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Novel Presentations Associated with a *PDHA1* variant – Alternating Hemiplegia in Hemizygote Proband and Guillain Barre Syndrome in Heterozygote Mother

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Abstract

We report a 5-year-old male with a *PDHA1* variant who presented with alternating hemiplegia of childhood and later developed developmental regression, basal ganglia injury and episodic lactic acidosis. Enzyme assay in lymphocytes confirmed a diagnosis of Pyruvate Dehydrogenase Complex (PDC) deficiency. His mother who was heterozygous for the same variant suffered from ophthalmoplegia, chronic migraine and developed flaccid paralysis at 36 years of age. *PDHA1* is the most common genetic cause of PDC deficiency and presents with a myriad of neurological phenotypes including neonatal form with lactic acidosis, non-progressive infantile encephalopathy, Leigh syndrome subtype and intermittent ataxia. The presentations in our 2 patients contribute to the clinical heterogeneity of this neurogenetic condition.

Introduction:

Pyruvate Dehydrogenase Complex (PDC) deficiency results from defects in the subunits (E1, E2, E3) of the enzyme complex, with pathogenic variants in *PDHA1* gene located on the X chromosome being the most common cause [1–3]. It encompasses a wide range of clinical manifestations ranging from severe neonatal lactic acidosis to developmental delay and intermittent ataxia. We report a hemizygous male who presented with alternating hemiplegia of childhood (AHC) - a phenotype most commonly linked to *ATP1A3* gene - and his heterozygous mother who had an episode of flaccid four limb paralysis, mimicking Guillain Barre Syndrome (GBS).

Cases:

Patient is a 5- year-old male with developmental delay, episodes of muscle weakness, dystonia, epilepsy and episodic lactic acidosis. He was born at 37 weeks gestational age via vaginal delivery to a 33-year-old primigravida. Pregnancy was complicated by pre-eclampsia and neonatal course was notable for hyperbilirubinemia. He passed his hearing screen and had a negative newborn metabolic screen. He started walking independently and saying his first words after his first birthday. At 14 months, he had acute onset of bilateral lower extremity weakness following which he was unable to walk for a few hours. He continued to have these episodes more and more frequently over the next few months, as frequently as daily and they could last from a few to several hours. The weakness involved a combination of any of four extremities, more commonly the right side. Subsequently, he developed dystonia and persistent weakness of right upper extremity. He was conscious during these episodes and did not seem to be in pain. Parents did not recall specifically if the weakness resolved during sleep.

He was admitted at an outside hospital at 18 months after an episode of hemiplegia in the setting of a viral syndrome. Brain and spine MRI were unrevealing. Cerebrospinal fluid (CSF) showed normal glucose, protein and cell count. Electromyography was non-diagnostic. Molecular testing of genes associated with alternating hemiplegia of childhood and dopa-responsive dystonia *(ATP1A2, ATP1A3, GCH1, SPR,* and *TH)* did not reveal any pathogenic or likely pathogenic variants. Treatment was started with trihexyphenidyl and levodopa-carbidopa which per parents, somewhat helped in stabilizing his dystonia and weakness. He presented to our institution at 4.5 years of age with right sided hemiplegia, right facial droop and slurred speech. Physical examination showed dystonia of the right upper extremity and spasticity in the lower extremities. He was alert but unable to speak in complete sentences. Repeat brain MRI showed bilateral hyperintensities in globus pallidi and substantia nigra (Figure 1) with elevated peak of lactate noted on spectroscopy. He was noted to have lactic acidosis ranging between 4 to 6 mM (normal range 1.0–2.4) and elevated alanine (1047 mM, normal range 110– 457) on plasma amino acids analysis. Lactate to pyruvate ratio was 16. He was started on intravenous 10% dextrose, levocarnitine, ubiquinol, thiamine and riboflavin. Due to concerns for poor oral intake, a gastrostomy tube was placed. He was noted to have episodic staring spells and unresponsiveness concerning for seizures. Electroencephalogram did not show any epileptiform discharges however there was evidence of encephalopathy and therefore, he was started on levetiracetam.

Trio exome sequencing revealed a maternally inherited novel single nucleotide variant (c.821G>C; p.R274T) in *PDHA1* gene. This variant was not reported in population database GnomAD and was predicted to be damaging to protein structure by PolyPhen-2. Activity of the pyruvate dehydrogenase complex (PDC) in blood lymphocytes was low at 0.91 nmol/min/mg protein (reference mean ± standard deviation 1.63 ± 0.53, range 0.98–2.72, n=596 [24]) with low PDC/E3 ratio of 1.3 (reference mean ± standard deviation 2.32 ± 0.59, range 1.41–3.55, n=596 [24]) confirming the diagnosis of PDC deficiency. Following his diagnosis, he was started on a ketogenic diet and thiamine supplementation was increased.

