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SERUM SOMATOMEDIN A AND NON-DIALYZABLE URINARY HYDROXYPROLINE IN GIRLS WITH IDIOPATHIC SCOLIOSIS

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Serum somatomedin A was determined by radioreceptor assay in 31 girls with idiopathic scoliosis and 30 controls, with ages ranging from 9.7–16.2 years. In the material as a whole no significant difference could be found between scoliotics and controls. Similarly no differences were found in the girls under 13 years of age. However, in girls older than 13 years the controls had significantly higher somatomedin A levels than the scoliotics.

In the second part of the study 26 girls with idiopathic scoliosis and 22 controls were examined with regard to the urinary excretion of non-dialyzable hydroxyproline, which has been suggested to be correlated with collagen synthesis. The percentage non-dialyzable fraction of the total hydroxyproline was found to be significantly higher in the control girls. The mean age was 12.8 years for both groups.

The results suggest a higher growth rate in the controls than in the scoliotics for girls over 12 years. There is, however, no definite evidence as to the function of the somatomedins or of the relationship between non-dialyzable hydroxyproline and growth.

Key words: adolescence; growth; idiopathic scoliosis; somatomedin A; urinary hydroxyproline

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The different patterns of growth (Willner 1974) and the difference in vertebral growth (Skogland & Miller 1980 a) in children with idiopathic scoliosis (IS) may be caused by differences in serum levels of growth hormone (GH) and testosterone (Skogland & Miller 1980 b). Salmon & Daughaday (1957) suggested that GH acts on the growth cartilage through secondary serum growth factors, so called somatomedins (Daughaday et al. 1972). Good correlation has been reported between the serum levels of somatomedin A (SMA) and the growth rate in healthy school children (Hall & Filipson 1975). Willner et al. (1976) found that the serum levels of SMA in IS patients were significantly higher than in healthy controls whereas Spencer & Zorab (1977) could not find differences in somatomedin activity (without referring to specific somatomedins) between scoliotics and normal controls. Further they observed no differences between the sexes or in different age groups. A bioassay technique was used in the estimation of somatomedin activity in both the latter investigations.

The purpose of the first part of this study was to find out if there was any difference between the serum levels of SMA in IS patients and non-scoliotic controls. A radioreceptor assay was used (Hall et al. 1974). This technique is thought to be more specific and sensitive than the bioassay technique (Van den Brande 1976).

There have been two reports of an increased urinary excretion of hydroxyproline (HP) in patients with IS, reflecting an increased collagen turnover (Benson 1965, Zorab et al. 1971). The

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excretion of total hydroxyproline (THP) is greater in normal children than in adults (Prockop & Kivirikko 1967) and it increases with increasing growth rate (Jasin et al. 1962, Jones et al. 1964, Smiley & Ziff 1964). The higher concentration of THP found in the urine of IS patients could be caused by an accelerated growth (Zorab et al. 1971).

THP in urine originates from several different sources; a major part of it is derived from collagen turnover in bone (Dull & Henneman 1963), but not all from the resorption of calcified bone (Rasmussen & Bordier 1975). Some of the urinary THP reflects the formation of new bone and Krane et al. (1970) have suggested that although most of the urinary THP represents low molecular weight peptides, a small portion is in the form of higher molecular weight material (polypeptides) probably representing fragments of collagen related to collagen synthesis. This HP constitutes part of the non-dialyzable fraction of urine and will be referred to as non-dialyzable hydroxyproline (NDHP).

The second part of this study was therefore designed to investigate whether there are differences between the different fragments of urinary HP in IS children and controls.

PATIENTS AND METHODS

Both studies were carried out in parallel with the investigations of hormones related to growth (Skogland & Miller 1980 b). The same IS patients and the same control cases served as the basic material (Table 1). Blood samples were collected from 31 IS girls and 30 controls, aged from 9.7–16.2 years, for the determination of SMA at the same time as the first sample for GH analysis. All patients and controls were hospitalized and the blood samples were obtained while they were still recumbent after an overnight fast (for a more detailed description of Material and Methods, see: Skogland & Miller 1980 b). The serum samples were stored at –25 degrees C until analyzed. SMA was determined by the radioreceptor method, as described by Hall et al. (1974). One unit SMA is defined as the activity in 1 ml of pooled normal human serum.

