A Novel PGK1 Gene Variant with Neurological Dysfunction, Haemolytic Anaemia and Myopathy: A Case Report from India

Dear Sir,

Phosphoglycerate kinase-1 enzyme (*PGK1*) deficiency is a rare X-linked recessive metabolic disorder with a prevalence of <1 per 100,000; 30 unrelated affected families have been reported so far.[1] Onset may be in childhood, adolescence or adulthood.

The cause is attributed to mutations in the PGK1 gene (Xq13.3), with 20 different disease-causing variants identified.[1] The *PGK* enzyme converts 1,3 biphosphoglycerate to 3-phosphoglycerate in the glycolytic pathway and helps in adenosine triphosphate (ATP) generation, among other functions. There are two isoforms: *PGK1 is* ubiquitous and *PGK2 is* unique to spermatogenic cells.[2]

Three phenotypes are known depending on the location of PGK1 enzyme deficiency; chronic non-spherocytic hemolytic anaemia (NSHA), neurological manifestations (seizures, intellectual disability, stroke, hemiplegic migraines, ataxia, tremors, behavioural abnormalities, attention deficit hyperactivity disorder, microcephaly, polyneuropathy, retinal dystrophy and ophthalmoplegia) and myopathy (exercise

intolerance, rhabdomyolysis, muscle weakness, myalgia and myoglobinuria).[2]

We report a 15-year-old boy with a novel PGK1 gene variant associated with a rare combination of all three phenotypes. This is also the first report from India.

Our proband was born uneventfully to non-consanguineous healthy parents and had apparently normal premorbid development. He had generalised convulsive status epilepticus [SE] and hemolysis at 3 ½ years of age with fever. Subsequently, he was on Phenobarbitone and soon after taper presented again with SE, intravascular hemolysis, and raised CPK at 7 years of age. During this episode, he had prolonged encephalopathy and increased tone in his right upper and lower extremities which resolved. At 10 years of age, he had recurrent focal seizures, encephalopathy with haemolysis and rhabdomyolysis triggered by fever. At 11 years of age, he had headache, lethargy and transient left hemiparesis with haemolysis triggered by fever Eventually, he developed refractory atypical absence seizures.

Initial interictal EEGs showed generalised spike-wave discharges with age-appropriate background activity. Interictal EEG at 11 years of age showed diffuse moderate asymmetric slowing (right > left), frontal epileptiform (left > right) discharges and occasional rhythmic 2–2.5 Hz bilateral slow waves [Figure 1]. Three months later, a repeat EEG showed markedly reduced epileptiform discharges with persistent background slowing. MRI brain revealed age-inappropriate cerebral atrophy.

Each acute episode was treated symptomatically, and once stable, he was discharged on oral anti-seizure medications (ASMs), which were taken regularly. Valproate was effective in controlling generalised tonic-clonic seizures. Atypical absences reduced on Ethosuximide and Clonazepam. Levetiracetam and Lamotrigine were tried and discontinued due to behavioural issues and skin reactions, respectively. Phenobarbitone was discontinued due to cognitive concerns.

He additionally had recurrent episodes of rhabdomyolysis and high creatinine phosphokinase values, ranging from 1555 to 8703 IU/L, during his hospital admissions. Echocardiography and electrocardiography studies were normal.

At 1 year of age, he was evaluated for pallor and low haemoglobin values (as low as 5.8 mg/dl) and was diagnosed with NSHA. He required multiple blood transfusions till he was 8 years of age. In view of haemoglobinuria and raised lactate dehydrogenase values, work up was done for intravascular haemolysis including red cell membrane disorders and red cell enzyme disorders (pyruvate kinase, glucose-6-phosphate dehydrogenase, glucose phosphate isomerase). These were found to be negative. Flow cytometry test for paroxysmal nocturnal haemoglobinuria was negative. *PGK* enzyme studies were not available and hence were not done. However, based on the triad of central nervous system (CNS) manifestations, high CPK and haemolysis, *PGK*1 deficiency was suspected

