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Serum Levels of Radioreceptor-assayable Somatomedins in Children with Minor Neurodevelopmental Disorders

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ABSTRACT

The somatomedins are a family of multitarget, growth-promoting hormones suggested to play a regulatory role in the central nervous system. Serum concentrations of somatomedins were determined by a radioreceptor assay in 26 patients (19 boys and 7 girls) with minor neurodevelopmental disorders. Five of these 26 patients showed high serum levels (> 2 S.D.) of somatomedins. It is concluded that patients with elevated concentrations of somatomedins might represent a pathogenetic subgroup.

INTRODUCTION

The somatomedins are a family of multitarget growth-promoting hormones. It has been suggested that the somatomedins play a regulatory role in the central nervous system (9). Sara et al. (6) has suggested that an embryonic form of somatomedin influences brain development by regulating cell proliferation and hypertrophic growth. These authors also propose that an adult form of somatomedin acts as a maintenance hormone regulating brain cell metabolism. Clinical investigations have revealed a disturbance in the serum levels of somatomedins in patients with Down's syndrome (11), in severe mental retardation without characterized genetic disorders (8) and in dementia of the Alzheimer type (10).

The aim of the present study was to investigate the serum concentration of somatomedins in patients with minor neurodevelopmental disorders (MND).

MND was defined as minor neurological dysfunction in the following fields: co-ordination of the extremities, associated movements, posture, balance, fine manipulative ability and gross motor functions (12). Patients who had a sibling also affected by MND were designated as familial type of MND. No patients with cerebral palsy or mental retardation were included.

METHODS

Blood samples were centrifuged and the sera stored at -80°C until assayed. The concentration of somatomedins was determined by a radioreceptor assay (RRA) using human fetal brain plasma membrane as matrix and somatomedin A (SMA) as ligand (fetal brain RRA-SMA). This assay, which has been described in detail earlier (7), measures predominantly insulin-like growth factors 1 and 2, which are 10 times more potent in cross-reaction than SMA. A serum standard, given the value 1 unit/ml was used as the reference. Samples were assayed in triplicate. Serum levels were determined using a symmetrical four-point system. The index of precision (λ) was < 0.2 for each sample determination (7).

In order to investigate whether protein binding in native serum might interfere with the levels of somatomedins determined by this RRA, serum samples were also examined in six of the patients after acid-ethanol extraction as described by Daughaday et al. (2).

A two-tailed t-test was applied in calculations of statistical significances.

PATIENTS

Since 1976 MND has been diagnosed in 109 patients at the Department of Pediatrics of the University Hospital in Uppsala. From this series, 12 patients of the non-familial type selected at random and all 14 patients of the familial type (1) participated in the present study.

Blood samples were collected from these 26 patients (19 males and 7 females) who had a mean age of 9.7±3.8 (S.D.) years (range 4-20 years). The birth data of the patients were as follows (mean values and ranges): gestational age 39.5 completed weeks (36-42 weeks), birth weight 3950 g (2250-4300 g), birth length 50 cm (47-55 cm), head circumference 34.5 cm (30-37 cm) and Apgar score five minutes after birth 9 (6-10). The mean deviations of the individual lengths and weights of the patients from the mean lengths and weights of the Swedish child population (3) were +0.8 S.D. (range -1.5 to +3.0 S.D.) and +0.8 S.D. (range -1.0 to +3.0 S.D.) respectively.

In normal children radioreceptor-assayable somatomedins increase during puberty (11). The results from the MND patients are therefore interpreted in relation to their stage of pubertal development rated according to Marshall and Tanner (4,5). Fifteen boys and five girls aged 4 to 13 years were in the preadolescent stage. Four boys and two girls had pubertal changes of stage 2 to 5. None of the patients were early or late maturers.

The control group consisting of 113 normal children aged 4 to 16 years and 29 normal adults aged 20 to 50 years (Table I and Fig. 1) has been described in detail before (11).

