.133, 1.023)	0.578 $\pm$ 0.145	(0.263, 0.911)	0.543 $\pm$ 0.132	(0.449, 0.637)	(0.359, 0.727)	(0.248, 0.838)	(0.181, 0.905)						
9.5-10.4	15	0.551 $\pm$ 0.255	(0, 1.116)	0.614 $\pm$ 0.219	(0.329, 1.099)	0.630 $\pm$ 0.163	(0.269, 0.991)	0.607 $\pm$ 0.135	(0.510, 0.704)	(0.419, 0.795)	(0.308, 0.906)	(0.241, 0.973)						
Girls																		
6.5-7.4	15	0.585 $\pm$ 0.246	(0, 1.130)	0.574 $\pm$ 0.165	(0.209, 0.939)	0.589 $\pm$ 0.164	(0.226, 0.952)	0.605 $\pm$ 0.144	(0.502, 0.708)	(0.405, 0.805)	(0.280, 0.924)	(0.215, 0.995)						
7.5-8.4	15	0.673 $\pm$ 0.304	(0, 1.346)	0.659 $\pm$ 0.204	(0.207, 1.111)	0.664 $\pm$ 0.160	(0.310, 1.018)	0.659 $\pm$ 0.145	(0.555, 0.763)	(0.458, 0.860)	(0.338, 0.980)	(0.266, 1.052)						
8.5-9.4	14	0.748 $\pm$ 0.340	(0, 1.501)	0.788 $\pm$ 0.267	(0.197, 1.379)	0.798 $\pm$ 0.234	(0.280, 1.316)	0.821 $\pm$ 0.247	(0.644, 0.998)	(0.473, 1.166)	(0.274, 1.368)	(0.143, 1.499)						
9.5-10.4	15	1.036 $\pm$ 0.588	(0, 2.351)	1.054 $\pm$ 0.388	(0.186, 1.922)	1.046 $\pm$ 0.328	(0.313, 1.799)	1.056 $\pm$ 0.329	(0.821, 1.291)	(0.599, 1.513)	(0.322, 1.792)	(0.164, 1.948)						

* Tolerance limits for the mean based on 1, 2, 3, or 4 determinations were obtained by taking the mean $\pm$ $t(1-\alpha/2, n-1)(SD) \sqrt{1 + 1/n}$ where t is the appropriate percentile of Student's t distribution and n is the number of children. For example, the 95% tolerance interval for 7-yr-old boys based on four determinations is $0.495 \pm t(0.975; 14) (0.125) \sqrt{1 + 1/15} = 0.495 \pm (2.145) (0.125) \sqrt{1 + 1/15} = 0.495 \pm 0.277$

Table 3 and Figure 1. Note the decrease in the width of the tolerance intervals as the number of determinations increased.

Figure 2 displays tolerance limits for girls and boys, age 7 to 10, for commonly used percentiles based on the average of four determinations at 6-wk intervals. These tolerance limits can be used to screen short children for GHD. If we define subnormal as the lower limit of the 95% tolerance intervals, then two or more SmCs per child are required before the lower limit of the 95% tolerance interval rises into a measurable range (>0.10 unit/ml) (Fig. 1). Since the lower limit rises progressively using the average of two, three, and four determinations (Fig. 1), it is likely that more children with partial or total GHD would be identified according to the order (4) $>$ (3) $>$ (2) $>$ (1). To test this hypothesis, we measured SmC at 6-wk intervals in seven GHD children (Table 4). If we define subnormal SmC as below the lower limit of the 95% tolerance intervals, then based on the mean of one, two, three, or four determinations we would classify, *a posteriori*, zero, three, three, and seven of the GHD children as hyposomatomedinemic, respectively. Thus, no less than four determinations were necessary in order to identify all seven GHD children as having abnormally low SmC levels.

Phase 2.

