Case Report

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# Pyruvate Dehydrogenase Deficiency: With More Phenotypes Than We Believe

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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 the production of energy on a cellular level; within these disorders we find pyruvate dehydrogenase (PDH) deficiency characterized by clinical neurological and systemic signs of varying severity, highlighting lactic acidosis, neurological and progressive neuromuscular deterioration.*

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

***Results:*** *The findings that made it possible to focus the diagnosis were elevated plasma and CSF lactate levels associated with persistent metabolic acidosis with accentuation of hyper intensity in the cortical sulci and in the in the bilateral basal ganglia and lenticular nuclei region of the brain on magnetic resonance imaging. Magnetic resonance imaging with spectroscopy showed 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 as well as elevated lactate in magnetic resonance spectroscopy of the brain. Unlike those affected by other subtypes, patients with E3-binding protein deficiency often survive childhood and even adulthood due to the presence of assembly to a certain extent of some of the pyruvate dehydrogenase complex. Prompt diagnosis opens the possibility of starting early supportive management, providing genetic counseling to parents, as well as establishing prognosis.*

## Keywords

Lactic acidosis, Pyruvate dehydrogenase, Mitochondrial diseases, Lactate, Ketogenic diet.

## Introduction

The pyruvate dehydrogenase complex (PDC) is a multienzymatic complex that is fundamental in the production of energy and carboohydrate metabolism, it oversees the conversion of pyruvate to Acetyl-CoA. Its deficiency (PDHD) afects the cells energy metabolism, especially those in the central (CNS) and peripheral (PNS) nervous systems [1].

It is an uncommon, inherited disease, with low prevalence of <1/1 000 000 per living births. It is caused by a mutation in the PDHA1 gene, located in chromosome X (Xp11.12) that codes for the E1-alpha subunit, with an X-linked inheritance pattern. It is more

frequent in men, nevertheless, due to the deactivation of one of the X chromosomes, in women it may be present with a more severe phenotype [2]. Other mutations have also been described, even though they appear to be less frequent; such as mutations in the E2 fraction (gene PDHA2), subunit E1-beta (gene PDHB), pyruvate dehydrogenase phosphatase (PDP1) and in protein E3BP (PDHX), this last one mentioned has an unknown prevalence, where up to this date approximately 20 cases have been reported [3].

The clinical manifestations present an ample spectrum depending on age and sex. Within the neurological phenotypes we find cerebral dysgenesis, encephalopathy, coma, epilepsy, motor deficits, dystonia, neuropathy and ataxia [4].

The diagnosis was previously based on the measurement of pyruvate in lymphocytes, fibroblasts or skeletal muscle cells with a 91% sensitivity and a much lower specificity [5]. Thus, today the definitive diagnosis is performed under genetic testing, that should be considered in cases of elevated lactate levels, elevated pyruvate plasma levels as well as in the CSF, associated to a clinical scenario of lactic acidosis of unknown cause [1].

In this article, we present the case of a female school aged patient with craniofacial dismorphologies, neurodevelopmental delay and episodes of neurologic deterioration accompanied by multisystem failure associated to metabolic acidosis, hyperlactatemia, hyperglycemia and evidence of bilateral hyperintensities on T2 and FLAIR in the basal ganglia region and in the lenticular nuclei. The elevation of lactate is later confirmed with a mutation of the PDHX gene.

## Materials and Methods

The case of a school aged girl was registered in a level IV pediatric hospital, located in the city of Bogotá, Colombia. In accordance with the protocols established by the hospital, authorization was requested from those responsible of the patient, for the publication of clinical data, which they accepted by signing an informed consent form.

## Case Report

A 9-year-old, school aged girl, with healthy, non-consanguineous parents, born at full term, normal delivery with immediate cry, weighed 2620 grams, 47 cm, presented neonatal jaundice with bilirubin values <14mg/dL, treated with phototherapy. From 5 months of age a delay in appropriate milestone acquisition was identified, generalized hypotonia and solids and semisolids dysphagia. At 9 months of age she is admitted to the hospital with an initial diagnosis of a respiratory infection that deteriorates rapidly to a multisystem failure. On neurological exam positive findings were craneofacial dysmorphology due to microcephaly, prominent metopic crest, bilateral epicanthus, anteverted and hypoplasic nares, oblique palpebral fissures, retrognatia, light skin and hair pigmentation, absent motor patterns expected for her age, hyporreflexia and generalized hypotonia.

