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Original Article - Case Study

Reversible mitochondrial infantile liver failure with hemophagocytic lymphohistiocytosis associated with a TRMU gene mutation

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ABSTRACT

Mitochondrial diseases are a clinically heterogeneous group of multisystem disorders caused by mitochondrial dysfunction. Hepatic involvement is a common feature in neonatal mitochondrial hepatopathies, which may manifest as acute liver failure, hepatic steatohepatitis, cholestasis, or even as chronic liver failure of insidious onset. Mitochondrial diseases are usually severe and rapidly progressive conditions and eventually fatal. However, some of the rare forms show remarkable spontaneous recoveries. The diagnostic process is complex, requiring clinical, biochemical, histological, and genetic investigations. Mutations in several mitochondrial DNA (mt-DNA) and nuclear genes involved in mt-DNA stability and mitochondrial protein synthesis machinery have been associated with mitochondrial disorders. Recently, mutations of *TRMU* gene encoding mitochondrial tRNA-specific 2-thiouridylase defines the pathomechanism of mitochondrial protein translation defect in the neonatal period presenting with early-onset, reversible liver disease. Here, we report the clinical, biochemical, and genetic findings from one Arab Yamani child presenting with hepatopathy, hyperlactatemia and respiratory chain defect associated with hemophagocytic lymphohistiocytosis, a feature which has not been described in previously reported cases. The aim was to have a prompt definitive genetic diagnosis to provide timely clinical management, decrease morbidity, and improve the survival of the patient. Utilizing next-generation sequencing techniques we identified the pathogenic biallelic mutation c.835G>A (p.Val279Met) in *TRMU* gene by whole exome sequencing. Since spontaneous recovery is a rare feature in mitochondrial liver disorders, early identification of underlying *TRMU* mutation can influence clinical management decisions. Our results add to the repertoire of a small number of cases with *TRMU* mutations reported in mitochondrial liver diseases, for further elaboration of genotype-phenotype correlation.

Keywords

Reversible liver disease, pathogenic mutation, hemophagocytic lymphohistiocytosis, autosomal recessive, *TRMU*.

Abbreviations

Mitochondrial DNA (mtDNA); respiratory chain deficiency (RIRCD); hemophagocytic lympho-histiocytosis (HLH); whole exome sequencing (WES); below the costal margin (BCM); aspartate aminotransferase (AST); alanine aminotransferase (ALT); gamma-glutamyl transferase (GGT); lactate dehydrogenase (LDH); creatine phosphokinase (CPK); prothrombin time (PT); partial thromboplastin time (PTT); international normalized ratio (INR); magnetic resonance imaging (MRI); American College of Medical Genetics and Genomics (ACMG); Human Gene Mutation Database (HGMD).

INTRODUCTION

Mitochondrial diseases are a clinically heterogeneous group of progressive, multisystem disorders, which are caused by mitochondrial dysfunction. Mitochondrial pathologies may be caused by mutations (acquired or inherited) in mitochondrial DNA (mtDNA), or in nuclear genes coding for mitochondrial elements. They can also be the result of acquired mitochondrial dysfunction due to drugs, infections, or other environmental causes. The prevalence of mitochondrial diseases is estimated to be at least 1:5000 individuals[1]. The clinical spectrum is very diverse, ranging from a multi-organ, life-threatening condition at birth to the onset of a single symptom in middle age, demonstrating interfamilial and intrafamilial variations even among family members with the same mutation. This makes the prognosis unpredictable. Mitochondrial dysfunctions are known to be linked to a large proportion of inherited human disorders, such as neurodegenerative disorders, neurometabolic diseases, cardiovascular disorders, cancer, and obesity[2]. The clinical heterogeneity is explained by the underlying genetic heterogeneity, and the genetic cause can be found in the mitochondrial or in the nuclear genome.

Mitochondrial disorders presenting in neonates have hepatopathy as a frequent clinical presentation[3]. The most commonly associated hepatic features include, but are not limited to: cholestasis, cirrhosis, coagulopathy, non-alloimmune neonatal hemochromatosis and fulminant hepatic failure[4]. In most of the cases, liver biochemical analysis shows a combined deficiency of mtDNA-dependent complexes (I, III, IV, and V), with depletion of mtDNA copy number, resulting in an overall reduction in respiratory competency of affected cells or tissue. These results are due to mutations in nuclear-encoded genes associated with mtDNA stability, mainly *DGUOK* (MIM 601465), *POLG* (MIM 174763), *SUCLG1* (MIM 611224) and *MPV17* (MIM 137960) genes[5-8]. The mtDNA depletion is a common cause of severe childhood hepato/encephalomyopathies and is accountable for 50% of combined respiratory chain deficiencies in childhood[9]. Less frequent cases are related to a defect in mitochondrial protein synthesis machinery, including mitochondrial maintenance, translation and/or transport, resulting in reduced activities of mtDNA-dependent complexes, but normal mtDNA copy number in the liver. Mutations of nuclear gene-encoding proteins *GFM1* (MIM 606639), *TUFM* (MIM 602389) and *TRMU* (MIM 610230), involved in mitochondrial protein translation, have been linked with the liver disorders in the neonatal period[10-12].