Distribution of SmC in 97 short children 7–10 yr old. In each child, plasma SmC was measured four times at 6-wk intervals, and the SmC status was represented as the average of the four values. Figure 3 compares the distribution of the mean of four SmC values in the 97 short children with those of the normal children determined in phase 1. A significant excess of low SmC values was found. When SmC was less than the lower 2.5 percentile established for normal children, the child was considered “hyposomatomedinemic.” Forty-five percent of the short children (44 of 97) were in this category.

Classification of the 44 hyposomatomedinemic short children. These children were evaluated for growth retardation as described in Reference 4. When the mean peak immunoreactive GH level was less than 4 ng/ml in four provocative tests, the child was classified GHD. If the mean value was 4–8 ng/ml, the child was classified as partial GHD. A mean value over 12 ng/ml was interpreted as a normal immunoreactive GH level and the child as non-GHD; mean values between 8 and 12 were classified as indeterminate.³ The numbers of children in the four groups were 12, 7, 20, and 5, respectively. Children in the indeterminate group will not be considered further in the present report.

Clinical characteristics for the GHD, partial GHD, and non-GHD groups. These characteristics are given in Table 2. Males predominated in all three groups. Anthropometric and auxologic features were similar. TSH or ACTH deficiency was common in GHD, but was not found in partial GHD or non-GHD subjects.

Responses to hGH by GHD and non-GHD children. There were sixty-five 6-month trials at one of the four standard doses as summarized in Table 5 (GHD and partial GHD are considered as one group). GHD children responded to all four doses of hormone; the responses to 0.43 and 0.70 unit/kg/wk were similar. In the non-GHD children, one trial at 0.16 unit/kg/wk was ineffective; average responses (increases in growth velocity) to 0.26, 0.43, and 0.70 unit/kg/wk were 50–90% as great as in the GHD group. At the two intermediate doses, the responses of non-GHD children were significantly less than by GHD children.

DISCUSSION

Defining the normal range for plasma SmC. A study similar to the present one, but based on only one SmC determination per child, was published by Bala *et al.* (9). We have estimated from their graphic data the mean SmC $\pm$ 1 SD for ages 7–9 to be 0.46 ± 0.30 unit/ml for boys, and 0.66 ± 0.31 for girls. Our results are in close agreement with those of Bala *et al.* For

Fig. 1. 95% tolerance intervals of plasma SmC by age for girls and boys based on one, two, three, and four determinations.

Fig. 2. Percentiles for plasma SmC based on the average of four determinations in normal children by sex and age.

Table 4. SmC values at 6-wk intervals of 7 GHD children (phase 1)

Subject no.	Individual SmC values			
1	0.14	0.26	0.29	0.19
2	0.13	0.14	0.26	0.15
3	0.25	0.19	0.28	0.16
4	0.25	0.24	0.21	0.19
5	0.20	0.22	< 0.10	0.22
6	0.11	0.25	0.36	0.20
7	0.33	0.14	< 0.10	0.24

example, in the present study, single determinations at age 7.5–8.4 resulted in a mean value of 0.57 ± 0.30 unit/ml for boys, and 0.67 ± 0.30 for girls.

Tolerance limits based on the average of four determinations at 6-wk intervals were clearly preferable to fewer than four determinations. For example, the widths of the 95% tolerance intervals for the 7-yr old boys were 0.934, 0.886, 0.714, and 0.554 unit/ml based on one, two, three, and four determinations,

³ As stated in “Methods,” if the mean peak value of the first two provocative tests was >12 ng/ml, no further tests were done; otherwise, four tests were done and the mean of the peak values was calculated.

Fig. 3. Distribution of plasma SmC values (average of four) among (i) 87 normal prepubertal children, age 7–10, between 5 and 95% in height for chronological age, and (ii) 97 prepubertal children of the same age, less than third percentile in height for chronological age.

