JIG Journal of Interdisciplinary Genomics

https://doi.org/10.22742/JIG.2019.1.2.15
Journal of Interdisciplinary Genomics 2019;1(2):15-18

Long-Term Clinical Course of a Korean Patient with Chronic Neuropathic (type III) Gaucher Disease

Jun Hwa Lee

Department of Pediatric Neurology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea

Gaucher disease (GD) is an autosomal recessive inborn error of metabolism resulting from a deficiency in β-glucocerebrosidase (GBA) activity that leads to the accumulation of glucocerebroside in macrophages in multiple organs, such as the bone marrow, liver, spleen, and brain. GD can be classified into three clinical types: type 1 (non-neuropathic form, OMIM #230800); type II (acute neuropathic form, OMIM #230900); and type III (chronic neuropathic form, OMIM #231000). Type III is the subacute form of neuropathic GD. The best available treatment for GD is long-term enzyme (imiglucerase) replacement therapy (ERT) performed every two weeks. This report describes the long-term clinical course of a patient with type III GD who was treated with ERT for 18 years.

Key words: Gaucher disease, Neuropathic, Clinical course, Korean

CASE REPORT

Received: September 19, 2019
Revised: October 22, 2019
Accepted: October 28, 2019

Correspondence to: Jun Hwa Lee
Department of Pediatrics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, 158 Paryong-ro, Masanhoewon-gu, Changwon 51353, Korea
Tel: +82-55-233-5310
Fax: +82-55-233-5329
E-mail: ljh3643@hanmail.net, ljh3643@skku.edu

ORCID
Jun Hwa Lee: https://orcid.org/0000-0001-9717-3677

INTRODUCTION

Gaucher disease (GD) is the most prevalent lysosomal disorder, and it results from mutation of beta-Glucosidase (GBA1) gene causing a deficiency in glucocerebrosidase activity, leading to accumulation of glucocerebroside in lysosomal macrophages. GD is a rare, pan-ethnic, autosomal recessive, genetic disease that involves multiple organs, such as the bone marrow, liver, spleen, and brain [1-3]. GD can be classified into three clinical types: type 1 (non-neuropathic form, OMIM #230800); type II (acute neuropathic form, OMIM #230900); and type III (chronic neuropathic form, OMIM #231000), which is the subacute form of neuropathic GD. The best available treatment for GD is long-term enzyme (imiglucerase) replacement therapy (ERT) performed every two weeks. This report describes the long-term clinical course of a patent with type III GD who was treated with ERT for 18 years.

CASE DESCRIPTION

A 20-year-old female patient with GD visited our pediatric outpatient center for ERT. She was born full term via spontaneous vaginal delivery with a birth weight of 4.0 kg to healthy nonconsanguineous Korean parents. Her family history included an older brother with suspected GD who died of status epilepticus at age 23, which was four years prior to presentation. The other family members had no history of metabolic disorders or neurologic diseases (Fig. 1). The patient showed normal development until 12 years of age when she first complained of leg pain.

