Globoid Cell Leukodystrophy: The First Case with Antemortem Diagnosis in Japan

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WADA, Y., ARAKAWA, Ts., CHIDA, N., ONUMA, A. NAKAGAWA, H., IINUMA, K., YOSHIMURA, Y., NAKAJIMA, S. and SUZUKI, Y. *Globoid Cell Leukodystrophy: The First Case with Antemortem Diagnosis in Japan*. Tohoku J. exp. Med., 1975, 115 (1), 53-59 — A Japanese boy was diagnosed as globoid cell leukodystrophy on the basis of a marked decrease in the galactocerebroside β -galactosidase activity in the leukocytes and the serum when one year and two months old. At autopsy when 1 year and 10 months, microscopic findings were characteristic for those of globoid cell leukodystrophy. Galactocerebroside β -galactosidase activities of leukocytes and sera of his father and mother were found to be half those of control subjects, thus it suggested the parents being heterozygotes of the disease. — globoid cell leukodystrophy; galactocerebroside β -galactosidase

The present paper deals with the first case of globoid cell leukodystrophy (GLD) in Japan which was diagnosed by the demonstration of a defective activity of galactocerebroside β -galactosidase in leukocytes and serum obtained from the patient when one year and two months old.

CASE REPORT

H.S., a one year and two months old Japanese boy was admitted to our clinic in the Tohoku University Hospital with a complaint of mental and physical deterioration.

The parents were not consanguineous, but the grandmother and great-grandfather on the maternal side were related. One of his aunts on the maternal side was mentally retarded and had frequent attacks of generalized tonic convulsions and died at the age of 11 years. An elder brother of the patient suddenly died of unknown origin on 2 days of life.

The proband was born on Jan. 17, 1971, after a full-term pregnancy and an uneventful delivery. His birth-weight and height were 4,150 g and 54 cm, respectively. The circumferences of the chest and the head were 36 and 35.5 cm, respectively.

There was no abnormality in his neonatal history. His progress had been entirely normal until 6 months of age, when difficulty in feeding developed. At that time his parents noticed that he became lean and weak to cry, and that his limbs were becoming progressively more "stiff".

Thereafter he showed an apathetic face and seemed to be indifferent to the surroundings.

An electroencephalogram, taken at the age of 7 months, suggested the presence of diffuse organic brain damage.

Since 11 months of age, he repeatedly suffered from episodic attacks of vomiting (probably due to acetonemic vomiting).

On the admission, when 1 year and 2 months old, he was extremely emaciated. His weight and height were 5.9 kg (normal 9.1 kg) and 69.5 cm (normal 74.1 cm), respectively. His extremities were of marked rigidity, with scissoring of his legs. His arms were flexed at the elbow with clenching fists. He could not hold his head up nor roll over himself. An only emotional expression observed was to cry weakly when some mechanical stimulation was given on his body.

His hair and eyes were black in color. The palate was high-arched and narrow. There was no lymphadenopathy. The anterior fontanel measured 1.5 cm×1.5 cm and was flat. There was no deformity in the skeletal systems including skull.

The heart and lungs were clear to auscultation. Abdomen was soft and flat. The liver and spleen were not palpable.

Deep tendon reflexes were not exaggerated, but Oppenheim's, Chaddock's and Babinski's reflexes were positive, while both nuchal rigidity and Kernig's sign were negative.

Laboratory data. Routine examinations of the urine and feces revealed no abnormality. The peripheral blood and bone marrow pictures showed no abnormality. The following laboratory tests gave normal findings: liver function tests, serum lipids, serum protein and its fraction, serum mucoprotein, blood ammonia nitrogen, serum electrolytes, blood sugar, serum acid and alkaline phosphatase activities, serum creatine phosphokinase, lactic dehydrogenase, urea nitrogen, serum amino acids, serum folic acid, non-volatile organic acids and amino acids in the urine and cerebrospinal fluid.

But protein content of the cerebrospinal fluid was found to be increased, being 230 mg per 100 ml.

Results of blood gas analysis were normal. Chromosomes were also normal in number as well as configuration.

There was a prolongation of PR interval in his electrocardiogram, but cardiomegaly was not observed in his X-ray film.

X-ray films of the bone revealed severe osteoporosis of the whole skeletal system, without any delay of the bone age.

Funduscopy revealed a marked optic atrophy and irregular reflexes on the retina bilaterally, but no cherry-red spots.

Clinical course. Within a few months after the admission, his extremities

became hypotonic. Since 1 year and 7 months of life, he was fed by tube-feeding, but he regurgitated frequently. He died on Nov. 11, 1972, when 1 year and 10 months old.

SPECIAL STUDIES

Methods

N- β -Acetylglucosaminidase activity in serum was assayed by O'Brien et al.'s method (1970).

Serum and leukocyte galactocerebroside β -galactosidase activities were assayed by means of Bowen and Radin's method (1969), with minor modifications (Suzuki and Suzuki 1971).