During her hospital stay she presented an unfavorable evolution of her symptoms with persistent metabolic acidosis with hyperlactatemia, hyperglycemia and hyperammonemia requiring prolonged invasive ventilatory support. Thus, organic acidosis in suspected and complementary studies are obtained, evidencing a slight increase in plasma alanine, without any other findings (Table 1). Magnetic resonance imaging of the brain (MRI) shows slight thinning of the corpus callosum. Her general condition progressively improved and outpatient monitoring was given.

**Table 1:** Lab and test results. Own authorship.

| Labs and Tests | Results |
|---|---|
| Auditive evoked potentials | Normal |
| Echocardiogram | Normo-functioning asymmetric trivalve aortic valve<br>Slight tricuspid insufficiency, good biventricular function. |
| 6 hr Video telemetry | Normal, no alteration. |
| Ammonium | 59 mmol/L |
| Plasma amino acid quantification using HPLC (high performance liquid chromatography) | Alanine 714 umol/l (Normal value <535)<br>No other relevant findings |
| Lactic acid in plasma | 3.01 mmol/L |
| Pyruvic acid in plasma | 0.25 mmol/L |
| Lactic acid in CSF | 2.9 mmol/L |
| Lactate/Pyruvate Ratio | 12.04 |
| Karyotype | 46 XX |

At 12 months of age the patient is readmitted due to an acute diarrheal ilness that quickly progresses to multiorgan failure,

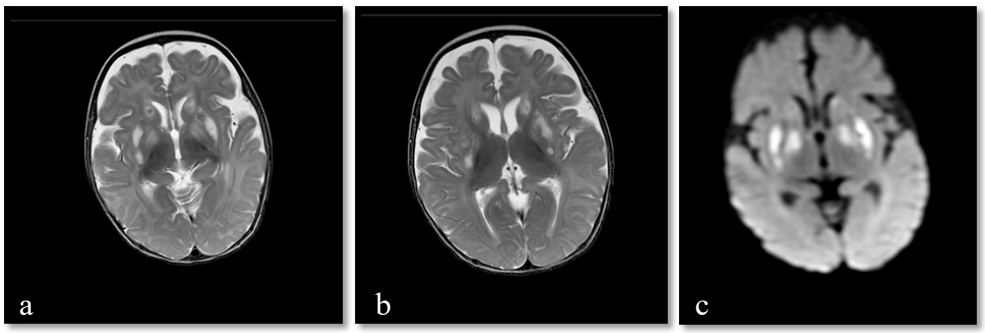


**Figure 1:** a. Bilateral hyperintensity in the caudate nucleus and putamen in an axial view of T2 sequence of MRI. b. Bilateral hyperintensity of the caudate nuclei, putamen, and globus pallidus in an axial view of T2 sequence of MRI. c. Bilateral restriction of diffusion in the basal ganglia region on DWI sequence.

additionally she also presents persistent metabolic acidosis with hyperlactatemia, hyperglycemia and hyperammonemia. A disease due to energy production failure is suspected and compementary tests evidenced hyperlactatemia on CSF (Table 1), a new MRI is ordered with findings of accentuated cortical sulci, hyperintensities in the basal ganglia and lenticular nuclei region on T2 and FLAIR (Figure 1), magnetic resonance imaging through spectroscopy (MRS) confirms a double negative peak of lactate with a prominent hill peak at the level of the lesion (Figure 2).

