Waleed Altwaijri et al, 2020;3(1):36–40.
https://doi.org/10.24911/JBCGenetics/183-1580893176

CASE REPORT

A new pathogenic homozygous variant in deoxyguanosine kinase gene cause vital progressive liver failure in a neonate: case report

Maher Mohammed Al-Hatlani[1*], Sharifah Ahmed Othman[2]

ABSTRACT

Background: Mitochondrial DNA-depletion syndromes (MDDS) usually present with a wide spectrum of clinical manifestations, such as weakness, hypotonia, developmental delay, and/or seizures, and are categorized as myopathic, encephalomyopathic, hepatocerebral, or multisystemic. The condition is typically fatal in infancy and early childhood although some with the myopathic variant have survived to their teenage years and some with the *SUCLA2* encephalomyopathic variant have survived into adulthood. There is currently no curative treatment for any form of MDDS.

Case Presentation: A female patient born at 37 weeks presented with intrauterine growth restriction, the infant was found to have jaundice, cataract, and metabolic diseases were suspected. Patient's liver enzymes continued to measure twice as high for the patient's age and the patient presented with mild cholestasis. At the age of 2 months, the patient was brought back by the parents because of fever, persistent crying, poor oral intake, and bloody stool. The following observations were noted: progressive liver failure, severe coagulopathy, ascites associated with the development of spontaneous bacterial peritonitis. Then, a homozygous variant c.763-766dup p.(Phe256*) in *DGUOK* was discovered.

Conclusion: We report a novel homozygous variant c.763_766dup p.(Phe256*) mutation discovered in the *DGUOK* gene (OMIM: 601465), causing fatal progressive liver failure in a three-month-old Saudi infant of asymptomatic consanguineous parents. This genotype is associated with a severe clinical presentation, and the infant died at the age of 3 months.

Keywords: Case report, mitochondrial diseases, hepatocerebral, syndrome, mitochondrial DNA depletion syndromes.

Introduction

Mitochondrial diseases in infants are a heterogeneous group of diseases and include mitochondrial DNA-depletion syndromes (MDDS), which are autosomal recessive disorders characterized by a primary alteration of the respiratory chain involving complexes encoded in nuclear and mitochondrial DNA (mtDNA) (1). These alterations lead to impaired synthesis of key subunits of respiratory chain complexes. MDDS usually present with a wide spectrum of clinical manifestations, such as weakness, hypotonia, developmental delay, and/or seizures, and are categorized as myopathic, encephalomyopathic, hepatocerebral, or multisystemic. The condition is typically fatal in infancy and early childhood although some with the myopathic variant have survived to their teenage years and some with the *SUCLA2* encephalomyopathic variant have survived into adulthood (2). There is currently no curative treatment for any form of MDDS although some preliminary treatments have shown a reduction in symptoms (3). Deoxyguanosine kinase (DGUOK) catalyzes the first step of the mitochondrial deoxypurine salvage pathway, which is the phosphorylation of purine deoxyribonucleosides.

Correspondence to: Maher Mohammed Al-Hatlani
*Division of Gastroenterology and Hepatology, Department of Pediatrics, Imam Abdulrahman Al Faisal Hospital, National Guard Health Affairs (NGHA) Dammam, Saudi Arabia.
Email: alhatlanima@NGHA.MED.SA
Full list of author information is available at the end of the article.
Received: 05 February 2020 | **Accepted:** 13 April 2020

It controls mtDNA maintenance, and variation in the gene can alter or abolish the anabolism of mitochondrial deoxyribonucleotides. Mutations in the *DGUOK* gene have been linked to inherited MDDS, neonatal liver failure, nystagmus, and hypotonia (3).