Proband’s mother is a 39-year-old female with a history of flaccid limb paralysis, progressive ophthalmoplegia and chronic migraine. At age 36, she had an episode of sudden

muscle weakness involving all four extremities, swallowing difficulties and respiratory failure and was given a diagnosis of GBS. Her prodrome began with tingling sensations in her feet and then proceeded to ascending weakness in legs and arms. Brain and spine MRI were normal as were glucose, protein and cell count in CSF. Due to her clinical presentation of ascending paralysis, she was treated with intravenous immunoglobulin (IVIG). She was intubated for respiratory failure for 2 weeks and then eventually had to undergo tracheostomy. A gastrostomy tube was placed for swallowing dysfunction. She completed 3 weeks of inpatient rehabilitation and was discharged with a wheelchair, able to feed by mouth and breathing on room air. She developed ankle contractures and needed reconstruction surgery.

She suffered from chronic migraine and associated double vision since her early twenties. She also endorsed easy fatigability and exercise intolerance. Physical examination showed ptosis and ophthalmoplegia (unable to adduct left eye) which per patient was notable as teenager and had gotten worse. She was born full term after an uneventful pregnancy and had typical development. She has an undergraduate degree and a full-time job. Trio exome of her son showed that she is heterozygous for the same *PDHA1* variant. Activity of PDC from her blood lymphocytes was within normal limits as was her lactate level. She was started on thiamine supplementation.

Discussion:

This is the first report of AHC as a presenting symptom of PDC deficiency. Proband's mother was a healthy woman with normal intelligence who suffered from an episode of flaccid paralysis imitating GBS. Both presentations are very novel and expand the phenotypic spectrum of this X-linked disorder. PDC deficiency is a clinically and genetically heterogeneous condition with a wide range of presenting neurological symptoms [1]. PDC deficiency due to pathogenic mutation in *PDHA1* which encodes the El-alpha subunit of PDC, predominate (82–88% of cases), but mutations in *PDHX, PDHB, DLAT, PDP1, LIAS* and at least 24 other genes have also been implicated [1, 4–6]. PDC links glycolysis with tricarboxylic acid cycle. It converts pyruvate to acetyl co-A and aberrations in any of the subunits leads to accumulation of pyruvate leading to lactic acidosis and failure of oxidative phosphorylation [2, 4].

PDC deficiency as a cause of lactic acidosis and progressive neurological symptoms has been recognized since 1976 [7]. The clinical presentation of PDC deficiency is highly variable and ranges from fatal congenital lactic acidosis and congenital brain abnormalities including corpus callosum abnormalities (15–55%), ventriculomegaly (35–85%) and Leigh syndrome (12–25%), to relatively mild ataxia or neuropathy with normal cognitive function and long survival [1, 2, 8–10]. Epilepsy (16–57%), hypotonia (46–89%), and developmental delay (57–83%) also are other common findings in subjects with PDC deficiency [1, 2, 8, 9, 11]. To our knowledge, AHC as initial presenting symptom has never been associated with PDC deficiency. The episodes started before the onset of seizures and developmental regression. In the subsequent years, he developed lactic acidosis and Leigh-like MRI changes. AHC is a neurodevelopmental disorder characterized by paroxysmal episodes of alternating weakness, dystonia, abnormal ocular movements and epilepsy in a subset of

patients [12]. Heterozygous variants in *ATP1A3* gene, which codes for sodium/potassium-transporting ATPase subunit alpha-3, was found to be causative in 75% of cases with neurological phenotype of AHC [13]. Patients who have AHC secondary to variants in this gene typically have normal MRI and no evidence of metabolic perturbations. Other genes have been implicated in AHC including *ATP1A2, SLC2A1, CACNA1A,* and *SCN1A* [12]. *TANGO2*- related neurological disorder has been stated to cause AHC accompanied with severe epileptic encephalopathy and rhabdomyolysis [14]. Gropman et al. also reported a 9-year-old boy with the classic clinical phenotype secondary to a dual diagnosis (with variants in *MT-TL2* and *PKND* genes) leading to mitochondrial dysfunction [15]. This report adds yet another neurometabolic entity which can lead to paroxysmal episodes of muscle weakness. Bilateral hyperintensities in basal ganglia and lactic acidosis helped guiding towards mitochondrial etiology in our case. Eventually exome sequencing and enzyme analysis confirmed the diagnosis enabling our patient to be started on the ketogenic diet and thiamine supplementation. The ketogenic diet has been shown to ameliorate symptoms of epilepsy, ataxia, sleep disturbance, speech/language development, and frequency of hospitalizations [16]. The ketogenic diet becomes an alternate fuel source when formation of acetyl CoA from pyruvate is disrupted. The E1 alpha subunit of PDC uses thiamine pyrophosphate as co-factor and supplementation with thiamine has been reported to improve outcomes as well [2, 17].

