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CLINICAL CASES

Pyruvate dehydrogenase deficiency: with more phenotypes than we think: A case report.

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Abstract

Introduction: The pyruvate dehydrogenase complex (PDC) is a multienzyme complex responsible for catalyzing the oxidative decarboxylation of pyruvate to acetyl CoA. A defect in any of its components can interfere with energy production at the cellular level; within these disorders is pyruvate dehydrogenase (PDH) deficiency characterized by clinical neurological and systemic signs of variable severity, highlighting lactic acidosis, neurological and progressive neuromuscular deterioration.

Objective: To describe the case of a school patient with characteristic craniofacial dysmorphology, neurodevelopmental delay, and episodes of metabolic decompensation due to infections, with a mutation in the PDHX gene, managed with a ketogenic diet, thiamine, lipoic acid, and carnitine.

Results: The findings that made it possible to focus the diagnosis are elevated plasma and CSF lactate associated with persistent metabolic acidosis with accentuation of hyperintensity cortical sulci in the bilateral basal ganglion region and lenticular nuclei in brain resonance imaging, with magnetic resonance spectroscopy showing a negative peak of lactate. Confirming the diagnosis with an exome of 6000 genes where a homozygous pathogenic variant is found in the PDHX gene position c.1426C> T.

Conclusion: PDH deficiency should be considered in cases of neurodevelopmental delay associated with intermittent episodes of neurological deterioration and elevated blood lactate and in brain magnetic resonance spectroscopy. Unlike those affected by other subtypes, patients with E3-binding protein deficiency often survive childhood and even adulthood due to the presence of some assembly of the pyruvate dehydrogenase complex. Early diagnosis opens the possibility of starting supportive management, providing genetic counseling to parents, and prognosis and early support measures.

Keywords:

MESH: Acidosis, Lactic; Pyruvate Dehydrogenase (Lipoamide); Mitochondrial Diseases, Lactic Acid; Diet, ketogenic.

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Introduction

The pyruvate dehydrogenase complex (PDC) is a multienzyme complex essential for energy production and carbohydrate metabolism and is responsible for the passage of pyruvate to acetyl-CoA; its deficiency (PDHD) affects cellular energy metabolism, especially of the central (CNS) and peripheral (PNS) nervous systems [1].

It is a rare hereditary disease with a prevalence of <1/1,000,000 live births. Its main etiology is a mutation in the PDHA1 gene on the X chromosome (Xp22.12), which encodes the E1-alpha subunit, with a pattern of X-linked inheritance. Being more frequent in men, however, due to inactivation of X, it can occur in women with a more severe phenotype [2]; less frequently, mutations have been described in the E2 fraction (PDHA2 gene), E1-beta subunit (PDHB gene), pyruvate dehydrogenase phosphatase (PDP1) and E3BP protein (PDHX); the latter with unknown prevalence, approximately 20 cases have been reported to date [3].

Clinical manifestations present a wide spectrum depending on age and sex. Neurological phenotypes include cerebral dysgenesis, encephalopathy, coma, epilepsy, motor deficit, dystonia, neuropathy, and ataxia [4].

Diagnosis was previously based on the measurement of pyruvate in lymphocytes, fibroblasts, or skeletal muscle cells with a sensitivity of 91% and a much lower specificity [5]; however, at present, the definitive diagnosis is made using genetic tests, which should be considered in cases of elevated plasma and CSF lactate and pyruvate levels associated with lactic acidosis of unclear etiology [1].

In this article, we refer to the case of a school patient with dysmorphologies, craniofacial disorders, neurodevelopmental delay and episodes of neurological deterioration and multisystemic failure associated with metabolic acidosis, hyperlactatemia, hyperglycemia with hyperintensities in T2 and FLAIR in the bilateral basal ganglia region and lenticular nuclei, and lactate elevation with subsequent confirmation of mutation in the PDHX gene.

The case of a female schoolgirl evaluated in a level IV pediatric hospital located in the city of Bogotá, Colombia, was recorded. Following the protocols established by the hospital, authorization for the publication of clinical data was requested from those responsible for the patient, which they accepted by signing an informed consent form.

