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Case Report

Enzyme Therapy in Gaucher Disease Type 2: An Autopsy Case

Tsutomu Takahashi, Yasuji Yoshida,[1] Wataru Sato, Tamami Yano, Yutaka Shoji, Yukio Sawaishi, Ikuro Sakuma,[2] Takashi Sashi,[2] Katsuhiko Enomoto,[3] Hiroyuki Ida[4] and Goro Takada

Departments of Pediatrics, [2]Radilogy, [3]Pathology, Akita University School of Medicine, Akita 010-8543, [1]Department of Pathology, Research Institute for Brain and Blood Vessels, Akita 010-0874, and [4]Department of Pediatrics, Jikei Medical School, Tokyo 105-0003

Takahashi, T., Yoshida, Y., Sato, W., Yano, T., Shoji, Y., Sawaishi, Y., Sakuma, I., Sashi, T., Enomoto, K., Ida, H. and Takada, G. *Enzyme Therapy in Gaucher Disease Type 2: An Autopsy Case.* Tohoku J. Exp. Med., 1998, **186** (2), 143-149 —— A Japanese patient with Gaucher disease type 2 was treated with enzyme therapy, alglucerase, from 7 to 22 months of age. Whereas hematologic parameters were normalized and hepatosplenomegaly was alleviated, no improvement in neurologic symptoms occurred, and the patient died of respiratory failure at age 22 months. Postmortem examination revealed massive intra-alveolar infiltration of Gaucher cells in lungs and in the central nervous system, i.e., the presence of Gaucher cells in the perivascular Virchow-Robins spaces in the cortex and deep white matter and extensive lamilar necrosis with reactive proliferation of blood vessels and macrophage infiltration of the cerebral cortex. It is suggested that enzyme therapy, with thus far recommended dose, does not prevent long-term respiratory and central nervous system involvement in severe varients of Gaucher disease. ———— Gaucher disease type 2; enzyme therapy; an autopsy case

Gaucher disease, an autosomal recessive inherited glycolipid storage disorder, is caused by deficiency of β-glucosidase (E.C. 3.2.1.45) (Beutler and Grabowski 1994). Three types of Gaucher disease have been delineated (Beutler and Grabowski 1994). Type 1, by far the most common, is distinguished from types 2 and 3 disease by the lack of primary central nervous system involvement. Type 2, the acute neuronopathic form of the disease, has an early onset with severe central nervous system involvement and death usually occurs within the first 2 years of life. Patients with type 3 Gaucher disease have neurologic symptoms

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Address for reprints: Tsutomu Takahashi, M.D., Department of Pediatrics, Akita University School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan.

with a later onset and a more chronic course than that observed in type 2 disease. Hepatosplenomegaly, bone lesions, and sometimes involvement of lungs and other organs occur in all forms of Gaucher disease. The use of enzyme therapy for Gaucher disease type 1 has revolutionized its treatment (Barton et al. 1991; Beutler et al. 1991; Fallet et al. 1992; Figueroa et al. 1992; Pastores et al. 1993). This therapy can clinically alleviate anemia, bone disease, and hepatosplenomegaly associated with the condition.

Although several patients with type 2 have received alglucerase therapy, only four reports documenting patient response appear in the literature (Brady et al. 1993; Erikson et al. 1993; Bembi et al. 1994; Bove et al. 1995). These reports concluded that the primary neuronopathic process in the central nervous system was unaffected by the therapy, but histological evaluation of the therapy have not been sufficiently discussed in the reports. We reported here an autopsied case of Gaucher disease type 2 treated with enzyme therapy for 15 months until just before death.

Case Report

The case was a boy born to healthy Japanese parents with an uneventful delivery. The patient developed normally until 4 months of age, when he was found to have an enlarged liver (3 cm) and spleen (4 cm palpable below the costal margin). At 7 months of age, he developed anemia caused by hypersplenism (hemoglobin level of 6.5 g/100 ml). Paresis of eye movement and retroflexion of the neck during waking also appeared. He was diagnosed with Gaucher disease, based on the existence of Gaucher cells in the bone marrow and on the deficient activity of acid β-glucosidase in the white blood cells (0.2 nmol/hour/mg vs. 4.6–5.6 nmol/hour/mg of normal). The genotype for the patient was determined as an L444P/unknown type from DNA isolated from peripheral blood leukocytes, as described (Ida et al. 1995).

