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Case report

Pathological fracture and pyogenic osteomyelitis in a patient with type 2 Gaucher disease

Anri Hayashi *, Rie Kawakita, Tomohiro Kumada, Fumihito Nozaki, Ikuko Hiejima, Tomoko Miyajima, Takashi Kusunoki, Tatsuya Fujii

Department of Pediatrics, Shiga Medical Center for Children, Moriyama, Shiga 524-0022, Japan

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Abstract

In Gaucher disease (GD), enzyme replacement therapy (ERT) results in the alleviation of hematological abnormalities and visceral infiltration as well as improvement in quality of life and life-span. However, several years may be required for skeletal manifestations, which are usually observed in type 1 and 3 GD, to respond to ERT. Infants with type 2 GD rarely present skeletal manifestations because most of these patients die within the first 2 years of life before they develop skeletal involvement. The use of ERT may prolong the lifespan of these patients and influence the natural history of the disease. The present study reports a new natural history of treated GD in which a 2-year and 7-month-old girl with type 2 GD who was receiving ERT developed valproate-induced Fanconi syndrome, pathological fractures, and pyogenic osteomyelitis. In conclusion, skeletal disease may occur in any type of GD, and Fanconi syndrome may lead to severe skeletal complications in patients with GD.
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Keywords: Gaucher disease; Fanconi syndrome; Pathological fracture; Pyogenic osteomyelitis

1. Introduction

Gaucher disease (GD) is a lysosomal storage disease caused by a deficiency of glucocerebrosidase. Patients with GD develop accumulation of glucocerebroside in macrophage lineage cells of the reticuloendothelial system, particularly those in the spleen, liver, bone marrow, and lung. The deficiency of β-glucocerebrosidase impairs the degradation of glucosylceramide and glucosylsphingosine, leading to their accumulation in the brains of patients with neuronopathic GD. GD can be categorized into 3 classical clinical types based on the presence or absence and rate of progression of neurologic manifestations.

Skeletal manifestations of GD usually occur later than visceral manifestations [1]. The skeletal aspects of GD include a diverse array of symptomatic and radiological findings, such as bone pain, bone crises characterized by as acute episodes of severe skeletal pain and fever accompanied by leukocytosis and elevated erythrocyte sedimentation rates, osteopenia, osteosclerosis, osteonecrosis, pathological fractures, bone marrow infiltration, Erlenmeyer flask deformity, and low signal intensity on T1- and T2- weighted magnetic resonance (MR) images. Skeletal manifestations are common in patients with type 1 and 3 GD, but rare in patients with type 2 GD, because most infants with type 2 GD die within the first 2 years of life [1–2].

Enzyme replacement therapy (ERT) has become available during the past decade, although the management of neuronopathic GD remains difficult [3]. In Japan, Cerezyme was approved as an orphan drug by

* Corresponding author. Fax: +81 775826304.
E-mail address: anri520@msn.com (A. Hayashi).

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the Japanese Ministry of Health and Welfare. Since September 1996, several patients with GD have received periodical intravenous ERT in medical institutions throughout Japan. Improvements in hematological parameters and reductions in visceral organ volumes are observed within 6–12 months after initiation of the ERT. However, the skeletal responses to ERT, such as a decrease in bone marrow glycolipid infiltration and an increase in bone mineral density, can take several years [4].

The present report describes the case of a 2-year and 7-month-old girl with type 2 GD who developed Fanconi syndrome, pathological fractures, and pyogenic osteomyelitis, despite receiving ERT for 17 months.

