Acta Orthop Scand 55, 135–140, 1984

Serum somatomedin A in Perthes' disease

Serum somatomedin A, determined by radioreceptor assay in 47 children with Perthes' disease, was significantly reduced as compared to normal children of the same age. Nine children underwent the l-Dopa tolerance tests to evoke growth hormone release; a normal response was found in eight.

Patients with Perthes' disease tend to be short in stature with "disproportionate skeletal growth" of the limbs; growth is less in the distal than in the proximal extremities. The low serum levels of somatomedin A suggest some growth disturbance during the development of Perthes' disease.

Key words: growth disturbance; growth hormone; Perthes' disease; skeletal growth; somatomedin A.

Hiroya Tanaka, Kiyoshi Tamura, Kazue Takano[1], Norihiko Inoue, Hideo Yoshioka, Kazumitsu Odera, Yasuyuki Takaya, Toshimichi Ono, Hiroyasu Ando & Yasushi Taguchi

Department of Orthopaedic Surgery, Kobe Central Municipal Hospital, Kobe, and [1]Department of Medicine, Tokyo Women's Medical College, Tokyo, Japan

In recent years the determination of various new growth factors has become possible and their roles have been discussed. According to one report, somatomedin A (SMA) is one of these growth-promoting polypeptides, secreted mainly from liver by the stimulation of growth hormone (GH). It is said to possess cartilage-stimulating and growth-promoting activities (Phillips & Vassilopoulou-Sellin 1980) and to act on the growth cartilage. Somatomedins were previously described as "sulphation factor" (Daughaday et al. 1972).

Perthes' disease has a complex etiology and can no longer be regarded as a focal disorder of the hip (Thompson & Woodrow 1981). Some investigators have paid attention to the presence of some kind of growth disturbance, and have studied various endocrine functions in affected children (Tachdjian 1972, Fisher 1972, Laron et al. 1973). The relation between Perthes' disease and somatomedin has also been discussed. Harrison & Burwell (1981) studied children with Perthes' disease, using bioassay (Van den Brande et al. 1974), and found raised levels of somatomedin in some affected boys. We determined the serum SMA in 47 children with Perthes' disease by radioreceptor assay (Takano et al. 1976), which was a more sensitive method, and obtained results different from those of Harrison & Burwell. On the basis of these results, we discuss the association of Perthes' disease with SMA and offer a new view on the etiology of Perthes' disease.

Patients and methods

The subjects were 47 patients with a diagnosis of Perthes' disease, who were hospitalized or regularly attended an outpatient clinic. Blood samples were collected after fasting from 42 boys and 5 girls with Perthes' disease, aged 4–14 years, for the determination of SMA. The serum samples were stored at −20 degrees C until analyzed. SMA was determined by the radioreceptor assay as described by Takano et al. (1976).

The controls were 86 healthy Japanese children without Perthes' disease (Table 1), who consulted us because of short stature. Their short stature was

Correspondence: Department of Orthopaedic Surgery, Faculty of Medicine, Kyoto University, Sakyo-ku, Kyoto 606, Japan