Most mitochondrial diseases are typically severe, progressive conditions with fatal outcome. However, a unique syndrome termed the reversible infantile respiratory chain deficiency (RIRCD; MIM 500009, previously called the reversible infantile cytochrome C oxidase deficiency) stands out by showing complete spontaneous recovery with the appropriate diagnosis and supportive treatment[13]. More recently, pathogenic biallelic homozygous or compound heterozygous *TRMU* gene mutations were identified by homozygosity mapping, followed by candidate gene sequencing, in a cohort of 13 cases of infantile reversible hepatopathy, predominately of Yemenite Jewish origin[12], postulating the possibility that mt-tRNA modifying factors may play an essential role in patients with combined respiratory chain deficiency.

Here, we report clinical, biochemical, and molecular findings in a 3 year-old-boy of Arab ancestry, presenting with hepatopathy associated with respiratory chain defect and hyperlactatemia, and a potential pathogenic biallelic *TRMU* mutation.

METHODS

A 3 years old patient with combined hepatic mitochondrial respiratory chain defect was presented to the Department of Genetics, at the King Saud Medical City, Riyadh, Saudi Arabia. He is an offspring of a consanguineous Yamani Arab couple with six healthy siblings and no history of abortions or deaths. Family history was without any preceding

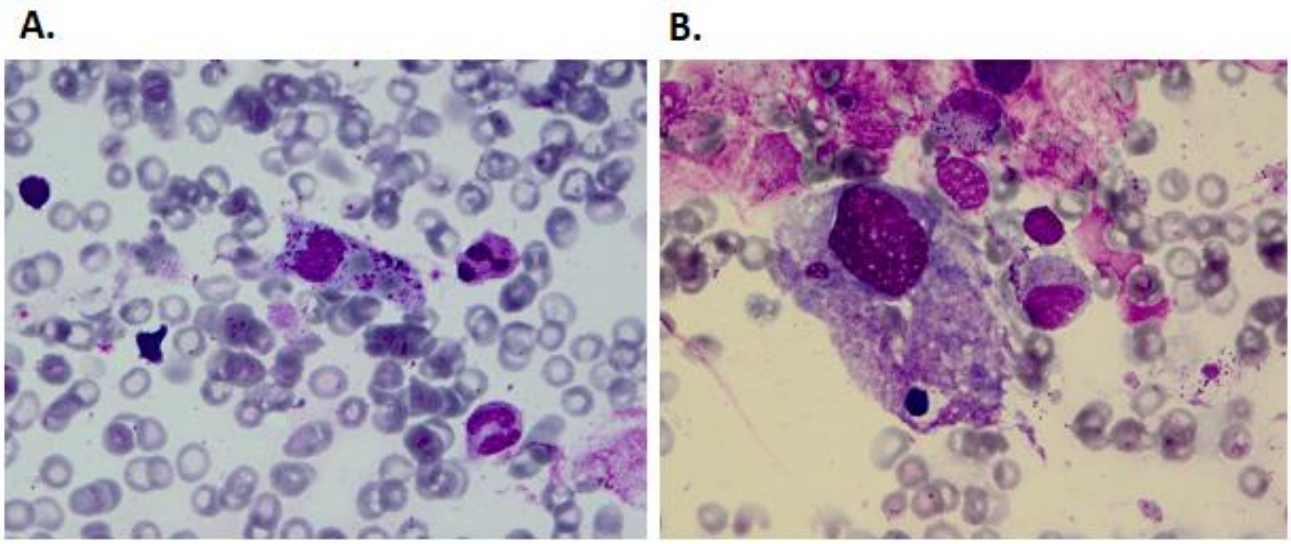

Figure 1. Stained macrophages with phagocytosis of blood cells;
A. A macrophage with phagocytosis of red blood cells and platelets; **B.** Macrophage with phagocytosis of blood elements (Wright stain, manually stained, King Saud Medical City Laboratories)

neurological or neuromuscular disorder or liver failure. He was born at full-term after an uneventful pregnancy and delivery (Apgar score 9/10) with no antenatal complaints. His weight was of 3.30 kg, the height of 48 cm and the head circumference of 34 cm. At 2 months of age, he presented with vomiting, poor feeding, fever, lethargy, and abdominal distension. No abnormal movement, skin lesions or rash was noticed. On clinical examination at 2 months of age, he was not dysmorphic and normal growth parameters were noted. He was pallor, having jaundice and generalized edema. There was no bleeding from any orifice with hepatomegaly (5 cm below the costal margin (BCM)), and splenomegaly (4 cm BCM) with rounded border, soft consistency, smooth surface, and ascites. Neurological examination revealed normal axial and peripheral tone and normal gait.

