Dehydrogenase (DLD) Deficiency in an Iranian Patient with Recurrent Intractable Vomiting: Successful Treatment with Thiamine Supplementation

How to Cite This Article: Moosavian T, Jamalipour Soufi G, Kamfar Sh. Dihydrolipoamide Dehydrogenase (DLD) Deficiency in an Iranian Patient with Recurrent Intractable Vomiting: Successful Treatment with Thiamine Supplementation. Iran J Child Neurol. Winter 2024; 18 (1) : 131-138

Toktam MOOSAVIAN, MD[1, 2], Ghazaleh JAMALIPOUR SOUFI, MD[3], Sharareh KAMFAR PhD[4]

1. Pediatric Neurology Department, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2.Metabolic Liver Disease Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
3.Radiology Department, Isfahan University of Medical Sciences, Isfahan, Iran
4.Pediatric Congenital Hematologic Disorders Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Dihydrolipoamide dehydrogenase (DLD) deficiency is a rare disease of genetic origin due to the malfunctioning of a shared subunit of three mitochondrial multi-enzyme complexes. Phenotypes of this disease are a set of clinical manifestations ranging from neonatal disorders to myopathy or recurrent episodes of liver failures, and vomiting for which no adequate or definitive treatment is currently available.

This study described a case involving a 16-year-old boy who had experienced recurrent vomiting of unknown cause from age two. Normal value ranges for the basic metabolic panel were reported in previous years. The patient was admitted with Wernicke's encephalopathy after the last vomiting attack, also indicating metabolites of organic acids compatible with DLD deficiency. Whole exome sequencing identified a known pathogenic mutation in the DLD gene, leading to a diagnosis of DLD deficiency. Our patient was treated with a high dose of thiamine supplementation and continued treatment, has not experienced any vomiting attacks or related problems in the last two years and has adequately responded to the treatment prescribed.

Normal urine organic acid levels in patients with recurrent vomiting cannot roll out DLD deficiency. However, although thiamine deficiency typically induces Wernicke's encephalopathy, it can also be implicated in pyruvate dehydrogenase complex (PDHc) deficiency, and high-dose thiamine therapy (with doses up to 30 mg/kg) is recommended for deficient patients.

Corresponding Author
Kamfar Sh. PhD
Pediatric Congenital Hematologic Disorders Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email: kamfarsharareh@gmail.com

Received: 25-Jul-2022
Accepted: 21- Jan-2023
Published: 18-Jan-2024

Keywords: Dihydrolipoamide Dehydrogenase Deficiency, Urine Organic Acid, Recurrent Vomiting, Wernicke's encephalopathy, Thiamin Supplementation
DOI: 10.22037/ijcn.v18i1.38971

Introduction

Dihydrolipoamide dehydrogenase (DLD) deficiency is a metabolic disorder with autosomal recessive inheritance, showing a different profile of clinical symptoms, age of onset, and severity among affected patients. This condition is caused by a defect in the gene encoding the DLD enzyme in 7q31 (1). The DLD, also called the E3 subunit, is a common enzymatic component of the mitochondrial-based multi-enzyme pyruvate dehydrogenase complex (PDHc) (2), converting pyruvate to acetyl-CoA to be eventually oxidized to produce energy. Therefore, its deficiency leads to the accumulation of pyruvate, lactate, and branched-chain amino acids in plasma and branched-chain alpha ketoacids in urine (3). Clinically, DLD deficiency phenotypes include severe conditions such as lactic acidosis, neurodegenerative dysfunction to encephalopathy, relatively mild phenotypes, including recurrent episodes of liver disease and vomiting, and rarely myopathic symptoms. Typically, the signs and symptoms of DLD deficiency may be triggered by various stimuli, such as illness, fever, injury, infection, or other stress-related health conditions. To date, based on molecular genetic data, t multiple variants of DLD have been identified in DLD-related causes of deficiency. Nevertheless c.685G > T, p.(Gly229Cys) is the most commonly reported variant in the DLD gene (4). Despite the rarity of DLD deficiency, a definitive treatment for the condition has yet to be established. (5).

The present case report presents the course of the illness, decisions related to diagnosis, and acceptable response to thiamin in a 16-year-old boy with a homozygous pathogenic variant in the DLD gene with a long history of unknown vomiting attacks.

