Pearls & Oy-sters: Paroxysmal Exercise-Induced Dyskinesias Due to Pyruvate Dehydrogenase Deficiency

Claudio M. de Gusmao, MD, Isabella Peixoto de Barcelos, MD, Anna L.R. Pinto, MD, PhD, and Laura Silveira-Moriyama, MD PhD

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Correspondence
Dr. de Gusmao
claudio.degusmao@childrens.harvard.edu

Abstract

Paroxysmal exercise-induced movement disorders may be caused by energy metabolism disorders, such as Glut 1 deficiency, pyruvate dehydrogenase deficiency, or mitochondrial respiratory chain disorders. A 4-year-old boy with a history of febrile seizures presented with paroxysmal dystonia, triggered by exercise, or occurring at rest. Additional investigations demonstrated pallidal hyperintensities on brain MRI and low CSF glucose. Pyruvate and lactate were elevated. The clinical presentation combined with neuroimaging abnormalities and biochemical profile (the lactate/pyruvate ratio) were clues to pyruvate dehydrogenase deficiency, a treatable metabolic disorder with neurologic presentations.

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Video

Pearls

- Paroxysmal exercise-induced movement disorders and seizures may be caused by energy metabolism disorders, such as Glut 1 deficiency, pyruvate dehydrogenase (PDH) deficiency or mitochondrial respiratory chain disorders.
- Abnormal MRI brain with Leigh-like features can be seen in mitochondrial respiratory chain disorders and pyruvate dehydrogenase deficiency.
- Lactate to pyruvate (L/P) ratio higher than 20 is suggestive of mitochondrial respiratory chain dysfunction. A normal L/P ratio (<20) is seen as PDH deficiency.

Oy-sters

- Low glucose CSF values do not necessarily equate Glut-1 deficiency. The level matters: in 90% of cases, it is <40 mg/dL.
- An elevated CSF lactate argues against Glut-1 deficiency.

Case Report

A 4-year-old boy presented with spells of imbalance associated with dystonic posturing of his legs. He was born at term with unremarkable antenatal and perinatal history. Hypotonia and plagiocephaly were noted in his first year of life, the latter improving with helmet therapy. He had mild motor delay but caught up on developmental milestones with occupational and physical therapy. He demonstrated normal language and social-emotional development. In his second year of life, he developed an upper extremity postural tremor and had 3 uncomplicated febrile seizures. Initial investigations including EEG, basic laboratory, and neuroimaging were nondiagnostic, and he was not treated.

At age 4, he presented with episodes of gait difficulty, manifested by "turning in" of one or both feet, sometimes with imbalance. The episodes would occur daily and could last several minutes. The most consistent trigger was exercise (e.g., walking a mile to school), but they could also occur in the setting of fatigue, after meals, or without a clear reason (Video 1). Occasionally, he voiced an

From the Department of Neurology (C.M.d.G., A.L.R.P.), Boston Children's Hospital, Harvard Medical School, MA; Neurology Department (C.M.d.G., L.S-M.), HC-FCM, University of Campinas, UNICAMP, Campinas, São Paulo, Brazil; Department of Neurology (I.P.d.B.), Children's Hospital of Philadelphia, PA; and Education Unit (L.S-M.), UCL Institute of Neurology, University College London, UK.

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ill-defined prodromal sensation that heralded an episode. Carbamazepine was tried empirically but was unhelpful and worsened his tremor.

On examination, he was a well-nourished boy, with age-appropriate language, motor, and social skills. There was a postural and kinetic tremor in the upper extremities, without dysmetria or gait ataxia. The remainder of the neurologic examination was normal. No dystonic events were elicited during the examination or after brief exercise. Family history was notable for a sibling with autism and ADHD; his mother had seizures secondary to a brain concussion. Laboratory investigations demonstrated elevation of serum pyruvate (0.221 mmol/L). CSF glucose was low at 48 mg/dL, CSF lactate (4.3 mmol/L), and alanine (59.2 mcmol/L) were elevated; full laboratory data detailed in eTable 1 (links.lww.com/WNL/C656). Brain MRI was notable for bilateral pallidal hyperintensities (Figure 1).

Based on the presence of paroxysmal exercise-induced dyskinesia (PED), a disorder of energy metabolism was suspected. Suspicion was highest for GLUT-1 deficiency syndrome (GLUT1-DS). Therefore, a targeted gene panel including the *SLC2A1* gene was ordered. However, it resulted negative. Follow-up testing with whole exome sequencing and mitochondrial DNA analysis demonstrated a pathogenic variant in *PDHA1* (NM_000284.4: c.214C > T; p.R72C), yielding the diagnosis of pyruvate dehydrogenase complex deficiency. The patient was placed on thiamine and a modified ketogenic diet, with complete improvement in his spells.