Case report

A 9-year-old female schoolgirl, healthy parents, not consanguineous, born at term of pregnancy and normal delivery with immediate crying, weight 2620 g and height 47 cm, presented with neonatal jaundice with bilirubin <14 mg/dl, managed with phototherapy. From 5 months of life, no gain of neurodevelopmental milestones, generalized hypotonia or dysphagia for solids and semisolids were identified. He was admitted to the hospital at 9 months with an initial diagnosis of respiratory infection that rapidly progressed to multisystem failure; in the neurological examination, dysmorphologies were noted craniofacial features given by microcephaly, prominent metopic crest, bilateral epicanthus, anteverted and hypoplastic nostrils, oblique palpebral fissure, retrognathia, skin pigmentation and light hair; absent motor patterns for age, hyporeflexia and generalized hypotonia.

During his hospitalization, he presented with torpid clinical evolution with persistent hyperlactatemic metabolic acidosis, hyperglycemia and hyperammonemia, requiring prolonged invasive ventilatory support. Organic acidosis was suspected. Complementary studies were requested that showed a slight increase in alanine in plasma, without other findings (Table 1) and MRI brain MRI (CMR) with slight thinning of the corpus callosum. The general condition improved progressively, and outpatient management was given.

Diagnostic workshop

The main studies are presented in Table 1.

Table 1. Main exams carried out.

Paraclinical	Outcome
Auditory Evoked Potentials	normal
Echocardiogram	asymmetric trileaflet aortic valve - mild tricuspid regurgitation, good biventricular function.
Video telemetry 6 hours	Normal, no alteration of background rhythms.
Ammonium	59 mmol/L
Plasma amino acids by HPLC	Alanine 714 umol/l (Vr up to 535) No other relevant finding
Plasma lactic acid	3.01 mmol/L
Plasma pyruvic acid	0.25 mmol/L
Lactic acid in CSF	2.9 mmol/L
Lactate/Pyruvate Ratio	12.04
Karyotype	46 XX

At 12 months, he was readmitted to the hospital with an acute diarrheal disease that quickly led to multiorgan failure. He again presented with persistent hyperlactatemic metabolic acidosis, hyperglycemia and hyperammonemia. Disease due to energy failure was suspected, and complementary tests showed hyperlactatemia in the CSF (Table 1). A new request was made. CMR found accentuation of cortical sulci, hyperintensities in T2 and FLAIR in the bilateral basal ganglia region and lenticular nuclei (Figure 1). Magnetic resonance spectroscopy (MRS) confirmed a double-negative lactate peak with a prominent choline peak at the lesion level (Figure 2).

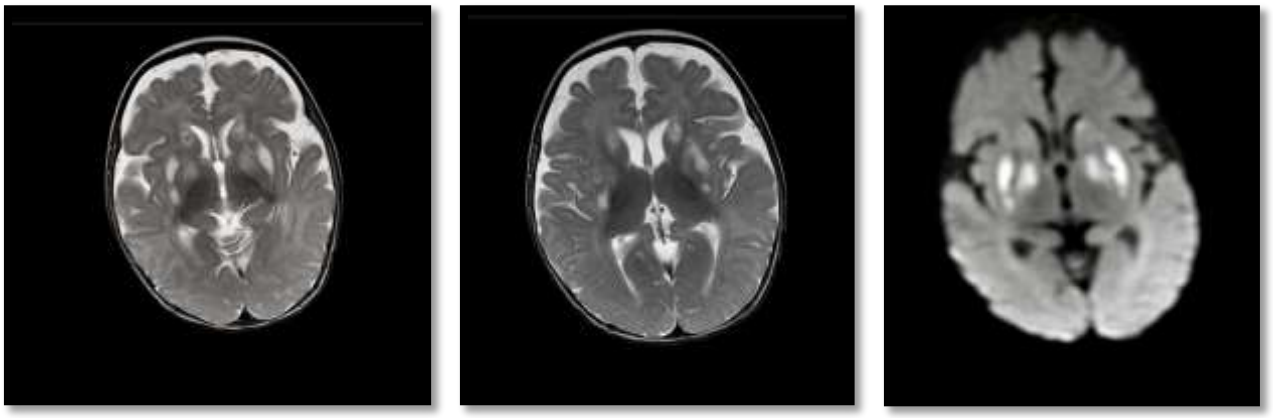

Figure 1. Hyperintensity in the caudate nuclei and bilateral putamen in T2 sequence of axial slice of CMR. b. Hyperintensity in the caudate nuclei, putamen and bilateral globus pallidus in T2 sequence of axial CMR slice. c. Diffusion restriction in bilateral basal ganglia region in DWI sequence.

