ECRONICON OPEN ACCESS

EC NEUROLOGY
Case Report

Novel GLB1 Mutation in Infantile GM1 Gangliosidosis-A Case Report

Nishant Gopaal[1], Dhan Raj Bagri[2]* and JN Sharma[3]

[1]*Senior Resident, Department of Pediatrics, SPMCHI, J K Lon Hospital, SMS Medical College, Jaipur, India*

[2]*Assistant Professor, Department of Pediatrics, SMS Medical College, Jaipur, India*

[3]*Senior Professior, SMS Medical College, Jaipur, India*

***Corresponding Author:** Dhan Raj Bagri, Assistant Professor, Department of Pediatrics, Sir Padampat Institute of Neonatal and Child Health, J K Lon Hospital, SMS Medical College, Jaipur, India.

Received: August 02, 2024; **Published:** September 04, 2024

Abstract

Background: GM1-gangliosidosis is a rare autosomal recessive disorder caused by mutations in the GLB1 gene and resultant functional deficiency of the lysosomal enzyme acid β-galactosidase with accumulation of keratan sulphate, glycolipids, and GM1 gangliosides in tissues.

Case Presentation: A 9-month-old male child with moderate hepatosplenomegaly, central hypotonia, a large Mongolian spot on the back and delayed verbal and motor milestones; based on clinical suspicion, through history, examination and MRI brain findings; was subjected to clinical genome sequencing. A novel homozygous missense variant (c.326G>C) in exon 3 of the GLB1 gene (NM_000404.3) that results in the amino acid substitution from arginine to proline at codon 109 (p.Arg109Pro) was identified.

Conclusion: The novel GLB1 mutation identified in this study will help to expand the spectrum of known GLB1 mutations and will be helpful in genetic counselling.

Keywords: *Novel GLB1 Mutation; GM1 Gangliosidosis; Central Hypotonia; Genome Sequencing; β-Galactosidase*

Key Messages

GM1 gangliosidosis is a severe LSD with complex pathophysiological mechanisms. Numerous diseases causing GLB1 mutations have been reported. However, genotype phenotype correlation has been difficult to establish. The clinical outcome of the disease in patients may vary from patient to patient. Cellular pathophysiology underlying this disease that may improve our understanding of the fundamental cell biology of GM1 ganglioside and the enzyme complex that regulates its catabolism in the lysosome needs more study. Multiple mouse models of this disorder have been instrumental for the pre-clinical testing of multiple therapies, several of which are currently in clinical trials. A novel GLB1 mutation causing GM1 gangliosidosis is identified in this study. This study helps to expand the spectrum of known GLB1 mutations and will be helpful in genetic counselling.

Introduction

Mutations in the GLB1 gene cause GM1-gangliosidosis (GM1; MIM# 230500); a rare autosomal recessive disorder, by resultant functional deficiency of the lysosomal enzyme acid β-galactosidase (GLB1; EC 3.2.1.23; GenBank M27507) [1]. This deficiency causes the accumulation of keratan sulphate, glycolipids, and GM1 gangliosides in several tissues including the neurons of peripheral and central nervous system. GM1 gangliosidosis has an estimated incidence of in 1 per 100,000 to 200,000 births [2].

Three clinical subtypes of GM1 gangliosidosis are classified by the age of onset. The infantile subtype (Type 1) combines the features of a neurolipidosis (i.e. macular cherry-red spots, neurodegeneration) and mucopolysaccharidosis (i.e. coarse facial features, dysostosis multiplex and visceromegaly). This form of GM1 gangliosidosis presents in early infancy but may be evident at birth and death usually occurs between the first and second year of life. The juvenile subtype (Type 2) is marked by a later age of onset and a less severe course. The adult subtype (Type 3) is marked by normal early neurologic development with no physical stigmata and subsequent development of a slowly progressive dementia with parkinsonian features, extrapyramidal disease, and dystonia [3]. Another disease, mucopolysaccharidosis IV B, is also associated with decreased β-galactosidase activity but, unlike GM1, is characterized by severe bone deformities without any CNS involvement.

Case History

A 9-month-old male child from Northern India was admitted with complaint of recurrent respiratory infections, inadequate weight gain and decreased movements of the limbs since birth. The patient was the first-born child out of a non-consanguineous marriage, with an uneventful birth history. The child had undergone a surgery for hydrocele at 4 months of age.