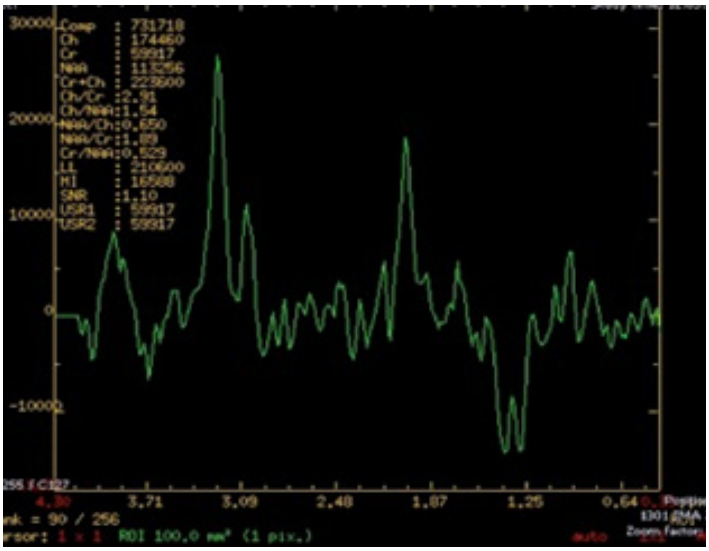


**Figure 2:** Magnetic resonance imaging through spectroscopy (MRS) confirms a double negative peak of lactate with a prominent hill peak at the level of the lesion.

Due to the clinical findings, laboratory and test results, and imaging; a neurodegenerative disease with multisystem compromise is considered as a primary diagnosis. A part of the inborn errors of metabolism, of the energy deficiencies group. Therefore, a complete exome of 6000 genes is obtained and confirms the mutation of the PDHX gene x. c.1426C>T in pathogenic homocygosis compatible with a pyruvate dehydrogenase deficiency. Acute management is begun with bicarbonate for management of acidosis, a ketogenic diet and thiamine supplementation.

At 18 months of age the patient begins cephalic support, she sits at 2 years of age, crawls at 3 years of age and stands at 5 years of age. Communicates through gestures and cry, she developed three more episodes of metabolic decompensation followed by the ingestion of rich carbohydrate foods that required management in the ICU, last episode was at 7 years of age.

Currently, the patient is stable, with an independent gait with short steps, severe cognitive disability, without acquisition of language. Her comprehensive care management is followed up by neurology, pediatrics, nutrition and genetics.

## Discussion

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

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

PDHD was first described in 1970 by John P. Blass and colaborators [6] on an 8-year-old child with balance and involuntary movement disorders associated with infections [6]. Nowadays, a prevalence of <1/1 000 000 live births has been described, with a varying inheritance pattern: autosomal recessive as is the case reported; or X-linked, in this case males who are affected are asymptomatic. And on the contrary, heterocygote women who present it have a varying pattern of X inactivation in different tissues, therefore displaying varied symptoms [7].

Over more than 50 mutations in patients with PDHD have been described (2). In this report, we evidenced a molecular variant of the PDHX c.1426C>T gene in pathogenic homocygosis compatible with pyruvate dehydrogenase defciency of the E3 binding protein. The most common cause (approximately 90%) is the mutation in the PDHA1 gene on chromosome X (Xp22.12) that codes for the subunit E1-alpha. Alterations in other subunits have also been identified but are much less frequent: subunits E1-beta, E2 (PDHB, DLAT), E3 binding protein (PDHX gene), subunit E3 and PDH phosphatase (DLD and PDP1). In table N°2 the most common mutations are presented with their clinical characteristics [8].

The mechanisms that make way for the manifestation of neurological symptoms include [2]: alteration of embryogenesis especially neuronal proliferation and migration which are processes that require a great amount of energy; this, causing partial or complete agenesis of the corpus callosum, heterotopy of gray matter especially in the periventricular area, dysplasia of the dented gyri and heterotopy of the Purkinje cells. On the other hand, acute energetic insufficiency causes post-natal lesions, mainly in areas of greater need for energy during development such as the tegmentum, the dented nuclei and basal ganglia, specifically in the putamen.

