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CASE REPORT

Spontaneous recovery in infantile mitochondrial hepatopathy due to TRMU gene mutation

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ABSTRACT

Background: Depending on the genetic mutation, mitochondrial hepatopathy has a variable presentation. Spontaneous recovery is a rare occurrence in these patients. However, complete recovery is possible in infants having t-RNA5-methylaminomethyl-2-thiouridylate methyl-transferase (TRMU) gene mutation.

Case presentation: A 53-day-old female child presented with hepatopathy and lactic acidosis. Genetic work up showed she has a mitochondrial respiratory chain disorder due to the TRMU gene mutation. Very few patients with isolated hepatic involvement have been described in the literature. We are reporting the first case from India of transient hepatopathy due to heterozygous TRMU gene mutation. Recovery was spontaneous at 4 months of age.

Conclusion: Complete recovery is possible in infants having TRMU mutation if they are supported through and survive the acute phase. The identification of TRMU mutation could impact clinical management.

Keywords: Infantile mitochondrial hepatopathy, TRMU, Hepatic failure, spontaneous recovery, case report.

Introduction

Viral infections and inborn errors of metabolism are the main causes of hepatopathy in infancy (1). This case report describes an infant who presented with hepatopathy and lactic acidosis. She made a spontaneous recovery after being administered intensive supportive care. A rare metabolic disorder was diagnosed. This communication will alert and remind the treating doctors of this rare diagnosis in suitable clinical situations.

Case Presentation

A 53-day-old female child, born of non-consanguineous union, presented with yellowish discoloration of the sclera and skin and high-colored urine for the last 15 days and cough with fast breathing for 4 days. The baby was delivered vaginally as a 34-week preterm baby appropriate for gestational age (birth weight: 2.1 kg). There was no history of fever, clay-colored stools, convulsions, or abdominal distension. There was no maternal history of fever, rash, jaundice, or swelling of feet during pregnancy. The active and irritable infant [Wt: 4.1 kg (Z score 0 to -2 SD), length: 54 cm (Z score 0 to -2 SD), with head circumference of 36.4 cm (Z score -1 SD to -2 SD)] and icterus had tachycardia (heart rate: 160/minute) and tachypnea (respiratory rate: 70/minute). The patient had stridor and suprasternal retractions and no facial dysmorphism. The abdomen was soft but distended with liver palpable, 2 cm below the right costal margin in the mid-clavicular line (span: 6.2 cm). It was soft in consistency and had a smooth surface and sharp margins. The spleen was not palpable and there was no clinical evidence of ascites. The rest of the examination was non-contributory. The child was admitted to the intensive care unit for monitoring and mechanical ventilation in view of respiratory distress, as the child had stridor due to laryngotracheomalacia and the respiratory rate was 70/minute. ABG analysis had features of metabolic acidosis. Serum creatinine and electrolyte levels were normal. Serum levels of hepatic transaminases, bilirubin, and alkaline phosphatase were raised (Table 1). Chest radiograph showed right middle lobe consolidation which developed while the child was on mechanical ventilation. Based on the clinical presentation with metabolic acidosis, the possibility of sepsis, neonatal hepatitis, or metabolic liver disease was considered. Simultaneously, samples were sent for the diagnosis of other etiologies. The TORCH panel test was negative. Viral work up for HBsAg was negative. Urine examination for reducing

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sugar was normal. Tandem mass spectroscopy was carried out to look for metabolic disease, but the test results were negative. Urine and blood cultures revealed no growth and C-reactive protein level was normal (2.1 mg/l). Thyroid function tests were normal [free T3- 2.7 pg/ml (1.4-4.4 pg/ml), free T4-1.1ng/ml (0.8-1.8 ng/ml), TSH- 0.9 μIU/ml (0.35-5.5 μIU/ml)]. The baby improved and was then extubated after 5 days. As shown in Table 1, the level of GGT was raised. Abdominal sonography was normal. Liver biopsy showed ballooning of hepatocytes with intrahepatic and canalicular cholestasis.