On examination the patient had moderate hepatosplenomegaly, central hypotonia, a large Mongolian spot on the back and delayed verbal and motor milestones (Figure 1). Fundus examination revealed a cherry red spot in the right eye. LFT showed elevated transaminases (SGOT:200; SGPT:270) with normal serum bilirubin. CBC, RFT, random blood sugar, thyroid profile, serum electrolytes, blood gas analysis serum ammonia and lactate were found to be within normal limits.

Figure 1: *Central hypotonia; Mongolian spot on the back.*

A 3.0 Tesla MRI Brain with contrast revealed diffused hyperintensities in the entire subcortical U fibres, periventricular and deep white matter of bilateral cerebral hemispheres with involvement of external capsules and corpus callosum, showing T2 hypointensity in bilateral centrum semiovale. MR spectroscopy showed an elevated choline peak. Overall MRI findings were suggestive of leukodystrophy, likely gangliosidosis or metachromatic leukodystrophy (Figure 2).

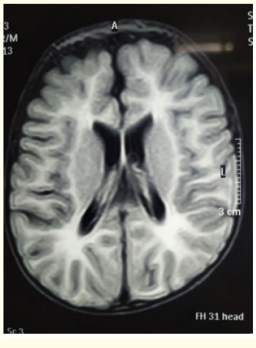

Figure 2: *MRI Brain-leukodystrophy.*

Based on history, clinical examination, ophthalmoscopic findings and MRI findings lysosomal storage disorder was suspected and clinical genome sequencing was done using illumina next generation sequencing (NGS) systems. Blood samples were collected from the patients after obtaining informed consent from the parents. Based on clinical suspicion through history, examination and MRI brain findings the patient's sample was subjected to clinical genome sequencing, done using illumina next generation sequencing (NGS) systems [4]. GATK best practice framework was followed for variant identification. BWA-mem aligner was used to align the obtain sequences to human reference genome (GRCh37/hg19). Blood samples were collected from the patients after obtaining informed consent from the parents [4].

Sention's Haplotypecaller module was used to identify the variants which are relevant to the clinical indications. Along with this deep variant analysis pipeline on google cloud platform was used as a secondary pipeline to look for genetic variants [5]. Quality checks (QC) were performed on all VCF files to exclude variants where sequencing is of poor quality. Additional QC metrics included total homozygous and heterozygous calls (SNVs and indels), proportion of variant calls that were common, number of variants falling into different annotated consequence categories, number of extreme heterozygotes (alternate allele proportion 0.8). Variant annotations were done using published databases like OMIM, GWAS, GNOMAD and 1000Genome [6-8] non-synonymous and splice site variants were used for clinical interpretation. Silent variations that do not result in any change in amino acid in the coding region were not reported.

Peripheral venous blood tested by stimulated peripheral blood lymphocyte culture by banding method (GTG) suggested no evidence of any structural or numerical abnormality in any of the cells studied with karyotype suggestive of a normal male chromosome complement. However, the possibility of the presence of sub microscopic or cryptic rearrangements couldn't be ruled out with karyotype: 46, XY [20] [ISCN 2016] reported (Figure 3).