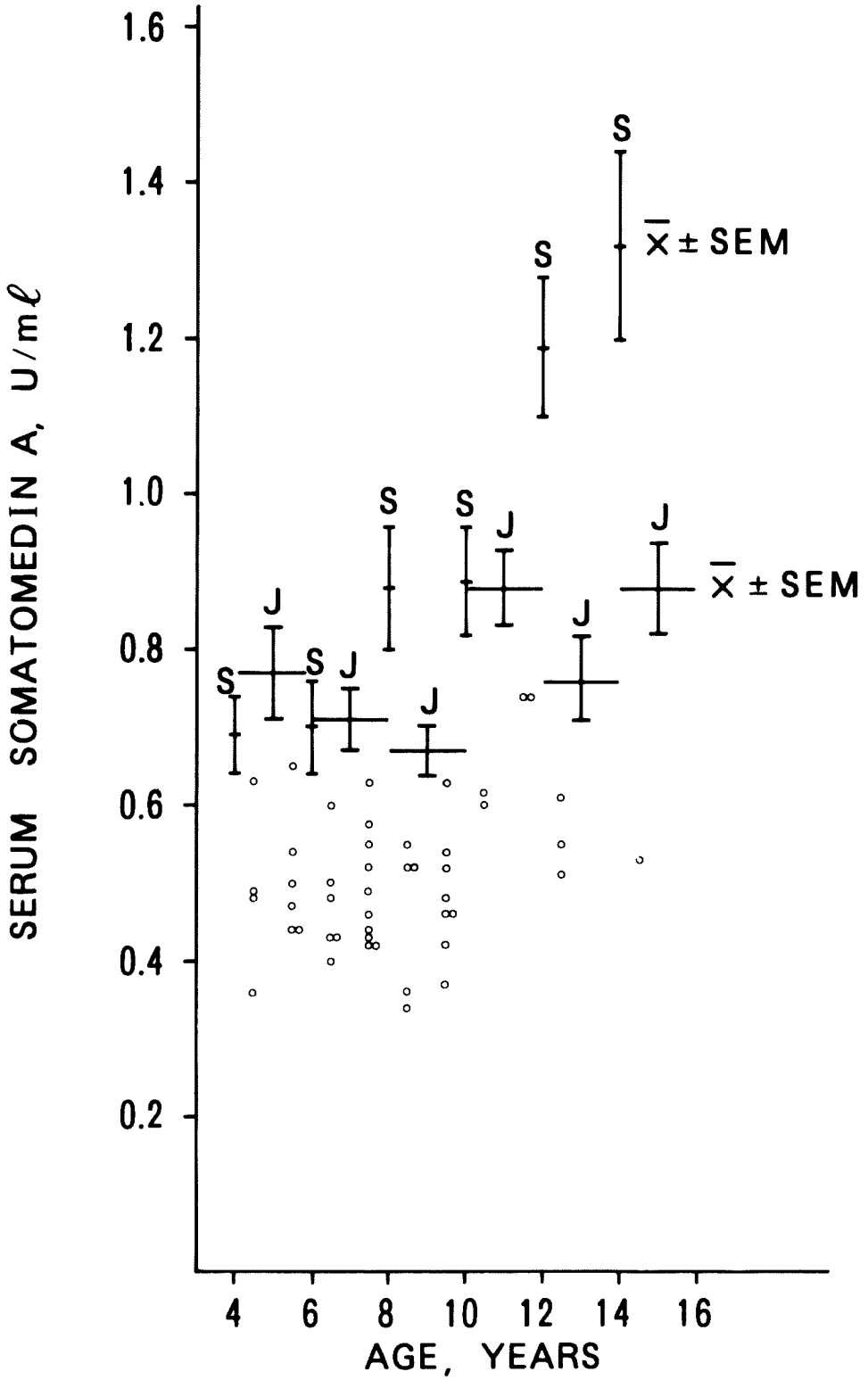

Figure 1. Serum somatomedin A determined by radioreceptor assay in relation to age in 86 healthy Japanese children (J), 188 healthy Swedish children (S) and 47 children with Perthes' disease (○). The bars indicate the mean value ± SEM for each 2-year group of healthy children.

Table 1. Serum somatomedin A (SMA) determined by radioreceptor assay in control groups (Japanese and Swedish controls) and children with Perthes' disease in 2-year age groups

Age group		Control group		Perthes' disease	
		n	SMA, U/ml, $\bar{x}\pm$SEM	*n*	SMA, U/ml, $\bar{x}\pm$SEM
4–5	Japanese	5	0.77±0.06	10	$0.50\pm0.03^{(**)}_{**}$
	(Swedish	20	0.69±0.05)		
6–7	Japanese	17	0.71±0.04	16	$0.48\pm0.02^{(**)}_{**}$
	(Swedish	20	0.70±0.06)		
8–9	Japanese	19	0.67±0.03	13	$0.47\pm0.02^{(**)}_{**}$
	(Swedish	31	0.88±0.08)		
10–11	Japanese	18	0.88±0.05	4	$0.67\pm0.04^{*}$
	(Swedish	26	0.89±0.07)		
12–13	Japanese	15	0.76±0.06	3	$0.56\pm0.03^{(*)}$
	(Swedish	29	1.19±0.09)		
14–15	Japanese	12	0.88±0.06	1	0.53
	(Swedish	21	1.32±0.12)		

** $p < 0.01$ & *$p < 0.05$: significant difference between Japanese control and patients with Perthes' disease. (**) $p < 0.01$ & (*) $p < 0.05$: significant difference between Swedish control and patients with Perthes' disease. Student's *t*-test.

within the normal range, and no clinical and laboratory abnormalities were found.

We also compared our data with SMA values of 188 healthy Swedish children which were measured by radioreceptor assay (Hall et al. 1980). Hall et al. generously offered us their standard serum, the SMA value of which was determined by our radioreceptor assay technique, which showed that 1 U/ml of Hall's SMA was equivalent to 0.98 U/ml of ours. Each of our 47 SMA values was recalculated. Mean values are expressed as $\bar{x} \pm$ SEM. Student's *t*-test was used for the analysis of differences. Furthermore, the Catterall classification (Catterall 1974) was used for the grouping of Perthes' disease, and the correlation between classes and SMA levels was investigated.