Discussion

Paroxysmal Exercise-Induced Dyskinesia

PED is a genetic heterogeneous condition characterized by recurrent episodes of sudden, involuntary movements induced by prolonged exercise.[1] Patients may present with variable combinations of dystonia and/or chorea, most notably in the limbs involved with the exercise.[2] The exact amount of exercise necessary to induce an attack is not well defined. Typical attack duration may range from 5-30 minutes; however, this can be quite variable.[3]

Pathogenic heterozygous mutations in the *SLC2A1* gene, encoding for the GLUT-1 transporter and causative of GLUT1-DS, are the main cause of PED.[3,4] Nevertheless, the differential diagnosis includes several other conditions. Of particular relevance to this case are disorders involving brain energy metabolism such as pyruvate dehydrogenase deficiency and mitochondrial dysfunction. The latter can occur either because of pathogenic mutations in nuclear genes relevant for mitochondrial function (such as *ECHS1*, *HIBCH*, and *PRKN*) or mtDNA mutations leading to respiratory chain defects.[3,5-7] In addition, pathogenic variants in genes associated with other paroxysmal dyskinesia subtypes (e.g., *PRRT2*, *MR1*, *ADCY5*, and *TBC1D24*) or dopaminergic deficits (e.g., *GCH1*) can also present with PED, often with additional phenomenology.

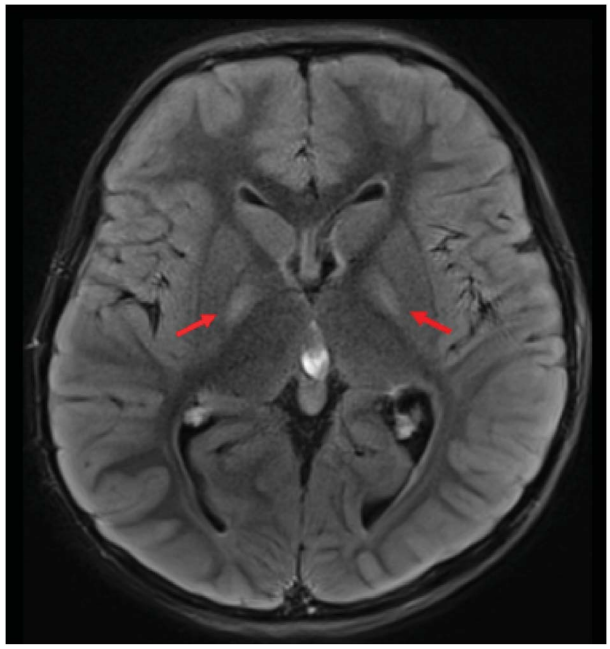
Diagnostic Traps and Tips

This case illustrates a few pitfalls when investigating patients with PED in the context of suspecting GLUT1-DS. First, imaging abnormalities are not typically seen in GLUT1-DS. Changes compatible with Leigh-like syndrome (symmetrical T2/FLAIR hyperintense lesions in the basal ganglia and/or brainstem), such as depicted in Figure 1, can be seen in pyruvate dehydrogenase deficiency and mitochondrial disorders.

Second, one should be careful about obtaining and interpreting CSF glucose results, especially if they are borderline. The absolute cutoff value for hypoglycorrachia in children is variable, so comparing values with age-normative data can be informative. Absolute CSF glucose values <10th percentile for age and CSF/serum glucose ratio ≤25th percentile for age have good discriminatory value for GLUT1-DS, with published reference values.[8] In this case, the CSF glucose level (48 mg/dL) was above the 10th percentile age cutoff value, and the CSF/serum glucose ratio (0.56) was exactly at the 25th percentile. Notably, in approximately 90% of confirmed GLUT1-DS cases, the absolute CSF glucose value is <40 mg/dL.

