Journal of Rare Diseases and Orphan Drugs, V4, 2023

Case Report

FIRST REPORTED LEBANESE PATIENT WITH DIHYDROLIPOAMIDE DEHYDROGENASE DEFICIENCY

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Received: 03-15-2023; Accepted: 03-30-2023; Published: 04-02-2023.

Abstract: Dihydrolipoamide dehydrogenase (DLD) deficiency is an autosomal recessive metabolic disorder characterized by an unpredictable pattern of presentation and a wide phenotypic spectrum. DLD is a common constituent of multiple mitochondrial complexes. It is also known as E3 (dihydrolipoamide: NAD+ oxidoreductase, EC 1.8.1.4). DLD, encoded by the DLD gene, is vital for catalysis. Thus, genetically induced deficiency of the enzyme, although very rare, is associated with failure to thrive, hypotonia, and metabolic acidosis [1,2].

In this report, we present the case of a 12-year-old Lebanese boy with a homozygous mutation in the DLD gene: c.685G>T p. Gly229Cys, who presented with liver failure, hyperammonemia, and encephalopathy. Genetic testing of his sibling revealed homozygosity for the same pathogenic variant.

Keywords: Dihydrolipoamide dehydrogenase deficiency, newborn, metabolic disorders

CASE PRESENTATION Herein we present the case of a previously healthy 12-year-old Lebanese boy with normal neurologic development, born to non-consanguineous parents, who initially presented to our institution in March 2021 for investigations of jaundice and elevated liver enzymes. The episodes were preceded by 20 days history of recurrent episodes of non-bloody, non-bilious, non-projectile vomiting associated with nausea, jaundice, and fatigue. On admission, vitals were stable; HGT: 99 mg/dL, BP: 90/60 mmHg (mean 62), HR: 77 beats/minute, Temperature: 36.5 C. The physical exam was remarkable for somnolence with a Glasgow coma scale of 12/15, jaundice, and icteric sclera. Laboratory tests on admission were significant for elevated liver enzymes (SGPT 1469 U/L, SGPT 5805 U/L, GGT: 771 U/L), hyperammonemia (82 mcg/dL), direct hyperbilirubinemia (Direct 6.11 and total 7.57 mg/dL) and prolonged coagulation studies. A provisional diagnosis of acute liver failure was made; he was managed conservatively by placing him on NPO and fluid restriction and by giving him lactulose, omeprazole, and antibiotics to prevent spontaneous bacterial peritonitis. A brain CT scan done for signs of encephalopathy was normal, with no signs of cerebral edema.

Brain MRI showed an abnormal signal in the basal ganglia with restricted diffusion and a high T2 abnormality and FLAIR abnormality (Figure 1). Spectroscopy showed a prominent myoinositol peak (Figure 2). Abdomen ultrasound showed a liver size of 16 cm, the upper limit in size, with normal echotexture and no evidence of focal hepatic steatosis or lesions and normal doppler. Investigations were done to exclude all possible causes of liver injury. HAV, HCV, HBV, EBV, and CMV tests were negative. Autoimmune workup negative, and protein electrophoresis normal. Lactic acid, pyruvic acid, and CPK

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were normal. A liver biopsy showed mild to moderate parenchymal inflammation and no evidence of cirrhosis.

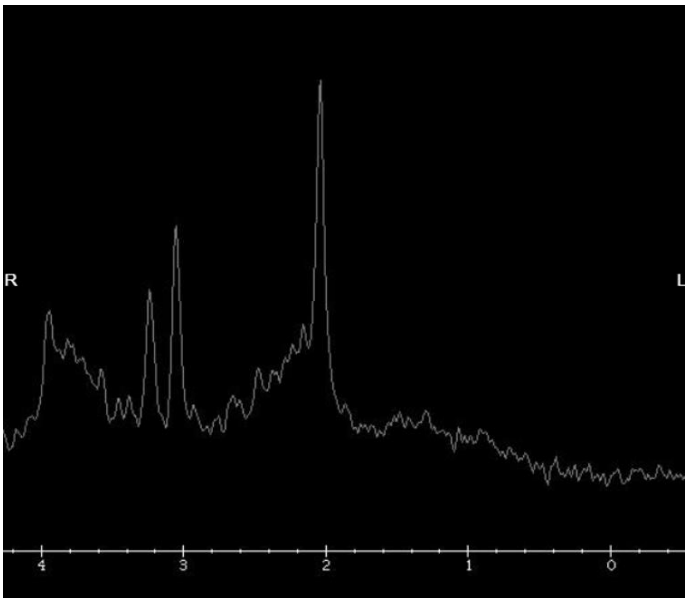

Figure 1. Prominent myoinositol peak on spectroscopy.

