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Case report

Compound heterozygous *TRMU* gene mutations in an infant with transient cholestasis and hyperlactatemia

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Abstract

The authors present an atypical case of an infant with unremarkable familiar, birth, and neonatal history who developed a mild/benign form of transient cholestasis. At admission, second- and third-level assessments were conducted, mitochondrial respiratory chain disorders were excluded. The patient was accurately and promptly diagnosed through a clinically driven genetic test. The genetic analysis evidenced a compound heterozygous mutation c.383A>G (p.Tyr128Cys) of maternal origin and c.835G>A (p.Val279Met) of paternal origin in the *TRMU* gene associated to transient infantile liver failure, a condition known for its progressive and sometimes fatal prognosis. Biochemical test and patient's clinical evolution were both good and there was no evidence of liver failure or dysfunction of other organs. This is the first-ever reported case of a patient with a *TRMU* pathological compound mutation with such good clinical evolution.

Keywords

Infant, cholestasis, genetic, *TRMU*, mutation, prognosis.

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Introduction

Neonatal cholestasis is never physiological; it is a rare disorder that affects about 1 in every 2,500 term infants and it is characterized by impaired bile flow [1]. Cholestatic disorders, most commonly presenting early in life with conjugated hyperbilirubinemia, should rise an alarm for hepatobiliary/metabolic disorders [2], such as glycogen storage disorders, mitochondrial disorders, and nonalcoholic fatty liver disease [3, 4].

The spectrum of liver involvement in metabolic disorders is wide, presentation may vary from acute liver failure, cholestasis, cirrhosis or chronic liver failure [5]. Acute liver failure accompanied by cholestasis and lactic acidemia has been associated with mitochondrial DNA (mtDNA) depletion [4]. Mitochondrial diseases (MD) collectively describe a diverse group of inheritable disorders that invariably affect mitochondrial respiratory chain function and cellular energy production. Together they represent the most common cause of inherited metabolic disease; the onset may occur at any age and with a wide spectrum of clinical manifestations. MD are caused by dysfunction of the mitochondrial oxidative phosphorylation system and can be the result of mutations both in mtDNA and in nuclear DNA (nDNA) [6].

Homozygous or compound heterozygous mutations of nuclear *TRMU* gene are responsible for a mitochondrial dysfunction called transient infantile liver failure (Liver Failure, Infantile, Transient – LFIT; OMIM #613070), which is a progressive and sometimes fatal condition [7]. Nuclear *TRMU* gene encodes for the transfer RNA (tRNA) 5-methylaminomethyl-2-thiouridylate methyltransferase, which is involved in mitochondrial tRNA (mt-tRNA) modification [7-9].

Custom, panel-based next-generation sequencing (NGS) strategies can be very successful in providing a rapid genetic diagnosis in cholestatic disorders, but this success depends on the degree of characterization to ensure that the appropriate candidate genes are targeted [8].

Clinical features, biochemical markers and specific tissue biopsy can guide the characterization and investigation toward a specific pathway or group of genes responsible for a given phenotype. In these cases, a targeted gene sequencing panel has proven efficient and cost-effective [8] to reach diagnosis, genetic counseling, and access to reproductive options for patients and their families [1-25].

Case report

The proband, first-born of healthy unrelated parents was born small for gestational age at 41 gestational weeks from spontaneous eutocic birth after an uneventful pregnancy. Birth weight was 2,950 grams, length and head circumference were 50 and 33 cm, respectively. The patient developed neonatal maladaptation syndrome with transient respiratory difficulty, resolved with continuous positive airway pressure. Apgar score was 5-8-9 at 1'-5'-10', respectively. Neonatal physiological jaundice was observed in the first days of life. Expanded newborn screening and maternal viral serology were negative.

At 2 months, the patient presented jaundice with pale stools and hyperchromic urine. Liver edge was palpable at 2 cm from the costal margin. Overall general conditions were unremarkable; no cutaneous stigmata of liver disease were evidenced.