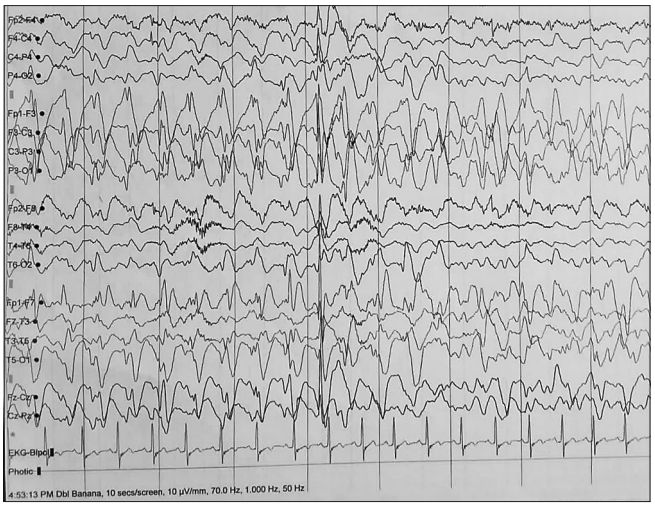

Figure 1: EEG findings showing diffuse bilateral moderate asymmetric delta slowing (3 Hz) and slow spike waves (left > right) over the frontal regions

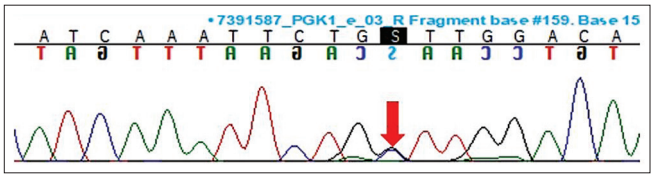

Figure 2: Results of chromatogram showing a hemizygous missense variant in exon 3 of the *PGK1* gene (chrX: g. 77369274C > G)

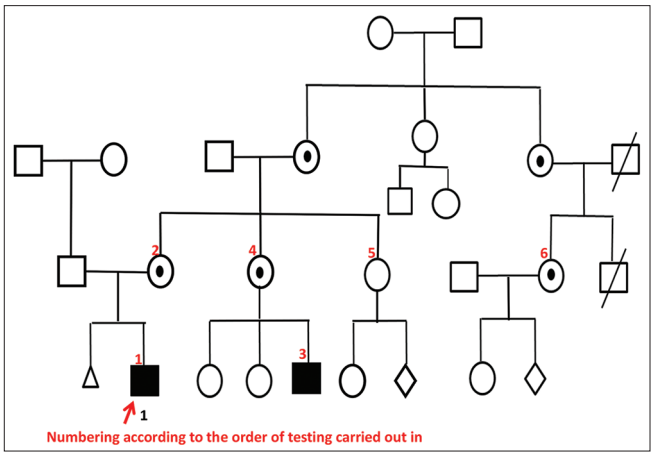

Figure 3: Family pedigree illustrating the proband's (1) family. His mother (2) and two maternal aunts (4, 6) are carriers and another maternal aunt (5) did not carry the variant. His maternal cousin (3) has the same variant and is symptomatic

and focused exome using next-generation sequencing was done to confirm the same.

A hemizygous variant c.150C > G that predicts a missense change p. Cys50Trp in exon 3 of the PGK1 gene (NM_000291.4) was detected [Figure 2]. The observed variation lies in the phosphoglycerate kinase domain of the *PGK*1 protein. The Cys50Trp variant has not been found in the 1000 gnomAD, ExAC and our internal databases. The in-silico predictions of

the variant are probably damaged by PolyPhen-2 (HumDiv) and by PROVEAN, SIFT, LRT and Mutation Taster 2. The reference codon is conserved across species. The variant was reported in the ClinVar database (ClinVar ID-1687119).[3]

Consequent to his genetic diagnosis, same *PGK1* variant was found in his maternal cousin with a similar phenotype who is being treated elsewhere. A heterozygous mutation of the same gene was found in his mother and two maternal aunts; however, they are asymptomatic [Figures 2 and 3]. The enzyme levels were not assessed.