In addition, the pituitary GH response to a provocative test with l-Dopa (10 mg/kg body weight) was observed in nine hospitalized patients with Perthes' disease. GH was measured with an HGH RIA kit (Dainabot Ltd.). One patient (weighing 28 kg) underwent additional provocative tests with arginine (14 g), insulin (0.1 U/kg), glucagon (0.84 mg) and propranolol (5 mg).

Results

Somatomedin A. Significantly lower SMA levels were observed in 39 patients with Perthes' disease, aged 4–9 years ($p < 0.01$) than in normal controls of the same age. The levels in eight patients aged 10–14 years were below the normal mean value, and generally a tendency to low SMA levels was found (Figure 1 and Table 1). However, no special relationship between SMA level and Catterall classification was observed (Figure 2).

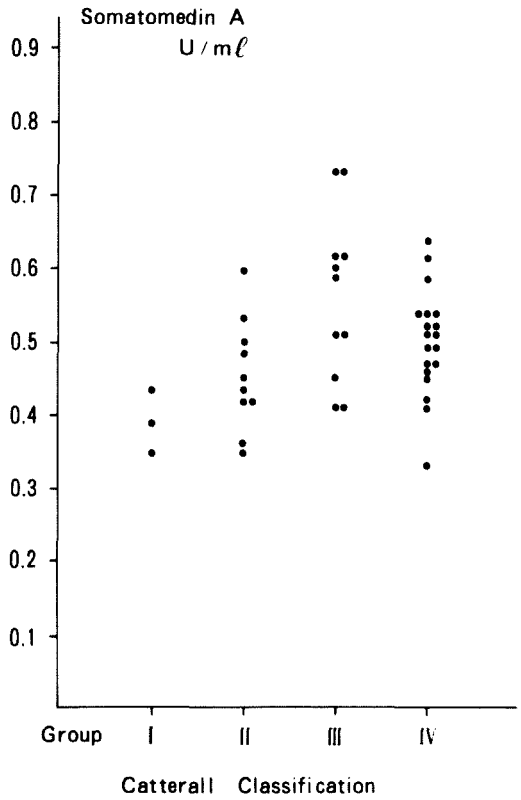

Figure 2. Catterall classification and somatomedin A in Perthes' disease.

Growth hormone. A normal GH rise was found in eight of nine patients during the l-Dopa tolerance test, but one patient did not respond to the test (Figure 3). This patient was a 9-year-old boy whose height and body weight were within the normal range for his age; his skeletal age was also normal. The serum SMA level, however, was extremely low, 0.37 U/ml. Various other provocative tests were performed and GH secretion was induced by a very powerful combination of glucagon and propranolol (Figure 4).

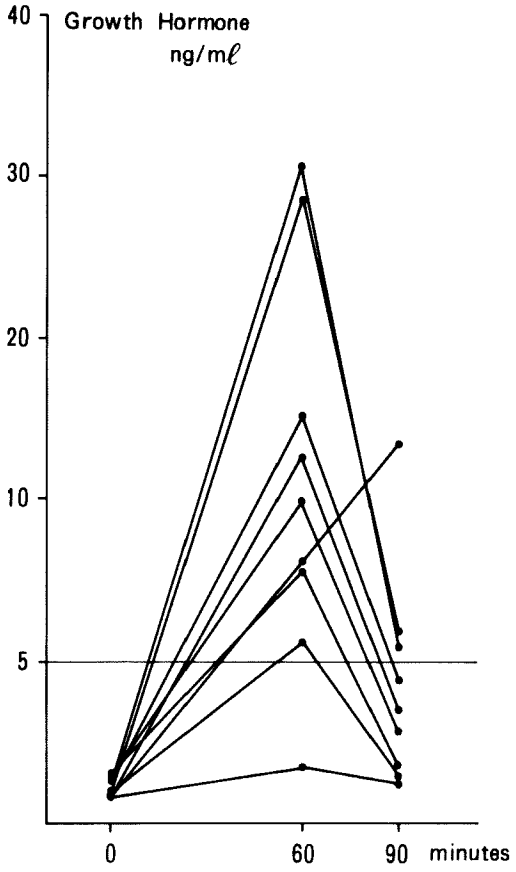

Figure 3. Growth hormone response to provocative test with l-Dopa (10 mg/kg body weight) in nine children with Perthes' disease.

