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IDENTIFICATION OF A LIKELY PATHOGENIC AGXT VARIANT IN A NON-CONSANGUINEOUS COUPLE WITH RECURRENT EARLY-ONSET RENAL DISEASE IN OFFSPRING: A CASE REPORT

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ABSTRACT

Background: Primary Hyperoxaluria Type 1 (PH1) is a rare autosomal recessive disorder caused by mutations in the AGXT gene, leading to hepatic deficiency of alanine-glyoxylate aminotransferase. This results in excessive oxalate production, renal damage, and systemic oxalosis. Early identification of carrier status is crucial for at-risk families. **Case Presentation:** A 40-year-old male and his 25-year-old wife from northern India presented for genetic evaluation after the death of their 6-month-old daughter, who had early-onset renal failure and seizures. The couple had a family history of chronic kidney disease and previous pregnancy loss. Whole exome sequencing revealed both partners to be heterozygous carriers of the likely pathogenic missense variant c.302T>C (p.Leu101Pro) in the AGXT gene, associated with PH1. Genetic counselling was provided, explaining the 25% recurrence risk in each pregnancy. The couple was advised on reproductive options including prenatal diagnosis and preimplantation genetic testing, and referred for nephrology evaluation and psychosocial support. **Conclusion:** This case demonstrates the utility of carrier screening in diagnosing autosomal recessive conditions like PH1 in non-consanguineous families. Genetic testing played a pivotal role in identifying the underlying cause of recurrent renal disease, enabling informed reproductive planning and timely intervention.

BACKGROUND-

Primary Hyperoxaluria is an uncommon inherited disorder passed down in an autosomal recessive pattern, characterized by the body's inability to properly manage oxalate—a compound naturally present in many foods. Under normal conditions, oxalate is removed from the body by the kidneys through urine. However, in individuals with this condition, mutations in specific genes cause the liver to produce excessive amounts of oxalate. This overproduction results from a deficiency in alanine: glyoxylate aminotransferase (AGT), a liver-specific enzyme that requires pyridoxal-5'-phosphate (PLP) to function and plays a key role in glyoxylate metabolism. The buildup of oxalate can lead to kidney stone formation and progressive kidney damage over time.[1,2]Some of the causes include Genetic mutations in the AGXT, GRHPR, and HOGA1 genes, deficiency or dysfunction of enzymes responsible for oxalate metabolism, excessive oxalate absorption due to intestinal disorders like Crohn's disease, Dietary factors, though less common, can contribute to oxalate buildup.[2]Though rare, this condition can have serious consequences. Clinical signs frequently appear during childhood or adolescence, with repeated episodes of kidney stones serving as an early indicator. Without timely intervention, oxalate accumulation may go beyond the kidneys and damage other organs. Treatment for Primary Hyperoxaluria generally includes pharmacotherapy, dietary modifications, and, in advanced cases, may require organ transplantation.[3]This case highlights the utility of carrier screening in identifying a shared likely pathogenic variant in the AGXT gene among a non-consanguineous couple with a history of recurrent early-onset renal disease in their offspring.

Case Details:

A 40-year-old male, and his 25-year-old wife, both residents of northern India, presented to the genetics clinic at PGIMER, Chandigarh, for carrier screening evaluation following the unexplained death of their infant daughter. The child, born at term after an uneventful antenatal period, began experiencing seizures at the age of 2 months. Over the next few weeks, she developed progressive renal dysfunction marked by persistent hyponatremia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Despite supportive medical management, she succumbed to end-stage renal failure at the age of 6 months. A presumptive clinical diagnosis of a metabolic or inherited renal tubulopathy, including infantile nephronophthisis or a related tubulointerstitial disorder, was made at the time, though confirmatory genetic testing was not performed. The lady also reported a bad obstetric history, including a medically terminated pregnancy at 10 weeks of gestation two years prior, due to early fetal demise with no identified structural anomaly. There is a significant family history of renal disease on the male partner's side; specifically, his twin brother's daughter (niece) was diagnosed with chronic kidney disease of unknown etiology and died in late childhood. Given the recurrence of early-onset renal disease in two closely related children from the paternal lineage and the recent neonatal loss, the couple underwent genetic counselling and were offered whole exome sequencing as part of a BPL-subsidized carrier screening . Blood samples were collected on 23rd December 2024 and analyzed using whole exome sequencing. On 7th February 2025, the results revealed that both individuals were heterozygous carriers of a likely pathogenic missense variant in the AGXT gene: c.302T>C (p.Leu101Pro), located in exon 2. This gene is associated with Primary Hyperoxaluria Type 1 (PH1), an autosomal recessive disorder (OMIM #259900). The variant identified is classified as "likely pathogenic" based on ACMG criteria and prior evidence from the literature and ClinVar databases, though it is rare in population databases (allele frequency <0.05%). In silico prediction tools (PolyPhen-2, SIFT, LRT) all support a damaging effect of the variant on protein function, and the altered amino acid is evolutionarily conserved.PH1 is caused by biallelic pathogenic variants in the AGXT gene, which encodes alanine-glyoxylate aminotransferase, a hepatic peroxisomal enzyme. Deficiency leads to accumulation of glyoxylate and subsequent overproduction of oxalate, resulting in calcium oxalate crystal deposition in renal tissue and other organs. The clinical spectrum ranges from recurrent urolithiasis to early-onset nephrocalcinosis, chronic kidney disease, and systemic oxalosis.In this couple's case, the presence of the same pathogenic variant in both partners places them at a 25% risk of having an affected child with PH1 in each pregnancy. Genetic counselling was provided, emphasizing the importance of prenatal or preimplantation genetic diagnosis (PGD) in future pregnancies. The couple was also referred for psychosocial support and further nephrological evaluation to rule out subtle renal dysfunction as carriers.

