CASE REPORT

A Novel Mutation in The GLA Gene Leading to Fabry Disease - A Case Report from Islamabad, Pakistan

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ABSTRACT

Fabry disease (OMIM #301500) is a rare X-linked lysosomal storage disease. Generally, lysosomal storage disease is identified by inappropriate lipid storage in lysosomes due to specific enzyme deficiencies. In case of Fabry disease, the defective enzyme is Alpha-Galactosidase A (Enzyme Commission No- 3.2.1.22). Alpha-Galactosidase A enzyme is involved in the hydrolysis of terminal, non-reducing Alpha-D-galactose residues in Alpha-D-galactosides, including galactose oligosaccharides, galactomannans, and galacto-lipids. The defect in the enzyme is usually due to pathogenic variants in the *GLA* gene, present on Human X chromosome (chrX:101397803-101407925, hg38). A mutation in the Alpha-Galactosidase A gene results in the accumulation of globotriaosylceramide and its derivatives throughout lysosomes in the body. A pathogenic, hemizygous Alpha-Galactosidase A variant identified through genetic testing usually confirms the diagnosis in male patients. In contrast, the presence of a heterozygous pathogenic variant may establish the diagnosis in female patients, as heterozygous females may be as severely affected as males or asymptomatic throughout a normal life span. To our knowledge, Fabry disease has not been reported from Pakistan. We report the first case of Fabry disease in a 13-year-old boy presenting with bilateral lower limb acroparesthesia and anhidrosis from Pakistan. At present, he does not have any additional symptoms, including cardiac and renal. Genetic testing through targeted panel sequencing revealed a novel pathogenic hemizygous mutation in the Alpha-Galactosidase A gene (c.779G>A, p.Gly260Glu) in this male patient. This variant is present in exon 5 of the Alpha-Galactosidase A gene, which comprises of 429 amino acids. We advised Injection Agalsidase beta, 1 mg/kg, I/V infusion every 2 weeks, which is a lifelong enzyme replacement therapy.

Keywords: *Fabry Disease, Hyperhydrosis, Missense Mutation*, *Paresthesia.*

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Introduction

Fabry disease (FD) is an X-linked lysosomal storage disease resulting from a mutation of the Alpha-Galactosidase A (*GLA)* gene.[1,2] There is reduced or absent activity of the enzyme α-galactosidase A, resulting in the lysosomal deposition of neutral sphingolipids such as globotriaosylceramide throughout the body, leading to progressive organ damage and a shortened life span.[3] Fabry disease affects multiple organs and results in various symptoms, including renal, cardiovascular, neurological, cutaneous, and ophthalmic manifestations.[4,5] This is due to the fact that lysosomes are present throughout the body and play a crucial role in catabolism and recycling of cytosolic compounds.[6] The chronic and progressive damage to the kidneys, heart, and central nervous system in later stages of the disease is one of the reasons for significant morbidity and mortality rate.[7] More than 1000 mutations in the *GLA* gene have been identified, promoting many different clinical pictures. For this reason, diagnosing FD can be difficult, mainly because of the great diversity of

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atypical clinical presentations that can simulate the disease.[8]

There are two variants of the disease, namely a severe classical form and a milder non-classical form. The classical form presents in males at an earlier age with a more severe progression, often with acroparesthesias, anhidrosis, and angiokeratomas.[9] Long-term complications include hypertrophic cardiomyopathy, cerebrovascular disease, and kidney impairment. Contrary to this, the non-classical form has a later onset and more variable progression due to the presence of some residual enzymes.[5] Although Fabry affects males more often, female carriers may also show some degree of involvement.[9] The availability of affordable panel genetic testing has enabled early diagnosis of rare inherited neurological disorders in Pakistan.[10]

Here, we report the case of a 13-year-old boy with Fabry disease. Genetic testing confirmed the presence of a hemizygous pathogenic *GLA* mutation in this patient. To our knowledge, this is the first case from Pakistan.

