The phenotypic spectrum of dihydrolipoamide dehydrogenase deficiency in Saudi Arabia

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Abstract

Background: Dihydrolipoamide dehydrogenase deficiency (DLDD) is a rare metabolic disorder inherited in an autosomal recessive manner. This heterogeneous disease has a variable clinical presentation, onset, and biochemical markers.

Materials and methods: We retrospectively reviewed the clinical and molecular diagnosis of eight cases with DLDD from four referral centers in Saudi Arabia.

Results: Remarkably, we found hepatic involvement ranging from acute hepatic failure to chronic hepatitis in five patients. In addition, neurological disorders in the form of seizures, developmental delay, ataxia, hypotonia and psychomotor symptoms were found in five patients, two of them with a combination of hepatic and neurological symptoms. In addition, only one patient had recurrent episodes of hypoglycemia. While most patients had the hepatic form of homozygous variant c.685G>T in the DLD gene, one patient was found to have a novel variant c.623C>T that had neurological and hepatic symptoms.

Conclusions: We describe the largest reported DLDD cohort in the Saudi population. Clinical, biochemical, radiological, and molecular characterization was reviewed and no clear genotype-phenotype correlation was found in this cohort.

Introduction

Dihydrolipoamide dehydrogenase deficiency (DLDD) is an extremely rare metabolic disorder with autosomal recessive inheritance [1]. The highest carrier rate for a pathogenic mutation of the DLD gene has been found in the Ashkenazi Jewish population (1:94 to 1:110, with a disease frequency of 1:35,000 to 1:48,000) [2]. The disease is less common in other populations, such as the Mediterranean population, although the exact incidence and carrier frequency are still unknown [3]. DLDD is caused by a deficiency of the enzyme the dihydrolipoamide dehydrogenase, which is encoded by the DLD gene in 7q31.1 [4]. This enzyme, a flavoprotein unit designated E3, is one of three mitochondrial multi-enzymatic complexes, which include a pyruvate dehydrogenase complex, an α-ketoglutarate dehydrogenase complex, and a branched-chain α-keto acid complex, and plays a role in the glycine cleavage system. [5]. The complexity of this enzyme and the multiple

Artificial Intelligence for Life Sciences: The Future of Drug Discovery and Development

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Abstract

The rapid advancement of artificial intelligence (AI) in life sciences has the potential to revolutionize drug discovery and development. This chapter provides an overview of the current state of AI in life sciences, highlighting the potential benefits and challenges of this technology. The chapter discusses the application of AI in drug discovery, including the identification of new drug targets and the prediction of drug properties. Additionally, the chapter explores the use of AI in drug development, such as the optimization of drug candidates and the prediction of drug metabolism. The chapter concludes with a discussion of the future of AI in life sciences and the potential impact on the pharmaceutical industry.

1. Introduction

AI has the potential to significantly enhance drug discovery and development by accelerating the pace of research and reducing the cost of drug development. AI can be used to analyze large datasets to identify new drug targets and predict drug properties, such as drug efficacy and toxicity. AI can also be used to optimize drug candidates by predicting drug properties and identifying potential side effects. In addition, AI can be used to predict drug metabolism, which is crucial for the development of drugs that can be efficiently absorbed and distributed in the body.

2. Applications of AI in Drug Discovery

AI can be used to identify new drug targets by analyzing large datasets of protein structures and gene expression data. AI can also be used to predict drug properties, such as drug efficacy and toxicity, by analyzing large datasets of drug properties and their associated protein structures. AI can be used to optimize drug candidates by predicting drug properties and identifying potential side effects. In addition, AI can be used to predict drug metabolism, which is crucial for the development of drugs that can be efficiently absorbed and distributed in the body.

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4. Future of AI in Life Sciences

The future of AI in life sciences is promising, with the potential to significantly enhance drug discovery and development. AI can be used to identify new drug targets, predict drug properties, optimize drug candidates, and predict drug metabolism. The potential impact of AI on the pharmaceutical industry cannot be underestimated, with the potential to significantly reduce the cost of drug development and accelerate the pace of research.
biochemical functions would explain the variability (clinical heterogeneity) in affected patients, with a remarkable variability in phenotype, onset, and severity [6]. Most cases occur in the first year of life, however neonates affected by DLDD also present with hypotonia, poor feeding, limb rigidity, and/or choreoathetoid movements [3,7,8]. Patients may suffer from recurrent episodes of encephalopathy triggered by infections, prolonged fasting, inadequate caloric intake and other catabolic stresses [9]. Previous reports have described exercise induced myopathy with persistent bilateral ptosis and lactic acidosis in some patients. An extremely rare case of myoglobinuria with a high creatinine kinase was observed in adults [10–12]. In addition, hepatocellular dysfunction and recurrent acute liver failure (Reye-like syndrome) have been well described in DLDD patients, associated with high transaminases, hepatomegaly, coagulopathy, and lactic acidosis [9,12]. Some patients with DLDD may have a milder course with fewer or no decompensatory episodes [13]. In a two-day-old neonate, myocardial dysfunction was observed to occur rarely, whereas several episodes of hepatic encephalopathy were noted in childhood [13].