During his routine follow-up, he had normal physical examinations. However, he has persistent atypical absences, learning disabilities and behavioural abnormalities including self-harm requiring treatment.

PGK1 deficiency is a very rare metabolic disorder, which is inherited in an X-linked recessive manner. Hence, males have full expression and females are usually asymptomatic carriers. Three main known phenotypes are known: a) chronic NSHA b) neurological manifestations (seizures, intellectual disability, stroke, hemiplegic migraines, ataxia and tremors) and c) myopathic syndrome (exercise intolerance, cramps, muscle weakness, myalgia and episodes of myoglobinuria). Patients may manifest with just one of these symptoms or a combination.

Earlier reports show that patients with PGK1 deficiency present with anaemia and CNS abnormalities, anaemia with myopathy, CNS abnormalities with myopathy, isolated myopathy or anaemia.[4] However, the presence of all three phenotypes in the same patient, with epilepsy being the dominant CNS manifestation, as seen in our patient, has not been reported. He also had behavioural abnormalities and learning disabilities described earlier.[4,5]

His epilepsy was polymorphic (GTCS, focal and atypical absences) and drug refractory, requiring multiple ASMs. Seizure semiology described in earlier cases is focal or generalised; however, atypical absences have not been described in children with *PGK1* deficiency.[5,6]

Less than 50 families affected by PGK1 deficiency have been reported. Among them, 25 different mutations (missense, loss of function and intronic) have been identified.[7] Our patient was found to have a novel *PGK1* missense variant.

To conclude, *PGK1* enzyme deficiency, though a very rare disorder, can be suspected in the presence of NSHA and neurological symptoms. It is confirmed by the identification of *PGK1* gene mutations by molecular analysis, which helps in genetic and reproductive counselling. We describe a case with a novel variant in *PGK1* gene with a triad of polymorphic refractory epilepsy (including atypical absence seizures), rhabdomyolysis and NSHA, it being the first report from India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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References

1. Orphanet: Glycogen storage disease due to phosphoglycerate kinase 1 deficiency. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en and Expert=713. [Last accessed on 2022 Jun 22].
2. Chiarelli LR, Morera SM, Bianchi P, Fermo E, Zanella A, Galizzi A, *et al*. Molecular insights on pathogenic effects of mutations causing phosphoglycerate kinase deficiency. PLoS One 2012;7:e32065. doi: 10.1371/journal.pone. 0032065.
3. National Centre for Biotechnology Information. ClinVar; [VCV001687119.1]. Available from: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV001687119.1. [Last accessed on 2022 Jun 21].
4. Garcia-Solaesa V, Serrano-Lorenzo P, Ramos-Arroyo M, Blázquez A, Pagola-Lorz I, Artigas-López M, *et al*. A novel missense variant associated with a splicing defect in a myopathic form of PGK1 deficiency in the Spanish population. Genes 2019;10:785. doi: 10.3390/genes10100785.
5. Matsumaru S, Oguni H, Ogura H, Shimojima K, Nagata S, Kanno H, *et al*. A novel PGK1 mutation associated with neurological dysfunction and the absence of episodes of hemolytic anemia or myoglobinuria. Intractable Rare Dis Res 2017;6:132-6.
6. Flanagan J, Rhodes M, Wilson M, Beutler E. The identification of a recurrent phosphoglycerate kinase mutation associated with chronic haemolytic anaemia and neurological dysfunction in a family from USA. British J Haematol 2006;134:233-7.
7. Beutler E. PGK deficiency. Br J Haematol 2006;136:3-11.

Submitted: 15-May-2023 **Revised:** 25-Jun-2023 **Accepted:** 26-Jul-2023
Published: 13-Oct-2023

DOI: 10.4103/aian.aian_428_23