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CASE REPORT

Newborn Genetic Screening: Significance in Early Diagnosis of an Infant with Mitochondrial DNA Depletion Syndrome-6

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Introduction

Newborn genetic screening assists in identifying the risk of having rare and serious medical conditions that can affect normal development so that preventable developmental delay, disability, morbidity, and mortality during infancy and childhood can be avoided [1].

Mitochondrial DNA maintenance defects (MDMDs) are a group of diseases, characterized by mtDNA depletion and/or multiple mtDNA deletions resulting from impaired mtDNA synthesis which is associated with pathogenic variants in the nuclear genes involved in mtDNA synthesis, mitochondrial nucleotide supply, or mitochondrial dynamics [2]. MPV17 gene encodes a mitochondrial inner membrane protein that plays an important role in mitochondrial deoxynucleotide homeostasis and maintenance of mtDNA [3]. MPV17-related Mitochondrial DNA depletion syndrome-6 (MTDPS6) is a rare autosomal recessive disorder characterized by the early onset of progressive liver failure, resulting in neonatal death within the first year of life [2].

Here we present a case of a newborn detected with MPV17 gene variant in a newborn genetic screening before the onset of symptoms which helped in early medical intervention.

Case Presentation

A 35 years old female visited Gupte hospital at the 20th week of her gestation due to abnormal ultrasound findings which were suggestive of fetal growth restriction and feto-placental insufficiency. This consanguineous couple had a history of two recurrent miscarriages, one Intrauterine death (IUD) at the gestational age of 8 months, and one neonatal death at the age of 2.5 months due to suspected metabolic disorder with clinical findings such as hepatosplenomegaly, renal failure, ascites, severe weakness, poor feeding, and low weight gain. Considering her ultrasound abnormality and advanced maternal age; a Noninvasive Prenatal screening (NIPS) test was referred which was suggestive of low risk. She delivered a healthy female child with no clinical diagnosis like her previous baby.

Due to the suspected metabolic disorder in the previous child, her baby was referred for newborn genetic screening (NBS) test post-delivery to rule out the possibility of any genetic disorder. After obtaining written informed consent from the couple, the NBS test was performed using Next Generation Sequencing (NGS), which screens for more than 400 congenital disorders. Homozygous pathogenic variant in exon 2 of MPV17 gene (c.22C > T; p.Gln8Ter) detected in the newborn was then confirmed with Sanger sequencing. The family pedigree and Sequencing chromatogram of a proband with MPV17 variation are shown in Fig. 1.

Genetic counseling was done to address the clinical condition and phenotype associated with the identified variant. The couple was advised to keep the newborn under proper medical surveillance having an increased risk of developing the mitochondrial condition associated with the identified gene variant.

In a routine medical check-up, the infant was diagnosed with failure to thrive at the age of 2.2 months and her physical examination suspected an enlarged liver. Further biochemical investigation revealed deranged LFT. The amino acid analysis reported moderate elevation of Alanine

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which could be due to lactic acidosis and elevated Histidine, Methionine, Ornithine, Phenylalanine, Tyrosine, and Valine were likely due to liver impairment [Table 1]. All these findings were suggestive of mitochondrial impairment. A regular follow-up with the pediatrician is being maintained to assess the progression of the condition. The baby is receiving symptomatic medical care until a liver transplant is performed.

Table 1 Biochemical test results (at 2.2 months) suggestive of mitochondrial impairment

Biochemical test		Observed value	Reference value
LFT	Total serum protein	4.1	5.6–7.5 g/dL
	Albumin	2.57	3.8–5.4 g/dL
	Globulin	1.53	2.3–3.2 g/dL
	A/G	1.68	1.2:1–2:1 g/dL
	Total Bilirubin	19.3	0.3–1.2 mg/dL
	SGOT/AST	150	5–35 IU/L
	SGPT/ALT	67	5–40 IU/L
Metabolic testing	Lactate	12.38	2–12 mg/dL
	Alanine	831.61	74–613 µM
	Citrulline	81.94	5–60 µM
	Histidine	344.14	60–215 µM
	Methionine	80.93	1–54 µM
	Phenylalanine	200.09	21–155 µM
	Tyrosine	626.27	17–250 µM
	Valine	375.48	41–233 µM
Blood Ammonia		191	31–123 µg/dL