Laboratory investigations showed elevated liver enzyme aspartate aminotransferase (AST) 462 U/L, alanine aminotransferase (ALT) 213 U/L, total bilirubin 49 µmol/L, conjugated bilirubin 21 µmol/L, gamma-glutamyl transferase (GGT) 13 U/L, and lactate dehydrogenase (LDH) 229 U/L. The creatine phosphokinase (CPK) and alpha-fetoprotein were 39 UI/L and 1102061 UI/mL, respectively, and serum ferritin was 1281 ng/dl. Coagulation profile showed prothrombin time (PT) of 48 sec, partial thromboplastin time (PTT) of 81 sec, and an international normalized ratio (INR) of 5.8 sec. The metabolic analysis revealed recurrent hypoglycemia and hyperlactatemia (11.0 mmol/L with elevated lactate/pyruvate ratios (L/P 33, N ¼ 7–15)). Uric acid 261 µmol/L, LDH 299 U/L, IL2/CD25 (2,630 U/ml), and NK cell activity were decreased. Bone marrow aspirate showed a marked increase in foamy macrophages with increased hemophagocytic activity. Abdominal ultrasound disclosed average sized liver with normal echo pattern and regular outline with moderate ascites. The skeletal survey was unremarkable, and cerebral magnetic resonance imaging (MRI) was not performed. The patient was seen by a hematologist, treatment for hemophagocytic lymphohistiocytosis (HLH) as per HLH 2004 protocol was started with an improvement of fever, cytopenia, and organomegaly gradually within 6 weeks. Besides the distinct clinical features which suggested HLH, the biopsy of bone marrow showed hemophagocytosis, including phagocytosis of nucleated cells, marked increase in foamy macrophages with an increased hemophagocytic activity which strongly correlated with a diagnosis of HLH (Figure 1). During the time of initial presentation, consent was taken from the parent for performing the whole exome sequencing.

Molecular Analysis

This study was approved by the Ethics Committee of the King Saud Medical City, Riyadh, Saudi Arabia.

A blood sample in EDTA was collected from the patient, and written informed consent was obtained from the patient's parents. The sample was sent for diagnostic whole exome sequencing (WES). Briefly, WES was performed on the genomic DNA, using the Agilent SureSelect Target Enrichment workflow, which targets regions of interest from the DNA fragment library. The whole exome was sequenced on the Illumina HiSeq 2500 sequencing system with a minimum coverage of 30X of 95% of the target regions. The proband's exome DNA sequences were then mapped and compared to the human genome build UCSC (GRCh37/hg19) reference sequence. Saudi Molecular Diagnostics Laboratories, KFSH&RC, analyzed and annotated the proband's sequence, employing a pipeline that was developed in-house. Coverage assessment and quality for targeted coding exons, including splice junctions of the known protein-coding RefSeq genes are assessed. Exome analyses interrogate thousands of genetic variants in a proband using proprietary reference databases specifically customized to the Arab populations. A subset of these genetic variants is categorized using the American College of Medical Genetics and Genomics (ACMG)[14] guidelines to classify their clinical significance.

WES revealed a homozygous c.835G>A transition resulting in a Val279-to-Met substitution in a highly conserved amino acid residue in *TRMU* gene (NM_018006.5). Sanger sequencing was performed for the validation of the variant identified by WES. The identified substitution was scored "as damaging" for protein function by Provean and SIFT and predicted "as disease-causing" by MutationTaster *in silico* pathogenicity prediction tools. The mutant residue is bigger in size than the wild-type residue. 3D-structure prediction analysis for p.Val279Met mutation by project HOPE[15] predicts that Val279 residue is located on the surface of the protein, this mutation will disturb interactions with other molecules or other parts of the protein, which might affect the function of the protein.