Biochemical parameters include hypoglycemia, lactic acidosis, and mild hyperammonemia. In addition, metabolic derangements such as high urinary pyruvate, organic acids with peak levels of 2-hydroxybutyric acid, 2-hydroxyisovaleric acid, glutaric acid, adipic acid, and 2-oxoglutaric acid, and moderate peak levels of 2-hydroxyglutaric acid and 4-hydroxyphenyllactic acid have been observed during acute episodes [9,14]. DLDD patients were found to have high levels of branched-chain amino acids (BCAAs) in amino acid plasma, with elevated citrulline, which was recently identified as a marker in symptomatic patients with DLDD [7,10,15,16]. MRI findings of the brain varied between abnormal signal intensity in different brain regions, including the basal ganglia brain stem, thalamus and/or frontal and occipital lobes, mild cortical atrophy with mild periventricular white matter abnormalities. Normal brain images have also been reported [10,13,17,18].

Because there is no established genotype-phenotype correlation, it is difficult to predict the patient’s phenotype based on the detected variant. The variability is directly related to the effects of the mutation on the activity of the enzymatic complex [10]. To date, there is no effective treatment, although the effect of dietary supplements on disease progression and the episode severity has been reported in the literature [19–22].

We retrospectively reviewed the clinical and molecular diagnosis of 8 cases with a confirmed diagnosis of DLDD from four participating centers in Saudi Arabia to describe the phenotypic spectrum of this rare disease, which may help to establish a consensus on a treatment protocol for such cases in the future.

2. Materials and methods

2.1. Ethical study approval and patient consents

This study was approved by the Institutional Review Board (IRB) of the King Abdullah International Medical Research Centre (KAIMRC) (IRB Number: IRBC/0366/19).

2.2. Patient data

We reviewed the charts of pediatric patients from four major referral centers in Riyadh, Saudi Arabia, with a diagnosis of DLDD. Data were collected from collaborating physicians at the four participating centers in Saudi Arabia. All available clinical data, laboratory data, and MRI data of the brain to confirm the diagnosis of DLDD were obtained from the medical records.

3. Results

3.1. Clinical findings

Eight patients (four males and four females) from eight unrelated families diagnosed with DLDD based on clinical and molecular tests, were included in this study. The age of the patients ranged from 2 years to 18 years, with a mean age of 8.5 years. Consanguinity was found in one family (12.5%). Symptoms occurred between birth and late childhood. In one of the patients, symptoms occurred in the neonatal period, in three patients in infancy, and in four in early and late childhood. The clinical phenotype included neurological manifestations with mental retardation in five patients, episodes of hepatocellular dysfunction in five patients, two of them with combined hepatic and neurological presentation (patients 4 and 8). One patient with hepatic presentation (patient 1) had episodic ketotic hypoglycemia with lactic acidemia during mild illnesses. Most of these episodes were triggered by infections, prolonged fasting, inadequate caloric intake, and catabolic stress. Patients with a hepatic manifestation had at least one episode of hepatic encephalopathy that recovered completely and had normal or near-normal mental functions with the exception of one patient (patient 8). In addition, mild hypertrophic cardiomyopathy was observed in two patients (patients 2 and 7) (Table 1).

3.2. Laboratory tests

Episodic lactic acidosis with metabolic acidosis occurred in six patients (75%), none of the cohort had sustained lactic acidosis but episodic elevations during decompensation, and hypoglycemia in only one case. Elevated levels of branched chain amino acids (BCAAs) with normal citrulline levels were observed in three patients (37%) with primary neurological presentations. No patients in this cohort underwent enzymatic testing.

3.3. Findings of images

MRI of the brain was performed in 6 of the patients. In the patients with isolated hepatic DLDD, the images showed a normal brain structure and normal myelination for age (2 patients). In the neurological DLDD group, the images varied between normal (1 patient), thin corpus callosum (1 patient), bilateral and symmetrical increased T2-weighted signal intensity involving the putamen and caudate nucleus with atrophic changes. (4 and 5) (Fig. 1). None of the patients who underwent MRI examination of the brain had significant MRS findings.