After all these tests, a conclusive diagnosis could not be achieved. As metabolic liver disease was suspected, genetic studies for mitochondrial respiratory chain were undertaken. The genetic test report showed a positive result for tRNA-modifying enzyme and tRNA5-methylaminomethyl-2thiouridylate methyl-transferase (TRMU) mutation. Next-generation sequencing (NGS) assay for targeted clinical exome sequencing detected heterozygous missense variation in exon 10 of TRMU gene (chr22: g.46751896T>C; depth :565×), with autosomal recessive inheritance that results in amino acid substitution of alanine for valine at codon 343 (p. Val343Ala; ENST00000290846.4). [Variant: ENST00000290846.4: c.1028T>C; p. (Val343Ala)].

TRMU gene mutation causes transient infantile liver failure. The child was treated with cefotaxime 50 mg/kg IV injection 8 hourly for 15 days, considering pneumonia and vitamin K supplementation was given for coagulopathy.

There was progressive improvement in clinical and biochemical parameters from the 20th day of hospital stay (age: 73 days). She was discharged on the 85th day of life. At the time of discharge, the patient was active, clinical manifestations were ameliorating (weight gain, reduced jaundice, no abdominal distention, and clear chest on auscultation), and the laboratory parameters were showing gradual change toward normalization (no metabolic acidosis, Table 1). The child was advised usual breastfeeding and no specific treatment was given. On follow-up on day 221 of life, the child was asymptomatic with normal growth. At the last examination, the patient weighed 7.1 kg (Z score 0 to -2 SD), head circumference was 42.6 cm (Z score 0 to -1 SD), and length was 66 cm (Z score 0 to -2 SD), and the biochemical parameters had returned to normal (Table 1).

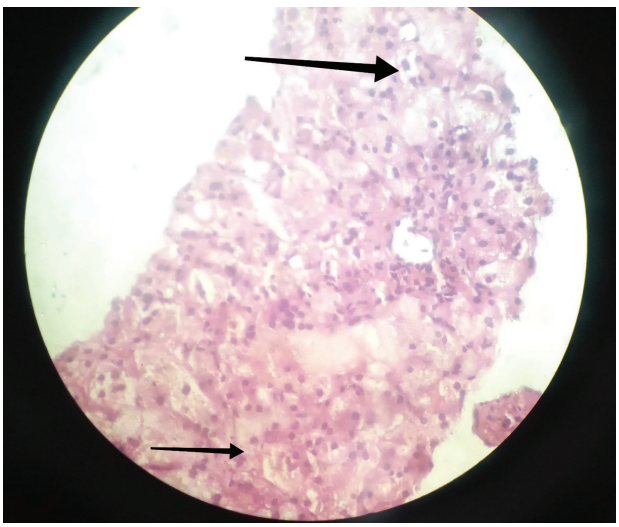

Figure 1. *Liver biopsy showing a) ballooning of hepatocytes (top arrow) with b) intrahepatic and canalicular cholestasis (bottom arrow).*

Discussion

This is the case of an infant, who presented with jaundice, hepatomegaly, irritability, lactic acidosis and laboratory features of hepatic dysfunction (raised hepatic transaminases, raised direct hyperbilirubinemia and coagulopathy). The patient was treated with supportive measures and the cause was determined to be related to mitochondrial respiratory chain disorder due to TRMU gene mutation. Mitochondrial diseases are clinically and genetically heterogeneous with highly variable outcomes. Other metabolic disorders, like congenital galactosemia and hereditary tyrosinemia type 1, can present with similar presentations. This association was first described in 13 cases in 2009 and so far, only 28 cases of reversible hepatic involvement secondary to this mutation have been reported (2). This is probably the first case from India of reversible hepatopathy due to TRMU.

The TRMU gene encodes mitochondria-specific t-RNA-modifying enzyme, tRNA5-methylaminomethyl-2thiouridylate methyl-transferase, and its mutation causes mitochondrial translation defect (3). The 421-aa-long protein encoded by the TRMU gene participates in the modification of mitochondrial t-RNAs. The encoded protein catalyzes the 2-thiolation of uridine, resulting in the formation of 5-taurinomethyl-2-thiouridine (4).