2. Case report

A 2-year and 7-month-old girl was born at 39 weeks of gestation through normal delivery to a non-consanguineous couple. At 3 months of age, she showed rapid head thrusts as an attempt to compensate when trying to visually track a moving object, this condition was later diagnosed as oculomotor apraxia. Developmental milestones had regressed since 6 months of age, and she developed opisthotonus and severe myoclonus at 7 months of age. When marked splenomegaly was noted at 11 months of age, she was diagnosed with type 2 GD based on neurologic symptoms and a decreased β-glucocerebrosidase activity in the skin fibroblasts (0.7 nmol/mg protein/h: normal range, 4.1–9.7 nmol/mg protein/h). Molecular genetic analysis of the GBA gene revealed a genotype of RecNci1/F213I. ERT (imiglucerase, 60 IU/kg of body weight, every 2 weeks) was initiated at 13 months of age, but she remained bedridden and required nasogastric feeding. She developed tonic clonic seizures at 14 months of age. Tracheotomy was performed because of laryngospasm at 20 months of age. Sufficient improvements in hematological parameters and reductions in hepatosplenomegaly were noted by 24 months of age (11 months after the initiation of ERT). In contrast, her convulsions and myoclonus were refractory to a combination of anticonvulsants and muscle relaxants (sodium valproate, clobazam, topiramate, dantrolene, and tizanidine hydrochloride).

At 30 months of age, she was hospitalized because of status epilepticus and severe incessant myoclonus. Pertinent laboratory data were normal. Treatment with intravenous midazolam and propofol could control the status but the myoclonus was unremitting. One month after admission, bilateral distal femoral swelling, erythema, and local heat were noted. Her body temperature was 40.0 °C, and heart rate was 170 beats/min. Conventional radiography demonstrated bilateral distal femoral fractures and an osteoporosis-induced relative increase in the cortical density of the femora (Fig 1a and b). No identifiable trauma or injury was observed. She

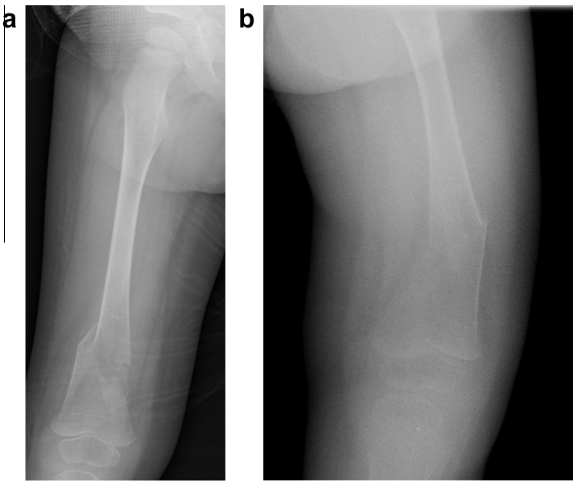

Fig. 1. (a) The pathological fracture of the right femur with osteoporosis. (b) Is the left side.

was treated with a hip spica cast. Laboratory evaluation revealed anemia and thrombopenia. The chemistry profile showed decreased levels of serum calcium, phosphorus, uric acid, and carnitine. Urinary β2-microglobulin level was markedly elevated and panaminoaciduria was present (Table 1). These laboratory findings were compatible with Fanconi syndrome. The patient had been treated with sodium valproate for 8 months (serum concentration of 80.2 μg/mL) with no effect on the progressive neural manifestation; this therapy was the most probable cause of Fanconi syndrome, so the treatment was changed to a regimen of potassium bromide, levetiracetam, and carnitine. The elimination of sodium valproate and supplementation with l-carnitine normalized serum levels of calcium (9.2 mg/dL), phosphorus (5.4 mg/dL), uric acid (2.3 mg/dl), and carnitine (total carnitine, 74.4 μmol/L; free, 65.7 μmol/L; and acyl, 8.6 μmol/L) and urinary levels of β2-microglobulin (56 μg/L) within 2 months. One month after the fracture, bone synostosis was detected, and the cast was removed. Oral alendronate sodium hydrate was started for osteoporosis. However, 2 months after the onset of the fracture, right distal femoral swelling, erythema, and localized warmth recurred, and the patient was diagnosed with osteomyelitis by femoral MR imaging (Fig. 2). Intravenous antibiotics and debridement were used for management, and culture of intraoperative samples revealed methicillin-resistant *Staphylococcus aureus*. Blood cultures showed no growth. Pathologic examination showed that the bone marrow was necrotic and infiltrated with numerous neutrophils and Gaucher cells (Fig. 3a and b). Her bone mineral density (BMD) examined 3 months after the fracture was 0.334 g/cm^2 at the lumbar spine measured by dural-energy X-ray absorptiometry. (reported control data from 3-to-10-year-old male children ($n = 12$) is 0.48 ± 0.08 g/cm^2 [5])

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