The other noteworthy aspect of this report is the presentation in the mother of our proband. The episode of ascending limb paralysis, swallowing dysfunction and respiratory failure masqueraded as GBS. Ophthalmoplegia is not typically associated with PDC deficiency. A GBS- like presentation in a 8-year-old boy with PDC deficiency presenting with recurrent proximal muscle weakness with evidence of mild sensorimotor neuropathy was reported [18]. Furthermore, GBS-like demyelinating polyneuropathy and ophthalmoplegia in a young infant with PDC deficiency due to *PDHA1* has also been described [19]. Lactate and/or other metabolic testing were not obtained on the proband's mother during her acute illness. The diagnosis was made retrospectively when we tested her son. The presentations of PDC deficiency in females can be varied [5, 20, 21] and for those with *PDHA1* mutations, the diagnosis can be challenging [22]. They can have severe neurological and metabolic phenotypes similar to males due to the unpredictability of skewed X-inactivation. Atypical presentation of PDC deficiency with exercise-induced dystonia in 19-year old female with normal intelligence was reported [23]. However, severe life-threatening complications in the third decade of life in a previously healthy heterozygous female appear to be unprecedented, raising a dilemma for counseling and long-term management. Our patient was started on thiamine and reported a subjective sense of increased energy levels. Unfortunately, the diagnosis could not be confirmed biochemically since enzyme activity in lymphocytes was within normal limits. This is not surprising given the diagnostic challenge of confirming low PDC activity using blood lymphocytes in female subjects with known pathogenic *PDHA1* mutation [24]. The mother declined to pursue enzymatic confirmation of PDC deficiency using cultured fibroblasts (from a skin biopsy) or skeletal muscle given her stable course.

Conclusion:

We report two very novel phenotypes associated with the X-linked form of PDC deficiency. PDC deficiency should be included on the differential for AHC, especially in patients who have abnormal brain MRI and metabolic decompensation. Asymptomatic carrier females should be counselled and made aware about risks for late-onset neurological manifestations of PDC deficiency.

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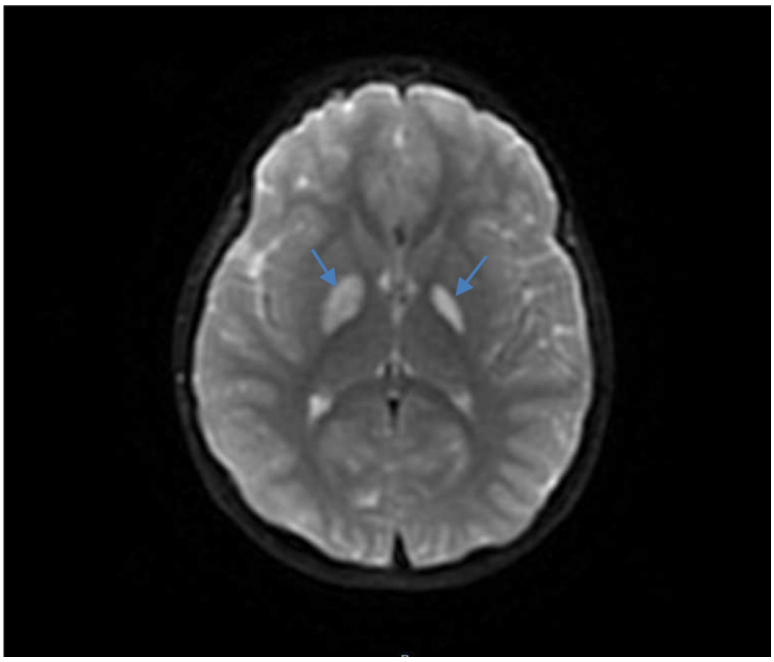

Figure 1:
DTI axial sequence showing acute metabolic stroke in bilateral globus pallidi (Leigh- like)

Table 1:

Comparison of phenotypes of proband and his mother

	Proband	Mother
Symptoms	Alternating hemiplegia, dystonia, developmental regression, epilepsy	Flaccid paralysis, chronic migraine, progressive ophthalmoplegia
Neuroimaging	Leigh syndrome with lactate peak on MR spectroscopy	Normal
Biochemical	Episodic lactic acidosis with increased alanine	Normal lactate
PDC, activated (+DCA) activity *	0.91 nmol/min/mg protein (56% of reference mean)	1.31 nmol/min/mg protein (80% of reference mean)
Treatment	Ketogenic diet, thiamine	Thiamine

* Blood lymphocyte-based activated PDC assay reference mean ± standard deviation is 1.63 ± 0.53, range 0.98–2.72, n=596. DCA, dichloroacetate.