Under a clinical perspective, varying states of severity exist that range from a severe state that leads to death during the neonatal period to very mild states that present symptoms until later in the

**Table 2**: Most common mutations of pyruvate dehydrogenase deficiency, genetic locations and clinical characteristics. Source: Own authorship.

| Gene | Location | Protein | Inheritance | Characteristics |
|---|---|---|---|---|
| PDHA1 | Xp22.12 | E1- alfa | X-linked | Present varied signs and symptoms that are classic to PDHD: lactic acidosis, poor nutrition, lethargy, tachypnea, neurodevelopmental delay, failure to thrive, poor acquisition or loss of previously obtained developmental milestones, hypotonia, convulsions, ataxia and dystonia. Structural brain lesions are frequently observed such as cortical atrophy, dilated ventricles, incomplete corpus callosum and olivary nuclei ectopy. |
| PDHB | 3p 14.3 | E1- beta | Autosomal recessive | Present with lactic acidosis and hypotonia at birth that are frequently preceded by consanguineous families. There are no specific clinical traits that differentiate this disease from the one due to E1- alpha subunit deficiency. |
| DLAT | 11q23.1 | E2 | Autosomal recessive | Present with movement disorders and lesions in the globus pallidus, similar to those found in patients with neurodegeneration associated to pantothenate kinase. |
| DLD | 7q31.1 | E3 | Autosomal recessive | Characterized by lactic acidosis with precocious onset and developmental delay, a neurological dysfunction of delayed onset or liver disease. |
| PDP1 | 8q22.1 | Pyruvate dehydrogenase phosphatase | Autosomal recessive | Extremely rare<br>Less than 5 cases have been documented. |
| PDHX | 11p13 | E3 binding protein | Autosomal recessive | Varying lactic acidosis, developmental delay and hypotonia during infancy.<br>That is why in the patient reported there is good survival during infancy as it allows some assembly of the pyruvate dehydrogenase complex.<br>More frequent than in DLAT, but less than in PDHA1 |

**Table 3:** PDHD Phenotypes; Based on Barnerias et al. [13].

| Phenotype | Characteristics |
|---|---|
| Neonatal encephalopathy and lactic acidosis | Abnormal cerebral development with microcephaly, agenesis of the corpus callosum and severe cortical atropy, causing encephalopathy with severe lactic acidosis, hypotonia and coma. Also, dismorphologies were made evident described as a long nasolabial groove and thin vermilion border. |
| Non progressive infantile encephalopathy | Clinical scenario of psychomotor delay in combination with neuropathy, paroxysmal dystonia or precocious epilepsy. Group of which our patient is a part of. |
| Leigh syndrome | Acute dysfunction of the cephalic trunk during infancy (central apnea, bradycardia, acute oculomotor anomalies with typical anomalies of the basal ganglia.) |
| Recurring ataxia | Deficits in proprioception and axonal neuropathy in previously healthy children, associated to pes cavus and a relapsing motor deficit without cerebelous compromise.<br>Ataxia is possibly the result of an acute combined motor and sensory deficit. |

adult life. In severe states symptoms may begin during the fetal period and affect the development of the CNS with alterations such as agenesis of the corpus callosum, microcephaly, dismorphology, and periventricular leukomalacia [9]. Most of the patients with PDHD manifest neurologic dysfunction; such is the case of our patient, she presented global neurodevelopmental delay associated to metabolic decompensations secondary to infections and craniofacial dysmorphologies. Additional symptoms may include hypotonia, early onset epilepsy, ataxia, chronic neuropathy and encephalopathy [10]. The dismorphologic alterations are an uncommon finding in PDHD, affecting only 11% of the patients, furthermore creating a greater interest in the case reported [11].

Clinically, our patient has presented a stable course of her condition, unlike other forms of pyruvate dehydrogenase deficiency. Often this subtype of patients' lives through infancy to adult life, due to the fact that to some extent some assembly of the pyruvate dehydrogenase complex exists, even with a total deficit of this protein [12].

In the study of Barnerias et al [13] four important neurologic phenotypes were identified.

Epilepsy in PDHD has been described as generalized epileptic seizures of delayed onset, sensitive to treatment and responsive to the ketogenic diet. Characteristically it has also been related to atypical absence seizures and myoclonic seizures that begin during infancy, associated to dystonic movements [14]. Pathophysiologically it has been suggested that PDHD may destabilize the equilibrium between neurotransmitters of a glioneuronal unit and within the neuronal networks, given that glutamate and GABA are obtained through the TCA cycle from alpha ketoglutarate [11]. Additionally the possible compromise of different regional networks and other neurotransmitters (dopamine) has been postulated, being the cause of the varying neurological phenotypes (paroxysmal dystonia, lesion in the ganglia and cerebellar ataxia) [15]; nevertheless it is not characteristic or pathognomonic and up to this moment it has not been reported in our patient.