DISCUSSION:

Ph1 is a rare autosomal recessive disorder of glyoxylate metabolism caused by mutations in the AGXT gene. It results in hepatic deficiency of alanine-glyoxylate aminotransferase, leading to overproduction of oxalate and progressive

deposition of calcium oxalate crystals in the kidneys and other tissues. Our case highlights the importance of carrier screening in a non-consanguineous Indian couple with a strong family history of early-onset renal failure and a deceased infant with presumed metabolic tubulopathy. Whole exome sequencing revealed that both partners are heterozygous carriers of the AGXT missense variant c.302T>C (p.Leu101Pro), classified as likely pathogenic. Several studies reinforce the variability in clinical presentation and genetic heterogeneity of PH1. Medina et al[4] described an 18-year asymptomatic follow-up of a patient diagnosed in infancy with nephrocalcinosis, who responded well to conservative therapy with pyridoxine. Similarly, Rather et al[5] reported Indian patients presenting with a range of manifestations—from asymptomatic siblings identified via family screening to individuals with end-stage renal disease requiring combined liver-kidney transplantation.[6]

Chanchlani et al[7] described cases of PH1 in very young children presenting with nephrocalcinosis, renal failure, and systemic features such as rickets and hypertension, further emphasizing the variable phenotypic spectrum. Mandrile et al[8] highlighted that genotype-phenotype correlation in PH1 remains inconsistent; even patients harboring the same mutations may have disparate outcomes, likely due to environmental or modifying genetic factors. Garrelfs et al[9] and Ganhal et al[10] reinforced the need for genetic diagnosis and long-term follow-up, especially in resource-limited settings, where biochemical screening may be inadequate. In our case, early identification of carrier status enabled timely genetic counselling and future reproductive planning. This case underscores the importance of preconception screening and consideration of prenatal or preimplantation genetic testing in families with unexplained renal losses.

CONCLUSION

This case stresses on the critical role of carrier screening and genetic testing in families with a history of early-onset renal disease, even in the absence of consanguinity. Identification of a shared likely pathogenic AGXT variant in a non-consanguineous couple emphasizes the need for broader awareness and access to genetic services.

REFERENCES:

1. Bouzidi H, Majdoub A, Daudon M, Najjar MF. [Primary hyperoxaluria: A review]. Nephrologie & therapeutique 2016;12(6):431-6.
2. Fargue S, Acquaviva Bourdain C. Primary hyperoxaluria type 1: pathophysiology and genetics. Clin Kidney J 2022;15(Suppl 1):i4-i8.
3. Groothoff JW, Metry E, Deesker L, Garrelfs S, Acquaviva C, Almardini R, et al. Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. Nature reviews Nephrology 2023;19(3):194-211.
4. Medina PG, Román LE. Importance of Assessing Compliance with Conservative Treatment of Primary Hyperoxaluria Type 1: A Case Report of a Patient with I244T/c.969-3C>G Mutation. The Permanente journal 2020;24(
5. Rather JI, Rasheed R, Wani MM, Bhat MA, Wani IA. Primary hyperoxaluria: a case series. J Med Case Rep 2023;17(1):421.
6. Batta G, Vishnuprasad R, Batta A, Santhanalakshmi D, Dwivedi A. Screening for Fabry disease in patients on Hemodialysis. International journal of applied & basic medical research 2024;14(3):187-92.
7. Chanchlani R, Sinha A, Gulati A, Agarwal V, Bagga A. Common mutation underlying primary hyperoxaluria type1 in three Indian children. Indian journal of nephrology 2012;22(6):459-61.
8. Mandrile G, Beck B, Acquaviva C, Rumsby G, Deesker L, Garrelfs S, et al. Genetic assessment in primary hyperoxaluria: why it matters. Pediatric Nephrology 2023;38(3):625-34.
9. Garrelfs SF, Rumsby G, Peters-Sengers H, Erger F, Groothoff JW, Beck BB, et al. Patients with primary hyperoxaluria type 2 have significant morbidity and require careful follow-up. Kidney International 2019;96(6):1389-99.
10. Ganhão I, Borges C, Amorim M, Braga da Cruz M, Nobre S, Francisco T, et al. Primary hyperoxaluria type 1–two case reports. Portuguese Journal of Nephrology & Hypertension 2020;34(1):55-7.