RESULTS AND DISCUSSION

The serum concentrations of radioreceptor-assayable somatomedins were significantly higher ($P < 0.05$) in the MND patients than in the normal controls at ages of 4 to 12 years (Table I) and 5 of these 26 patients showed serum levels higher than +2 S.D. (Fig. 1).

In order to exclude the possible interference of somatomedin binding proteins in the RRA, the following six MND patients had levels determined in both whole and acid-ethanol extracted serum: (sex and age: value in whole serum/value in acid-ethanol extracted serum in U/ml).

male 5 years: 1.21/1.14, male 6 years: 0.94/0.84,

male 8 years: 1.21/1.14, male 12 years: 1.81/1.67,

male 13 years: 1.06/1.21, male 16 years: 1.17/1.59.

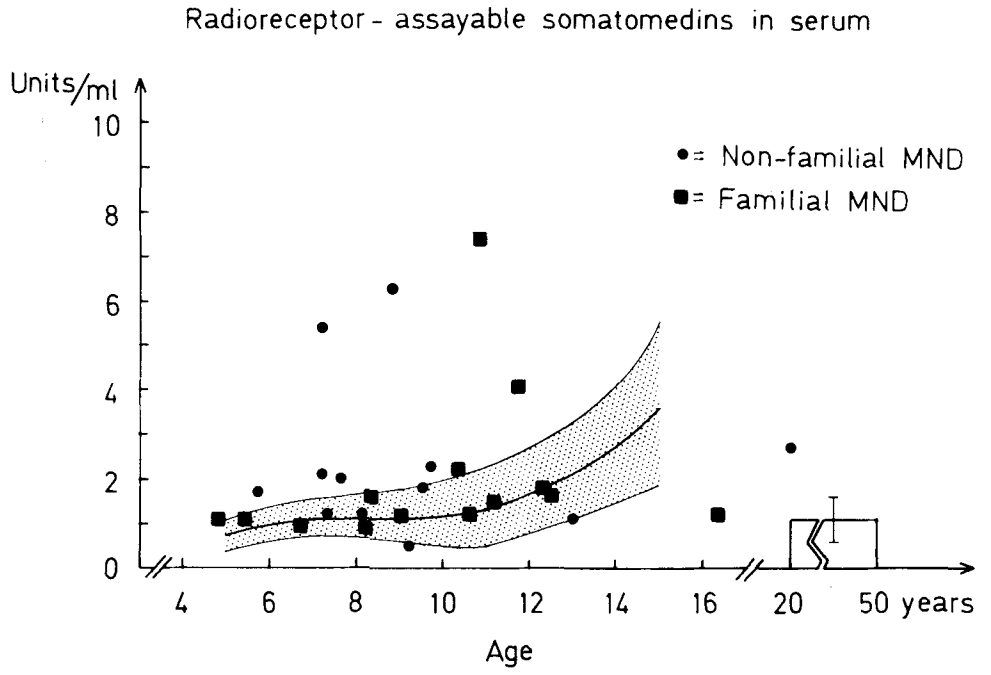

Fig. 1. Concentrations of radioreceptor-assayable somatomedins determined by fetal brain RRA-SMA in whole serum from 14 patients with the familial type (■) and 12 patients with the non-familial type (●) of minor neurodevelopmental disorders (MND). The mean levels ±1 S.D. of 113 normal children are indicated by the hatched area and of 29 normal adults by the bars.

Table 1. Concentrations of radioreceptor-assayable somatomedins (fetal brain RRA-SMA) in 19 males and 7 females with minor neurodevelopmental disorders, 113 normal children and 29 normal adults.