Discussion and Conclusion

Newborn genetic screening significantly improves and expands the scope of conventional biochemical Newborn screening (NBS) enabling comprehensive and presymptomatic testing which will aid in better diagnosis of genetic conditions and early medical intervention as well as personalized treatment [4]. MPV17 encodes a mitochondrial inner membrane protein which plays a significant role in mtDNA maintenance. A pathogenic variant of the MPV17 gene leading to loss of function causes mtDNA depletion in affected individuals with characteristic clinical phenotypes such as progressive liver dysfunction, metabolic impairment, failure to thrive, neurological symptoms. At present, no curative treatment is available for this disorder; and the management is mainly symptomatic. Liver transplantation, Nucleoside supplementation and HSCT are potential treatment options. Liver transplant is relatively effective preventing liver failure in affected individual with milder phenotypes and no neurological manifestations but remains controversial in case of multisystem involvement[2,5]. Early diagnosis of the disorder and identification of the cause may help in better management and personalized treatment.

We detected a homozygous pathogenic variant c.22C > T; p.Gln8Ter of the MPV17 gene in an asymptomatic newborn as a result of newborn genetic screening. Later the infant presented with clinical symptoms that correlated with the mitochondrial condition associated with the identified gene variant.

In conclusion, this case implies the impact of newborn genetic screening in early diagnosis of a rare genetic disorder that NIPS, a prenatal diagnostic test failed to identify. It further helped in on-time medical intervention reducing the severity and progression of the disorder leading to better life prognosis.

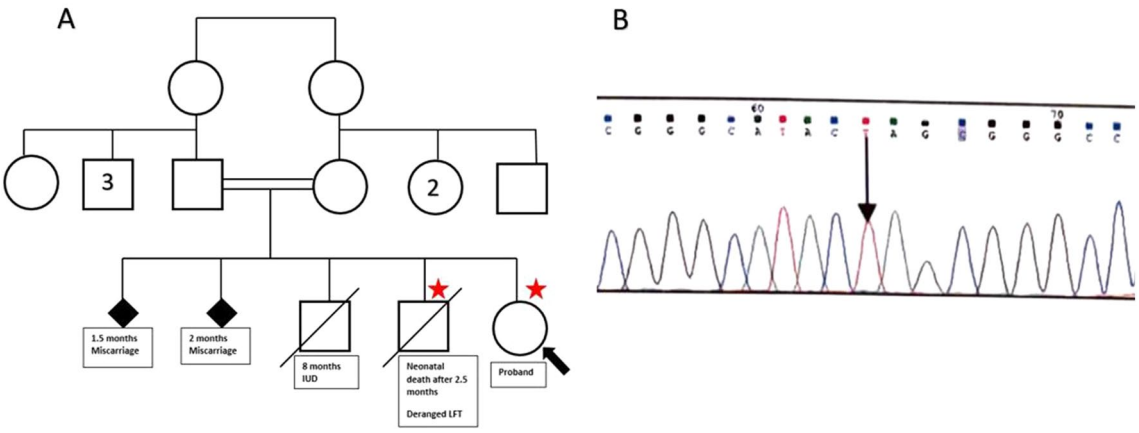

Fig. 1 **A** Pedigree that shows the presence of a MPV17 gene-associated phenotype within a family across generations represented with ★ mark. **B** Sanger chromatogram of an identified variant in a neonate

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Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical statement We ensure that this work is original and has not been published elsewhere, nor it is currently under consideration for publication elsewhere. We also acknowledge, that all authors have substantially contributed to the underlying research and drafting of this manuscript and agree with the content of the manuscript. We have no conflicts of interest to disclose.

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