Given clinical, paraclinical and imaging findings, neurodegenerative disease with multisystem involvement, inborn error of metabolism of the energy deficit group, for which a complete exome of 6000 genes is requested, confirming mutation of the PDHX c.1426C>T gene, is considered the first possibility. in pathogenic homozygosity compatible with pyruvate dehydrogenase deficiency. Acute management with bicarbonate is started to manage acidosis, a ketogenic diet and thiamine supplementation.

At 18 months, he started head support, seated at 2 years, 3 years of crawling, bipedal at 5 years, sign language and crying. He presented three episodes of metabolic decompensation after ingesting foods rich in carbohydrates, which required management in intensive care, with the last event at 7 years.

At the time of the report, stable patient walking independently with short steps, severe cognitive disability, without language acquisition, under management by neurology, pediatrics, nutrition and genetics.

Discussion

The pyruvate dehydrogenase complex (PDC) is a multienzyme mitochondrial complex composed of three enzymatic subunits: pyruvate dehydrogenase (E1), which is a heterotetramer of 2 subunits (alpha and 2 beta), dihydrolipoamide transacetylase (E2) and dihydrolipoamide dehydrogenase (E3). involved in the aerobic oxidation of glucose catalyzes the irreversible decarboxylation of pyruvate in acetyl-CoA to start the tricarboxylic acid (TCA) cycle, which is fundamental for the production of energy and metabolization of carbohydrates [4].

The decrease in the availability of acetyl-CoA reduces the production of cofactors nicotinamide adenine dinucleotide and flavin adenine dinucleotide, whose main function is to provide the respiratory chain with electrons for oxidative phosphorylation, promoting the cytoplasmic reduction of pyruvate to lactate [4].

PDHD was first described in 1970 by John P. Blass and colleagues [6] in an 8-year-old boy with balance disorders and involuntary movements associated with infections [6]. Currently, a prevalence of <1/1,000,000 live births has been described, with a variable inheritance pattern, autosomal recessive, as in the reported case, or X-linked; in the latter, affected males are symptomatic. In contrast, heterozygous females exhibit a variable pattern of X inactivation in different tissues; thus, their symptomatology is variable [7].

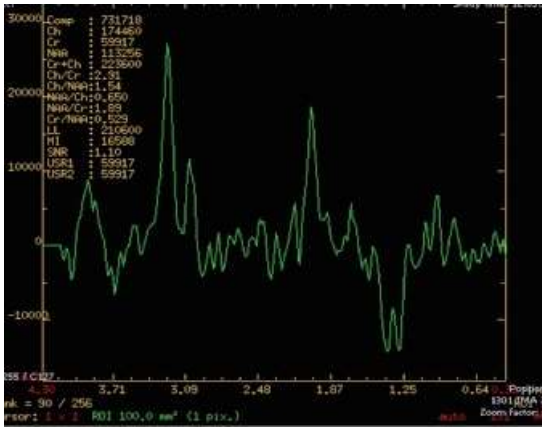

Figure 2. Magnetic resonance spectroscopy (MRS) confirms double negative lactate peak with prominent choline peak at lesion level.

More than 50 mutations have been described in patients with PDHD (2). In this report, we show a molecular variant in the PDHX c.1426C>T gene in pathogenic homozygosis compatible with pyruvate dehydrogenase deficiency of the E3 binding protein. The most common cause (approximately 90%) is mutation in the PDHA1 gene on the X chromosome (Xp22.12), which encodes the E1-alpha subunit. Alterations in the other subunits have been identified but are much less frequent: E1-beta and E2 subunits (PDHB, DLAT); E3 binding protein (PDHX gene); E3 subunit and PDH phosphatase (DLD and PDP1). Table 2 shows the main mutations and clinical characteristics [8].

Mechanisms in the genesis of neurological symptoms include [2]: Altered embryogenesis, especially neuronal proliferation and migration, which require a large amount of energy, causing complete or partial agenesis of the corpus callosum, gray matter heterotopias in the periventricular area, dentate gyrus dysplasia and Purkinje cell heterotopias.