RESULTS AND DISCUSSION

To date, more than 250 nuclear genes have been linked to mitochondrial diseases[16]. Once a mitochondrial disorder is suspected, the diagnostic procedure is challenging as there is no specific test to exclude or confirm the diagnosis. Nevertheless, it is of considerable significance for the patients and their families to establish a precise genetic etiology. Patients with acute infantile liver failure usually present with a clinically heterogeneous phenotype, often rapidly progress and could be a life-threatening condition. Patients often present with poor feeding, nausea, vomiting, distended abdomen, jaundice, hemorrhagic diathesis, irritability, and hypoactivity. Definite diagnosis is difficult due to non-specific clinical phenotypes, technical difficulties in obtaining and interpreting mitochondrial respiratory chain studies and underlying genetic heterogeneity of the mitochondrial defects. Improvement in the diagnostic pathway of rare mitochondrial respiratory chain defects has been possible with the advent of WES, which has revolutionized the diagnostic paradigm for patients with mitochondrial disease.

Mitochondrial tRNAs need to undergo several modification steps for their optimal function[17]. Nuclear *TRMU* gene on chromosome 22q13 encodes the mt-tRNA modifying enzyme mt-tRNA5-methylaminomethyl-2- thiouridylate methyltransferase (EC 2.1.1.61), which catalyzes the 2-thiolation of uridine at the wobble position of mitochondrial tRNALys, tRNAGlu, and tRNAGln[18]. This post-transcriptional modification of the uridine located at the wobble position has a pivotal role in the structure and function of tRNAs, including structural stabilization, aminoacylation, and thus contributes to efficient and precise codon recognition at the decoding site of small rRNA[19-21]. Defects of TRMU protein lead to a reduced 2-thiolation and decreased levels of mitochondrial tRNA, that may result in impaired translation of mtDNA-dependent complexes.

Mutations in *TRMU* gene have been identified as the etiology for acute liver failure in the patients at the time of birth until the age of 6 months. The availability of cysteine as an essential amino acid in the neonatal period is limited because of the physiologically low activity of the cystathionine gamma-lyase (cystathionase) enzyme in infants[22]. There is a window of time during 1 - 4 months of age whereby patients with *TRMU* mutations are at an increased risk of developing liver failure, as proposed by Zeharia et al.[12]. If left untreated without supportive care, it results in a fatality in infancy. When onset was later in infancy, and the liver failure could be successfully treated, no relapse occurred later in life. The early molecular diagnosis is significant as this could help to provide appropriate, timely clinical management, decrease morbidity, and