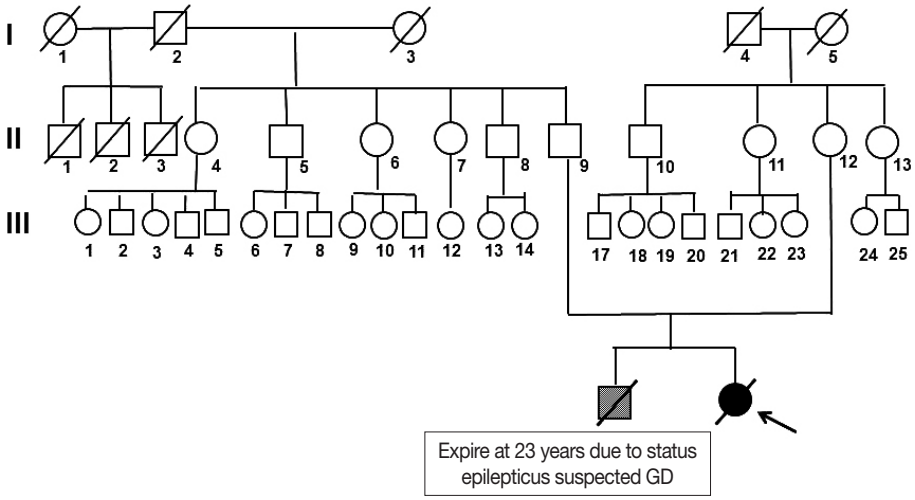

Fig. 1. Family pedigree of the patient with Gaucher disease. The solid circle represents the patient (proband), and the square represents her older brother, a suspected GD patient who expired with status epilepticus at age 23.

Fig. 2. Serial photographs of the patient. She had a normal development and lived an almost normal life except for intermittent seizures. However, at 27 years of age, her seizures worsened, and she required multiple antiepileptic medications. The disease slowly progressed until she was quadriplegic with sluggish speech and altered mental status. She was bedridden after age 30.

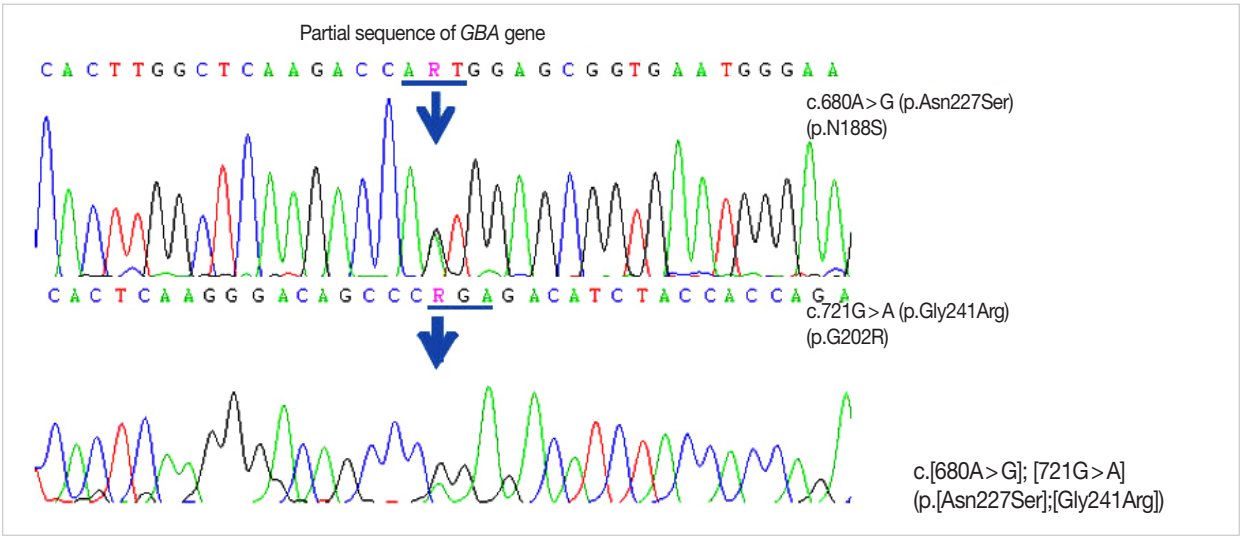

Fig. 3. Sanger sequencing analysis for the GBA gene. The patient was confirmed to have p.N188S and p.G202R mutations in the GBA gene mutation test, findings consistent with GD.

The initial suspicion was osteomyelitis, and she was treated with antibiotics. However, the leg pain progressed, and she developed bilateral hip pain. She was subsequently treated with medication for rheumatoid arthritis until age 18, although her symptoms waxed and waned. Her elder brother died due to status epilepticus when she was 16 years old.