Case presentation

A 16-year-old boy was admitted to the Mofid Children's Hospital, Tehran, Iran, with severe attacks of vomiting for a few days. The vomiting was projectile, without any concomitant symptoms or signs, such as diarrhea, abdominal pain, or constitutional symptoms. Furthermore, he was the first offspring of related parents and had a healthy 10-year-old sister. The course of psychomotor developmental and constitutional symptoms was normal, without any problems in neonatal and

infantile periods. Additionally, no family history of vomiting or significant health conditions was observed. He had recurrent vomiting with frequent hospital admissions since he was two years old and had never had gastrointestinal problems or a history of vomiting-related disorders. Besides, neurological, immunological, endoscopic, and psychiatric evaluations were normal. Basic metabolic assessments, including serum amino acid profiles and urine organic acids, along with liver enzyme tests and brain MRI scans, revealed no identifiable abnormalities that could lead to disease. Our patient was misdiagnosed as a migraine patient for years, treated with amitriptyline and CoQ10 at regular doses, but with no responses. Despite efforts, there was no response decrease in either the frequency or length of the periods. Occasionally, vomiting attacks are accompanied by increases in liver enzymes or a minimal increase in ammonia and lactate. Likewise, the lactate to pyruvate ratio was elevated to more than 25. After each attack, our patient returned to his original condition without any apparent neurological deficit. Attacks frequently occurred every three months with periods of one to three days before nine years old. At this age, vomiting attacks were triggered by a high fever without any functional or infectious disease. Marked behavioral changes were a notable concern observed on admission, leading to hospitalization. High levels of liver enzymes ALT and AST (increased to 1000 U / l), PT, and bilirubin indicate abnormal liver function. Laboratory tests were negative for autoantibodies, viral hepatitis panel, serum ceruloplasmin, and vasculitis. Advanced diagnostic laboratory tests were negative, including autoantibodies, viral hepatitis panel, serum ceruloplasmin, and vasculitis. Liver biopsy was normal, and endoscopy and colonoscopy evaluations were unremarkable. In addition, the studied patient was diagnosed with hepatic encephalopathy based on Reye-like syndrome.

Then, treatment started with ursodeoxycholic acid (Ursobil), cloxacillin, metronidazole, and FFP. According to the mentioned protocol, he recovered and was discharged after a month. As the patient aged, his recovery was followed by a shift in his vomiting episodes. Initially occurring about once a week, these episodes would last at least three days. Over time, they became both more frequent and more prolonged. Episodes of vomiting, whether the patient was hospitalized or not, usually resolved spontaneously after a while. Notably, though, the patient underwent nothing by mouth (NPO) management. Specialized metabolic tests were requested at intervals between normal vomiting episodes, including plasma acylcarnitine, plasma amino acid profiles, and urinary organic acid profiles. Occasionally, only a slight increase was observed in ammonia levels, so sodium benzoate was recommended as adjunctive therapy. The patient's lactate level was typically above normal limits and sometimes returned to normal. In addition, an increased lactate-pyruvate ratio of more than 20 was observed in our patient. Three years later, a similar hepatic encephalopathy occurred with an increase in liver enzymes (AST 1250 IU/L, ALT 1640 IU/L) and the PT/INR ratio in the patient, but no CPK was observed.

The lack of a definitive diagnosis for this patient caused him to suffer from recurrent vomiting for unknown reasons. He was admitted to the hospital