First-tier laboratory tests confirmed the suspicion of cholestatic jaundice with 12.6 mg/dL of total bilirubin and 9.5 mg/dL of conjugated bilirubin, mild hypoalbuminemia, mild metabolic acidosis with hyperlactatemia and mild coagulopathy that gradually responded to vitamin K (**Tab. 1**). Abdominal ultrasound documented an enlarged liver with coarsened texture without focal lesions. Intra- and extra-hepatic bilious tracts were not dilated.

Serum alpha-1-antitrypsin, erythrocyte galactose-1-phosphate urydyltransferase and thyroid

Table 1. Summary of the patient's main laboratory tests at the first hospitalization.

Laboratory test		Patient's values	Normal values
pH		7.328	7.36-7.42
HCO_3-		20.5	24-32
Base excess		–3.9	–1.5-+2.5
Lactate		7.2 mmol/L (up to 9.6 mmol/L)	0.5-1.6 mmol/L
ALT		143 U/L	21-72 U/L
AST		125 U/L	17-59 U/L
Total bilirubin		12.6 mg/dL	0.2-1.3 mg/dL
Direct bilirubin		9.5 mg/dL	-
GGT		145 U/L	10-71 U/L
Serum bile acids		2,250 µmol/L	0-10 µmol/L
Alkaline phosphatase		571 U/L	145-320 U/L
Albumin		2.1 g/dL	3.5-5 g/dL
PT INR		2.01	< 1.15
PTT ratio		1.74	0.80-1.2
Creatinine kinase		36 U/L	55-170 U/L
Ammonia		41 µmol/L	9-30 µmol/L
Alpha-1-antitrypsin		94 mg/dL	100-200 mg/dL
Alpha-fetoprotein		> 90,000 IU/mL	323 ± 278 IU/mL
Infective serologies (CMV, EBV, *Toxoplasma gondii*, HSV1, HSV2)		negative	NA
Plasma alanine		862 µmol/L	239-345 µmol/L
Urinary organic acids	**Lactic acid**	677 mM/M ur creat	0-35 mM/M ur creat
	Pyruvic acid	330 mM/M ur creat	0-12 mM/M ur creat

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CMV: Citomegalovirus; EBV: Epstein Barr virus; GGT: gamma-glutamyl transpeptidase; HSV1: Herpes simplex virus 1; HSV2: Herpes simplex virus 2; INR: international normalized ratio; NA: not applicable; PT: prothrombin time; PTT: partial thromboplastin time; ur creat: urinary creatinine.

function were normal. Viral serologies for CMV, EBV, *Toxoplasma gondii*, HSV1 and HSV2 were negative. Echocardiogram (*ostium secundum*), spine radiogram and ophthalmological examination ruled out Alagille syndrome stigmata. The child was fed with medium chain triglycerides-enriched formula and started ursodeoxycholic acid and liposoluble vitamins supplementation. Transient hyperlactatemia (up to 9.6 mmol/L) and poor fasting tolerance with episodes of morning hypoglycemia were evidenced; growth hormone and cortisol levels were normal.

Second-tier biochemistry tests included a metabolic work-up (see **Tab. 1**). High levels of alanine (862 µmol/L) related to hyperlactatemia, with increased levels of glycine, proline and branched chain amino acids (leucine, valine, isoleucine), tyrosine and methionine. Urinary organic acids revealed ketonuria with increased excretion of lactic and pyruvic acids (677 and 330 mM/M urinary creatinine, respectively), high levels of 3-OH butyric and 3-OH isovaleric acids and dicarboxylic aciduria.

A liver biopsy was conducted. The liver histology did not show any signs of cholangiopathy; biliary atresia and alpha-1-antitrypsin deficiency were excluded. Polymorphic hepatocytes with vacuolated cytoplasm, biliary metaplasia in periportal area and PAS-positive diastase-sensitive intracytoplasmic inclusions, suggestive of a metabolic disease, were evidenced. Macro-micro vesicular steatosis of 5%, Kupffer cells hyperplasia, some canalicular thrombi and focal parenchymal siderosis of grade 1-2 were also detected (**Fig. 1**).

