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Case Report

Late-Infantile GM1 Gangliosidosis Presenting with Rapid Neuroregression: A Case Report

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Abstract

GM1 gangliosidosis is a rare autosomal recessive lysosomal storage disorder caused by a deficiency of β-galactosidase due to pathogenic variants in the *GLB1* gene. Late-infantile GM1 gangliosidosis typically presents after a period of normal development with progressive neuroregression and variable systemic involvement. We report an 18 months male child born to non-consanguineous parents, with normal early development, who presented with rapid neuroregression, central hypotonia, seizures, and hepatosplenomegaly, without coarse facial features, dermal melanocytosis (Mongolian spots), or cherry-red macula. Neuroimaging revealed bilateral thalamic signal abnormalities with diffuse white-matter involvement. Whole exome sequencing identified a homozygous missense variant in exon 10 of the *GLB1* gene (c.1024G>T; p.Asp342Tyr), classified as a variant of uncertain significance. The clinico-radiological and molecular findings supported a probable diagnosis of late-infantile GM1 gangliosidosis. This case highlights the phenotypic overlap between infantile and late-infantile GM1 gangliosidosis and emphasises the diagnostic challenges associated with atypical presentations.

Keywords: Gangliosidosis; Lysosomal; Late Infantile; Neuroregression

Introduction

GM1-gangliosidosis (GM1) is a progressive neurodegenerative disorder of autosomal recessive inheritance with an incidence of 1 in 100,000–200,000 live births worldwide [1]. It is a lysosomal storage disorder resulting from pathogenic variants in the *GLB1* gene, which encodes the lysosomal enzyme β-galactosidase. Deficiency of this enzyme leads to impaired degradation and subsequent intracellular accumulation of β-galactose–containing glycoconjugates, most prominently the glycosphingolipid GM1 ganglioside, within neuronal cells [2]. Among the pediatric phenotypes, the infantile form of GM1 gangliosidosis is the most frequent andmanifests within the first year of life with early developmental delay, seizures, and characteristic ophthalmologic findings such as cherry-red spots, often progressing rapidly to severe neurodegeneration. In contrast, children with the late-infantile form usually demonstrate normal early development, followed by the onset of neuroregression between 12 and 18 months, predominantly affecting motor functions and subsequently progressive cognitive decline. The juvenile form presents later, most commonly between 3 and 5 years of age, and is characterised

by gradual motor and language regression with a slowercourse. The adult form represents the mildest end of the spectrum and follows a slowly progressive trajectory marked by spasticity, ataxia, dysarthria, and insidious cognitive deterioration [3]. We report a case of late infantile GM1 gangliosidosis showing mixed features of infantile and juvenile subtypes.

Case Report

An 18months male child, second born to non-consanguineous parents, who was developmentally normal until 15 months of age, presented with progressive weakness of all four limbs and loss of speech for three months, followed by recurrent generalised tonic seizures for two months and increasing lethargy over the preceding two weeks.

The illness had an insidious onset, initially manifesting as reduced activity and frequent falls. Over the subsequent weeks, the child progressively lost the ability to walk, stand, and sit without support, and eventually became unable to hold his neck or roll over. Language regression was also noted, with loss of previously acquired meaningful words. In addition, there was a marked decline in social interaction; the child lost interest in his surroundings and was unable to recognise his mother. He was born at term by spontaneous vaginal delivery with an uneventful perinatal period and had been immunised appropriately for age. Family history was non-contributory.

On general physical examination, the child was found to have severe acute malnutrition, with a normal head circumference for age (Figure 1). There were no coarse facial features, neurocutaneous stigmata, or skeletal abnormalities. Systemic examination revealed central hypotonia with quadriparesis, along with hepatosplenomegaly.

Figure 1: Malnourished child.

Laboratory investigations revealed microcytic hypochromic anaemia on peripheral smear. Arterial blood gas analysis, blood glucose, electrolytes, thyroid profile, and liver and renal function tests were within normal limits. Cultures were sterile, and serological testing for HIV was non-reactive. Ophthalmological and hearing evaluation was normal. Chest and spinal radiographs were unremarkable.

Magnetic resonance imaging of the brain demonstrated diffuse and symmetrical white matter hyper-intensities involving subcortical U-fibres, suggestive of dysmyelination, along with symmetric hypointense signals in the bilateral thalami on T2-weighted images, whereas T1-weighted images showed corresponding thalamic hyperintensity (Figure 2, 3).

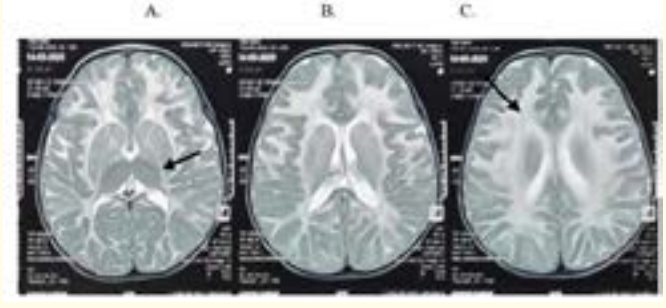

Figure 2: Axial T2-weighted MRI images showing bilateral thalamic hypointensity (arrow in A) with diffuse periventricular and subcortical white-matter hyperintensity (B, C).