at 16 years old with the same recurrent vomiting periods, and the vomiting periods lasted for hours and even up to seven days. The patient's condition gradually deteriorated shortly after admission. Some significant changes, such as decreased consciousness (GCS12-13) and hyperammonemia, were reported for him. Around three weeks after symptoms onset and hospitalization, the patient was diagnosed with rhabdomyolysis based on elevation in CPK levels (Table 1). In addition, the individual exhibited progressive hearing loss, vision impairment accompanied by irregular eye movements, weakness in the lower limb muscles, and a diminished deep tendon reflex response. A comprehensive metabolic panel and simultaneous plasmapheresis were performed every other day for disease management. However, this treatment did not improve the patient's condition or reduce the disease's symptoms. Brain MRI revealed high signal intensity on T2, FLAIR, and DWI sequences in the dorsal aspect of the medulla oblongata, midbrain tectum, dorsomedial aspect of both thalami, medial occipital, and perirolandic cortex (Figure 1). Hence, treatment was started with 500-700 mg intravenous thiamine per day due to suspected Wernicke's encephalopathy. significant improvment in hearing clinically and level of consciousness (GCS 15) was indicated in the patient, along with a slight increase in muscle strength after three days of thiamine treatment. However, no change in vision impairment was observed. The patient was conscious for one month after starting treatment but had vision problems, and subsequently, the vomiting attacks gradually improved. Because the patient was suspected of thiamine deficiency, discharged on a 300 mg thiamine diet daily. Large large amount of 2 hydroxyadipic acid ,2 ketoadipic acid,2 ketoglutaric acid,pyrovic acid, becides increase of alloisoleucine and normal 2 aminoadipic acid were detected during metabolic analysis in the acute phase of the disease. Pyruvate dehydrogenase Complex 3 deficiency was diagnosed based on phenotype information, and whole-exome sequencing (WES) was requested for the patient. Based on the evidence, a pathogenic homozygous variant in the DLD gene was identified during WES (Table 2). This variant has been reported many times in previous publications and the ClinVar database.

Discussion

DLD deficiency, a hereditary metabolic disorder, reveals various clinical manifestations among patients. Hence, predicting the genotype-based DLD phenotype is challenging when factors such as severity and biochemical consequences are variable (6). In the case of vomiting, the overall causes of the disease can be a challenging process that can lead to misdiagnosis. The studied patient did not have specific metabolic abnormalities based on metabolic assessments during all previous years. Interestingly, before the last attack and the onset of Wernicke's encephalopathy, the metabolic analysis showed normal levels of urinary organic acids, and an increase in metabolites associated with DLD deficiency was observed only in the patient's last vomiting attack. The delayed diagnosis of DLD deficiency in the patient was due to these normal values. Therefore, normal urine organic acid levels in patients with recurrent vomiting cannot roll out DLD deficiency. However, despite the normal

Table 1: Laboratory results during the last vomiting attack of reported patient

Laboratory results		
Laboratory test	**Result**	**Normal range**
Total bilirubin	2 (mg/dl)	Below 1.3 (mg/dl)
Direct bilirubin	0.5 (mg/dl)	Below 0.3 (mg/dl)
ALT	356 (IU/L)	19-33 (IU/L)
AST	570 (U/L)	19-29 (IU/L)
INR	1	Below 1.1
PT	12	11-13.5 sec
CPK	10000 (U/L)	26-192 (U/L)
CSF WBC	5 (mm3)	Less than 5
CSF protein	40 (mg/dl)	20-40 (mg/dl)
Lactate	35 (mg/dl)	4.5-19/8 (mg/dl)
Pyruvate	1.2 (mg/dl)	Below 1(mg/dl)
Ammonia	120 (mcg/dl)	15-60 (mcg/dl)

Table 2: Detected pathogenic variant of DLD gene in reported patient.

Whole Exome Sequencing				
Major findings				
Gene	**Protein**	**cDNA**	**Class**	**Matching phenotype**
DLD	p. Gly229 Cys	NM_000108.5 c.685G>T	Pathogenic	Dihydrolipoamide dehydrogenase deficiency (AR)

