

A novel MPV17 gene mutation in a Saudi infant causing fatal progressive liver failure

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We describe in this report the clinical, biochemical, and molecular features of a Saudi infant with hepatocerebral MDS secondary to a novel homozygous mutation in the MPV17 gene. An automated sequencing of the nuclear MPV17 gene was performed. The coding region (7 exons) of the MPV17 gene was amplified using an M13-tagged intronic primer and screened by direct sequencing of the PCR-amplified products (GenBank Association Number NM_002437.4). The sequencing of the entire coding region and intron-exon boundaries of MPV17 gene revealed a single homozygous variant, -c.278A>C(p.Q93P), which predicts the substitution of a highly conserved amino acid. This particular sequence variant has not been previously reported as a single-nucleotide polymorphism (SNP) or pathogenic mutation. Diagnostic workup for neonatal liver disorders should include mutation screening for known genes. The new advances in molecular genetics can help clinicians establish the diagnosis in a timely fashion, which may prevent a child from undergoing invasive and expensive investigations.

Mitochondrial DNA depletion syndromes (MDSs) are autosomal recessive inherited disorders characterized by a severe decrease in mitochondrial DNA content, which leads to dysfunction of the affected organ. Liver failure is well described in these disorders. Several genes have been identified as causes for MDS; the most recent one is MPV17 gene mutation. We describe in this report the clinical, biochemical, and molecular features of a Saudi infant with hepatocerebral MDS caused by a novel homozygous mutation in the MPV17 gene.

CASE

The proband was the eighth child of non-consanguineous Saudi parents, who was born at term after an uneventful pregnancy. His birth weight was 3 kg (25th percentile), birth height was 52 cm (75th percentile), and head circumference was 34 cm (25th-50th percentile). He was admitted at the age of 2 months with a history of jaundice and diarrhea and was found to have microcephaly, failure to thrive, hypotonia, and hepatosplenomegaly. The family history was unremarkable.

His investigations revealed the following: total bilirubin: 128 µmol/L (<205); direct bilirubin 86 µmol/L; alkaline phosphatase: 837 U/L (<500); albumin: 28 g/L (38-54); aspartate aminotransferase (AST): 132 U/L (5-34); alanine aminotransferase (ALT) 59 U/L (5-55); GGT 115 U/L (12-65); lactic acid 9.8 mmol/L (0.5-2.2); prothrombin time 28 seconds (control 7.2-10.4); international normalized ratio 2.8 (0.8-1.2); partial thromboplastin time 55 (28.1-42.9); ferritin 543 µg/L (21.8-274); virology screening for hepatitis B, C, CMV, and EBV were negative; blood and urine metabolic screen were normal; POLG1 and DGUOK gene mutations for mitochondrial disorders were negative; echocardiogram was normal; a slit lamp eye exam showed retinal pigmentation; a liver biopsy showed marked distension of hepatocytes, few periportal glycogen nuclei, portal and perisinusoidal fibrosis, microvesicular steatosis, and portal inflammation (**Figure 1**). Magnetic resonance imaging showed subtle subcortical white matter changes. Screening of MPV17 gene revealed a single novel homozygous gene mutation (c.278A>C (P.Q93P)).

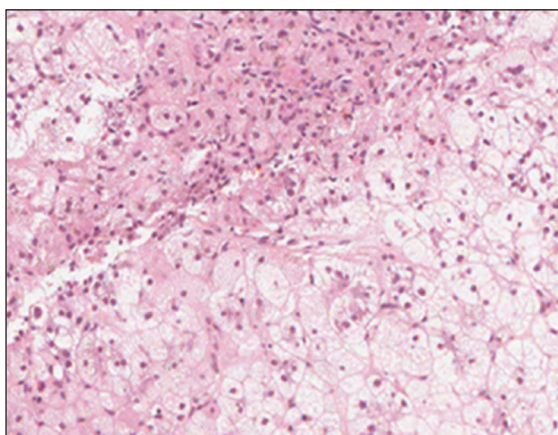


Figure 1. A liver biopsy showing marked distension of hepatocytes, few periportal glycogen nuclei, microvesicular steatosis and portal inflammation (Hematoxylin and eosin stain, original magnification $\times 10$).