Case Presentation

The female patient was born at 37 weeks (Apgar score at 1 minute: 9; 5 minutes: 10) and presented with intrauterine growth restriction (IUGR) (weight: 1,806 g, head circumference: 30, height: 46 cm) (Figure 1). Upon examination, the infant was found to have jaundice and cataract, but normal neurological, cardiovascular, musculoskeletal, and genitourinary systems, and all primitive reflexes were present. Owing to the presence of jaundice and cataract, metabolic diseases were suspected. Therefore, additional laboratory tests were conducted. The patient was screened for congenital adrenal hyperplasia using the 17-hydroxyprogesterone test, biotinidase deficiency, congenital hypothyroidism, galactosemia, and tyrosinemia. Additionally, Tandem MS and organic acids tests were performed to exclude inborn errors of metabolism. Abdominal and head ultrasounds were performed and the results were considered unremarkable. Liver/ Hepatobiliary iminodiacetic acid (HIDA) scans were performed, which suggested reduced hepatocellular function with the patent biliary system, showing the tracer into the gut. After all the negative initial metabolic screening test results, the patient was discharged, and close follow-up appointments with hepatology and neonatal clinics were scheduled. After discharge, the patient's liver enzymes continued to measure twice as high for the patient's age and the patient presented with mild cholestasis. Clinically, minimum ascites was observed and was treated with diuretics. At 2-month old, the patient was brought back by the parents because of fever, persistent crying, poor oral intake, and bloody stool, and was admitted into the pediatric intensive care unit. An abdomen ultrasound was performed, which showed increased parenchymal echogenicity of the liver, echogenic foci within the collecting system of both kidneys (likely representing medullary calcification), echogenic debris in the urinary bladder, and moderate ascites. The patient was screened for metabolic diseases again, wherein high levels of methionine were observed using Tandem MS, which indicated liver disease (Table 1).

Figure 1. *Picture of the patient at three days old (permission obtained from the parents).*

After testing at 2-month old, the patient's condition continued to deteriorate over time. The following observations were noted: progressive liver failure, severe coagulopathy [International normalized ratio (INR) > 9.0 seconds], ascites associated with the development of spontaneous bacterial peritonitis (e.g., Gram-negative bacilli, heavy growth of *Pseudomonas aeruginosa*), and anemia (hemoglobin measured as low as 68 g/l; normal range: 110–147 g/l). Throughout the patient's stay in the intensive care unit (ICU), multiple units of packed red blood cells were administered owing to hemodynamic instability, hypoglycemia, and persistent lactic acidosis.

The patient developed hepatorenal syndrome and hepatic encephalopathy stage II, resulting in septic shock, cardiopulmonary arrest, and death after four weeks of ICU care.

WES was performed at the age of two months and the results are summarized in Table 2. A homozygous variant c.763-766dup p.(Phe256*) in *DGUOK* (OMIM: 601465) was discovered. This variant is a stop-gain mutation, which causes a premature stop codon and subsequent mRNA degeneration (nonsense-mediated decay) or truncation of the protein. Although this variant has been previously described in the literature with regard to families with mitochondrial hepatopathies (PMID: 14568816, 17073823, 19265691), it is only found in 0.002% of the overall population (5 heterozygous, 0 homozygous; gnom AD). This case is unique, as it is the first time that this mutation has been detected in the homozygous state.

Previous publications have classified this variant as pathogenic. Pathogenic variants in *DGUOK* cause autosomal recessive mitochondrial DNA depletion syndrome 3 (hepatocerebral type) (MTDPS3; OMIM: 251880), which is characterized by the onset of progressive liver failure, neurologic abnormalities, hypoglycemia, and increased lactate in the body fluids in infancy. Affected tissues show both decreased activity of the mtDNA-encoded respiratory chain complexes (I, III, IV, and V) and mtDNA depletion. Based on the available information, the patient's phenotype appears to be MTDPS3. Considering the homogenous pathogenic variant in *DGUOK* and the

***Table 1**. Comparison between laboratory test at birth and at 2-month-old.*

	At birth	2-month-old "At admission"
TSB	183 mg/dl	62.7 mg/dl
Bili D	76.9 µmol/l	35.4 µmol/l
AST	104 U/l	131 U/l
ALT	81 U/l	124 U/l
Alb	25 g/l	29 g/l
GTP	256 U/l	366 U/l
INR	NA	>9.0 seconds
PT	NA	>94.0 seconds
PTT	90.0 seconds	>60.0 seconds
Lactic acid	4.16 mmol/l	5.50 mmol/l
Hgb	179 gl	138 g/l
Ferritin	677.84 µg/l	NA
Ammonia	101 µmol/l	45 µmol/l
Bile acid	81.0 µmol/l	>200.0 µmol/l
Random blood glucose	2.5 mmol/l	5.6 mmol/l

***Table 2**. Whole exome sequencing (WES).*

Gene (Isoform)	OMIM-P (mode of inheritance)	Variant	Zygosity	MAF gnomAD (%)	Literature [PMID]	Classification
DGUOK	251880	c.763-	hom.	0.002	14568816,	Pathogenic
(NM_080916.2)	(AR)	766dup			17073823,	
		p.(Phe256*)			19265691	
		chr2:				
		74185326				

supportive phenotype of the patient, a genetic diagnosis of mitochondrial DNA depletion syndrome 3 was confirmed.