Uric acid levels in plasma, urine and cerebrospinal fluid were determined by Henry et al.'s method (1957). Phosphoribosyltransferase activities were assayed by Kelley et al.'s method (1967).

Results

Phospholipids in the erythrocytes (2.0 mg/ml packed erythrocytes) and

TABLE 1. *Galactocerebroside β -galactosidase activity in leukocytes*

	Galactocerebroside β -galactosidase activity (nmoles/mg protein/hr)
Our own patient (H.S.) (1y. 5m. ♂)	0.06
His father (35y. ♂)	0.66
His mother (25y. ♀)	0.58
Control	
T.T. (1y. 11m. ♂)	1.69
M.S. (3y. 8m. ♀)	1.35
Adult 1	1.49
Adult 2	1.11

TABLE 2. *Galactocerebroside β -galactosidase activity in the serum*

	Galactocerebroside β -galactosidase activity (nmoles/hr/100 ml)
Our own patient (H.S.) (1y. 5m. ♂)	1.1
His father (35y. ♂)	3.4
His mother (25y. ♀)	5.7
Controls	
H.Y. (0y. 5m. ♂)	9.0
K.O. (0y. 4m. ♂)	16.0
Infant 1	18.0
Infant 2	24.4

TABLE 3. *Phosphoribosyltransferase (PRT) activity in erythrocytes*

	Adenine-PRT	Guanine-PRT	Hypoxanthine-PRT
Our own patient (H.S.) (1y. 5m. ♂)	30.3	104.2	101.3
Mean±S.D.	29.1±6.8	103.9±20.7	100.5±21.6
(Number of cases)	(93)	(93)	(93)

Activities are given in nmoles/mg protein/hr

TABLE 4. *Results of chemical analysis of the cerebrospinal fluid of our patient (H.S., 1y. 2m. ♂)*

Cell count	8/3
Protein	230 mg/100 ml
Uric acid*	1.0 mg/100 ml
Sugar	58 mg/100 ml
Chloride	123 mEq/liter
GOT	14 (R.F.)
GPT	3 (R.F.)
LDH	75

* (normal range 0.15–0.3 mg/100 ml)

urinary sulfatides were found to be within normal ranges.

The galactocerebroside β -galactosidase activity of the patient was found to be markedly decreased in both leukocytes and serum, and that the enzyme activity in both leukocytes and sera obtained from the parents was found to be about half that of control subjects (Tables 1 and 2).

Uric acid levels in the plasma and urine from the patient were 2.8 mg/100 ml and 140.8 mg/day, respectively. Phosphoribosyltransferase activities in the erythrocytes were found to be within normal limits (Table 3). But uric acid in the cerebrospinal fluid of our patient was 1.0 mg/100 ml, which was remarkably increased as compared with the normal range (Table 4).

AUTOPSY FINDINGS

Macroscopic findings

The brain was small in size, weighing 580 g. Frontal area of the cerebrum appeared extraordinarily narrow in shape. Gyli were shrunken and sulci were widened.

On the frontal section, the white matter appeared remarkably atrophic, while the gray matter was not so, and a plenty of small cysts were seen in the bulk (Figs. 1 and 2).

The cerebellum was also small, the weight of the cerebellum with brain stem being 75 g.

The spinal cord was also thin and wax-colored.

There were multiple necroses of millet-seed size in both lungs, which were diffusely edematous.

Fig. 1. Remarkable atrophy of the white matter of the brain of our patient (H.S.).

Fig. 2. Small cysts in the bulk of the brain of our patient (H.S.).

The liver was uniformly fatty.

Microscopic findings

In the white matter of the cerebrum, oligodendroglia decreased in number and plenty of epithelioid cells and globoid bodies were found (Fig. 3).

There were diffuse demyelination and gliosis as well as loss of ganglion cells especially in nucleus olivaris, nucleus pontis and nucleus dentatus. Perivascular lymphocytic infiltration was found in the cerebral cortex and its bundles.

In some place of the deep white matter, there were cystic structures especially

Fig. 3. Typical globoid body seen in the white matter of the brain of our patient (H.S.).

in the perivascular areas.

In the gray matter, most of the nerve cells showed more or less necrotic changes, which was the most severe in nucleus ruber.

DISCUSSION

Defective activity of galactocerebroside β -galactosidase in GLD was first reported by Suzuki and Suzuki (1970).

The cases with antemortem diagnosis of this disorder by the demonstration of the defective activity of the enzyme in leukocytes and/or serum have been reported in 9 cases up to date (Suzuki and Suzuki 1971; Young et al. 1972; Suzuki 1973).

The present report of ours was the first case with antemortem diagnosis of this disorder in Japan, in which autopsy confirmed microscopic findings of the brain characteristic for this illness (Andrews et al. 1971; Jacob et al. 1973; Norman et al. 1973).

An abnormally high concentration of uric acid was found in the cerebrospinal fluid of our patient, but its significance remains obscure. Uric acid levels in the serum and urine were found to be within normal ranges and hypoxanthine-guanine phosphoribosyltransferase activity of erythrocytes was also normal in our patient.

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