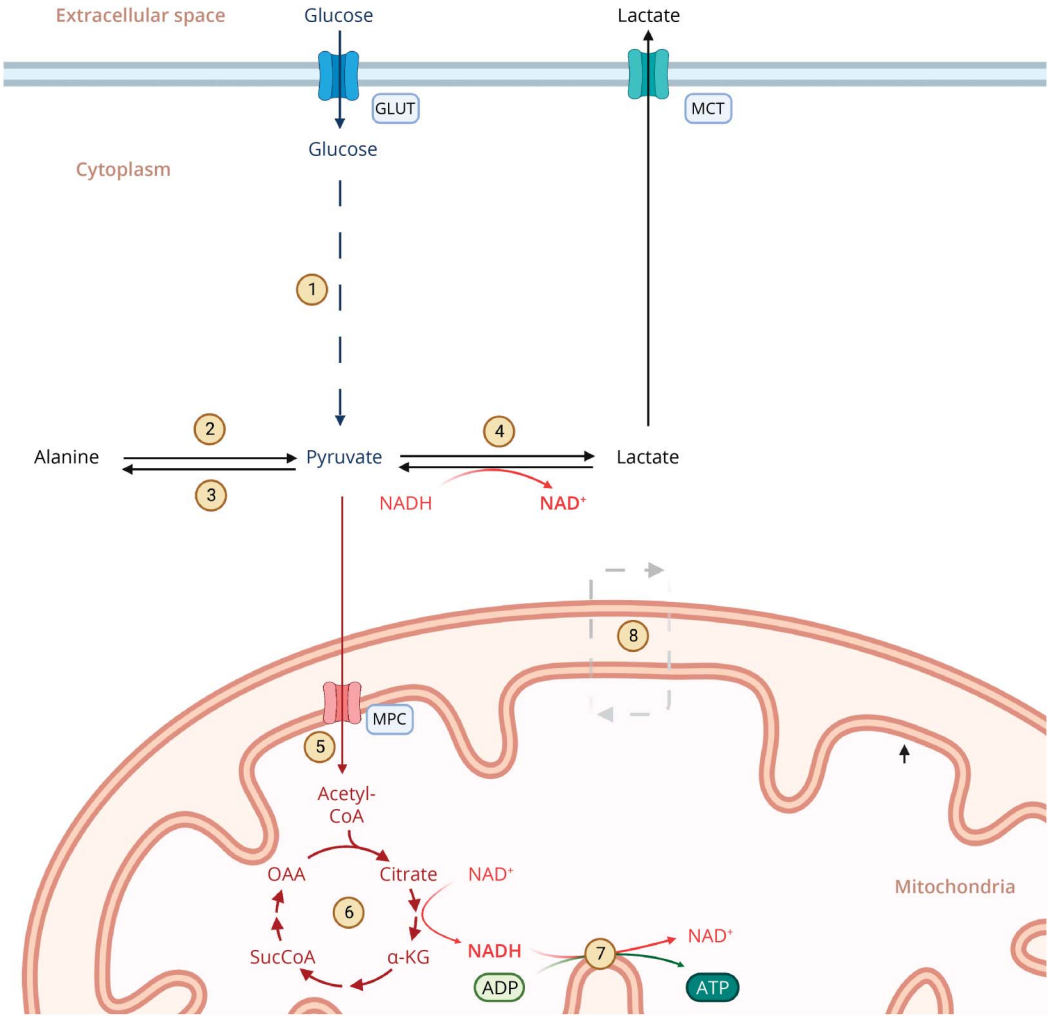
Finally, CSF lactate levels may be helpful. In this case, CSF lactate was elevated, whereas in GLUT1-DS, it is usually low or normal.[8,9] Elevations in lactate can be seen in variety of acquired or genetic conditions. To aid in the differential diagnosis, the lactate to pyruvate (L/P) ratio can be informative.[10] As with glucose, simultaneous serum measurements may be helpful as a comparison.

Figure 1 Brain MRI



Red arrows indicate symmetrical abnormal T2/FLAIR hyperintensity within the bilateral globi pallidi.

Figure 2 Glycolytic Pathway and the Metabolic Steps Involving Its By-product Pyruvate



Three alternative pathways of pyruvate metabolism are depicted: conversion into acetyl-CoA through PDH to enter the Krebs cycle, conversion to alanine through alanine dehydrogenase and conversion to lactate through LDH. The LDH enzyme is influenced by the cytoplasmic concentrations of NADH and NAD+. When there is dysfunction of the electron transport chain, NAD+ production decreases. The shift in NADH/NAD+ equilibrium drives the production of lactate and increases the lactate/pyruvate ratio. KEY: (1) Glycolytic enzymes, (2) alanine aminotransferase, (3) alanine dehydrogenase, (4) lactate dehydrogenase, (5) pyruvate dehydrogenase, (6) Krebs cycle, (7) electron transport chain, and (8) NAD/NADH shuttles. Abbreviations: GLUT: Glut1 transporter; MPC: Mitochondrial Pyruvate Carrier; MCT: Monocarboxylate Transporter. Created with BioRender.com.