Case Presentation

The case report was approved by the Intuitional Review Board and Ethics Committee of the hospital vide IRB letter no: 261-24, dated: 25th March 2025.

A 13-year-old boy from Sawabi, Khyber Pakhtunkhwa (KPK) province, presented to Neurology OPD of Shifa International Hospitals Limited, Islamabad, Pakistan with a four-year history of acroparesthesias, localized to his toes. The pain was severe, burning, and tingling in nature, and the family had sought medical attention in the years prior, with local doctors dismissing it as non-significant. The pain had no aggravating or relieving factors, but impaired the boy's daily life such that there was difficulty in walking. His mother also gave a history of heat intolerance in the summer. Prior autoimmune workup for systemic lupus erythematosus, sharp syndrome, Sjogren syndrome, scleroderma, polymyositis, dermatomyositis, primary biliary cirrhosis, autoimmune hepatitis, and polymyositis/dermatomyositis was all negative.

On examination, he was a pleasant young boy who looked his age. His weight and height were 26 kg and 140 cm respectively, yielding a BMI of 13.3. He was alert and oriented. Speech, gait and cranial nerve examination was unremarkable. Muscle power was MRC grade 5/5 in all four limbs. Deep tendon reflexes were ++ and symmetrical, plantar responses were flexor. There was no sensory loss to pin prick bilaterally. Differential diagnoses included erythromelalgia and painful small fiber neuropathies. Prior to presentation at our facility, several investigations were carried out. (Table 1).

Additionally, the urine detailed report was normal and negative for protein, blood, glucose, ketones, and epithelial cells. The electrocardiogram (ECHO) was also unremarkable. However, plasma levels of globotriaosylsphingosine (Lyso-Gb3) were not checked in this patient (Not available in Pakistan).

Table 1: Presentation of biochemical findings in the patient

Parameter	Reported Values	Unit	Reference Values
Hemoglobin	11	g/dL	12.5-16.1
Platelet Count	251,000	µL	150,000-400,000
Folic Acid	5.2	ng/mL	3.1-20.5
Vitamin B12	100	pmol/L	25-165
Aldolase	6.7	U/L	=<7.6
TSH	1.34	µlU/mL	0.7-6.4
CPK	77	U/L	39-308
Creatinine	0.52	mg/dL	0.72-1.25

Genetic testing: Targeted Panel Sequencing (Comprehensive Neuropathies Panel, Invitae, USA) was used in this patient (III-2, Figure 1). A novel hemizygous, pathogenic variant, c.779G>A, p.Gly260Glu, (X-101398803-G-A, GRCh38), was identified in *GLA* (Alpha-Galactosidease A) gene, present in exon 5 of the gene (http://genome.ucsc.edu/). Minor allele frequency of this variant is not available (https://gnomad.broadinstitute.org/). The *GLA* (MIM- 300644) gene is associated with X-linked Fabry disease (MedGen UID: 8083). This result

is consistent with a diagnosis of Fabry disease. Both asymptomatic siblings, a sister and a brother (III-1 and III-3, Figure 1) underwent genetic testing at Invitae, USA, and found negative for identified *GLA* variant (data not shown).

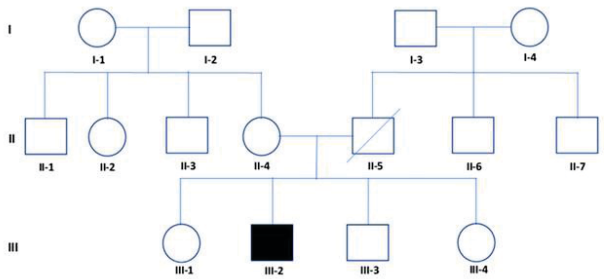

Fig.1: Pedigree of the family of the patient with Fabry Disease (III-2). One of his paternal uncles (II-6) has a neurological condition (details not known) while one maternal uncle (II-3) has epilepsy. Squares represent males while circles represent females. Filled square represent affected male. Diagonal line represents deceased individual

The patient was advised to take low-dose aspirin daily and has been advised to restrict activity in the heat. The patient was advised to take frequent cold showers in the summer to provide symptomatic relief for the acroparasthesias. We have also advised Injection Agalsidase beta, 1 mg/kg, I/V infusion every 2 weeks, which is a life-long enzyme replacement therapy.