At 18 years of age, the patient developed hepatosplenomegaly and seizures with eyeball deviation as well as generalized tonic-clonic type of seizures. Treatment with antiepileptic drugs, such as valproic acid and topiramate, was unsuccessful, and she underwent tests for an accurate diagnosis at a tertiary hospital. The patient was found to have Gaucher cells in the bone marrow and decreased leukocyte GBA activity (1.32 mM/hr/ng protein, reference range: 5.11-11.32), and she was finally diagnosed with GD. She received ERT at age 20, and the bone pain and hepatosplenomegaly significantly improved. The laboratory evaluation revealed: hemoglobin 12.3 g/dL, hematocrit 35.9%, WBC 4,300/mm^3, platelets 177,000/mm^3, segment neutrophil 65.1%, eosinophil 2.1%, basophil 0.1%, lymphocyte 27.9%, monocyte 1.5%, immature cell 0%, GOT/GPT 11/9 IU/L, calcium 9.3 mg/dL, phosphorus 2.9 mg/dL, BUN/Cr 8.2/0.7 and PT/aPTT 13.8/45.5 seconds. Brain MRI findings were non-specific. Electroencephalography (EEG) showed focal epileptiform discharges from right temporo-occipital or left occipital areas. Abdominal MRI findings at age 21 were normal shape and size of liver and spleen.

Except for uncontrolled intermittent seizures, she lived an almost normal life until the age of 27. However, the myoclonic seizures worsened despite the use of multiple antiepileptic medications, such as zonisamide, clobazam, pregabalin, Levetiracetam and phenobarbital. Over time, the disease slowly progressed, and she had abnormal eye movements (such as supranuclear gaze palsy), quadriplegia, sluggish speech and altered mental status despite continued ERT (Fig. 2). A GBA gene mutation test found that she had a heterozygote p.N188S and p.G202R genotype mutations (Fig. 3). Although she had been using ambroxol chaperon therapy with starting dose ranging from 1.5 mg/kg/day up to 24 mg/kg/day in combination with ERT treatment since age 37 and 5 months to improve her neurological symptoms, she was repeatedly hospitalized and discharged due to infectious diseases such as pneumonia and sepsis. She died of septic shock and pneumonia at age 38 and 4 months.

DISCUSSION

GD is a rare, pan-ethnic, autosomal recessive, lysosomal storage disorder resulting from a beta-Glucosidase (*GBA1*) gene defect. Patients with GD have a glucocerebrosidase enzyme deficiency and an increased accumulation of glycolipid glucocerebroside inside cell lysosomes. GD involves multiple organs, such as the bone marrow, liver, spleen, eyes and brain, so affected patients generally exhibit various clinical symptoms. To date, there are nearly 460 known mutations in the *GAB1* gene [1-3]. The incidence rate in the general population varies from approximately 1 in 40,000 to 1 in 60,000 births, and is

as high as 1 in 800 births among Ashkenazi Jews [4].

GD can be classified into three clinical types: type 1 (non-neuropathic form), type II (acute neuropathic form), and type III (chronic neuropathic form). Among the three types, type 1 is the most common and is characterized by a wide variety of clinical symptoms ranging from asymptomatic to severe manifestations. The most common symptoms are anemia, thrombocytopenia, splenomegaly and/or hepatomegaly, and potentially severe bone involvement. Type 1 GD carries a particularly high risk of hematologic diseases such as multiple myeloma, Parkinson's disease, and some solid cancers. Its treatment includes enzyme replacement therapy or substrate reduction therapy [1,4]. Type 2 GD is the most severe and progressive form, and patients manifests symptoms prenatally or in the first month of life and die in the first year of life [5]. Type 3 GD, known as chronic neuropathic disease, is a milder but chronically progressive variant that is characterized by hepatosplenomegaly, anemia, thrombocytopenia, bone alterations and central neurological manifestations, including seizure, myoclonic epilepsy, and progressive neurodegeneration [2,6,7]. Type 3 GD also has ocular features and gaze abnormalities, including saccadic eye movement abnormalities, corneal clouding, ocular deposits and pigmentary changes in the macula [8, 9]. Although the main treatment for GD is ERT, it is not effective for neurological symptoms. Ambroxol in combination with ERT has been suggested as a promising therapy for patients with Type 3 GD [10].