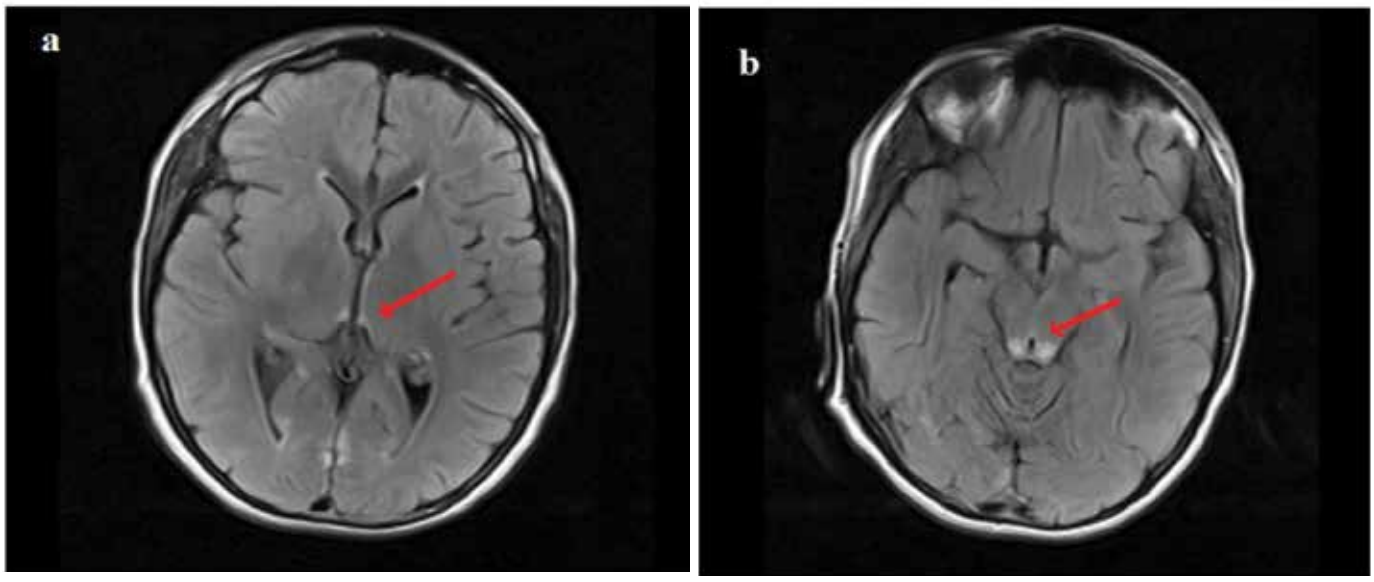

Figure 1. *Brain MRI findings: (a) increased signal intensity on flair in dorsomedial aspect of both thalami. (b) increased signal intensity on flair in dorsal aspect of medulla oblongata, midbrain tectum.*

levels of organic acids, the lactate/pyruvate ratio was more than 25 in 2 attacks, which enhanced the suspicion of DLD deficiency.

The obtained results confirmed the diagnosis by biochemical laboratory values, serum amino acid profiles, urinary organic acid, and molecular analyses found in the acute phase of the last vomiting attack. Investigations showed a pathogenic homozygous mutation in the DLD gene, c.685G>T, p. (Gly229Cys), that, based on previous reports, this variant is responsible for causing disease (7). DLD is a common component of three mitochondrial enzyme complexes: branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, α-ketoglutarate dehydrogenase (αKGDH) complex, and pyruvate dehydrogenase (PDH) complex, playing a crucial role in the glycine cleavage system (8). Therefore, due to the vital role of DLD in various metabolic pathways, its deficiency management faces many challenges (9).

Typically, the signs and symptoms of DLD deficiency due to the homozygous variant differ from those of the heterozygous variant (10). Homozygous c.685G>T mutation has been reported in a late-onset DLD deficiency with liver failure or neurologic presentation (11). In the late-onset type of disease, patients have hepatic encephalopathy or Wernicke's encephalopathy. Both types were observed in our patient during all the years of his illness. Mutations in the X-linked PDHA1 gene and subsequent defects in activating PDHc and decreased affinity for thiamin pyrophosphate (TPP) are considered the primary causes of thiamine-responsive PDHc deficiency (12). After the patient was diagnosed with DLD deficiency, he received a thiamine diet (20 mg/kg /day). Accordingly, he continued this treatment protocol with supervision for two years after discharge from the hospital with a good response and no vomiting attacks. In addition, co-administration of riboflavin with thiamine may be more effective in reducing the symptoms of DLD deficiency with myopathic manifestations because riboflavin acts like a chaperone (13).

Despite the previous essay,this resault of the present study,based on a two- year follow- up of the patient,demonstrated that prescribing high-dose thiamine regiments,lone, cn effectively control and treat certain types of DLD deficiency (14)

In Conclusion

DLD deficiency can be presented only with refractory recurrent vomiting without any abnormality in urine organic acid. Although thiamine deficiency usually induces Wernicke's encephalopathy, thiamine can also be notably implicated in PDHc deficiency. Therefore, high-dose thiamine (30 mg/kg) is recommended to treat patients with DLD deficiency.

Acknowledgment

The authors would like to thank Dr. Mahin Hashemipour and their colleagues at Isfahan Endocrine and Metabolism Research Center. The authors also thank the Metabolic Liver Disease Research Center colleagues at Isfahan University of Medical Sciences for their collaboration.