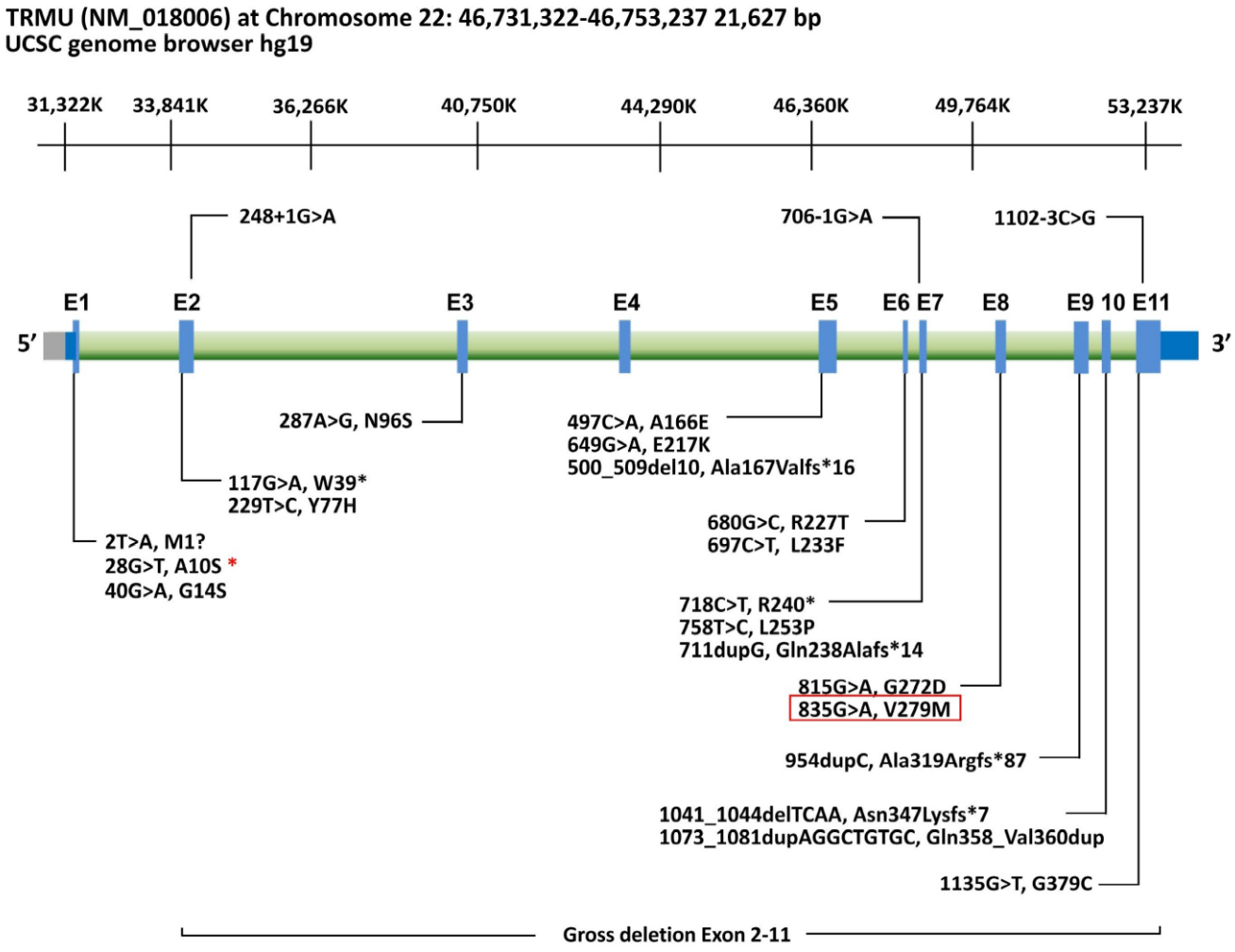

Figure 2. Schematic representation of the reported TRMU gene mutation in the Human Gene Mutation Database (HGMD; http://www.hgmd.cf.ac.uk). TRMU mutation with sign (*) acta as a modifier in patients with sensorineural deafness, carrying the homoplasmic m.1555G>A mutation in the mtDNA. Homozygous pathogenic TRMU mutation identified in our patient, c.835G>A (p.Val279Met) is boxed in red.

potentially improve survival rates. With supportive care, patients who survive the initial acute episode can recover and show normal development.

The clinical presentation of our infant is similar to other reported cases associated with *TRMU* mutations[12,23-25]. Our infant patient presented with acute hepatic failure and had a mild deficiency of MRC Complex IV on liver samples. This is a unique case since we found the first associated HLH with reversible acute liver failure in *TRMU* mutation in an Arab Yamani patient. Our patient required the supportive nutrition, and blood products were given as compensation for coagulopathy. HLH was managed according to HLH protocol 2004. He showed good response to treatment with HLH protocol 2004, initially for 8 weeks, and extend to continue more than 15 weeks with dexamethasone, which was tapered gradually plus etoposide and cyclosporine. No significant side effect has been reported, and his condition dramatically improved, resulting in a complete recovery. While he is still on regular follow up with routine blood investigations and radiological assessment at every 3 months, showing normal liver functiona, coagulation profile and normalized abdominal scan. No acute issues were reported, and no recent hospitalization was required. In the last visit to the clinic, about 2 months back, he was 3 years old, gaining 15.7 kg in weight and his height was 102 cm, all on 5th centile and with good psychomotor and developmental performance.

KEY POINT

- **This study found the first associated hemophagocytic lymphohistiocytosis with reversible acute liver failure with a TRMU gene mutation in an Arab Yamani patient.**

The missense homozygous mutation p.Val279Met identified in our patient has been previously reported in compound heterozygous with other variants; p.Val279Met/p.Ala167Valfs*16, p.Val279Met/c.1102-3C>G, and p.Val279Met/c.248+1G>A[12,25,26]. Together with the mutation identified in our patient, a schematic representation of *TRMU* gene with all previously reported mutations in the Human Gene Mutation Database is presented in Figure 2.

Considering the emerging genotype and phenotype correlation for *TRMU* mutations, it is postulated that the patients harboring two missense mutations (except in first Met residue) have a better chance of surviving than the patients carrying at least one frameshift or splicing mutation[25]. The patient in our study carrying a biallelic missense variant recovered in a few months, providing further evidence that this condition is one of the few mitochondrial disorders with a life-threatening onset, although the liver failure can still be reversed due to the timely intervention and appropriate supportive treatment.

CONCLUSION

This case highlights the importance of a prompt diagnosis and highlights the *TRMU* mutations as a potential cause of acute liver disease in infants. Proper diagnosis of mitochondrial disorders is essential for the treatment of these patients, prognosis, and to provide informed counseling. Further reports of additional patients with TRMU anomalies are necessary to fully elucidate the prognostic factors, constituting further progress in the field of mitochondrial medicine.

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Conflict of Interest

The authors declare no conflict of interest.

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