Table 2. Most common mutations in pyruvate dehydrogenase deficiency, genetic location and clinical characteristics.

gene	Location	Protein	Inheritance	Characteristic
PDHA1	XP22.12	E1- alpha	Bound to the X chromosome	They present with a variety of classic signs and symptoms of PDHD: lactic acidosis, poor feeding, lethargy, tachypnea, developmental and growth retardation, poor acquisition or loss of motor milestones, hypotonia, seizures, ataxia, and dystonia. Structural lesions are frequently seen in the brain including cortical atrophy, dilated ventricles, incomplete corpus callosum, absence of medullary pyramids, and ectopia of the olivary nucleus.
PDHB	3p 14.3	E1-beta	autosomal recessive	They present lactic acidosis and hypotonia at birth and often come from consanguineous families. There are no specific clinical features that differentiate this disease from E1-alpha subunit deficiency.
DLAT	11q23.1	E2	autosomal recessive	They present movement disorders and globus pallidus lesions similar to those found in patients with pantothenate kinase-associated neurodegeneration.
DLD	7q31.1	E3	autosomal recessive	Characterized by early-onset lactic acidosis and developmental delay, late-onset neurologic dysfunction, or liver disease.
PDP1	8q22.1	Pyruvate dehydrogenase phosphatase	autosomal recessive	Extremely rare. Less than 5 documented cases
PDHX	11p13	Protein binding to E3	autosomal recessive	Variable lactic acidosis, developmental delay and hypotonia during childhood. As in the reported patient, there is good survival in childhood, since there is a certain assembly of the pyruvate dehydrogenase complex. More common than DLAT, but less than PDHA1

On the other hand, acute energy insufficiency causes postnatal lesions, mainly in areas of high energy consumption during development, such as the tegmentum, dentate nuclei, and basal ganglia, especially the putamen.

From the clinical point of view, there are different degrees of severity, from severe forms leading to death in the neonatal period to mild forms with symptoms presenting in adulthood. In severe cases, the symptoms can start during the fetal period and affect the development of the CNS, appearing as alterations such as agenesis of the corpus callosum, microcephaly, dysmorphologies and periventricular leukomalacia [9]. Most patients with PDHD manifest neurological dysfunction, as in the case of our patient, where global neurodevelopmental delay associated with metabolic decompensation secondary to infections and craniofacial dysmorphologies was identified. Additional symptoms may include hypotonia, early-onset epilepsy, ataxia, chronic neuropathy, and encephalopathy [10]. Dysmorphological alterations are a rare finding in PDHD, affecting only 11% of patients and causing greater interest in the reported case [11].

Clinically, our patient presented stabilization during her course; unlike other forms of pyruvate dehydrogenase deficiency, patients with this subtype often survive well from childhood to adulthood, since there is some assembly of the pyruvate dehydrogenase complex, even with a total deficiency of this protein [12]. In the study by Barneiras et al [13], four important neurological phenotypes were identified.

Epilepsy in PDHD has been described as late-onset generalized epileptic seizures that are drug-sensitive and respond adequately to a ketogenic diet. Characteristically, atypical absences and childhood-onset myoclonic seizures associated with dystonic movements have been linked [14].

Pathophysiologically, it has been suggested that PDHD could destabilize the neurotransmitter balance in the glioneuronal unit and in neuronal networks, since glutamate and GABA are obtained from the TCA cycle through alpha ketoglutarate [11].

Table 3 Phenotypes in PDHD; Based on Barnerias et al (13) .

Phenotype	Characteristic
neonatal encephalopathy and lactic acidosis	Abnormal brain development with microcephaly, agenesis of the corpus callosum, and severe cortical atrophy, causing encephalopathy with severe lactic acidosis, hypotonia, and coma. In addition, clear dysmorphologies with a long nasolabial fold and a thin upper lip were described.
encephalopathy childish nonprogressive	Psychomotor retardation combined with neuropathy, paroxysmal dystonia or early epilepsy. Group to which our patient belongs.
Syndrome by Leigh	Acute brainstem dysfunction in childhood (central apnea, bradycardia, and acute oculomotor abnormalities, with typical abnormalities of the basal ganglia.
Ataxia recurrent	Proprioceptive deficit and axonal neuropathy in previously normal children, associated with pes cavus and recurrent motor deficit without cerebellar involvement Ataxia is possibly the result of a combined acute motor and sensory deficiency.

Additionally, the possible involvement of different regional networks and other neurotransmitters (dopamine) has been postulated, which may cause variable neurological phenotypes (paroxysmal dystonia, ganglia injury and cerebellar ataxia [15]; however, it is neither characteristic nor pathognomonic and even thus far it has not been reported in our patient.

In relation to the paraclinical tests that allowed guiding the diagnosis of DPHD in the present, the presence of hyperlactatemia in plasma and CSF stands out, with a lactate L/P index in blood ≤ 20, associated with a picture of metabolic acidosis, thus becoming a differential diagnosis in hyperlactatemic metabolic acidosis of unclear cause. In newborns and infants, there are several causes of metabolic acidosis, including perinatal asphyxia, hypovolemia, sepsis, congenital heart disease, kidney disease, respiratory distress syndrome, and IEM [13].