3.4. Molecular genetic study data

Using Whole Exome Sequencing (WES), a homozygous pathogenic, probable pathogenic and a variant of unknown significance in the DL D gene were detected in all patients: NM_0001083. The homozygosity inheritance related to the high consanguinity in our population. All variants detected were missense. The most frequently reported variant was c.685G > T, p.(Gly229Cys) which was detected in 5 patients (62%), mostly with hepatic form. In addition, c.1436A > T, p.(Asp479Val) was detected in two patients. Finally, one patient in this cohort has a novel variant c.623C > T, p.(Ser208Phe). This variant was not present in our local database, furthermore ACMGG classifies this variant as PM2, PP2, PP3. The substitution was classified as deleterious by computerized prediction tools (PolyPhen2, MutationTaster, FATHMM, PROVEAN, and SIFT).

4. Discussion

We reported the clinical phenotype, biochemical tests, and molecular tests of 8 patients with confirmed DLDD. The phenotype spectrum of this disease ranges from early-onset neurologic manifestations to late-onset...
liver involvement and, rarely, myopathic manifestations. The clinical and biochemical variability proved to be unpredictable on the sole basis of the genotypic characteristics or loss of enzymatic activity of the E3 component. This could be due to many factors related to the degree of increase in reactive oxygen species (ROS) especially during acidosis. The most frequently detected variant in the sample was c.685G > T p. (Gly229Cys), which showed dramatic improvement after being treated with nutritional supplements (Carnitine, Coenzyme Q10, Thiamine, Riboflavin, and Biotin). She was not hospitalized for three years after diagnosis and treatment. Neurological symptoms varied among the five patients, with two patients (patients 4 and 8) having a combination of hepatic and neurological presentation and abnormal neurological imaging findings when available. To date, the only affected DLDD patients with hepatic presentation who had neurological symptoms had experienced severe episodes associated with deep coma. This sometimes makes the distinction between the two types difficult and may explain the overlap of symptoms in cases 4 and 8.

In this cohort, one female patient (patient 6) had neonatal onset neurological manifestations due to c.1436A > T, p.(Asp479Val). The seizures occurred shortly after birth, were rapidly progressive, and were frequently recorded. She had microcephaly, developmental delay, mild behavioral disturbances, cerebellum signs, hypotonia, but no dystonia or cardiac involvement. Remarkably, her MRI scans were within normal structure and myelination for her age. Her clinical condition improved after the introduction of thiamine, biotin, carnitine, and dichloroacetate (DCA), which showed as a decrease in the number of crisis and admissions to the hospital. We discovered the same mutation in one patient in

### Table 1

| Demography | Onset | Molecular test | Clinical phenotype | HCM | OPC | BCAA | LA | Brain images | Treatment |
|------------|-------|----------------|-------------------|-----|-----|------|----|--------------|-----------|
| Patient 1  | Male  | Homozygous, c.685G > T p. (Gly229Cys) (Pathogenic) | Mild course with mild ketotic hypoglycemia, lactic acidosis, and mild persistent elevated AST / ALT during catabolic stress. He has normal psychomotor function with no neurological symptoms. | UK  | N   | Normal | Yes | UK           | Carnitine, Coenzyme Q10, Thiamine, Riboflavin, and Biotin. |
| Patient 2  | Female | Homozygous, c.685G > T p. (Gly229Cys) (Pathogenic) | Episodic cyclic vomiting with mild persistent elevated AST / ALT. She had two episodes of Reye-like syndrome. She has normal psychomotor function with no neurological symptoms. | Yes | N   | Normal | Yes | Normal       | Carnitine, Coenzyme Q10, Thiamine, Riboflavin, and Biotin. |
| Patient 3  | Male  | Homozygous, c.685G > T p. (Gly229Cys) (Pathogenic) | Recurrent acute hepatic failure, encephalopathy, with mild persistent elevated AST / ALT, associated with metabolic acidosis. He has normal psychomotor function with no neurological symptoms. | No  | N   | Normal | Yes | Normal       | Carnitine, Coenzyme Q10, Thiamine, Riboflavin, and Biotin. |
| Patient 4  | Female | Homozygous, c.685G > T p. (Gly229Cys) (Pathogenic) | She has psychomotor dysfunction (DD/ID), seizures with mild persistent elevated AST / ALT. | No  | Micro | Elevated | No | Bilateral and symmetrical increased T2-weighted signal intensity affecting the putamen and caudate nuclei with atrophic changes. | Antiepileptic: Levetiracetam Rehabilitation. |
| Patient 5  | Male  | Homozygous, c.685G > T p. (Gly229Cys) (Pathogenic) | She has psychomotor dysfunction and (DD/ID) | UK  | Micro | Normal | No | Bilateral and symmetrical increased T2-weighted signal intensity affecting the putamen and caudate nuclei with atrophic changes. | Supportive |
| Patient 6  | Female | Homozygous, c.1436A > T p. (Asp479Val) (Pathogenic) | She has psychomotor dysfunction (DD/ID, seizures, and hypotonia). | No  | N   | Normal | Yes | Normal Carnitine, Thiamine, Biotin and Dichloroacetate |
| Patient 7  | Male  | Homozygous, c.1436A > T p. (Asp479Val) (likely pathogenic) | She has psychomotor dysfunction (DD/ID, seizures (focal), hypotonia, dystonia and optic atrophy) | Yes, mild | N | Elevated | Yes | Thin corpus callosum | Carnitine, Riboflavin, Thiamine, Biotin, and Sodium bicarbonate |
| Patient 8  | Female | Homozygous, c.623C > T p. (Ser208Phe) Variant of unknown significance | She has psychomotor dysfunction (mild hypotonia and DD), Recurrent acute hepatic failure (Reye-like syndrome) and metabolic acidosis. | UK  | N   | Elevated | Yes | UK            | Carnitine, Coenzyme Q10, Thiamine, Riboflavin, and Biotin. |

