ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 06 | June - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CASE REPORT ON RARE DISEASE: TRMU DEFICIENCY-TRANSIENT INFANTILE LIVER FAILURE (LFIT)

Paediatric Medicine

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ABSTRACT

Transient infantile liver failure (LFIT) is a rare genetic disorder which has autosomal recessive inheritance and is characterized by acute hepatic failure. It is due to TRMU gene mutation, which encodes a mitochondrial enzyme. We report a case of a 7-month-old infant with Transient infantile liver failure (LFIT) and discuss its clinicopathological features, diagnostic workup and also the available therapies. LFIT generally presents in the first six months of life as acute hepatic failure with jaundice, vomiting, ascites, poor feeding, and failure to gain adequate weight; along with biochemical hepatic derangements. Since it is due to defect in the mitochondrial respiratory chain, an important investigation which points towards the diagnosis is elevated serum lactate. Management of this condition is challenging; however, results are encouraging with appropriate supportive treatment.

KEYWORDS

Transient infantile liver failure (LFIT); acute hepatic failure; TRMU gene mutation

INTRODUCTION

Transient infantile liver failure (LFIT) is a genetic disorder caused due to defect in the mitochondrial respiratory chain. It is due to mutation in the TRMU gene located on chromosome 22q13, and results from substitution of methionine in place of valine at codon 279. The TRMU (tRNA mitochondrial 2-thiouridylase) gene encodes a mitochondrial tRNA-modifying enzyme, and a defect in this mechanism results in hepatic dysfunction, resulting in hepatic failure. *TRMU* mutations in infantile mitochondrial hepatopathy were first reported by Zeharia et al. in 2009 by homozygosity mapping in a cohort of 13 patients of predominately Yemenite Jewish origin (OMIM 610230) (Zeharia et al. 2009). To date, 62 individuals (60 probands and two at-risk sibs) have been identified with biallelic pathogenic variants in *TRMU* [Zeharia et al 2009, Schara et al 2011, Uusimaa et al 2011, Gaignard et al 2013, Grover et al 2015, Indolfi et al 2017, Gil-Margolis et al 2018, Sala-Coromina et al 2020, Murali et al 2021, Vogel et al 2023].

CASE REPORT

A 7-month-old male child, presented to emergency department with the complaints of fever, abdominal distention, vomiting and yellowish discoloration of eyes and urine. Patient had similar complaints at 3 months of age for which parents had consulted paediatric gastroenterologist. Patient's liver functions were deranged at that time and USG abdomen was normal except for mild hepatomegaly. Patient was managed for cholestasis and advised further workup for metabolic liver disease. Patient was a single child, born out of a 3rd degree consanguineous marriage and mother had two spontaneous abortions previously. Birth events were uneventful, and patient had normal growth and development till 3 months of age, after which there was inadequate weight gain.

On examination, patient had icterus, mild pallor and abdominal distention due to ascites. Patient was admitted in PICU. Relevant investigations were sent and were suggestive of acute hepatic failure-elevated liver enzymes, deranged prothrombin time (PT) and activated partial thromboplastin time (aPTT), raised bilirubin (conjugated), raised blood ammonia. USG abdomen was suggestive of hepatomegaly with gross ascites. Ascitic tapping was done and fluid investigations were suggestive of transudative type of ascites. Paediatric gastroenterologist opinion was also taken and advised to rule out tyrosinemia, galactosemia, PFIC and hepatic vein obstruction. Hepatic and portal vein doppler were within normal limits. CECT abdomen was done which was suggestive of hepatomegaly with liver have irregular margin and gross ascites. Serum GGT levels were elevated along with elevated alpha feto protein. Blood gas analysis was within normal limits. Serum lactate was raised. Urinary succinyl acetone levels were sent due to suspicion of tyrosinemia and were within normal limits. There was no evidence of any other system involvement. While the above-mentioned investigations were being done, patient was kept under galactose free diet. Management of cholestasis was continued, and Vitamin K given and fresh frozen plasma transfused. Therapeutic ascitic tapping done to relieve respiratory distress due to gross ascites. Patient's whole exome sequencing was sent.

Whole exome sequencing reports were suggestive of Transient infantile liver failure (LFIT). Hence patient has been started on N-acetyl cysteine. His clinical condition has improved post initiation of this therapy, although biochemical derangements are yet to improve. Liver transplantation was originally planned, however it has been deferred for now in view of improvement.