According to a report of 20 Korean patients with GD (11 type 1, two type 2, and 7 type 3), most patients presented with hepatosplenomegaly, thrombocytopenia, and short stature, and atypical symptoms included B cell lymphoma, protein-losing enteropathy, and hydrops fetalis. In the same study, the neuropathic group manifested variable neurological features, such as seizures, tremor, gaze palsy and hypotonia at age 8.7 ± 4.3 years. L444P was the most common mutation. N188S and G202R variants that are known to be retained in the endoplasmic reticulum, is also amenable to chemical chaperoning. The L444P variant is not chaperoned by any of the active site-directed molecules tested, likely because this mutation destabilizes a domain distinct from the catalytic domain [11].

The patient in the present case had typical type 3 GD clinical symptoms, and despite 18 years of ERT treatment and 1 year of ambroxol chaperone therapy, her neurological symptoms did not improve. She expired with pneumonia and sepsis.

This study was approved by the Institutional Review Board of Samsung Changwon Hospital (IRB study #SCMC 2019-01-007).

CONFLICT OF INTEREST

There are no potential conflicts of interest relevant to this article.

ACKNOWLEDGMENTS

I would like to thank my patient's parents for agreeing to this study, and I express my deepest condolences for the patient.

REFERENCES

1. Nguyen Y, Stirnemann J, Belmatoug N. Gaucher disease: A review. Rev Med Interne 2019;40:313-22.
2. Eghbali A, Hassan S, Seehra G, FitzGibbon E, Sidransky E. Ophthalmological findings in Gaucher disease. Mol Genet Metab 2019;127:23-7.
3. Sheth J, Bhavsar R, Mistri M, Pancholi D, Bavdekar A, Dalal A, et al. Gaucher disease: single gene molecular characterization of one-hundred Indian patients reveals novel variants and the most prevalent mutation. BMC Med Genet 2019;20:31.
4. Stirnemann J, Belmatoug N, Camou F, Serratrice C, Froissart R, Caillaud C, et al. An review of gaucher disease pathophysiology, clinical presentation and treatments. Int J Mol Sci 2017;17:18(2).
5. Weiss K, Gonzalez A, Lopez G, Pedoeim L, Groden C, Sidransky E. The clinical management of Type 2 Gaucher disease. Mol Genet Metab 2015;114:110-22.
6. Emanuel AJ, Holman N, Presnell SE, Welsh CT, Pai S, Sun S. Small bowel mucosal involvement and mesenteric mass formation in a young female with Type 3 Gaucher disease. A case report. J Gastrointestin Liver Dis 2018;27:459-63.
7. Sechi A, Deroma L, Dardis A, Ciana G, Bertin N, Concolino D, et al. Long term effects of enzyme replacement therapy in an Italian cohort of type 3 Gaucher patients. Mol Genet Metab 2014; 113:213-8.
8. Kim EA, Lim YT, Hah JO, Sohn YB, Kim YK, Choi JH, et al. Neuronopathic Gaucher disease presenting with microcytic hypochromic anemia. Int J Hematol 2019;109:361-5.
9. Bremova-Ertl T, Schiffmann R, Patterson MC, Belmatoug N, Billette de Villemeur T, Bardins S, et al. Oculomotor and vestibular findings in Gaucher disease Type 3 and their correlation with neurological findings. Front Neurol 2018;8:711.
10. Charkhand B, Scantlebury MH, Narita A, Zimran A, Al-Hertani W. Effect of Ambroxol chaperone therapy on Glucosylsphingosine (Lyso-Gb1) levels in two Canadian patients with type 3 Gaucher disease. Mol Genet Metab Rep 2019;20:100476.
11. Lee JY, Lee BH, Kim GH, Jung CW, Lee J, Choi JH, et al. Clinical and genetic characteristics of Gaucher disease according to phenotypic subgroups. Korean J Pediatr 2012;55:48-53.