The family history was reviewed and no congenital anomaly or neonatal death due to gene disorder was reported. The patient died because of a cardiopulmonary arrest secondary to septic shock, while in the ICU at the age of 3 months.

Discussion

Mitochondrial diseases in infants are a heterogeneous group of diseases that includes MDDS. This disease is characterized by a reduction in the number of mitochondrial DNA, leading to impaired synthesis of key subunits of the respiratory chain complexes. MDDS are inherited in a Mendelian fashion and can be a dominant or recessive trait (1). In the past MDDS were classified into two groups: the hepatocerebral form (affecting the liver and the central nervous system) and the myopathic form (affecting the skeletal muscles) (2).

Now, there are three well-established forms of MDDS, including the new encephalomyopathic form (1). Infants with hepatocerebral syndrome show hepatomegaly and neurological manifestations, such as hypotonia, nystagmus, and psychomotor retardation. Some infants also present with lactic acidemia and respiratory chain dysfunction (3). Approximately, 1 in 20,000 infants is affected by this disorder (4). The primary role of mitochondria is energy production in the form of ATP to meet the energy demands of the cell. This metabolism process is called oxidative phosphorylation and requires both nuclear and mitochondrial DNA. Mutations in either type of DNA can cause mitochondrial disorders. Mutations are caused by alternations in the nucleotides essential for mtDNA synthesis, or alternations of enzymes that have a direct role in mtDNA replication (5).

A common mutation observed in childhood is reduced mtDNA copy number, which has been linked to various clinical presentations. Cormier-Daire V et al. (6) evaluated 1,041 children, where 22 out of 234 patients (10%) had respiratory chain deficiency associated with liver failure and 10 out of the 22 patients had liver dysfunction in the early neonatal period. The diagnosis of MDDS is difficult, as the clinical manifestations vary in patients, resulting in the underestimation of the prevalence of MDDS.

Patients with MDDS present with several symptoms, the most common being hepatomegaly with progressive

liver failure. Other symptoms include vomiting, severe gastroesophageal reflux disease, delay in growth, and developmental delay. In these patients, liver enzyme tests usually indicate raised serum alanine aminotransferase and aspartate aminotransferase, and liver function test shows a coagulopathy profile in addition to elevated total and conjugated bilirubin with significant hypoglycemia. Other neurological manifestations, such as hypotonia, Leigh syndrome, nystagmus, psychomotor delay, pyramidal signs, seizures, and cataracts may be observed as well (7,8). In this case report, the patient had IUGR with progressive liver failure, but no neurological manifestations.

Maciej Pronicki et al. (10) evaluated liver biopsies of patients with the hepatocerebral form of MDDS. The histopathological pattern of this form of MDDS, caused by *DGUOK* mutations, showed typical diffuse scarring and neocholangliolisation reflecting liver failure in the late stages. Furthermore, liver histology of patients with *DGUOK* mutations during the early stages showed the classical cirrhosis pattern with prominent steatosis (11). For our patient, liver biopsy was not performed owing to severe coagulopathies.

MDDS are typically fatal in infancy and early childhood, though some patients have survived to their teenage years with the myopathic variant, and some have survived into adulthood with the *SUCLA2* encephalomyopathic variant. There is currently no curative treatment for any form of MDDS although some preliminary treatments have shown a reduction in symptoms. The clinical management of MDDS is mostly conservative; this is a severe condition with poor prognosis in most cases. Currently, no effective therapies are available for MDDS because of their complexity that involves the dysfunction of multiple organs, and therefore, the involvement of several different subspecialties is required to provide effective care. There are, however, various options to provide supportive treatments, such as dietary modulation, cofactor supplementation, liver transplantation, and stem cell transplantation, which can assist in managing complications in patients (11).

Extensive and regular evaluation of patients diagnosed with MDDS should be performed to better understand the multiple organ involvement, such as the neuromuscular, hepatic, gastrointestinal, cardiac, and renal systems (11). Nutritional support in these disorders is crucial to prevent hypoglycemia and involves frequent feeding of uncooked cornstarch (12). Although liver transplantation is one of the treatment options for MDDS, it does not increase survival and does not offer a cure for these patients.