Author's Contribution

Toktam Moosavian was responsible for designing and implementing the research and analyzing the

results and also revised it critically for important intellectual content. Sharareh Kamfar wrote the manuscript and contributed the version to be published. Ghazaleh Jamalipour Soufi was responsible for preparing and interpreting medical imaging data. All authors discussed the results and commented on the manuscript.

Conflict of Interest

The authors declared no conflicts of interest.

References

1. Pons G, Raefsky-Estrin C, Carothers DJ, Pepin RA, Javed AA, Jesse BW, et al. Cloning and cDNA sequence of the dihydrolipoamide dehydrogenase component human alpha-ketoacid dehydrogenase complexes. Proceedings of the National Academy of Sciences. 1988;85(5):1422-6.
2. Cameron JM, Levandovskiy V, MacKay N, Raiman J, Renaud DL, Clarke JT, et al. Novel mutations in dihydrolipoamide dehydrogenase deficiency in two cousins with borderline-normal PDH complex activity. American Journal of Medical Genetics Part A. 2006;140(14):1542-52.
3. Hong YS, Kerr DS, Craigen WJ, Tan J, Pan Y, Lusk M, et al. Identification of two mutations in a compound heterozygous child with dihydrolipoamide dehydrogenase deficiency. Human Molecular Genetics. 1996;5(12):1925-30.
4. Alfarsi A, Alfadhel M, Alameer S, Alhashem A, Tabarki B, Ababneh F, et al. The phenotypic spectrum of dihydrolipoamide dehydrogenase deficiency in Saudi Arabia. Molecular Genetics and Metabolism Reports. 2021;29:100817.
5. Staretz-Chacham O, Pode-Shakked B, Kristal E, Abraham SY, Porper K, Wormser O, et al. The Effects of a Ketogenic Diet on Patients with Dihydrolipoamide Dehydrogenase Deficiency. Nutrients. 2021;13(10):3523.
6. Quinonez SC, Leber SM, Martin DM, Thoene JG, Bedoyan JK. Leigh syndrome in a girl with a novel DLD mutation causing E3 deficiency. Pediatric neurology. 2013;48(1):67-72.
7. Odièvre MH, Chretien D, Munnich A, Robinson BH, Dumoulin R, Masmoudi S, et al. A novel mutation in the dihydrolipoamide dehydrogenase E3 subunit gene (DLD) resulting in an atypical form of α-ketoglutarate dehydrogenase deficiency. Human Mutation. 2005;25(3):323-4.
8. Wang J, Nemeria NS, Chandrasekhar K, Kumaran S, Arjunan P, Reynolds S, et al. Structure and function of the catalytic domain of the dihydrolipoyl acetyltransferase component in Escherichia coli pyruvate dehydrogenase complex. Journal of Biological Chemistry. 2014;289(22):15215-30.
9. ShiQ,KaruppagounderS,XuH,PechmanD,Chen H, Gibson G. Responses of the mitochondrial alpha-ketoglutarate dehydrogenase complex to thiamine deficiency may contribute to regional selective vulnerability. Neurochemistry international. 2007;50(7-8):921-31.
10. Patel MS, Harris RA. Mammalian α-keto acid dehydrogenase complexes: gene regulation and genetic defects 1. The FASEB journal. 1995;9(12):1164-72.
11. Hong YS, Kerr DS, Liu T-C, Lusk M, Powell BR, Patel MS. Deficiency of dihydrolipoamide

dehydrogenase due to two mutant alleles (E340K and G101del): analysis of a family and prenatal testing. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 1997;1362(2-3):160-8.

12. Naito E, Ito M, Yokota I, Saijo T, Matsuda J, Ogawa Y, et al. Thiamine-responsive pyruvate dehydrogenase deficiency in two patients caused by a point mutation (F205L and L216F) within the thiamine pyrophosphate binding region. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2002;1588(1):79-84.
13. Carrozzo R, Torraco A, Fiermonte G, Martinelli D, Di Nottia M, Rizza T, et al. Riboflavin responsive mitochondrial myopathy is a new phenotype of dihydrolipoamide dehydrogenase deficiency. The chaperon-like effect of vitamin B2. Mitochondrion. 2014;18:49-57.
14. Quinonez SC, Thoene JG: Dihydrolipoamide Dehydrogenase Deficiency. In: GeneReviews(®). edn. Edited by Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A. Seattle (WA): University of Washington, Seattle Copyright © 1993-2023, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.