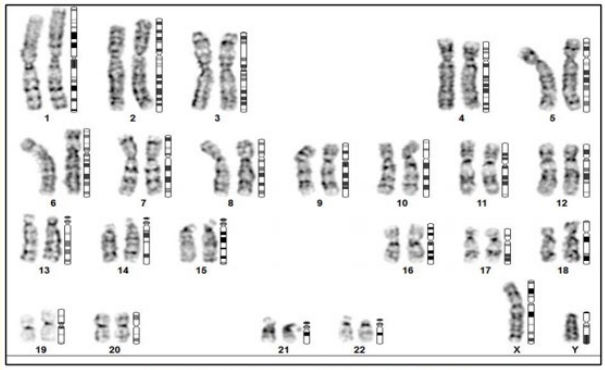

Figure 3: *Peripheral venous blood karyotyping sample.*

A novel homozygous missense variant (c.326G>C) in exon 3 of the GLB1 gene (NM_000404.3) that results in the amino acid substitution from arginine to proline at codon 109 (p.Arg109Pro) was identified. The observed variant is not present in the 1000 genomes [7] and has a minor allele frequency of 0.0004% in the gnomAD database. The reference base is conserved across the species and *in-silico* predictions by Polyphen and SIFT were found to be damaging. Such homozygous mutations in the GLB1 gene have been previously reported to be the genetic cause of GM1 gangliosidosis. Based on the above evidence this variant was classified as variant of uncertain significance according to the ACMG guidelines [8,9]. β-galactosidase enzyme activity in peripheral blood leukocytes was found to be 0.8% of normal enzyme activity which confirmed the diagnosis of GM1 gangliosidosis type 2.

Discussion and Conclusion

Our patient presented at 9 months of age. The most severe infantile form of GM1 gangliosidosis presents with onset of symptoms before 6 months of age and early death [10]. One of the earliest signs in infantile form is hydrops fetalis on prenatal testing [11]. Early diagnosis of infantile onset disease is necessary for successful therapeutic interventions. Our patient has normal antenatal ultrasonograms though the child had undergone a surgery for hydrocele postnatally at 4 months of age.

Our patient had diffuse hyperintensities in the entire subcortical U fibres, periventricular and deep white matter of bilateral cerebral hemispheres with involvement of external capsules and corpus callosum, showing T2 hypointensity in bilateral centrum semiovale, with an elevated choline peak on MR spectroscopy. Type II consists of late infantile and juvenile subtypes with onset of symptoms between 1 to 2 years of age. The normally developing infant suddenly loses the ability to ambulate and have difficulty swallowing and handling secretions. Late infantile patients present in mid second decade with variable clinical features [12]. Progressive atrophy in the cerebrum and cerebellum with unpredictable clinical course due to variability in regulatory, and post-translational mechanisms that modulate GM1 catabolism is noted in both late infantile and juvenile subtypes [13].

Most patients with GM1 gangliosidosis are compound heterozygotes with no association of any specific phenotypes to any single mutation. GM1 gangliosidosis reflects poor genotype-phenotype correlation even in siblings. This variability may be due to polymorphisms or mutations in the other genes of the β-GAL complex, protective protein/cathepsin A (PPCA) and neuraminidase 1 (NEU1). Mutations associated with type I/infantile onset GM1 gangliosidosis are mostly located in the core protein region causing β-gal instability & mutations associated with milder phenotypes, such as types II and III GM1 gangliosidosis, on the protein surface [13]. Variable expressivity of genotype-phenotype correlation and incomplete penetrance complicate it further [14].

The GLB1 gene is present on chromosome 3 at 3p21.33 and consists of 16 exons which encode for 677 amino acid residues. More than 160 disease causing mutations have been identified in GLB1 gene [15]. The severity of the disease phenotype depends on the residual activity of the beta-galactosidase enzyme. Our case study of novel GLB1 mutation in infantile GM1 gangliosidosis and phenotype of patient will enrich the knowledge pool. Out of the total 261 reported pathogenic variants associated with a phenotype of GM1 gangliosidosis and/or Morquio B disease, most of them are missense/nonsense (194), and the rest are splicing substitutions (20), small deletions (25), small insertion/duplications (17), small indels (2), gross insertion/duplications (2), and a single large deletion. Previous reports implicate exons 2, 6, and 15 as hot spots for mutations, with largest number of mutations in exons 2 (26 variants) and exon 16 (24 variants) respectively [16].

In our study, a patient with an infantile GM1 gangliosidosis has been identified with a novel homozygous missense variant (c.326G>C) in exon 3 of the GLB1 gene (NM_000404.3) that results in the amino acid substitution from arginine to proline at codon 109 (p. Arg109Pro). There is a moderate physicochemical difference between arginine and proline. The phenotypic manifestations of the patient correlate with previous studies demonstrating the adverse functional effects of missense mutations of the GLB1 gene [17].

This article provides critical research insights in complex neuro-medicine field with GLB1 mutation in infantile GM1 gangliosidosis. Moreover, the biochemical/metabolic cross-talks amongst the enigmatic array of TLRs sphingolipids/ceramide and autophagy signaling components offer fascinating neuro-immuno-oncology-based therapeutic avenues for elegant development of predictive and/or prognostic biomarkers in timeline-driven cost-effective risk-stratification and management of gangliosidosis in susceptible populations worldwide in the Covid-19/Omicron pandemic post-vaccination era [18-20].

