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PYRUVATE DEHYDROGENASE COMPLEX-E2 DEFICIENCY CAUSES PAROXYSMAL EXERCISE- INDUCED DYSKINESIA

Paroxysmal exercise-induced dyskinesia (PED) is a rare disorder characterized by episodes of choreoathetosis or dystonia triggered by several minutes of exercise such as walking or running.¹ Mutations in various genes have been associated with PED.¹ We report a patient with intellectual disability and this unique phenotype associated with homozygous missense mutation in the *DLAT* gene (c.470T>G; p.Val157Gly) that encodes the E2 component of the pyruvate dehydrogenase complex (PDC). This case of PED associated with *DLAT* mutations broadens the phenotypic spectrum for this ultra-rare condition and widens the range of potentially treatable PEDs.

Case report. The proband presented at age 8 years with intellectual disability and exercise-induced gait abnormalities. He was the uncomplicated term product of a consanguineous Iraqi union. He sat at 8 months, walked at 18 months, and was slow to speak. Cognitive assessment (age 8) revealed IQ 44. At age 3, he developed paroxysmal episodes after 5–15 minutes of ambulation characterized by dystonic arm and leg posturing, sometimes with leg shaking, and with progressive inability to stand (video at Neurology.org). Occasionally there was dysarthria and mental status change without loss of consciousness. Spells resolved after 5 minutes rest but would recur multiple times daily with repeated exertion. In addition to intellectual disability, baseline examination showed microcephaly, disconjugate gaze with limitation of upward right eye excursion, mildly increased tone, brisk lower extremity reflexes without clonus, and left Babinski sign. Gait was mildly wide-based with foot eversion. Extensive evaluation revealed normal brain and spine MRI and ictal EEG. EMG showed probable myopathic features. CSF lactate and pyruvate were slightly elevated. Creatine phosphokinase, lactate, muscle histology, electron microscopy, and respiratory chain enzyme analysis were normal (table e-1).

The patient's sister had global delays with intellectual disability, cautious gait, and inability to walk long distances. She declined further neurologic and biochemical evaluation.

Institutional approval and informed consent were obtained. Exome sequencing revealed novel, homozygous, likely pathogenic, missense (c.470T>G; p.Val157Gly) mutations in *DLAT* in the patient and sister. PDC enzyme activity in blood lymphocytes was below the reference range (53% of mean on activation with dichloroacetate/fluoride and PDC/E3 ratio 56% of mean), consistent with previously reported cases of PDC-E2 deficiency.^{2–5} (table e-1).

After diagnosis, the patient was prescribed typical treatments for PDC deficiency; thiamine, with which he was intermittently adherent; and modified Atkins diet, which was not tolerated. At age 22, he developed mental status change including anxiety, decreased ability to follow commands, and reduced oral intake. Brain MRI revealed changes consistent with metabolic insult (figure). Thiamine level was low (7 nmol/L; normal 8–30 nmol/L). Thiamine (200 mg/d) and α -lipoic acid (300 mg/d) were started with return to baseline with reversal of behavioral abnormalities and normalization of appetite. Exercise-induced symptoms persisted without change despite treatment with α -lipoic acid (600 mg/d) and high-dose thiamine (1000 mg/d).

Discussion. PDC is a multienzyme complex that, utilizing thiamine as a cofactor, converts pyruvate to acetyl coenzyme A, and serves as a key regulator of energy metabolism.^{2,3,6} PED has been described in patients with mutations in genes encoding the E1 α and E3 binding protein subunits of PDC^{1,6} but not the E2 subunit encoded by the *DLAT* gene.

The *DLAT* (c.470T>G; p.Val157Gly) mutation encodes a missense change that affects an evolutionarily conserved residue through zebrafish and is predicted to be damaging using in silico prediction tools SIFT and PolyPhen2. CSF and MRI findings are consistent with, and reduced PDC enzymatic activity confirmed, the diagnosis of PDC deficiency.^{2–5} Treatment with thiamine reversed the patient's deterioration but not exercise-induced paroxysmal symptoms.

Only 7 genetically confirmed cases and 1 biochemically defined PDC-E2 deficiency case have been reported.^{2–5} Four of eight displayed episodic dystonia triggered in some by stress or fever, but none by exertion,^{3,4} as in our patient. Ketogenic diet, not

Supplemental data
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(A) Axial diffusion-weighted image shows 1.5-cm focus of reduced diffusivity in the midline and left paramedian splenium of the corpus callosum. (B) Axial fluid-attenuated inversion recovery image shows corresponding T2-hyperintense edema. (C) Axial susceptibility-weighted image shows abnormal symmetric hypointensity in the bilateral globi pallidi for the patient's age, likely representing premature mineralization.

tolerated by our patient, in others, caused dramatic improvement in episodic symptoms.⁴ Ketogenic diet may also benefit other genetic PEDs (PDC deficiency [*PDHX* and *PDHAI*] and glucose-transport deficiency [*SLC2A1*]),^{1,7} suggesting that impaired brain glucose delivery or metabolism may be a factor more generally in the pathogenesis of PED. Future studies may evaluate whether ketogenic diet may be considered more broadly in PED regardless of genetic etiology.

PDC-E2 deficiency may result in broad symptoms ranging from profound developmental delay with lactic acidemia² to mild motor manifestations and moderate intellectual disability.³ As in our case, peripheral biomarkers of deficient energy metabolism may be absent and imaging may be normal, posing a diagnostic challenge and suggesting need for considering this disorder in patients with paroxysmal dystonia. Genomic sequencing may increase recognition of this partially treatable condition.

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