		Age in years							
		4-6	6-8	8-10	10-12	12-14	14-16	16-18	20-50
Patients	Number males/females	2/1	4/1	5/3	3/2	3/0	0	1/0	1/0
	Fetal brain RRA-SMA U/ml mean ± 1 S.D.	1.30±0.37	2.32±1.78	1.97±1.84	3.28±2.55	1.48±0.38	—	1.17	2.71
Controls	Number males/females	10/10	9/10	11/14	9/10	9/8	6/7	0	29
	Fetal brain RRA-SMA U/ml mean ± 1 S.D.	0.77±0.41	1.08±0.42	1.12±0.59	1.29±0.93	2.16±1.09	3.59±1.77	—	1.09±0.53

There was no statistically significant difference ($P > 0.05$) between the results obtained from native and extracted serum. Thus, the elevated concentrations of fetal brain RRA-SMA found in some of the present MND patients cannot be attributed to the presence of binding proteins.

Since all the patients in this study showed normal pubertal changes for their age, the high concentrations of fetal brain RRA-SMA found in some of the cases cannot be explained by early pubertal maturation. The implications of the high serum levels of fetal brain RRA-SMA found in five of the patients are not known. They could not be distinguished on the basis of clinical data (e.g. developmental language disorder or learning disability) from those with levels within the normal range, and included both cases of the familial and the non-familial type of MND. However, MND is a heterogeneous condition and the patients with high concentrations of radioreceptor-assayable somatomedins might represent a pathogenetic subgroup.

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REFERENCES

1. Bergström, K., Bille, B., & Rasmussen, F.: Computed tomography of the brain in children with minor neurodevelopmental disorders. Accepted for publication in Neuropediatrics, 1983.

2. Daughaday, W.H., Mariz, I.K., & Blethen, S.L.: Inhibition of access of bound somatomedin to membrane receptor and immuno-binding sites: a comparison of radioreceptor and radioimmunoassay of somatomedin in native and acid-ethanol extracted serum. J. Clin. Endocrinol. Metab. 51:781-788, 1980.

3. Karlberg, P., Taranger, J., Engström, J., Karlberg, T., Landström, T., Lichtenstein, H., Lindström, B., & Svennberg-Redegren, I.: Physical growth from birth to 16 years and longitudinal outcome of the study during the same period. Acta Paediatr. Scand. Suppl. 258, 1976.

4. Marshall, W.A., & Tanner, J.M.: Variations in Pattern of Pubertal Changes in Girls. Arch. Dis. Childh. 44:291-303, 1969.

5. Marshall, W.A., & Tanner, J.M.: Variations in Pattern of Pubertal Changes in Boys. Arch. Dis. Childh. 45:13-23, 1970.

6. Sara, V.R., Hall, K., & Wetterberg, L.: Growth hormone dependent polypeptides and the brain. In: de Wied D., van Keep P.A., eds. Hormones and the

Brain. London: MTP Press, 63-72, 1980.

7. Sara, V.R., Hall, K., Rodeck, C.H., & Wetterberg, L.: Human embryonic somatomedin. Proc. Natl. Acad. Sci. 78:3175-3179, 1981.

8. Sara, V.R., Hall, K., Rutter, M., & Wetterberg, L.: Hormonal regulation of brain growth: Implications for mental retardation. In: Perris, C., Struwe, G., Jansson, B., eds. Biological Psychiatry. Elsevier/North Holland Biochemical Press. 1316-1319, 1981.

9. Sara, V.R., Hall, K., & Wetterberg, L.: Fetal brain growth: A Proposed Model for Regulation by Embryonic Somatomedin. In: Ritzen, A., Aperia, A., Hall, K., Larsson, A., Zetterberg, A., Zetterström, R., eds. The Biology of Normal Human Growth. New York: Raven Press, 241-252, 1981.

10. Sara, V.R., Hall, K., Enzell, K., Gardner, A., Morawski, R., & Wetterberg, L.: Somatomedins in aging and dementia disorders of the Alzheimer type. Neurobiol. of Aging 3:117-120, 1982.

11. Sara, V.R., Gustavson, K.-H., Annerén, G., Hall, K., & Wetterberg, L.: Somatomedins in Down's Syndrome. Biological Psychiatry (in press), 1983.

12. Touwen, B.C.L.: Examination of the child with Minor Neurological Dysfunction: Clinics in Develop. Med. No. 71, 1979.

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