Conclusion

Here, we report a novel homozygous variant c.763_766dup p.(Phe256*) mutation discovered in the DGUOK gene (OMIM: 601465), causing fatal progressive liver failure in a three-month-old Saudi infant of asymptomatic consanguineous parents. This genotype is associated with a severe clinical presentation and the infant died at the age of 3 months.

List of Abbreviations

DGUOK	Deoxyguanosine kinase
HIDA	Hepatobiliary iminodiacetic acid
ICU	Intensive care unit
INR	International normalized ratio
IUGR	Intrauterine growth restriction
MDDS	Mitochondrial DNA-depletion syndromes

Funding
None.

Declaration of conflicting interests
The authors of this article have no affiliations or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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

Consent for publication
Written informed consent was obtained from the parents of the patient for publication of this case report and any accompanying images.

Author details
Maher Mohammed Al-Hatlani[1], Sharifah Ahmed Othman[2]
1. Division of Gastroenterology and Hepatology, Department of Pediatrics, Imam Abdulrahman Al Faisal Hospital, National Guard Health Affairs (NGHA) Dammam, Saudi Arabia.
2. MBBS, Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia.

References

1. Spinazzola A. Mitochondrial DNA mutations and depletion in pediatric medicine. Semin Fetal Neonatal Med. 2011;16(4):190–6. https://doi.org/10.1016/j.siny.2011.04.011
2. Di Re M, Sembongi H, He J, Reyes A, Yasukawa T, Martinsson P, et al. The accessory subunit of mitochondrial DNA polymerase γ determines the DNA content of mitochondrial nucleoids in human cultured cells. Nucl Acids Res. 2009;37(17):5701–13. https://doi.org/10.1093/nar/gkp614
3. Sezer T, Ozçay F, Balci O, Alehan F. Novel deoxyguanosine kinase gene mutations in the hepatocerebral form of mitochondrial DNA depletion syndrome. J Child Neurol. 2014;30(1):124–8. https://doi.org/10.1177/0883073813517000
4. Skladal D. Minimum birth prevalence of mitochondrial respiratory chain disorders in children. Brain. 2003;126(8):1905–12. https://doi.org/10.1093/brain/awg170
5. Spinazzola A, Zeviani M. Disorders from perturbations of nuclear-mitochondrial intergenomic cross-talk. J Intern Med. 2009;265(2):174–92. https://doi.org/10.1111/j.1365-2796.2008.02059.x

6. Cormier-Daire V, Chretien D, Rustin P, Rötig A, Dubuisson C, Jacquemin E, et al. Neonatal and delayed-onset liver involvement in disorders of oxidative phosphorylation. J Pediatr. 1997;130(5):817–22. https://doi.org/10.1016/S0022-3476(97)80027-3
7. Morris A, Taanman J, Blake J, Mark Cooper J, Lake B, Malone M, et al. Liver failure associated with mitochondrial DNA depletion. J Hepatol. 1998;28(4):556–63. https://doi.org/10.1016/S0168-8278(98)80278-X
8. Labarthe F, Dobbelaere D, Devisme L, De Muret A, Jardel C, Taanman J, et al. Clinical, biochemical and morphological features of hepatocerebral syndrome with mitochondrial DNA depletion due to deoxyguanosine kinase deficiency. J Hepatol. 2005;43(2):333–41. https://doi.org/10.1016/j.jhep.2005.03.023
9. Lee W, Sokol R. Mitochondrial hepatopathies: advances in genetics and pathogenesis. Hepatology. 2007;45(6):1555–65. https://doi.org/10.1002/hep.21710
10. Pronicki M, Piekutowska-Abramczuk D, Rokicki D, Iwanicka-Pronicka K, Grajkowska W. Histopathological liver findings in patients with hepatocerebral mitochondrial depletion syndrome with defined molecular basis. Polish J Pathol. 2018;69(3):292–8. https://doi.org/10.5114/pjp.2018.79549
11. El-Hattab A, Scaglia F. Mitochondrial DNA depletion syndromes: review and updates of genetic basis, manifestations, and therapeutic options. Neurotherapeutics. 2013;10(2):186–98. https://doi.org/10.1007/s13311-013-0177-6
12. Parini R, Furlan F, Notarangelo L, Spinazzola A, Uziel G, Strisciuglio P, et al. Glucose metabolism and diet-based prevention of liver dysfunction in MPV17 mutant patients. J Hepatol. 2009;50(1):215–21. https://doi.org/10.1016/j.jhep.2008.08.019