After supportive treatment and a complete diagnostic workup, the patient was discharged but was readmitted at the age of 4 months with intractable ascites. Despite full support, the patient's condition deteriorated and progressed to severe liver failure and neurological depression. He succumbed at the age of 5 months.

METHODS

After obtaining consent from the parents, genomic DNA was extracted from the peripheral blood. An automated sequencing of the nuclear-encoded deoxyguanosine kinase (DGUOK) gene showed no pathogenic mutation; therefore, further screening on the same sample for MPV17 gene mutation was done by automated sequencing of the whole nuclear MPV17 gene. The coding region (7 exons) of the MPV17 gene was amplified using an M13-tagged intronic primer and screened by direct sequencing of the PCR-amplified products (GenBank Association Number NM_002437.4).

RESULTS

Sequencing of the entire coding region and intron-exon boundaries of MPV17 gene revealed a single homozygous variant, c.278A>C(p.Q93P), which predicts the substitution of a highly conserved amino acid. Unfortunately, we were not able to confirm the carrier status of this novel mutation in the parents; however, this particular sequence variant has not been previously reported as an SNP or pathogenic mutation, but is likely to be of pathological significance in the observed presentation that fits the clinical picture of MPV17 gene defects.¹

DISCUSSION

MDS are well-established causes of liver failure in infancy. They are autosomal recessive disorders caused by mutations in nuclear genes encoding proteins with a specific function targeted to mitochondria, rather than primary mutations in the mitochondrial genome.¹ MDS are characterized by multisystemic involvement with phenotype heterogeneity. Liver involvement has been associated with mutations in Twinkle (POE1), POLG1, DGUOK genes and recently with mutations in the MPV17 gene.² MPV17 encodes a mitochondrial inner membrane protein; it has been postulated that the absence or malfunction of MPV17 plays a role in oxidative phosphorylation failure and mtDNA depletion, which subsequently causes progressive hepatocerebral disease.²

Patients with MDS typically present with rapidly progressive liver failure, hypoglycemia, lactic acidosis,

Table 1. Clinical features of patients with MPV17 gene mutations.

Demographics	
Age at onset	Early presentation (2-6 mo)
Gestational age	Full term, normal birth weight
Consanguinity	+
Family history	+
Ethnicity	Reported from different parts of the world (Navajo population, Middle East, Italy, Hispanics, and Caucasians) (1-7)
Clinical features	
Dysmorphic features	Non-specific
Failure to thrive	+
Hepatic manifestations	Early in the course: cholestasis, hepatomegaly, liver failure, cirrhosis, hepatocellular carcinoma (6)
Splenomegaly	+
Hypoglycemia	+ (almost all the reports)
Neurology manifestations	Late in the course: hypotonia, microcephaly, ataxia, nystagmus, seizures, psychomotor delay, muscle weakness, and peripheral neuropathy (2,4,8)
Ophthalmological examination	Normal – pigmented retinopathy (8,TR)
Other manifestations	Diarrhea, renal tubulopathy (6,8), nephrolithiasis (3,7), hypoparathyroidism (6,8)
Outcomes	Death in infancy from rapidly progressive liver failure. Mixed outcomes with liver transplantation (survival rate of <50%) (3)

TR; This report.

growth retardation, and neurological symptoms during the first year of life. Unlike the other types of MDS, neurological manifestations in patients with MPV17 mutation are mild early in the course, mainly with hypotonia, and then manifest further as the disease progresses.^{1,3} **Tables 1 and 2** summarize the clinical, biochemical, radiological, and histological features of this disorder. Its incidence is not well known; the reasons is partly related to the rarity of the condition (less than 30 cases published worldwide so far) and the diversity of its clinical presentation.