He had a normal slit eye exam with normal serum ceruloplasmin and copper levels. Full recovery was achieved after supportive management with a return to baseline. He was discharged home on ursodeoxycholic acid.

the DLD gene was found: DLD: NM_000108.4:c.685G>T p.Gly229Cys. Outpatient management included avoidance of fasting and catabolic stressors, as well as hepatotoxic drugs.

Unfortunately, the patient was re-admitted to our institution in October 2022 for recurrent vomiting and elevated liver enzymes. Laboratory tests were significant for elevated liver enzymes, hyperammonemia, direct hyperbilirubinemia, and prolonged coagulation studies. An urgent brain CT scan showed normal findings with no signs of cerebral edema. Supportive management was started with lactulose, rifaximin, sodium benzoate, omeprazole, and L-carnitine (50mg/kg/day). He required intubation because of central apnea. His ammonia level reached 600 mcg/dL, non-responsive to medications, requiring four hemodialysis sessions. However, the patient was clinically deteriorating and had disseminated intravascular coagulopathy and passed away after repetitive cardiac arrest and EEG showing suppressed brain activity.

DISCUSSION DLD is a very rare condition that varies widely in age, severity, and clinical manifestations. It is an autosomal recessive inherited disorder caused by a mutation in the DLD gene. DLD functions as the E3 subunit of three different mitochondrial enzyme complexes: the pyruvate dehydrogenase complex (PHD), the branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, and the ketoglutarate dehydrogenase (KGDH) complex

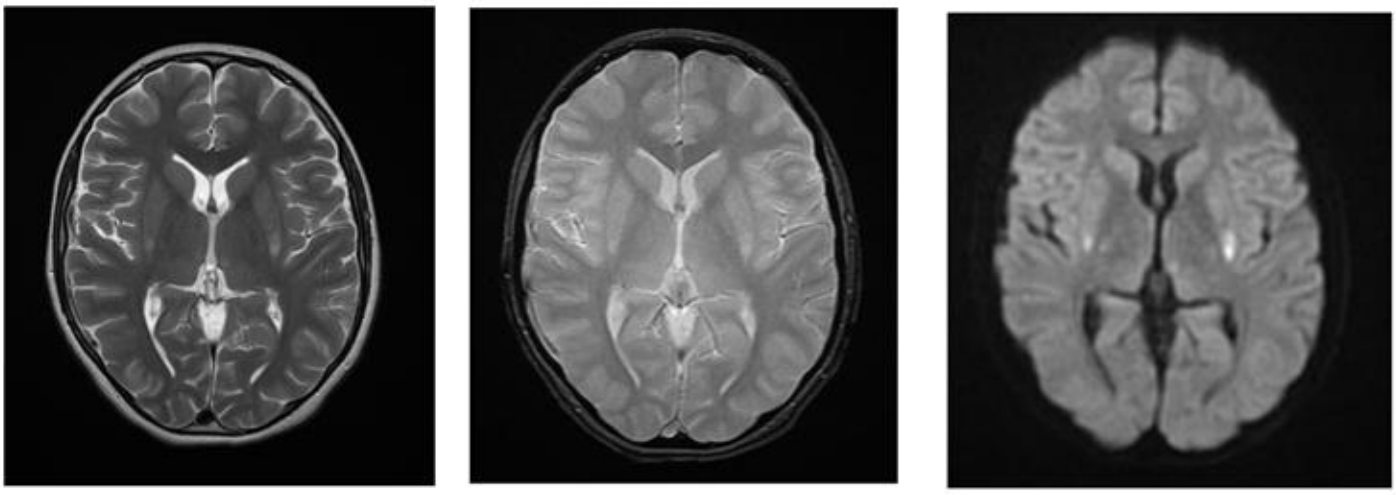

Figure 2. Abnormal signal in the basal ganglia with a restricted diffusion

Four weeks after discharge, whole exome sequencing detected a pathogenic variant at the homozygous state in