In previous studies, patients having heterozygous mutations were either compound heterozygous or had the second mutation on another allele.

The heterozygous mutation in the TRMU gene has previously been reported in a patient affected with acute liver failure due to non-expressing maternal allele (4). Patients carrying two missense mutations seem to have a better prognosis than patients carrying at least one frameshift or splicing mutation. Our case had only one missense mutation (3).

The presence of increased serum lactate is consistent with mitochondrial respiratory function defect. With supportive care, patients who survive the initial acute episode can recover and show normal development (5).

The TRMU protein requires sulfur for its activity, supplied by the cysteine desulfurase enzyme. Cystathionase is the rate-limiting enzyme for the synthesis of L-cysteine from L-methionine (6). The activity of the rate-limiting enzyme cystathionase is very low at birth and increases slowly during the first few months of life. Metallothionein, a source of cysteine, is at its peak at birth and declines rapidly during the first month of life (7). Cysteine supplementation increases sulfur availability for TRMU activity and thus increases thiouridylation levels of mt-tRNAs. Dietary- and metallothionein-derived cysteine may provide some protection during the first month of

Table 1. *Results of the serial investigations.*

Parameter	Unit	Ref. Range	Age of the Child				
			Day53	Day 60	Day 75	Day 150	Day 221
ALP	IU/L	80-310	915	679	618	703	196
AST	IU/L	0-40	143	147	406	124	38
ALT	IU/L	0-40	82	112	269	114	26
S. bilirubin (T)	mg/dl	0-1	7.6	7.9	6.7	0.4	0.76
S. bilirubin (D)	mg/dl	0-0.3	4.3	4.3	3.9	0.2	0.35
S. Protein	g/dl	6-7.5	4.8	4.7	5	5.5	6.9
PT	Seconds	11-15	28.27	24.84	22.32	13.32	13.1
INR	-	<1.5	2.1	1.87	1.76	1.01	0.99
S.GGT	U/L	10-73	138				
S. Ammonia	µg/dl	18-86	109				
ABG (pH)		7.35-7.45	7.12	7.31	7.39		
P_{CO2}	mmHg	35-45	29	31	38		
HCO_3^-	mEq/L	22-26	9.1	15	23		
Anion Gap	mEq/L	12-16	22	18	12		
Chloride	mEq/L	97-107	107	106	104		
Sodium	mEq/L	135-145	136	139	139		
S. Lactate	mmol/L	0.2-2	12.3		1.4		

ALT Alanine aminotransferase; ALP Alkaline phosphatase; ABG Arterial blood gas analysis; AST Aspartate aminotransferase; D Direct; GGT Gamma glutamyl transpeptidase; S Serum; T Total.

life. After 3-4 months of age, cystathionase enzyme activity rises. L-cysteine powder (300 mg/kg/day) and N- acetylcysteine (70 mg/kg/day) can be considered in infants diagnosed with TRMU deficiency as it reduces the need of liver transplantation (2).

Most patients with TRMU gene mutation present at 2-4 months of age (8). Typical age of presentation, absence of multi-organ involvement, transient involvement, and lactic acidosis are clues to the diagnosis. The infants with TRMU mutation are managed with supportive measures. Once the patient survives this period, the recovery could be complete and the child is expected to have normal development. Our patient followed this pattern.

Conclusion

The treating doctors need to consider the diagnosis of TRMU mutation as a cause of hepatopathy when the above-mentioned diagnostic clues are present. This will ensure that time and other resources are not unnecessarily spent and attention is focused on the management of hepatopathy, as this alone can provide gratifying results. If the recovery is delayed or slow, therapeutic measures such as supplementation with L-cysteine powder and N-acetylcysteine can be considered in selected patients to obviate the need for liver transplantation.

Limitation

We could not find the second allele carrying the mutation, as sensitivity of NGS assay to detect large heterozygous deletions/duplications is low. Whole exome sequencing would have been ideal for confirmation. Also, sequencing the variant in parents and other family member would be helpful to confirm the significance.

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Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication
Informed consent was obtained from the patient.

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