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Original article

Diagnostic challenge for the rare lysosomal storage disease: Late infantile GM1 gangliosidosis

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Abstract

Background: GM1 gangliosidosis is a rare lysosomal storage disorder caused by GLB1 mutations. Because of its extreme rarity and symptoms that overlap with other neurodegenerative diseases, its diagnosis is sometimes challenging, especially in the late infantile form with less severe phenotype. We aim to expand the clinical and genetic spectrum of late infantile GM1 gangliosidosis.

Methods: We confirmed a diagnosis of GM1 gangliosidosis based on *GLB1* mutations and/or the deficiency of β-galactosidase activity. We identified the first two cases by whole-exome sequencing, and then the other six cases by direct sequencing of *GLB1* with enzyme analysis.

Results: All eight patients presented with developmental delay or regression during late infancy and later developed epilepsy, mostly intractable generalized tonic seizures. No clinical signs of storage disorders were noted except for skeletal abnormalities. Interestingly, we found aspartate transaminase (AST) elevations alone with normal alanine transaminase (ALT) levels in all patients. The recurrent mutation, p.D448V in GLB1, accounted for 50.0% of total alleles in our cohort.

Conclusions: With a high index of clinical suspicion, skeletal survey and AST level would be important for early diagnosis of GM1 gangliosidosis. In addition, we would highlight the clinical usefulness of whole-exome sequencing in the diagnosis of non-classical presentation of ultra-rare neurodegenerative disease in children.
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Keywords: GM1 gangliosidosis; *GLB1*; Whole-exome sequencing; Aspartate transaminase

1. Introduction

GM1 gangliosidosis (MIM 230500) is a lysosomal storage disorder caused by β-galactosidase deficiency, which is classified into three clinical forms with various ages of onset and clinical phenotype, infantile,

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late-infantile/juvenile, and adult/chronic, although the classification is arbitrary and there may be clinical overlaps [1,2]. Among these, the late infantile/juvenile type usually starts between 7 months and 3 years of age with slowly progressive neurological signs including early motor problems, strabismus, muscle weakness, seizures, lethargy, and susceptibility to infections. Dysmorphisms and skeletal changes are less severe than in infantile form, therefore, early diagnosis is sometimes a challenge.

GM1 gangliosidosis is a rare neurodegenerative disorder with an incidence of about 1:100,000–1:200,000 live births worldwide, although increased prevalence or founder mutations have been found in some populations [3–6]. Most cases have been reported in the white populations of European descent, while adult/chronic form is highly prevalent in the Japanese population [7–9]. In Korea, there has been only one report of Morquio syndrome or mucopolysaccharidosis type IVB, an allelic form of GM1 gangliosidosis [10]. Because of its rareness and clinical features that overlap with other neurodegenerative diseases, the diagnosis of GM1 gangliosidosis is sometimes challenging and the patients go through diagnostic odyssey, especially in the late infantile form with less severe phenotype.

Here we aim to expand the clinical and genetic spectrum of late infantile form GM1 gangliosidosis by reporting eight cases in a cohort of patients with unexplained white matter changes from our center, in which whole-exome sequencing (WES) gave insight into the rare neurodegenerative disease entity with atypical presentation and its diagnosis.

2. Methods

2.1. Subjects

This study included 19 patients with unexplained white matter changes seen in their brain MRI at Seoul National University Children's Hospital. In this cohort, no abnormalities were revealed from comprehensive blood tests including metabolic screening with blood ammonia, lactate, amino acids, urine organic acids, thyroid function tests, tandem mass screening, arylsulfatase A and β-galactosylcerebrosidase activities, very long chain fatty acid profiles, and a *PLP1* genetic test. After performing WES and Sanger sequencing to validate genetic variations, we identified *GLB1* mutations in two patients (Patient 1 and 2). Thereafter, we selected four additional patients (Patient 3–6) and two siblings (Patient 7 and 8) among our cohort with high likelihood of having neurodegenerative disease with unexplained white matter changes. For these six patients, we confirmed the diagnosis by β-galactosidase activity assay with targeted direct sequencing of *GLB1*.

We retrospectively reviewed the medical records of eight patients, including EEG findings. We performed brain magnetic resonance imaging (MRI) for all six patients and MR spectroscopy (MRS) for one. This study was approved by the Seoul National University Hospital Institutional Review Board (approval No. 1406-081-588), and blood samples were obtained from enrolled patients and their parents who provided informed consent.

2.2. Whole-exome sequencing

Preparation of genomic DNA, whole-exome capture using NimbleGen V2 array, sequencing by Illumina HiSeq, read alignment, variant calling and filtering have been described previously [11].

2.3. Direct Sanger sequencing

We performed PCR amplification using 10 pmol of primer pairs designed by the authors (available upon request). Sanger sequencing reactions were run on an ABI 3730XL DNA Analyzer (Applied Biosystems).

2.4. Chromosomal microarray

An array comparative genomic hybridization (CGH) using Agilent Human Genome oligonucleotide CGH microarray 4×180 K (Agilent Technologies, Santa Clara, CA) was conducted with 13 Kb overall median probe spacing.

2.5. mRNA test

Reverse transcription-PCR and gel electrophoresis were done using primer pairs designed by the authors to investigate presence of abnormal mRNA products. Amplified PCR fragments were purified using ExoSAP-IT^{TM} (USB, Cleveland, OH, USA), when single band was observed in gel electrophoresis. In samples containing two or more bands, 100ul of PCR products were loaded on the gel and separated by electrophoresis. Each band seen in UV illuminator was cut out of the gel slices and purified using silica spin columns. Then sequences were confirmed by direct Sanger sequencing.

2.6. Gene dosage test

For measuring the copy number of the exons 11 and 12 of *GLB1* (Patient 3), we performed a quantitative PCR using fluorescently labeled primers [12,13]. The multiplex PCR was done for the target exons (exon 10–13) and the reference gene (β_2-microglobulin). Amplified PCR products were measured for size and signal intensity of fluorescent dye with the electrophoresis

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