From 7 to 11 months of age (for 3 months), he was given 30 U of alglucerase per kilogram per week (recommended dosage) in divided doses 3 times per week (the first protocol). This protocol did not show any improvement in his clinical or laboratory findings, and then the patient was given 30 U per kilogram 1 time per week (the second protocol). The last dose was administered at 22 months of age, 2 weeks before death. Although his Hb level did not increase during the first protocol (5.0 g/100 ml), it was normalized during the second protocol (12.5 g/100 ml) (Fig. 1). Platlet counts were within normal limits from the beginning and did not differ between the 2 protocols. Total serum acid phosphatase levels elevated initially (349.5 units/liter vs. 10–20.6 units/liter of normal) and then reduced to some extent (100–170 units/liter). Initially, the level of angiotensin converting enzyme was markedly increased (93.2 IU/liter/37°C vs. 8.3–21.4 IU/liter/37°C of normal), and then decresed during the treatment (50–70 IU/liter/37°C). Volumes of the liver and spleen were determined by established computer-

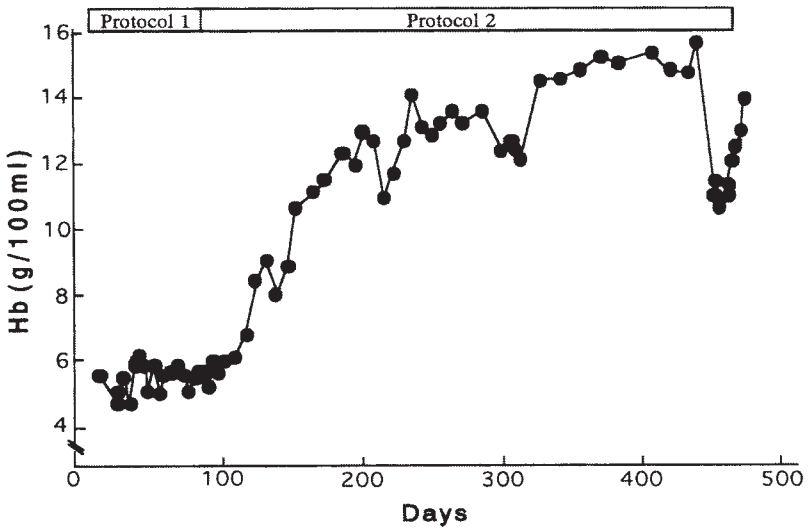

Fig. 1. The effect of alglucerase treatment on the hemoglobin level. From 7 months to 11 months of age, he was given 30 U per kilogram per week in divided doses 3 times per week (protocol 1). Then, he received 30 U per kilogram 1 time per week (protocol 2).

ized tomographic techniques. The liver volume was reduced from 340.8 cm^3 to 263.7 cm^3 (after 3 months of therapy) and increased to 276.3 cm^3 (after 6 months). The spleen volume changed from 260.2 cm^3 to 182.2 cm^3 and to 188.72 cm^3 after 3 and 6 months of therapy, respectively. Despite the effectiveness against hepatosplenomegaly, the patient's central nervous system involvement increased markedly, and finally he exhibited fixed strabismus, severe retroflexion of the neck, intermittent laryngeal spasms leading to apnea, and severe uncoordinated swallowing. Although the chest x-ray photos of the patient were normal, the levels of arterial blood gas gradually deteriorated throughout the course. At 13 months of age, blood gas studies in F_{IO_2} 0.21 were: pH 7.40, P_{aco_2} 42.1 mmHg, P_{ao_2} 60.5 mmHg, and base excess 1.1. Alveolar-arterial O_2 difference, P_{AO_2}-P_{aO_2}, calculated from the above data was high (38.7 mmHg vs. 15–25 mmHg for normal). At 17 months of age, blood gas studies in F_{IO_2} 0.21 were: pH 7.47, P_{aco_2} 33.1 mmHg, P_{ao_2} 65.3 mmHg, base excess 0.4, and P_{AO_2}-P_{aO_2} 44.7 mmHg. His death occurred at 22 months of age because of bulbar palsy and progressive respiratory insufficiency in a cachectic state. During the treatment period, there were no untoward reactions and no development of antibodies against the enzyme.

Autopsy was performed 3 hours postmortem. The liver (245 g) and spleen (140 g) were markedly enlarged. The kidneys were congested, weighing 20 g respectively. No malformation was detectable in any organ, including the heart. Right ventricular hypertrophy was absent. In the brain, atrophic and lacunar changes were observed, weighing less than normal (735 g vs. 1100 g of normal). Histologically, alveolar consolidation and filling of alveolar space by Gaucher cells were clearly observed, suggesting that severe infiltration of Gaucher cells in the lung had contributed to the respiratory failure as the cause of death (Fig. 2).

