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Case Report

Somatic mosaicism for a novel *PDHA1* mutation in a male with severe pyruvate dehydrogenase complex deficiency

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ABSTRACT

Pyruvate dehydrogenase complex (PDC) deficiencies are mostly due to mutations in the X-linked *PDHA1* gene. Males with hemizygous *PDHA1* mutations are clinically more severely affected, while those with mosaic *PDHA1* mutations may manifest milder phenotypes. We report a patient harboring a novel, mosaic missense *PDHA1* mutation, c.523G > A (p.A175T), with a severe clinical presentation of congenital microcephaly, significant brain abnormalities, persistent seizures, profound developmental delay, and failure to thrive. We review published cases of *PDHA1* mosaicism.

1. Introduction

The mitochondrial multi-enzyme pyruvate dehydrogenase complex (PDC) is the gateway for oxidative metabolism of carbohydrates, catalyzing oxidative decarboxylation of pyruvate into acetyl-CoA as the primary substrate for the tricarboxylic acid cycle and oxidative phosphorylation. It is comprised of multiple catalytic components: including E1α (encoded by *PDHA1*), E1β, E2, and E3 subunit proteins; and the vitamin coenzyme thiamine pyrophosphate (TPP) [1]. PDC deficiency is a

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major cause of primary lactic acidemia. The clinical presentation of PDC deficiencies are quite variable and may include severe neonatal lactic acidosis (often with early lethality), neurological involvement ranging from intermittent ataxia to persistent seizures, developmental delay, structural brain anomalies, and degenerative encephalopathy [1–3].

About 90% of PDC deficiencies in genetically confirmed patients result from mutations in the X-linked *PDHA1* [2,3]. More than 100 different mutations have been described [2–7]. Although similar numbers of affected males and females have been identified, there is a disproportionate distribution of mutation types between genders [2,3,6]. Deletion/insertion mutations in exons 10 and 11, which result in premature termination codons, are often observed in females, whereas missense/nonsense mutations in exons 3, 7, 8 and 11 are predominant in males [6]. Hemizygous males with deleterious *PDHA1* mutations are often clinically more severely affected (including lethality in infancy). Females with the same mutation may show variable clinical manifestations and greater survival due to skewed X-inactivation [1–3]. Mosaicism of *PDHA1* mutations has been documented in only a few patients.

We report a case of *PDHA1* mosaicism in a male patient with functional PDC deficiency. This is the seventh reported case of male mosaicism for *PDHA1* mutation; and this patient notably has a severe clinical phenotype.

2. Case report

This male child was born to a healthy non-consanguineous couple with normal pregnancy and delivery. At birth, the infant was microcephalic, hypotonic, and required some ventilatory support. Brain CT scan MRI revealed marked hydrocephalus with partial agenesis of the corpus callosum and colpocephaly. At 14 months of age, an intercurrent respiratory illness precipitated eye deviations and tonic–clonic movements of his upper extremities. Seizures were confirmed by EEG and he was started on antiepileptic medications. Repeat brain MRI at two years of age revealed severe hypoplasia of the corpus callosum, ventriculomegaly, hypoplasia of the cerebellar vermis consistent with the Dandy Walker variant, marked volume loss of the brain parenchyma and prominence of the cortical sulci, and absence of the cavum septum pellucidum (Fig. 1A). Follow-up evaluations revealed severe microcephaly with bitemporal narrowing and a shallow, sloping forehead, and no progression of developmental milestones. Karyotype and chromosomal microarray analysis were normal. Testing for storage disorders, peroxisomal disorders, purine processing disorders, and disorders of creatine processing and transport were all negative. Family history was non-contributory.

3. Results

The patient exhibited persistent lactic acidosis and hyperalaninemia with normal lactate to pyruvate ratio, suggestive of PDC deficiency. Biochemical analysis revealed metabolic acidosis (bicarbonate 10 mmol/L; reference range (RR) 17–29), elevated blood lactate (3.5–5.5 mmol/L, n = 10; RR 0.5–2.2), pyruvate (0.34–0.35 mmol/L, n = 2; RR 0.03–0.08), and alanine (565 μmol/L; RR: 143–439) levels with normal lactate to pyruvate ratio (ranging 10–13). Increased lactate and pyruvate were also noted in urine specimens. Activity of PDC in cultured skin fibroblasts (SFs) was 26% and 31% of the mean (0.63 and 0.76 nmol/min/mg protein; control mean 2.42; range 1.26–4.42 (3rd–97th %tile); n = 329).

PCR and Sanger sequencing of all exons and intron/exon boundaries of the *PDHA1* gene were performed on genomic DNA from cultured SFs, peripheral blood and buccal mucosa. The patient was mosaic for a novel, missense mutation, c.523G > A (p.A175T) (Fig. 1B, NM_000284.3). c.523G > A results in a substitution of a highly conserved alanine to threonine at position 175 of E1α (Fig. 1C). Different ratios of mutant adenine (A) and wild-type guanine (G) alleles were observed in the fibroblasts, peripheral blood and buccal cells, indicating a different mutant allele burden among different tissues (Fig. 1B). *In silico* prediction of structural changes of the alanine to threonine at 175 showed a potential disturbance of protein structure that may affect its overall interaction with E1β (Fig. 1C). Sequencing of the *PDHA1* gene from the peripheral blood and buccal cells of the proband's mother did not reveal any mutation, indicating a *de novo* event in this patient.