Glycemia and insulin levels were normal before and after meals, blood lactate was slightly increased. A fasting test followed by glucagon administration showed low response to glucagon (serum glucose raised from 57 mg/dL to 76 mg/dL), blood lactate values remained mildly elevated but stable (2.43-3.06 mmol/L); modest ketonuria with dicarboxylic aciduria was evidenced.

Plasma acylcarnitines were normal under stress, excluding beta-oxidation deficiency. Chitotriosidase indicative for Gaucher or Niemann Pick

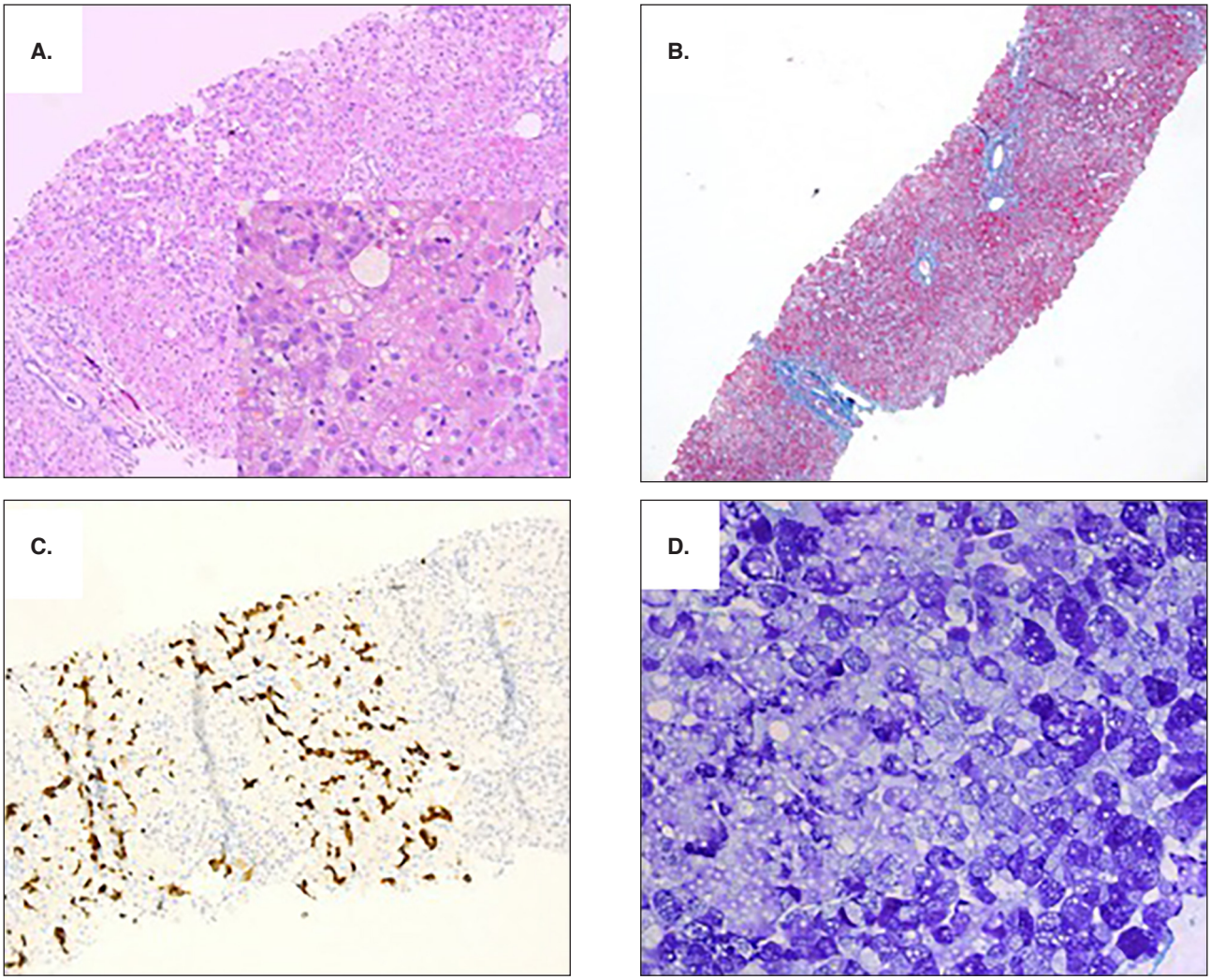

Figure 1. A. Hematoxylin and eosin, 10-20x: polymorphic hepatocytes with enlarged, eosinophilic vacuolated cytoplasm, aspects of canalicular cholestasis and rosette formation. **B.** Trichrome stain, 5x: conserved lobular architecture with mild portal fibrosis. **C.** Cytokeratin 7 stain, 10x: ductular proliferation and biliary metaplasia of periportal hepatocytes. **D.** Periodic Acid-Schiff (PAS), 20x: PAS-positive, diastase-sensitive hepatocyte cytoplasmic inclusions.

diseases were also normal. Molecular analyses for glycogen storage disease types Ia, Ib, III and IXa were negative.

The anomalies of plasma amino acids and urinary acids suggested mitochondrial impairment; therefore, NGS-based targeted gene panel was performed. The analysis evidenced biallelic variants c.383A>G (p.Tyr128Cys) of maternal origin and c.835G>A (p.Val279Met) of paternal origin in *TRMU*, associated to LFIT.

Therapy with ubidecarenone and vitamin C supplementation was started. Serum bilirubin decreased spontaneously until normalization at the age of 4 months. At 1-year-old, gamma-glutamyl transpeptidase and transaminases reached near-normal serum concentrations.

After over 2 years of clinical follow-up, the patient's general condition is good, with adequate growth parameters, psychomotor development, normal glycemic controls and good fasting tolerance. At physical examination and abdominal ultrasound, there is still evidence of mild hepatomegaly.

Discussion