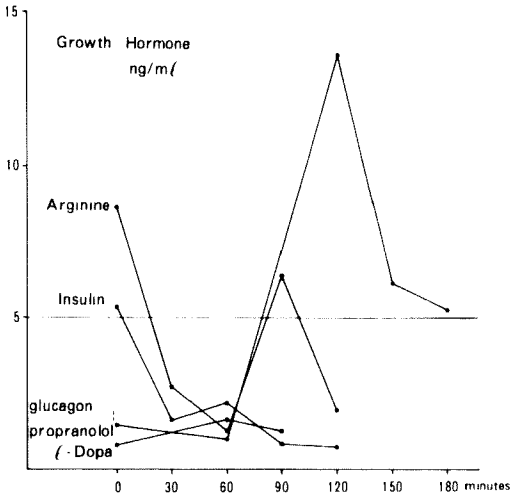

Figure 4. A patient (weighing 28 kg) underwent additional provocative tests with arginine (14 g), insulin (0.1 U/kg), glucagon (0.84 mg) and propranolol (5 mg). Growth hormone secretion was induced by a combination of glucagon and propranolol in high doses.

Discussion

Children affected with Perthes' disease are generally shorter than average (Tachdjian 1972). The presence of some kind of growth disturbance is suspected, and some aspects of endocrine function have been investigated in affected children. Thyroid function, growth hormone, follicle-stimulating hormone, luteinizing hormone and 17-ketosteroids in children with Perthes' disease have been reported to be normal (Tachdjian 1972, Laron et al. 1973, Fischer 1972). However, Harrison & Burwell (1981) reported raised levels of somatomedin in young (3–5-year-old) boys with Perthes' disease, but not in those aged 6–11 years, on the basis of bioassay findings (Van den Brande et al. 1974). This is quite different from the results of our radioreceptor assay studies, in which we found that children with Perthes' disease generally have low serum SMA levels. Increased somatomedin levels reported by Harrison & Burwell seem to be due to insufficient sensitivity of the bioassay (Van den Brande 1976).

The results of serum SMA determination by radioreceptor assay in 47 patients with Perthes' disease, together with GH evaluations in nine subjects, suggest that there is a pattern of normal immunoreactive GH and low SMA in Perthes' disease. On the other hand, we know of various types of growth disturbance due to abnormal GH and growth factor (Table 2). In addition to Laron's dwarfism (Laron et al. 1966) which is considered to be due to abnormal GH receptors, there are Kowarski's dwarfism, which may be caused by secretion of a biologically inactive but immunoreactive GH

Table 2. Growth hormone and somatomedin level in various growth disturbances

	Growth hormone	Somatomedin
Pituitary growth hormone deficiency	low	low
Laron's dwarfism (1966)	high	low
Kowarski's dwarfism (1978)	normal	low
Lanes' dwarfism (1980)	normal	high

(Kowarski et al. 1978), and Lanes' dwarfism (Lanes et al. 1980), which is suspected to be induced by defects in somatomedin responsiveness. In Kowarski's dwarfism there are normal immunoreactive GH and low somatomedin levels, resembling the pattern of Perthes' disease in our evaluation. Thus from the standpoint of growth disturbance, the following two possibilities will be considered to be related to the development of Perthes' disease. First, children with Perthes' disease have an underlying growth disturbance similar to that of Kowarski's dwarfism; however, the patients are not dwarfs because the growth disturbance is only slight. Second, in children with Perthes' disease, transient growth disturbance which may lower the biological activity of GH has occurred before the development of clinical signs. If there is abnormal endogenous GH in children with Perthes' disease, there is a possibility that the disease can be treated with exogenous GH.

There is a marked predominance of boys in Perthes' disease (Tachdjian 1972). No sex difference in the SMA values of our patients and our Japanese control could be evaluated, because of the small number of girls. However, a tendency to lower mean SMA values in normal boys than in normal girls has been observed (Hall et al. 1980). A predominance of boys in Perthes' disease may be associated with lower basal levels of SMA values in boys than in girls. But other factors, including differences in daily activities, will contribute to the male predominance.

There was no special relationship between the SMA level and the Catterall classification. SMA level may be one of the important factors which trigger Perthes' disease but may not be the factor which decides the grade of the disease.