Pyruvate is the by-product of glycolysis (Figure 2). Depending on homeostatic balance, a fraction of the cytoplasmic pyruvate is interconvertible to alanine or to lactic acid. However, to carry out cellular respiration, pyruvate must be transported to the mitochondrial matrix where it is converted to acetyl-CoA through the pyruvate dehydrogenase enzyme complex (PDH). Acetyl-CoA then enters the Krebs cycle, which produces reducing equivalents such as nicotinamide adenine nucleotide (NADH), a high-energy electron carrier to the electron transport chain (ETC). The multiple subsequent electron transfers in the ETC occurring during oxidative phosphorylation ultimately produce ATP, with oxygen as the final electron acceptor and generating NAD+ as a by-product.

Typically, pyruvate and lactate are in equilibrium in the cell cytoplasm. This balance is influenced by the concentrations of NADH and NAD+. If oxidative phosphorylation is dysfunctional (because of genetic or acquired ETC defects), there is a decrease in NAD+ production. This shifts the cellular NADH/NAD+ equilibrium and drives the lactate dehydrogenase enzyme to produce more lactate with consequent increase in the L/P ratio. For many authors, an L/P ratio >20 is generally indicative of a defect in the ETC.[6] On the other hand, defects in PDH do not affect the cellular NADH/NAD+ balance. Therefore, when there is dysfunction of the PDH enzyme, there are proportional accumulations of pyruvate and lactate, and the L/P ratio tends to be normal (i.e., < 20). In our patient, the serum lactate/pyruvate ratio was 7.

PDH

The PDH complex is an enzyme assembled of different subunits encoded by the *PDHA1*, *PDHB*, *DLAT*, *PDHX*, and *DLD* genes. In 84% of cases, defects are caused by mutations in

the *PDHA1* gene, which is X-linked—although women may present with disease depending on the pattern of X inactivation. Clinically, PDH deficiency affects mainly the CNS with findings of congenital microcephaly, hypotonia, epilepsy, ataxia, and variable degrees of developmental delay. Although there may be some clinical overlap, 4 clinical phenotypic subtypes have been previously identified: paroxysmal motor symptoms and developmental delay; episodic ataxia with peripheral neuropathy; acute brainstem/basal ganglia dysfunction with a "Leigh-Like" MRI and neonatal lactic acidosis with encephalopathy, facial dysmorphisms, and brain malformations.[7] Nevertheless, the clinical spectrum of PDH disorders is expanding with next-generation sequencing. Brain MRI may show dysgenesis of the corpus callosum, and bilateral basal ganglia with or without brainstem T2 hyperintensities, suggestive of a Leigh-like pattern. Metabolic abnormalities such as increased plasma pyruvate, lactic acidemia, increased lactate in CSF, and metabolic acidosis can be present.[6,7]

Treatment of PDH deficiency can be attempted by supplementing its cofactor thiamine or substances that enhance PDH activity, such as dichloroacetate and phenylbutyrate.[6,11-13] In addition, the ketogenic diet may provide an alternative energy supply to the brain. In our patient, since instituting a modified Atkins diet (a less restrictive form of the ketogenic diet), his paroxysmal symptoms improved significantly. His tremor was controlled with propranolol.

This case exemplifies the importance of clinical phenotyping to inform pretest and posttest probabilities when ordering and interpreting genetic testing results, which bear a direct impact on management. A low CSF glucose level led to an anchoring cognitive bias, overlooking clinical clues such as neuroimaging and laboratory abnormalities. It also underscores that confirmation of the molecular diagnosis in PED, as genotype informs treatment. For example, the ketogenic diet can be useful in PDH deficiency and GLUT-1 DS, but can be detrimental in patients with pathogenic mutations in *ECHS1*.[6,14,15] Other genetic paroxysmal movement disorders may benefit from specific treatment modalities, such carbamazepine in *PRRT2* mutations, caffeine in *ADCY5*, and levodopa in *GCH1* and *PRKN*.

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Appendix Authors

Name	Location	Contribution
Claudio M. de Gusmao, MD	Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA; Neurology Department, HC-FCM, University of Campinas, UNICAMP, Campinas, São Paulo, Brazil	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Isabella Peixoto de Barcelos, MD	Department of Neurology, Children's Hospital of Philadelphia, PA	Analysis or interpretation of data
Anna L.R. Pinto, MD, PhD	Department of Neurology, Boston Children's Hospital, Harvard Medical School, MA	Major role in the acquisition of data
Laura Silveira-Moriyama, MD, PhD	Neurology Department, HC-FCM, University of Campinas, UNICAMP, Campinas, São Paulo, Brazil; Education Unit, UCL Institute of Neurology, University College London, UK	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data

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