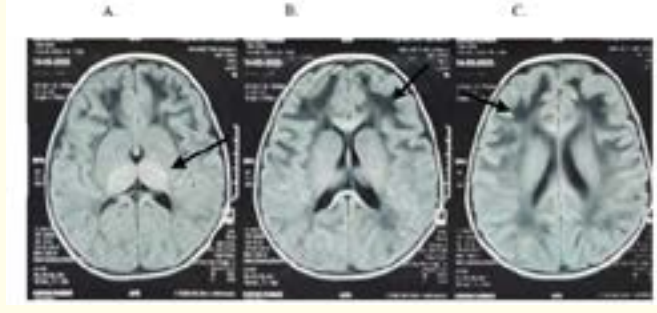

Figure 3: Axial T1-weighted MRI images showing bilateral thalamic hyperintensity (arrow in A) with abnormal periventricular and subcortical white-matter signal (arrows in B and C).

To further evaluate the suspected diagnosis, whole exome sequencing was performed, which identified a homozygous missense variant in exon 10 of the *GLB1* gene (c.1024G>T),

resulting in an amino acid substitution p.Asp342Tyr in the β-galactosidase enzyme. The variant was classified as a variant of uncertain significance (PM2, PP3) and was compatible with an autosomal recessive inheritance pattern.

Discussion

GM1 gangliosidosis is a rare lysosomal storage disorder and accounts for approximately 5% of lysosomal storage disorders in an Indian cohort of children presenting with hepatosplenomegaly [4]. The disease is classically divided into infantile, late-infantile, and juvenile forms based on age at onset; however, multiple cohort and natural history studies have demonstrated substantial phenotypic overlap, with many patients not fitting clearly into a single subtype [2,5,6].

Our findings align with previous reports indicating that rapid neuroregression, cognitive decline, central hypotonia, and seizures are more commonly observed in infantile and late-infantile GM1 gangliosidosis [5,7-10]. In contrast to our patient, dystonia and ataxia have been frequently reported across GM1 subtypes, particularly in late-infantile disease [5,11].

Our patient had hepatosplenomegaly without coarse facial features, skeletal abnormalities, dermal melanocytosis, or cherry-red macula, a pattern consistent with reports showing that these somatic features are common in infantile but less frequent in late-infantile and juvenile GM1 gangliosidosis [2,5,6].

Neuroimaging in our case showing dysmyelination and bilateral thalamic involvement is characteristic of infantile GM1 gangliosidosis [12]. However, similar thalamic involvement and white-matter changes have also been reported in rapidly progressive late-infantile cases supporting radiological overlap between infantile and late-infantile forms [1,13]. Hypomyelination refers to deficient formation of structurally normal myelin, whereas dysmyelination is characterised by the deposition of abnormal or malformed myelin. On MRI, hypomyelination typically demonstrates relatively preserved or mildly hyperintense white matter on T1-weighted images with hyperintensity on T2-weighted sequences, whereas dysmyelination shows abnormal T1 hypointensity along with marked T2 hyperintensity of the white matter. In contrast, demyelination refers to destruction of previously formed normal myelin and usually appears as patchy or confluent T2/FLAIR hyperintense lesions with corresponding T1 hypointensity in affected white matter [14]. Based on the clinical and radiological profile, the differential diagnoses included inherited metabolic and lysosomal storage disorders such as GM1/GM2 gangliosidoses, metachromatic leukodystrophy, Alexander disease, and Canavan disease. Metachromatic leukodystrophy was considered because of the symmetric periventricular white-matter changes and normal head circumference; however, the absence of tigroid or leopard-skin patterns made it less likely. The absence of frontal predominance and macrocephaly argued against Alexander disease, while lack of macrocephaly and diffuse spongiform white-matter degeneration made Canavan disease less likely. In addition, hepatosplenomegaly is uncommon in primary leukodystrophies [14].

The *GLB1* gene is located on chromosome 3p21.33, comprises 16 exons, and encodes a protein of 677 amino acids [15]. GM1 gangliosidosis exhibits poor genotype–phenotype correlation, reflected by wide variability in age at onset and disease progression. Among approximately 261 pathogenic variants associated with GM1 gangliosidosis, the majority are missense or nonsense mutations [2]. In our patient, whole exome sequencing identified a homozygous missense variant in exon 10 of the *GLB1* gene (c.1024G>T), resulting in an aspartic acid to tyrosine substitution at codon 342 (p.Asp342Tyr). The variant was classified as a variant of uncertain significance, but was extremely rare and absent from major population databases including 1000 Genomes, gnomAD, and TOPMed. In-silico prediction tools (SIFT, LRT, and MutationTaster2) consistently predicted a deleterious effect on protein function, and the affected codon was evolutionarily conserved across species, supporting its potential functional relevance. Missense variants in *GLB1* have previously been associated with impaired β-galactosidase activity and variable clinical phenotypes [2]. Enzymatic confirmation of β-galactosidase deficiency could not be performed due to resource limitations. 2Nevertheless, the combination of characteristic clinical features, supportive neuroimaging, and molecular findings supported a probable diagnosis of late-infantile GM1 gangliosidosis rather than a genetically confirmed diagnosis. Parental segregation analysis and enzyme activity testing would further strengthen variant classification and are recommended where feasible, particularly for variants initially labelled as of uncertain significance [11].

The management of GM1 gangliosidosis remains largely supportive and symptomatic, focusing on airway protection, nutritional support through nasogastric feeding, and antiepileptic therapy for seizure control. Meanwhile, disease-modifying approaches, including gene therapy, enzyme replacement therapy, substrate reduction therapy, and stem cell transplantation, are under active investigation.

Conclusion

This case underscores the phenotypic variability of GM1 gangliosidosis and the importance of integrating clinical features, neuroimaging, and genetic findings for diagnosis, particularly in patients with overlapping subtype characteristics. Early recognition of such presentations is essential for appropriate management and genetic counselling.

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