[1,2,3]. DLD mutations affect the proper functioning of the mitochondrial enzyme complexes**,** which prevents them

from breaking down amino acids in the body, leading to lactic acidosis. DLD deficiency has a variable phenotypic spectrum that can present anywhere between the neonatal period and the third decade of life, with either early-onset neurologic presentation, a primarily hepatic presentation, or a primarily myopathic presentation [1,2]. In the neurologic form, patients present with early onset hypotonia and lethargy. Many affected infants die after their first metabolic decompensation, and those who survive it exhibit different neurologic manifestations. In the hepatic form, patients present anytime between the neonatal period and third decade with recurrent liver injury preceded by emesis, with normal intellectual function and no neurologic deficit between the episodes unless neurologic damage ensued. The last form is myopathic, where patients present with muscle weakness and elevated creatinine kinase [1]. Our patient presented with the hepatic form in the first decade of his life. He had normal development and intellect until neurologic damage occurred secondary to hyperammonemia. He presented with liver failure, preceded by nausea and emesis and accompanied by encephalopathy and coagulopathy. The hepatic manifestations are typically present during the acute episodes, with a return to baseline between episodes.

Diagnosis can be made by molecular genetic testing, either by approaching single-gene testing or using a multigene panel. DLD is caused by pathogenic variants in the DLD gene, located on chromosome 7 at 7q31.1. Around 20 pathogenic variants have been reported. Some correlations have been reported for individuals who have at least one c.685G>T (p.Gly229Cys) pathogenic variant [4]. Brassier *et al.* (2013) report that patients with the hepatic presentation were homozygous for the c.685G>T (p.Gly229Cys) pathogenic variant. The most common mutation in the Middle East is the p.Gly229Cys mutation, which is often associated with the hepatic form [4], which is detected and seen in our Lebanese patient.
Since DLD is considered one of the variants phenotypes of maple syrup urine disease type III, newborn screening for DLD deficiency is recommended by Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) [4,5].

Consensus recommendations for the management of DLD are currently absent in the literature. The acute management of liver injury secondary to DLD includes treating any precipitating factor and avoidance of hepatotoxic drugs, nutritional support, correction of metabolic and lactic acidosis, with consideration of dialysis in case of persistent acidosis and encephalopathy, and fresh frozen plasma for coagulopathy [1]. No current data exists for the chronic management of patients with hepatic disease. However, between acute episodes, avoiding fasting, catabolic stressors, and hepatotoxic drugs is important.

It is essential to test at-risk family members to allow early diagnosis and management and avoid precipitating factors. Screening for family members was done, and the sibling of our patient was found to be homozygous for the same pathologic variant in the DLD gene. The sibling had an initial screening level of ammonia level reaching 305 mg/dL, for which he was started on pheburane, and his elevated ammonia level has returned to the normal range (40 mg/dL) since then. Pheburane is a medication that contains the active substance sodium phenylbutyrate, which is used for the treatment of patients with urea-cycle disorders. The accumulation of nitrogen waste products in the form of ammonia is toxic, especially for the brain. Sodium phenylbutyrate is converted into phenylacetate, which combines with glutamine to form a substance that the kidneys can excrete. Thus, increasing nitrogen excretion reduces the amount of ammonia produced [6].

Congenital inherited metabolic diseases are common in societies with very high consanguinity rates, such as Lebanon [7]. The consanguinity rate in Lebanon is elevated, reaching 35% in a report by Barbour *et al.* (2009) [8]. Lebanon's high consanguinity rate increases the risk of genetically inherited disease. Therefore, genetic counseling and screening are paramount to help consanguineous parents make informed choices and screen early on for preventable and treatable diseases. Nair *et al.* (2018) report that among the patients tested for genetic disorders in Lebanon, a high number of autosomal recessive disorders is noted, pointing out the impact of the high consanguinity rate [3].

CONCLUSION Managing and diagnosing patients with unexplained liver failure is challenging. However, DLD deficiency should be considered as a possible rare etiology, even in the absence of neurologic and developmental symptoms. Here we present the first report of a Lebanese patient affected with DLD deficiency. Early genetic testing is crucial for appropriate management. At-risk family members should be tested for timely, appropriate early intervention and trial of medications that can aid in the excretion of nitrogen waste products.

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