A number of patients refused to participate in the HP study because they disliked the collagen-free diet; in addition, some patients had to be excluded for various technical reasons. After including 9 additional cases, the total series consisted of 26 IS girls and 22 female controls aged from 9.2–15.8 years. They were all given a collagen-free diet the day before and during the day of collection. The urine samples were collected under 30 ml of toluene and stored at –25 degrees C until analyzed. THP was determined by using a modified method of Firschein & Schill (1966) as described by Gordeladze et al. (1978). The amount of non-dialyzable hydroxyproline (NDHP) was determined after dialysis for 48 hours against distilled water which was changed after 24 hours.

Table 1. Control groups. List of diagnoses and number of girls

	Somato-medin A	Hydroxy-proline
Cong. dislocation of the hip	8	2
Cong. scoliosis/kyphosis	5	4
Spondylolisthesis	2	4
Scheuermann's disease	3	3
Postopr. spine deformity	2	1
Anisomelia		2
Recurrent dislocation of patella	2	
Anteversion of fem. neck	2	1
Others	6	5
	30	22

The skeletal (skel.) age was determined by the Greulich & Pyle (1970) method. All results were evaluated according to skel. as well as chronological (chr.) age. The results of SMA analyses were also evaluated for age groups under and over 13 years. When necessary, age-matching was accomplished using random deletion from the tails of the age histograms.

The data analysis was run on a Digital Equipment Corporation "DEC-10" computer, using a statistical program ("Stat-pack" Western Michigan University). Significance testing was carried out using the Mann-Whitney U-test. The two-tailed test was used in all cases. For correlation analyses the rank correlation coefficient (r_s) due to Spearman was calculated (Snedecor & Cochran 1978).

RESULTS

Somatomedin A: No significant difference could be found between IS patients and controls in the total sample of girls, although the mean serum level of SMA was markedly higher in the control group (Figure 1 and Table 2). It did not make any difference whether the populations were compared on the basis of chr. or skel. age. When the different age groups are considered the SMA levels were found to be significantly higher

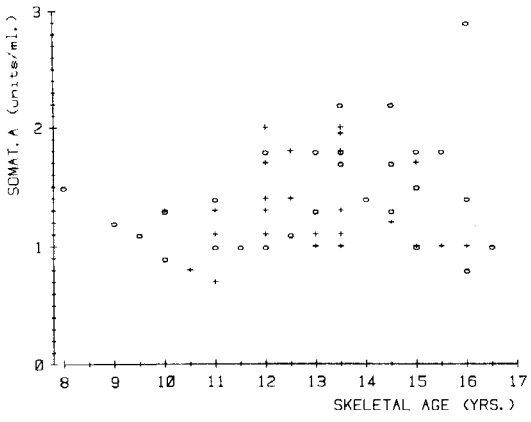

Figure 1. Somatomedin A plotted against skeletal age in IS girls (+) and controls (○).

($P < 0.05$) in the control group for girls over 13 years (skel.) (Table 4), whereas no difference could be demonstrated in girls of or younger than 13 years (skel.) (Table 3). Similar results were found when evaluating the data on the basis of chr. age. No significant correlation could be found between SMA on the one hand and GH fasting values or pituitary GH response to the provocative test (Skogland & Miller 1980 b) on the other.

Non-dialyzable hydroxyproline: The amount of THP excreted during 24 hours was markedly higher in the IS group (36.8 per cent) than in the controls but the difference was not statistically significant (Table 5). Whether the comparison was based on chr. or skel. age did not affect this result (Table 6) and normalization of the THP values on the basis of body surface area had a negligible effect on the results. The IS patients

Table 2. Serum level of somatomedin A in the total groups of scoliotic girls (IS) and female controls (C). In this and the following tables the values are given in means ± standard deviation

	n	mean chr.age years	mean skel.age years	Somat. A Units
IS	31*	13.1±1.4	12.9±1.5	1.30±0.37
C	30*	13.3±1.9	13.0±2.2	1.47±0.46
				N.S.

* Due to the age matching of the sub-groups, the sum of the samples in Tables 3 and 4 is not equal to the total number of cases in this table.

Table 3. Serum level of somatomedin A in scoliotic girls and female controls less than or equal to 13 years of skeletal age

	n	mean skel.age years	Somat. A Units
IS	13	11.7±1.0	1.22±0.32
C	12	11.5±1.3	1.26±0.30
			N.S.