When metabolic acidosis is unexplained, persistent, and severe, further evaluation, including blood and CSF lactate, pyruvate, ammonia, glucose, plasma amino acids, and urine organic acids, should be considered [13]. Other etiologies must be ruled out, especially in those patients with neurological deterioration associated with infections, such as organic acidemia, Leigh syndrome, Complex I deficiency, cytochrome oxidase deficiency due to mutation in the SURF1 gene and a series of mutations in mitochondrial DNA [16]. At this point, neuroimaging acquires great importance since it allows an imaging approach in the initial approach.

Brain MRI shows accentuation of cortical sulci, hyperintensities in T2 and FLAIR in the bilateral basal ganglia region and lenticular nuclei; although they are not pathognomonic, they were found in anatomical regions characteristic of this disease. Different brain abnormalities have been reported in the literature, including cortical atrophy, ventriculomegaly, dysgenesis of the corpus callosum, and subacute necrotizing encephalomyopathy [17]. Normal CMR is not a common finding; however, a study of 371 patients reported normal CMR in only 7 (2%) patients, all of whom had E1α deficiency [4].

Magnetic resonance spectroscopy (MRS) allows biochemical and functional assessment of tissues; in this case, MRS allows us to evaluate lactate, a fundamental metabolite of anaerobic glycolysis. MRS is generally found in low concentrations at the brain level under normal conditions, and high concentrations are indicative of alterations in oxidative phosphorylation and energetic dysfunction, as in the case of mitochondrial characteristics. [18].

The rapid progress in genetic tests has allowed a more accurate and earlier diagnosis; next-generation sequencing (NGS) has revealed a large number of genetic mutations and has been essential for the diagnosis of DPHD, as in this case [19].

Regarding treatment, there is no curative or preventive treatment for the disease. Several strategies have been implemented, with variable success, such as the use of vitamins, coenzymes and trace elements that favor chemical reactions in the mitochondria, among which thiamine, carnitine and lipoic acid stand out [20], used in our patient, with subsequent stabilization in their acute decompensations. A limited number of patients with mutations in the PDHA1 gene respond to thiamine and usually have better clinical outcomes [21].

One of the advances in treatment is the ketogenic diet, which has been used to provide an alternative energy source to the CNS through the formation of ke-

tones and to help control epilepsy and recurrent episodes of paroxysmal dystonia or ataxia [13]; dietary treatment implies risks of dyslipidemia, urolithiasis, pancreatitis, cardiac disorders or thrombocytopenia. The administration of dichloroacetate is responsible for inhibiting the kinase of pyruvate dehydrogenase, activating the complex

Conclusions

PDH deficiency should be considered in cases of neurodevelopmental delay associated with intermittent episodes of neurological deterioration and elevated blood lactate and by spectroscopy. Unlike those affected by other subtypes, patients with E3-binding protein deficiency often survive childhood and even adulthood because of some assembly of the pyruvate dehydrogenase complex. Hyperlactatemia is a frequent, but not universal, finding that is associated with a blood lactate:pyruvate ratio ≤ 20 and morphological alterations in neuroimaging and is part of the diagnostic keys. Although there is still no curative medical management, interventions must be adapted to signs and symptoms individually, advising parents on care and help, as well as psychological and social support for the family group.

Abbreviations

HDPD:
NGS: Next Generation Sequencing.
PDH: pyruvate dehydrogenase.
PDHD: pyruvate dehydrogenase deficiency

Supplementary information

Supplementary materials are not declared.

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Author contributions

Divahia García Martín: Conceptualization, Data Retention, Fundraising, Research, Resources, Software, Writing - original draft.
Natalia Martinez Córdova: Data curation, research, fundraising, supervision, methodology.
Eugenia Espinosa García: Curation of data, research, acquisition of funds, supervision, methodology.
All authors read and approved the final version of the manuscript.

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Availability of data and materials

The data sets generated and/or analyzed during the current study are not publicly available due to participant confidentiality but are available through the corresponding author upon reasonable academic request.

Statements

Ethics committee approval and consent to participate

It was not needed.

Publication consent

We have written permission from the patient's guardian for the publication of this case.

Conflicts of interest

The authors declare no conflicts of interest.

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