The pathophysiology of MD is complex and involves genetic mutations in mtDNA and nDNA. MD are clinically heterogeneous, can occur at any age and can manifest with a wide range of clinical symptoms. Diagnosis often relies on genetic testing, in addition to histochemical and biochemical analysis of tissue biopsies [6].

Mitochondrial hepatopathies in early infancy are generally associated to biallelic pathogenic variants in nuclear genes *MPV17*, *POLG1* and

DGUOK (OMIM *137960, *174763 and *601465) with a defect in the mtDNA maintenance, resulting in depletion of the mtDNA [5, 25]. The clinical presentation of mitochondrial hepatopathies is very variable and may present as neonatal acute liver failure, hepatic steatohepatitis, cholestasis or cirrhosis with chronic liver failure of insidious onset with extrahepatic involvement often accompanied by neurodevelopmental delay [5].

Homozygous or compound heterozygous mutations in the nuclear *TRMU* gene are responsible of LFIT. Nuclear *TRMU* gene, located in the short arm of chromosome 22 in the region 13, encodes for the tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase. This enzyme participates in the modification of mt-tRNAs, catalyzing the addition of a sulfur-containing thiol groups to the wobble position of some specific mt-tRNAs.

Particularly, the tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase is responsible for the thiouridylation of mitochondrial encoded glutamate tRNA (mt-tRNAGlu), mitochondrial encoded glutamine tRNA (mt-tRNAGln) and mitochondrial encoded lysine tRNA (mt-tRNALys). A defect in this protein may impair the translation of mtDNA-dependent complexes and cause a combined mitochondrial respiratory chain defect [7, 15].

LFIT is characterized by distended abdomen with hepatomegaly, jaundice, vomiting, poor feeding and hypotonia in the first months of life. The disease is usually progressive and eventually fatal; if the patient survives the acute liver failure, a clinical and biochemical improvement is evidenced after 2-3 weeks of supportive care and the liver's function returns normal within the next 3 to 4 months. However, the normalization of the liver volume may take longer, from 3 months to 3 years [7, 15, 17].