Acknowledgements

We acknowledge the trust of parents.

Bibliography

1. Nishimoto J., *et al*. "GM1-gangliosidosis (genetic beta-galactosidase deficiency): identification of four mutations in different clinical phenotypes among Japanese patients". *American Journal of Human Genetics* 49.3 (1991): 566-574.

2. Armstrong-Javors A and Chu CJ. "Child neurology: Exaggerated dermal melanocytosis in a hypotonic infant: a harbinger of GM1 gangliosidosis". *Neurology* 83.17 (2014): e166-e168.

3. Suzuki Y., *et al*. "Beta-galactosidase deficiency (beta-galactosidosis): GM1 gangliosidosis and Morquio B disease". In: Scriver CR, Beaud*et al*, Sly WS, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill (2001): 3775-3809.

4. Freed D., *et al*. "The Sentieon Genomics Tools-A fast and accurate solution to variant calling from next-generation sequence data". BioRxiv (2017): 115717.

5. https://cloud.google.com/life-sciences/docs/tutorials/deepvariant

6. Landrum MJ., *et al*. "ClinVar: public archive of interpretations of clinically relevant variants". *Nucleic Acids Research* 44.D1 (2015): D862-D868.

7. Welter D., *et al*. "The NHGRI GWAS Catalog, a curated resource of SNP-trait associations". *Nucleic Acids Research* 42 (2014): D1001-1006.

8. 1000 Genomes Project Consortium., *et al*. "A global reference for human genetic variation". *Nature* 526.7571 (2015): 68-74.

9. Kalia SS., *et al*. "Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics". *Genetics in Medicine* 19.2 (2017): 249-255.

10. Lang FM., *et al*. "The natural history of type 1 infantile GM1 gangliosidosis: a literature-based meta-analysis". *Molecular Genetics and Metabolism* 129.3 (2020): 228-235.

11. Iyer NS., *et al*. "Lysosomal storage disorders as an etiology of nonimmune hydrops fetalis: a systematic review". *Clinical Genetics* 100.5 (2021): 493-503.

12. Tonin R., *et al*. "Pre-diagnosing and managing patients with GM1 gangliosidosis and related disorders by the evaluation of GM1 ganglioside content". *Scientific Reports* 9.1 (2019): 17684.

13. Rha AK., *et al*. "GM1 gangliosidosis: mechanisms and management". *Application of Clinical Genetics* 14 (2021): 209-233.

14. Gorelik A., *et al*. "Structure of the murine lysosomal multienzyme complex core". *Science Advances* 7.20 (2021): eabf4155.

15. Quakenbush Alex. "Analysis of the Ovine NEU1 Gene in a Unique Model of GM1 Gangliosidosis". Biology Undergraduate Publications, Presentations and Projects (2015).

16. Brunetti-Pierri N and Scaglia F. "GM1 gangliosidosis: review of clinical, molecular, and therapeutic aspects". *Molecular Genetics and Metabolism* 94.4 (2008): 391-396.

17. Karimzadeh P., *et al*. "Case reports of juvenile GM1 gangliosidosisis type II caused by mutation in GLB1 gene". *BMC Medical Genetics* 18.1 (2017): 73.

18. Saumya Pandey. "Toll-like receptors-autophagy immuno-inflammatory networks as "molecular rheostats" in hypoxic tumor microenvironment in complex neurological diseases primarily glioblastoma and spinal meningioma: translational research perspective with public health impact in genetically susceptible population-pools in Covid-19/Omicron pandemic era". *EC Neurology* 14.7 (2022): 01-02.

19. Pandey S. "IL-6 induced upregulation of T-type Ca^{2+} currents and sensitization of DRG nociceptors is attenuated by MNK inhibition: Translational Research Perspective". *Journal of Neurophysiology* 124.1 (2020): 305-306.

20. Pandey S., *et al*. "Recent advances in the immunobiology of ceramide". *Experimental and Molecular Pathology* 82.3 (2007): 298-309.

Volume 16 Issue 9 September 2024