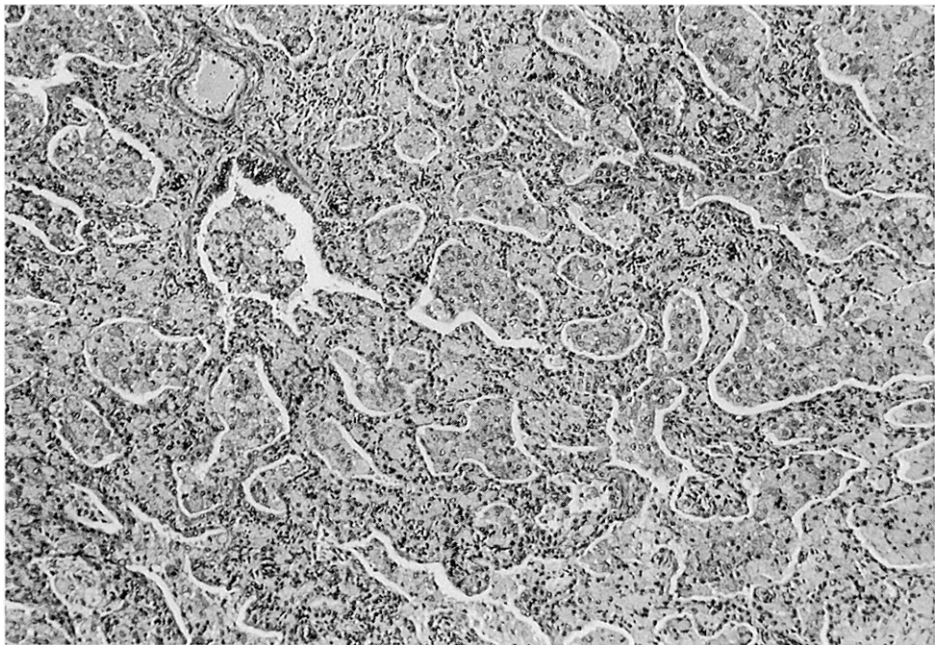

Fig. 2. Lung tissue showed massive intra-alveolar infiltration by Gaucher cells. (hematoxylin-eosin stain; original magnification ×100)

Accumulation of Gaucher cells within either the alveolar septa or the perilobular septa was not marked, nor was there any evidence of Gaucher cell infiltration in the small blood vessels. The infiltration of Gaucher cells was marked in the liver but scattered in the sinusoids, which was consistent with the reduction of the hepatic volume after the enzyme therapy. Severe infiltrations of Gaucher cells were recognized in other organs such as the spleen, visceral lymph nodes, and thymus.

Histological studies were also performed in the central nervous system. Cortical laminar necrosis of the layers IV and V was extensive in the whole cerebrum. Additional laminar necrosis was also observed in the layer II of the cortices in the temporal and occipital lobes. In the calcarine cortex, laminar necrosis existed in the layer IVa. The laminar necroses were composed of neuronal loss, reactive astrocytosis, macrophage infiltration with multinuclear giant cells (Langerhans type), and microvascular proliferation. Neuronophagia, glial nodules, confluent necrotic foci with astrocytosis and macrophage infiltration were observed in the mamillary bodies, substantia nigra, pontine nuclei and dentate nuclei. Perivascular accumulation of Gaucher cells was observed in the subcortical white matter, putamen, globus pallidus, thalamus, substantia nigra and brain stem tegmentum. No evidence of degeneration of the basal ganglia, cerebellar cortex and medulla oblongata was recognized. Severity and location of central nervous system abnormalities in the patient were summalized in Table 1. The severity of the abnormalities range from normal (0) to very extensive changes (3+). Spinal cord was not available for examination.

TABLE 1. *Histological evaluation of central nervous system*

	Degeneration and cell reaction		Perivascular Gaucher cells	
	Gray M.	White M.	Gray M.	White M.
Frontal lobe	2+	0	0	1+
Parietal lobe	2+	0	0	1+
Occipital lobe	3+	1+	1+	2+
Temporal lobe	3+	0	1+	2+
Ammon	2+ (focal)	0	0	0
Basal ganglia				
Putamen	0	0	0	1+
Claustrum	0	0	0	–
Globus pallidus	0	0	0	1+
Caudate nucleus	0	0	0	–
Basal nucleus of Meynert	0	0	0	0
Thalamus				
Anterior nuclear group	0	0	2+	–
Dorso median nucleus	0	0	1+	–
Lateral nucleus	0	0	0	–
Internal Capsule	–	0	–	0
Optic tract	–	0	–	0
Midbrain				
Substantia nigra	2+	0	1+	–
Cerebral peduncle	–	0	–	0
Red nucleus	1+	1+	0	0
Trochlear nucleus	1+	–	0	0
Oculomotor	0	–	0	–
Pons				
Tegmentum	0	0	1+	1+
Superior cerebellar peduncle	–	1+	–	0
Pontine nuclei	2+	1+	1+	1+
Medulla oblongata	0	0	1+	0
Cerebellum	0	0	0	0
Dentate nucleus	2+	1+	0	0