Burwell et al. (1978) pointed out the presence of "disproportionate skeletal growth" in children with Perthes' disease; that is, growth of the distal upper and lower extremities is more impaired than that of the proximal. This impaired growth pattern is exactly opposite to that of acromegaly, in which SMA levels are high (Takano & Shizume 1980). The disproportionate growth may also affect the hip joint with disproportion between the acetabulum and the femoral head (Harrison & Burwell 1981). Since children with the disease have low SMA levels, a lowering of growth-promoting activity is predicted. The hypothesis of Harrison & Burwell (1981), who regard Perthes' disease as "chronic stress fracture" due to the skeletal immaturity and limb disproportion, agrees with our view that children with this disease have low SMA levels.

Acknowledgements

We would like to express our gratitude to Prof. Takao Yamamuro, Department of Orthopaedic Surgery, Kyoto University, for his continued interest and guidance in this investigation. We also thank Drs. Masao Tomi, Shingo Morishita and Takashi Hamamoto for referring patients to us for our study, and Dr. Alice Cary for help with the manuscript.

References

Burwell, R. G., Dangerfield, P. H., Hall, D. J., Vernon, C. L. & Harrison, M. H. M. (1978) Perthes' disease. An anthropometric study revealing impaired and disproportionate growth. *J. Bone Joint Surg.* **60**-B, 461–477.

Catterall, A. (1971) The natural history of Perthes' disease. *J. Bone Joint Surg.* **53**-B, 37–53.

Daughaday, W. H., Hall, K., Raben, M. S., Salmon, W. D. Jr., Van den Brande, J. L. & Van Wyk, J. J. (1972) Somatomedin: proposed designation for sulphation factor. *Nature* **235**, 107.

Fisher, R. L. (1972) An epidemiological study of Legg-Perthes' disease. *J. Bone Joint Surg.* **54**-A, 769–778.

Hall, K., Enberg, G., Ritzén, M., Svan, H., Fryklund, L. & Takano, K. (1980) Somatomedin A levels in serum from healthy children and from children with growth hormone deficiency or delayed puberty. *Acta Endocrinol. (Kbh.)* **94**, 155–165.

Harrison, M. H. M. & Burwell, R. G. (1981) Perthes' disease: concept of pathogenesis. *Clin. Orthop.* **156**, 115–127.

Kowarski, A. A., Schneider, J., Ben-Galim, E., Weldon, V. V. & Daughday, W. H. (1978) Growth failure with normal serum RIA-GH and low somatomedin activity: somatomedin restoration and growth acceleration after exogenous GH. *J. Clin. Endocrinol. Metab.* **47**, 461–464.

Lanes, R., Plotnick, L. P., Spencer, E. M., Daughaday, W. H. & Kowarski, A. A. (1980) Dwarfism associated with normal serum growth hormone and increased bioassayable, receptor-assayable, and immunoassayable somatomedin. *J. Clin. Endocrinol. Metab.* **50**, 485–488.

Laron, Z., Pertzelan, A. & Mannheimer, S. (1966) Genetic pituitary dwarfism with high serum concentration of growth hormone. A new inborn error of metabolism? *Isr. J. Med. Sci.* **2**, 152–155.

Laron, Z., Axer, A. & Drezner, Z. (1973) Growth and development of children with Legg-Calvé-Perthes syndrome in Israel. *Isr. J. Med. Sci.* **9**, 612–616.

Phillips, L. S. & Vassilopoulou-Sellin, R. (1980) Somatomedins. *N. Engl. J. Med.* **302**, 371–380.

Tachdjian, M. O. (1972) *Pediatric orthopedics*, Vol. 1, pp. 384–406. W. B. Saunders Company, Philadelphia.

Takano, K., Hall, K., Ritzén, M., Iselius, L. & Sievertsson, H. (1976) Somatomedin A in human serum, determined by radioreceptor assay. *Acta Endocrinol. (Kbh.)* **82**, 449–459.

Takano, K. & Shizume, K. (1980) Growth and growth factors. *Proceedings of the international symposium on growth and growth factors, held June 4 and 5, 1979* (Eds. Shizume, K. & Takano, K.), pp. 119–134. University of Tokyo Press, Tokyo.

Thompson, S. K. & Woodrow, J. C. (1981) HLA antigens in Perthes' disease. *J. Bone Joint Surg.* **63**-B. 278–279.

Van den Brande, J. L. & Du Caju, M. V. L. (1974) An improved technique for measuring somatomedin activity *in vitro*. *Acta Endocrinol. (Kbh.)* **75**, 233–242.

Van den Brande, J. L. (1976) Growth hormone and related peptides. *Proceedings of the 3rd International Symposium, Milan, September 17–20, 1975* (Eds. Pecile, A. & Muller, E. E.), pp. 271–285. Excerpta Medica, Amsterdam, Elsevier Publ. C., Inc., N.Y.