| (DD) developmental delay, (ID) intellectual disability, (HCM) hypertrophic cardiomyopathy, (UK) unknown, (OPC) head circumference, (BCAA) branched chain amino acid, (LA) lactic acidosis and (Micro) microcephaly. | (ALT) Alanine transferase, (AST) Aspartate aminotransferase, (AST) Aspartate aminotransferase, (N) Normal. |
the current cohort (patient 7). His symptoms began at 7 months of age in the form of epilepsy, dystonia, optic atrophy, severe developmental delay, hypotonia, and a thin corpus callosum, in addition to an elevated BCAA levels, and lactic acidosis. Later in the course of the disease, he developed mild hypertrophic cardiomyopathy. This variant was reported in a patient with neonatal manifestations including episodes of apathy, metabolic acidosis, and lactic acidosis. At 9 months of age, he showed neurological symptoms in the form of developmental delay, hypotonia, microcephaly and mild hypertrophic cardiomyopathy [23].

Only one patient (patient 8) had a variant of unknown significance, c.623C>T p. (Ser208Phe), which had not been reported previously. This patient had mild developmental delay and hypotonia, showed episodic hepatic dysfunction, and metabolic derangements (hyperammonemia, elevated BCAAs, high lactic acidosis (2.45–8.70 mmol/l), organic urine and was unremarkable. Elevated BCAAs occurred in three patients in this cohort (37%). Episodic lactic acidosis with metabolic acidosis in six patients (75%), and hypoglycemia in only two cases (25%). Quinonez et al. studied the phenotype, biochemical markers, and genetic variant of 25 patients with different molecular outcomes in a larger cohort. Lactic acidosis was observed in 5 of the 25 patients (20%), elevated BCAA in 11 patients (44%), and hypoglycemia in only 4 patients (16%) [24]. To date, there are no consistent recommendations for the management of DLDD. In general, effective treatment depends not only on lowering the concentrations of pathological metabolites, but also on controlling the underlying metabolic derangement. Several strategies (e.g., restriction of proteins/BCAAs, oral BCAAs, thiamine, and lipoic acid supplementation, and nutritional therapy and consideration of a gastrostomy tube for persistent feeding problems) that have been tried in neurologic presentation do not appear to significantly alter disease progression. Lipoic acid is an essential cofactor for the E2 subunits of BCKDH, αKGDH, and PDH as well as to the glycine cleavage system. It has been reported in the literature that in some individuals with myopathic and hepatic presentation, laboratory values and/or clinical condition improved with supplementation alone or in combination with a low-protein diet [11,20,21]. In this cohort, most patients were started on supplementation with variable response. A systematic evaluation of the effect of available therapies is needed.

5. Conclusions

In this descriptive study, we describe the pattern of presentation and molecular characterization in eight DLDD patients. The correlation between genotype and phenotype cannot be predicted in DLDD patients. To date, there is no effective treatment for this disorder, so early detection, molecular confirmation, and prenatal testing are needed to prevent severe disease such as DLDD.

Consent for publication

Informed consent to conduct the research study and to publish the cases was signed by the patients’ fathers.

Availability of data and materials

All data generated or analyzed as part of this study are included in this published article. Any additional data/files can be requested from the corresponding author.

Authors’ contributions

ALF, FAM prepared and summarized the literature, drafted the table, and wrote the manuscript. MAF, SAL, ALH, ITB, FAB, ALF edited the manuscript, collected the data, and contributed to the clinical diagnosis and management of the patients.

Declaration of Competing Interest

The authors declare that they have no competing financial interests.

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