The severity of the abnormalities range from normal (0) to very extensive changes (3+). –, not examined.

DISCUSSION

In Gaucher disease, enzyme therapy is known to markedly reduce the sizes of the liver and spleen, increase blood counts, and reverse bony changes, but the effects on the pulmonary system have been conflicting. Beutler et al. (1991) reported that 2 patients with pulmonary involvement of moderately severe Gaucher disease type 1 responded to enzyme replacement and modestly improved

in pulmonary function tests. Barranger (1984) described that a patient with Gaucher disease, who underwent liver transplantation (a kind of enzyme replacement therapy), showed a marked improvement in oxygenation immediately after surgery. However, Bove et al. (1995) reported autopsy findings of 2 patients with Gaucher disease type 2, treated with acid β-glucosidase infusion, who showed massive intra-alveolar accumulation of characteristic Gaucher cells. In our case, the enzyme therapy improved the levels of Hb level, acid phosphatase, and angiotensin converting enzyme, and decreased the sizes of the liver and spleen. However, the respiratory function did not improve during the treatment, it deteriorated instead. The alveolar-arterial O_2 difference, the elevation of which implies the presence of ventilation/perfusion impairment or a decrease in diffusing capacity, deteriorated from 38.7 mmHg to 44.7 mmHg after 4 months of therapy. We suspected that the respiratory involvement caused respiratory failure leading to death for 2 reasons. Firstly, 12 hours before death, the blood gas studies in F_{IO_2} 1.0 were: pH 7.39, P_{aco_2} 47.8 mmHg, P_{ao_2} 140.2 mmHg, base excess 2.6, and the alveolar-arterial O_2 difference was 515.4 mmHg. Secondly, the pathology of the lung showed a massive intra-alveolar accumulation of characteristic Gaucher cells. Accumulation of Gaucher cells within the alveolar septa, perilobular septa, or small blood vessels was not markedly observed in our case, which supports the absence of right ventricular hypertrophy of the heart. Therefore, in addition to central nervous system dysfunction, the extensive intra-alveolar accumulation of Gaucher cells with resultant respiratory insufficiency was considered to be one of the major causes of death. The pathological findings of our patient's respiratory system were similar to 2 cases reported by Bove et al. (1995). Thus, we believe that enzyme therapy is ineffective in treating both the central nervous system and the intra-alveolar accumulation of Gaucher cells. As Bove et al. (1995) speculated potential obstacles in obtaining effective interaction between alglucerase and alveolar macrophages, pulmonary tissue, with a specific type of infiltration, i.e., alveolar-space filling, may have a higher dose-response threshold than those of other organs needing a different modality of treatment.

Because histological findings of the central nervous system is heterogeneous in Gaucher disease, it is difficult to make a histological evaluation of the central nervous system in the enzyme therapy. In contrast to the decreased number of Gaucher cells observed in hepatic sinusoids of the patients, Gaucher cells were abundant in the central nervous system, especially in the perivascular spaces. Although the basal ganglia, cerebellar cortex or medulla oblongata was not histologically degenerated, massive accumulation of Gaucher cells showed apparent ineffectiveness of enzyme therapy on the central nervous system.

A characteristic finding of our case, extensive cortical laminar necrosis in the cereberum and additional laminar necrosis in the layer II of the temporal and occipital lobes, have not been described in the reported cases. Although the finding could be caused by hypoxic brain damage, we believe that the finding is

a primary lesion of Gaucher disease due to the reason that characteristic finding of hypoxic brain damage, loss of Purkinje cells in the cerebellum and degeneration of basal ganglia and Sommer's secta, were not observed in our case. The laminar necrosis in the layer II of the cortex should be described as a primary finding of neuropathology in Gaucher disease.

To understand the tissue effects of alglucerase for Gaucher disease, more detailed studies of biochemical and histochemical analyses should be important components of new and ongoing therapy protocol.

Acknowledgments

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