Gene (Transcript)	Location	DNA/ Protein Change	Zygosity	Inheritance	Classification	Associated Diseases / OMIM
TRMU (+) NM_018006	Exon 8	c.835G>A p.(Val279Met)	Homozygous	Autosomal Recessive	Pathogenic	Liver failure, transient infantile (#613070)

DISCUSSION

Acute liver failure (ALF) is a rapid deterioration of liver function in a person who has no pre-existing liver disease. Acute liver failure in infancy is a life-threatening condition manifested by poor feeding, vomiting, jaundice, distended abdomen, haemorrhagic diathesis, irritability, and hypoactivity.[1] It can be due to various causes such as infectious, toxic, inborn errors of metabolism and genetic. Metabolic and genetic disorders need to be considered in infants with poor weight gain and positive family history who present with the above manifestations once infections and toxins have been ruled out.

Among these disorders, defects in the mitochondrial respiratory chain can induce a heterogeneous range of clinical and biochemical manifestations. Hepatic involvement includes acute fulminant hepatic failure, microvesicular steatosis, neonatal non-alloimmune haemochromatosis and cirrhosis.[2] The finding of hyperlactatemia directs the diagnosis toward mitochondrial respiratory chain disorders, and in about half of the patients there is a defect in the mtDNA synthesis machinery, resulting in mtDNA depletion.[3] The genes for these include *POLG*, *DGUOK*, and *MPV17*. Mutations in these genes results in liver failure often manifested in the first year of life, hence termed as infantile liver failure. However, in recent years, mutations in *TRMU* gene encoding the mitochondrial tRNA-specific 2-thiouridylase have also been found related to infantile liver failure related to mitochondrial respiratory chain defects.[4] In this, there is a combined defect of respiratory chain complexes without

mitochondrial DNA depletion.

TRMU gene defect results in Transient infantile liver failure (LFIT), a genetic disease with autosomal recessive inheritance. Patients with LFIT generally become symptomatic at 2 to 4 months of age, and have acute liver dysfunction, presenting with jaundice, vomiting, poor feeding, poor weight gain, ascites. Laboratory parameters include elevated hepatic enzymes, deranged coagulation profile, decreased liver synthetic function, hyperammonemia, hyperlactemia, hypoglycemia. There can be hepatomegaly with/without ascites. The liver dysfunction progresses to acute hepatic failure if untreated. However, with proper supportive treatment, liver functions and metabolic derangements improve. Clinical and biochemical improvement starts after 2–3 weeks, and liver functions return to normal within 3-4 months.[1] An encouraging feature of this clinical presentation is that the hepatic failure can be reversible with appropriate supportive treatment. However, long-term neurological and hepatic outcomes are yet to be defined.[2]

This disease has no cure. Supportive therapies are the mainstay of management. These include nutritional support, treatment of metabolic acidosis, hypoglycemia, hypoalbuminemia, coagulopathy, associated comorbidities, as well as genetic counselling and physiotherapy. [5] Medications to avoid include those increase metabolic demand (such as corticosteroids) or inhibit mitochondrial activity (such as valproic acid and prolonged propofol infusion) and fasting, as it increases metabolic demand and may exacerbate hypoglycemia. Consider avoiding acetaminophen (paracetamol) during episodes of liver dysfunction based on theoretical concerns for oxidative stress. [6]

Cysteine is being evaluated as a possible therapy for this disorder. L-cysteine, with or without N-acetylcysteine (NAC), should be initiated as soon as a diagnosis of TRMU deficiency is suspected. Because the endogenous supply of cysteine is normally low in the first few months of life and because the enzyme TRMU requires adequate amounts of cysteine to enable the essential function of thiolating mitochondrial transfer RNAs, the initial manifestations of TRMU deficiency (primarily hepatopathy) may be reversed, ameliorated, or in some cases prevented by exogenous oral cysteine supplementation in infants with TRMU deficiency.[6] In a study conducted by Murali et al (2021) six patients with TRMU deficiency were started on cysteine (either N acetylcysteine and/or L-cysteine), including two who were diagnosed pre-symptomatically, and of these 4 have survived the initial hepatic insult and are on cysteine.[7] However, no studies have been conducted on the long term implication of cysteine supplementation.

Orthotopic liver transplantation is indicated when hepatopathy does not respond to medical interventions. However, there was no difference in overall individual survival based on liver transplantation.[8]

CONCLUSION

Transient infantile liver failure (LFIT) being a rare genetic disorder presents a diagnostic as well as therapeutic challenge to the treating physician. A high index of suspicion is required in patients with infantile liver failure of suspected metabolic origin with persistent lactic acidosis. Use of cysteine as a therapeutic modality appears to be promising.

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