Table 4. Serum level of somatomedin A in scoliotic girls and female controls older than 13 years of age

	n	mean skel.age years	Somat. A Units
IS	11	14.5±0.9	1.25±0.33
C	13	14.4±0.8	1.62±0.41
			$P < 0.05$

Table 5. Total (THP) and non-dialyzable hydroxyproline (NDHP) excretion in scoliotic girls and female controls with matched mean chronological ages

	n	mean chr.age years	THP mg/24 h	NDHP mg/24 h	Percentage NDHP/THP
IS	19	12.8±1.5	97.05±53.73	7.2±3.0	7.9±1.6
C	19	12.8±1.9	70.95±43.50	6.4±3.9	9.3±1.9
			N.S.	N.S.	$P < 0.02$

Table 6. Total (THP) and non-dialyzable hydroxyproline (NDHP) excretion in scoliotic girls and female controls with matched mean skeletal ages

	n	mean skel.age years	THP mg/24 h	NDHP mg/24 h	Percentage NDHP/THP
IS	19	12.5±2.1	97.05±53.73	7.2±3.0	7.9±1.6
C	18	12.3±2.3	72.56±44.17	6.5±3.9	9.2±1.9
			N.S.	N.S.	$P < 0.02$

had a non-significantly higher quantity of NDHP in their urine samples but the percentage NDHP/THP was significantly increased in girls without scoliosis.

A statistically significant correlation ($P < 0.05$) could be found between percentage NDHP/THP and age both in the IS girls and in the controls, for skel. as well as chr. ages ($0.44 < r_s < 0.49$). No significant correlation could be demonstrated between THP or NDHP/THP on the one hand and SMA on the other, neither in the IS group nor in the controls. Neither could a significant correlation be demonstrated between NDHP and GH values.

DISCUSSION

The results of the SMA determinations did not shed any further light on the question of accelerated growth in children with IS. The significantly increased serum level of SMA in the control patients over 13 years of age might indicate that non-scoliotic girls have a more intensive growth at this particular age (mean = 14.5 years skel.) than girls with IS. However, this is not in agreement with previous reports on growth in normal and scoliotic girls. According to measurements made on Norwegian school girls (Brundtland et al. 1975) they had their maximum growth rate between 11 and 12 years of age whereas the growth rate between the ages 14 and 15 years was low, the mean height-gain being 6.9 and 2.2 cm, respectively. Skogland & Miller (1980 a) found that the peak growth rate of the spine occurred between 11 and 12 years of age in scoliotic girls and 1 year later in the controls. There seemed to be less growth of the spine in the controls than in the IS girls after the age of 14 years. A higher growth rate in healthy girls compared with scoliotics after the age of 13 years is not compatible with Willner's (1972, 1974) findings. In addition, the lack of correlation between GH (Skogland & Miller 1980 b) and SMA supports the suggestion that the blood level of SMA as measured in the present study is not, as a matter of course, indicative of body growth rate.

The function of peptide growth factors like SMA is still not clear. Even if somatomedin levels have been shown to be higher during puberty than in adults (Almquist & Rune 1961) and good correlation between SMA levels and growth rate has been reported (Hall & Filipson 1975), there are several observations indicating a disturbed relationship between growth and GH on the one hand and somatomedin on the other. During infancy, the period of most intensive growth, GH levels are high while somatomedin levels are low (Van den Brande 1976). A possible explanation for this could be the existence of a special fetal form of the somatomedins, which is "not fully detected by conventional assay procedures" (Sara et al. 1980), but this remains to be verified. Almquist & Rune (1961) found maximum levels of somatomedin in children at ages 8 and 15 years whereas the values at 11 years of age, i.e. in a period of increased height gain, were about the same as in 25 and 75 year old persons. Thorngren et al. (1977) reported a lack of effect on the longitudinal bone growth when hypophysectomized rats were given SMA in the form of subcutaneous injections, whereas a significant increase in longitudinal bone growth could be observed when the rats were given GH.

The results of the latter investigations should be interpreted with some reservation due to the

insufficient sensitivity of the bioassay (Van den Brande 1976) and possible problems with short half-life of SMA (Moses et al. 1976), but there are still indications that the relationship between GH and SMA is not fully clarified. Haug et al. (1977) induced GH-producing tumors in rats and found a decrease in SMA levels with increasing concentration of GH. It also remains to be proved that SMA can promote growth during treatment *in vivo* (Hall et al. 1977).