Regarding the lab test results that oriented the diagnosis of DPHD, the presence of hyperlactatemia in plasma and CSF is highlighted; with a Lactate/Plasma ratio in blood of $\leq 20$, associated to a clinical scenario of metabolic acidosis, becoming in this way metabolic acidosis with hyperlactatemia of unclear cause a differential diagnosis. In newborns and infants there are many causes of metabolic acidosis in which we find: perinatal asphyxia, hypovolemia, sepsis, congenital cardiopathy, renal disease, respiratory difficulty syndrome and EIM [13]. When the metabolic

acidosis is inexplicable, persistent and severe; additional evaluation must be considered that includes blood and CSF lactate, as well as pyruvate, ammonia, glucose, amino acids in plasma and organic acids in urine [13]. Other causes must be discarded, especially in those patients who present neurologic deterioration associated to infections as organic acidemias, Leigh syndrome, Complex 1 deficit, cytochrome oxidase deficit due to mutation in the SURF1 gene and a series of mutations in the mitochondrial DNA [16]. At this point, neuroimaging acquires great importance, given that it allows an approach with imaging from the initial assessment.

Magnetic resonance imaging of the brain evidences accentuation of the cortical sulci, hyper intensities in T2 and FLAIR and in the bilateral basal ganglia and lenticular nuclei region; although these are not pathognomonic, they were found in characteristically anatomical regions of this disease. Literature has reported different cerebral anomalies, among which we find cortical atrophy, ventriculomegaly, dysgenesis of the corpus callosum, subacute necrotizing encephalomyopathy [17]. A normal MRI is not a usual finding, nevertheless, in a study of 371 patients a normal MRI was only reported in 7 (2%) of patients, all of whom had a deficiency of E1α (4). Magnetic resonance imaging through spectroscopy (MRS) allows the biochemical and functional assessment of the tissues, in this particular case it allows us to evaluate the lactate, a fundamental metabolite of anaerobic glycolysis; generally, under normal conditions, it is found in low concentrations in the brain, by finding it elevated this is indicative of an alteration in oxidative phosphorylation and energetic dysfunction, as is in this case of mitochondrial characteristics [18]. The rapid advance in genetic testing has allowed a more certain and early diagnosis; new generation sequencing (NGS) has revealed a great number of genetic mutations and it has been fundamental for the diagnosis of DPHD, as is in this case [19].

Concerning treatment, there is no curative or preventive treatment for the disease. Several strategies have been implemented with varying success rates as is the use of vitamins, coenzymes and oligo elements that favor chemical reactions in the mitochondria, in which thiamine, carnitine and lipoic acid stand out [20], that were used for our patient with posterior stabilization of her 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 the treatment is the ketogenic diet, which has been widely used to provide the CNS with an alternative source of energy, through the formation of ketones, like in the control of epilepsy or in recurring episodes of paroxysmal dystonia or ataxia [13]; the dietary treatment implies risks of dyslipidemia, urolithiasis, pancreatitis, cardiac alterations or thrombocytopenia. The administration of dichloroacetate is in charge of inhibiting the kinase of pyruvate dehydrogenase, activating the PDC [3,22]; it is implemented to decrease the elevated lactate levels in the case of an acute decompensation, although the significant secondary side effects have limited its use.

## Conclusion

PDH deficiency must be considered in cases of neurodevelopmental delay associated to intermittent episodes of neurologic deterioration and elevation of blood lactate levels through spectroscopy. Unlike those affected by other subtypes, patients with deficit of the E3 binding protein often survive infancy and live to adulthood given that to a certain extent some assembly of the pyruvate dehydrogenase complex exists. Hyperlactatemia is a common finding, but it is not universal, which is associated with a lactate ratio: blood pyruvate ≤ 20 and to morphologic alterations on neuroimaging; being key for diagnosis. While still there is no curative medical management, interventions must be adapted to signs and symptoms of each patient individually, performing an assessment with the parents in regards to comprehensive care, as well as psychological and social support of the family group.

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