MPV 17 gene mutation was also found to cause an old disorder known as Navajo neurohepatopathy (NNH), which is an autosomal recessive disorder that is prevalent in the Navajo population at the southwest of the United States.⁴ The major clinical features of this disorder are hepatopathy, sensorimotor neuropathy, corneal ulcerations, acral mutilation, cerebral leukoencephalopathy, failure to thrive, and recurrent metabolic acidosis with serious systemic infections.^{4,5} This may represent a milder form of neurologically predominant picture of MVP17 disorder.

Several mutations have been reported in MPV17 gene from different parts of the world including our area.^{1,3,6-7} Recently, El-Hattab et al reported 7 novel MPV17 gene mutations in 8 patients,⁶ in addition to 13 previously reported mutations in 21 patients.¹⁻⁷ We report in this case an additional single homozygous mutation, $-c.278A>C(p.Q93P)$, in the MPV 17 gene. The clinical presentation in our patient was similar to that in the previously reported cases, with a neonatal onset of progressive liver failure, hypotonia, lactic acidosis, and early death from liver failure. Previous reports did not find a clear phenotype-genotype correlation, which suggests that other factors may contribute to the severity of the disease such as concurrent infections.⁸

Diagnostic workup for neonatal liver disorders with neurological involvements should include mutation screening for known genes of mitochondria depletion syndrome like MPV 17, Twinkle (POE1), POLG1, and DGUOK. The new advances in molecular genetics can help clinicians establish the diagnosis early in its course; this may prevent a child from undergoing invasive and expensive investigations. In addition, this will provide physicians with more accurate information in regard to prognosis, thus providing better counseling. This may prevent the family from having another affected child in future pregnancies with cur-

Table 2. Biochemical, histopathological, radiological, and genetic features of patients with MPV17 gene mutations.

Liver enzymes	Mild to moderate increase of transaminases (AST>ALT), high GGT almost in all reports.
Lactic acid	High (almost in all reports)
Coagulopathy	++ (almost in all reports)
Histopathology	Swollen hepatocytes with coarse cytoplasmic granules, multinucleated giant cells, cholestasis, microvesicular steatosis, portal inflammation, portal and perisinusoidal fibrosis (1,3,9, TR)
Neuroimaging	Variable (normal MRI, leukoencephalopathic lesions [2-4,7,TR]), elevated lactate in MRS (3)
Echocardiography	Normal (1, TR)
Genetic mutation	More than 20 gene mutations have been reported in the MVP gene (6). $c.278A>C(p.Q93P)$ is a novel mutation in our patient. The homozygous $p.R50Q$ mutation is associated with a less severe form of the disease (4,6).

MRI: Magnetic resonance imaging, MRS: magnetic resonance spectroscopy, TR: this report, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase.

rent advances in pre-implantation genetic diagnosis.

Supportive therapy is the mainstay intervention in the management of hepatic failure in MDS. So far, liver transplant is controversial in patients with MPV 17 mutations. The effect of liver transplantation seems to be variable among different MPV 17 mutations where almost half of the patients progressed to multi-organ failure post-transplantation.⁶ Parini et al found that regular glucose intake at short intervals may be beneficial in preventing hypoglycemia and slowing the progression of liver disease, particularly, in patients waiting for liver transplantation.⁹ Other report found that some patients may benefit from lipid-rich, carbohydrate-restricted diet, in addition to succinate and coenzyme Q supplementation.¹⁰

In conclusion, we reported the occurrence of novel MPV17 gene mutation in a Saudi infant who experienced rapidly progressive liver failure and death. We recommend considering testing for known genetic mutations of the MDS in infants with progressive liver failure and neurological involvements, which will help significantly in establishing the etiology of liver disease in a timely fashion.

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