The natural history of LFIT suggests a possible pathophysiological explanation to the spontaneous recovery within the first years of life. Cystathionase, which role is to break down cystathionine into cysteine, does not reach mature levels of activity until 3 months of age. Cysteine levels are thus low in the first months of life. Cysteine provides sulfur for the TRMU activity. Therefore, the combination of temporally low levels of cysteine and the presence of pathogenic variants in *TRMU* correlate with poor thiouridylation of mt-tRNAs, which interferes with mitochondrial protein translation, and leads to clinical manifestation of acute liver failure in infants [18, 19]

At least 30 cases of LFIT due to mutations in *TRMU* have been reported. Apart from the typical findings, one child was described with an isolated reversible myopathy, another patient with a fatal Leigh syndrome and cardiomyopathy without liver involvement, and a recently reported case with concomitant ichthyosis [16, 20, 21].

The overall good clinical conditions of our patient, the absence of hypotonia and progression to liver failure are very peculiar. The patient's first-tier blood tests documented cholestasis, hypertransaminasemia, high alpha-fetoprotein, hypoglycemia and hyperlactatemia (**Tab. 1**), as reported in the scientific literature, that improved through time and there was no evidence of the typical evolution to liver failure. The presence of liver enlargement has been reported in all cases, including our own.

Only 2 infants with TRMU deficiency were reported with a history of severe cholestasis without liver failure, both in a context of an advanced liver disease with cirrhosis at the histological examination in patients carrying at least one frameshift or splicing mutation. Milder presentations [15] have been reported in patients with missense mutations. Our patient is the mildest case ever reported, with primarily cholestatic liver disease, hepatomegaly and acholic stools that mimicked a biliary atresia, with a synthetic function within normal range.

The biochemical analysis suggested a mitochondrial defect (hyperlactatemia with increased levels of glycine, proline, and branched chain amino acids) but this was not enough to rule out a surgical cause, therefore liver biopsy was retained necessary. Liver histology is seldom contributory in intrahepatic forms of cholestasis. In our case, polymorphic hepatocytes with PAS-positive diastase-sensitive intracytoplasmic accumulation with no signs of cholangiopathy were described. Liver histology of children with LFIT are generally characterized by fibrosis, irregular cirrhosis with nodulation, cholestasis, macrovesicular steatosis with oncocytic hepatocytes [7, 15. 16].

Atypical findings at the biopsy were reported by Schara et al. who reported the case of a patient with moderate reticular fibrosis and incomplete cirrhosis with micronodular structure and swollen hepatocytes [17]. Another atypical finding, described by Grover et al., was a notable copper deposition in periportal hepatocytes, portal fibrosis, cholangiopathy and some evidence of steatosis [22].

A clinically oriented genetic approach with genetic variant filtering and analysis driven by phenotype should be indicated in children with persistent cholestasis after biliary atresia and alpha-1-antitrypsin deficiency are excluded [2]. This type of protocol enhances accurate diagnosis and adequate treatment in children with liver disease of unknown etiology, providing at the same time an appropriate family counseling [12, 23].

Regarding treatment, Soler-Alfonso et al. suggested that L-cysteine supplementation may improve liver function and reduce the need for liver transplantation in patients with TRMU deficiency [24]. A recent study concluded that, when a TRMU deficiency is suspected, exogeneous cysteine should be administered until this condition is ruled out, as this is a low-risk approach that may increase survival and mitigate the severity of the disease course [25]. A diagnosis of LFIT in an infant due to mutations in *TRMU* does not preclude the patient from listing for liver transplantation. As for other metabolic multi-organ diseases, the decision to list such patients should be taken case-by-case, according to ethical issues and prognosis [8].

Conclusions

A mitochondrial respiratory chain disorder should be suspected and ruled out in children with transient cholestatic hepatopathy, especially if hyperlactatemia is evidenced at the laboratory work-up. To reach diagnosis promptly and accurately, a clinically oriented genetic approach is recommended. In the presented case, the genetic analysis evidenced a compound heterozygous mutation in *TRMU* associated with liver failure specifically in the first months of life. This condition may be fatal, but luckily it is transient in most patients, with a complete clinical and biochemical resolution within the next months or years of life. However, mutations in these gene may not necessarily evolve to liver failure, it may sometimes be associated to a much milder presentation, as evidenced in our case, where the patient presented only with transient cholestasis and hyperlactatemia.

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Declaration of interest

The Authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. The Authors report no involvement in the research by any sponsors that could have influenced the outcome of this work.

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