Table 5. Linear growth responses of GHD and non-GHD hypsomatomedinemic short children to 6-month courses of 4 different doses of hGH (phase 2) (values are mean $\pm$ SE)

Dose hGH (units/kg/wk)	Increase in growth velocity (cm/yr)	
	GHD	Non-GHD
0.16	4.35 $\pm$ 0.66 (n = 8)	0.2 (n = 1)
0.26	7.43 $\pm$ 1.15 (n = 9)	3.44 $\pm$ 0.69* (n = 16)
0.43	8.68 $\pm$ 0.89 (n = 12)	5.43 $\pm$ 0.66* (n = 12)
0.70	8.25 $\pm$ 1.09 (n = 4)	7.27 $\pm$ 1.96 (n = 3)

* Statistically different from GHD group, $p < 0.02$.

respectively. The width of the 95% tolerance interval based on five determinations at 6-wk intervals was estimated to be 0.495, by modifying the estimate of the SD to be based on five instead of four determinations. Because the estimated width of the tolerance interval would be reduced by only about 0.06 unit/ml by adding a fifth determination, we recommend tolerance intervals based on four determinations at 6-wk intervals.

The tolerance limits are influenced not only by the number of determinations per child, but also by the number of children in each age group. Our tolerance limits are based on 14–15 subjects per group. The tolerance limits will, in theory, decrease with an increase in the number of subjects per group. For example, had we chosen thirty 7-yr-old boys instead of 15, the tolerance interval would be (0.235, 0.755) assuming that the mean and SD

based on 15 subjects would remain the same if 30 subjects were observed and by using 30 instead of 15 for n . Comparison of this interval to that based on 15 subjects (0.218, 0.772) shows that only a small reduction would be achieved by increasing the group size from 15 to 30.

The prevalence of subnormal SmC among short children. Our data show that in children below the third percentile in height, there is a 20-fold excess of low SmC levels for chronological age (45% versus 2%, Fig. 3). About 40% of the excess of low SmC in the present series is caused by either total or partial GHD. About 40% of the excess cannot be ascribed to GHD, and the following possibilities can be considered. First, the low SmC could be related to the delayed maturation. As Bala *et al.* (8) showed and we have confirmed, plasma SmC increases in prepubertal children with chronological age. The normal mean SmC level for 5-yr olds, for example, is substantially less than for 10 yr olds. The excess of low SmC values in our short, non-GHD 7–10 year olds, therefore, could be related to their retarded bone age (average bone age/chronologic age, 0.66).

A second possibility is a failure of nocturnal secretion of hGH as described by Wise *et al.* (9); this has been ruled out by the nocturnal serum GH data (10). Other causes cannot be excluded: Impaired hepatic production of SmC; nutritional disorders (11); abnormally rapid clearance of SmC; an altered SmC binding system (12); or a bioinactive GH (3–5) are possible, but are generally outside the scope of the present data. Average weight was appropriate for height (Table 2), tending to rule out severe malnutrition. The possibility of a bioinactive GH is considered in the accompanying report (10).

The linear growth response. If we take a 5 cm/yr or greater increment in growth velocity as a satisfactory response to GH treatment, then at the 0.26 unit/kg/wk dose about 25% of the non-GHD hypsomatomedinemic short children were responders. At the next higher dose, the proportion of satisfactory responses increased to 60%. Thus our data support the recent series of reports (2–6) that linear growth response to hGH is not a unique feature of GHD children but can be elicited in many non-GHD hypsomatomedinemic short children. At conventional GH treatment doses (up to 0.43 unit/kg/wk), the magnitude of the response by such children was less than 60% as great as that of their GHD counterparts. At the highest dose of 0.70 unit/kg/wk, the response by the non-GHD hypsomatomedinemic short children resembled that of the GHD patients, but only a few in each group (three and four, respectively) were tested at this dose.

Van Vliet *et al.* (13) have shown that some short stature children with normal SmC respond to hGH with accelerated linear growth. Such children were not included in phase 2 of the present study.

The prevalence of GHD in our series of 97 short children was 20%, while in four cities of England and Scotland the prevalence was less than 2% (14, 15). This difference suggests selectivity in the referral of children to this study by the collaborating pediatricians.

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