Discussion

Fabry disease is a hereditary, progressive, multisystemic lysosomal storage disorder caused by a functional deficiency of the enzyme α-galactosidase A (α-GalA), with a global prevalence between 1:40,000 and 1:60,000 in males.[8,11] In Fabry Disease, the primary metabolic defect is [a] deficiency of lysosomal alpha-galactosidase A (alpha-Gal A), which is required for the breakdown of the terminal galactose from globotriaosylceramide (Gb3).[11] Mutations in the *GLA* gene lead to the accumulation of Gb3 in various cells and tissues, including skin, eye, kidney, heart, brain, and peripheral nervous system.[12,13]

Genetic testing through Targeted Gene Panel (Comprehensive Neuropathies Panel, Invitae, USA) revealed a novel hemizygous mutation in the *GLA* gene c.779G>A, p.Gly260Glu, in exon 5 of the gene (X-101398803-G-A, GRCh38). To the best of our knowledge, this is the first reported *GLA* gene mutation in a Fabry disease patient from Pakistan. Rare genetic disorders are challenging to diagnose in Pakistan due to limited access of patients to tertiary care facilities, and the cost of genetic and metabolic testing.

This patient's only complaint was paresthesias in the limbs and heat intolerance with normal laboratory tests, which delayed his diagnosis by four years. With the increasing availability of genetic testing at an affordable cost, it may be easier to diagnose such rare genetic diseases at an earlier stage.

Identification of mutations in symptomatic patients is indicative of Fabry disease, and expands the molecular comprehension of the *GLA* gene, providing invaluable insights to physicians in the diagnosis and management o the disease.[13-15] In this study, we have identified a novel mutation in *the GLA gene c.779G>A, p.Gly260Glu* (X-101398803-G-A, GRCh38) in a patient of Fabry's disease from Pakistan. To our knowledge, this is the first genetically confirmed case from Pakistan. We recommend early genetic testing and referral to tertiary care academic centers in such rare, undiagnosed cases.

Currently, enzyme replacement therapy is the approved treatment for Fabry disease.[16-18] Treatment regimens include agalsidase alfa, agalsidase beta or pegunigalsidase alfa every other week intravenously or, if a responding ('amenable') α-galactosidase A mutation is present, oral pharmacological chaperone therapy.[16,17,19,20] We have advised life-long enzyme replacement therapy to this patient (Injection Agalsidase beta, 1 mg/kg, I/V infusion every 2 weeks).

Conclusion

Fabry disease one of the very few treatable genetic diseases caused by mutations in the *GLA* gene. A life-long enzyme replacement therapy is available in different forms, which needs to be started before 16 years of age (Injection Agalsidase beta, 1 mg/kg, I/V). Early genetic testing is highly suggested to aid the replacement therapy and to prevent long-term complications, including hypertrophic cardiomyopathy, cerebrovascular disease, and kidney impairment.

Patient Perspective: The patient's family is relieved

to have received a diagnosis and explanation for his symptoms. Although the disease has impacted his quality of life, our patient and his family are determined to access enzyme replacement therapy and have requested donor agencies for assistance.

Patient Consent: The patient in this case report was 13 years old (minor) so the clinical and laboratory details were shared after taking written informed consent from guardian.

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Conflict of Interest: The authors declare no conflict of interest

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Author Contributions

AAM: Concept and design of work and data acquisition, curation and statistical analysis
MJH: Manuscript writing for methodology design and investigation, and validation of data, interpretation, and write up of results
AA: Revising, editing and supervising for intellectual content, and writing the original draft, proofreading and approval for final submission

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