According to Van den Brande (1976) the bioassay does not distinguish between the different components of somatomedins; this might be the explanation for the increased SMA levels in IS patients as demonstrated by Willner et al. (1976). The radioreceptor assay is not specific for SMA either (Hall et al. 1974), though it is thought to be more sensitive than the bioassay. A radioimmuno-assay for SMA has been developed; this is a more sensitive technique and Hall et al. (1980) has found that the levels of SMA increase during the prepubertal growth spurt. Perhaps SMA determinations by radioimmuno-assay would give more reliable and different results in IS children? On the other hand, it is possible that somatomedin receptors change both in affinity and in numbers during development. This could be more or less pronounced in pathological states and it would therefore be of more interest to examine cartilage receptors from biopsy specimens rather than serum levels of somatomedins.

Scoliosis is frequently observed in association with connective tissue disorders (James 1970, Nordwall 1973, Nachemson & Sahlstrand 1977) and it has been suggested that patients with IS might have a generalized collagen disease (Francis et al. 1977, Bushell et al. 1978). Even if Nordwall (1973) was unable to find any difference in elastic stiffness of tendons or ligaments between scoliotics and controls, the experimental results of Francis et al. (1977) suggest an abnormal cross-link formation and maturation in the collagen of patients with adolescent IS. They suggested that the finding could be related to the reported growth abnormality of these patients (Willner 1972, 1974, Nordwall & Willner 1975).

THP excretion in urine is thought to be a good indicator of collagen turnover in general (Prockop & Kivirikko 1967) and is correlated with the growth rate of children (Clark & Zorab 1978). A higher growth rate in children with IS could be the reason for their increased THP excretion (Zorab et al. 1970). During growth the formation and resorption of bone are concurrent processes, but in periods of intensive growth (like the prepubertal growth-spurt) bone formation should predominate and NDHP, which is thought to be correlated with bone formation (Haddad et al. 1969, 1970, Kalu 1975) should be increased.

No information about growth rate was available in the present material. However, in a longitudinal study Willner (1974) found that both IS girls and controls had their maximum growth rate at the age of 11 years, but the scoliotics were taller at this age. His findings implied that "prescoliotic" girls grew more rapidly during their 8th and 9th year of life. Zorab et al. (1971) found a maximum urinary excretion of THP between 12 and 13 years of age in scoliotic as well as in normal girls.

In the present study of girls with a mean age of 12.8 years, the mean THP excretion was higher in the scoliotics although the difference was not statistically significant. The percentage NDHP was, however, significantly higher in the controls so that if this indicates a higher growth velocity, it is not incompatible with Willner's (1974) findings for this age group. The significant correlation between percentage NDHP/THP and age is in agreement with the THP data of Zorab et al. (1971) but is not fully in agreement with previously published growth velocity data (Willner 1974, Brundtland et al. 1975).

Even if the relatively high urinary excretion of NDHP at the mean age of 12.8 years (chr.) in the controls seems to be in agreement with the higher SMA levels at a mean age of 14.5 years (chr.) in the same group, no significant correlation could be found between percentage NDHP/THP and SMA.

According to Van den Brande & Du Caju (1973) it is important to correct the SMA determinations for age in order to allow group comparison. In the present study all age groups were carefully matched by random deletion (Skogland & Miller 1980 a).

The results taken as a whole may indicate that

the IS girls had a growth rate different from that of the controls at the time of investigation, at least this would appear to be the case for girls over 12 years. However, it should be noted that there is no definite evidence as to the function of somatomedins in growth and similarly the interpretation of NDHP findings is uncertain on the basis of current knowledge.

CONCLUSIONS

The determinations of serum somatomedin A and the urinary content of non-dialyzable hydroxyproline did not confirm the suggestion that girls with idiopathic scoliosis have a growth pattern which is different from non-scoliotic controls during early adolescence. However, the results did suggest a difference in growth rate after the age of 12 years, since the mean values of somatomedin A and non-dialyzable hydroxyproline both were higher in the controls after this age. Due to the uncertainty regarding the exact function of serum growth factors and the relationship between non-dialyzable hydroxyproline and growth, a reliable interpretation of the results must await further advances in this field.

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