Mutations of The E3 Beta Subunit of The Pyruvate Dehydrogenase Complex (PDC) Gene: A Case Report

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INTRODUCTION

The pyruvate dehydrogenase complex (PDC) is a multienzyme complex to aerobic oxidation and catalyzes the irreversible decarboxylation of pyruvate to acetyl-CoA. Nervous tissue is normally reliant on aerobic oxidation of glucose for its energy generation. A deficiency of this enzyme complex impairs the aerobic oxidation of glucose. PDC deficiency (PDCD) can result from modifications in any of the genes encoding its several subunits. While the great majority (≈ 77%) of patients with PDCD have mutations in the *PDHA1* gene encodes the E1α subunit, Dihydrolipoamide dehydrogenase (E3) and E3 binding protein (*E3BP*) defects contribute 10.7% of patients. It commonly manifests with congenital microcephaly, hypotonia, epilepsy, developmental delay, and/ or ataxia. Metabolic abnormalities like increased plasma pyruvate, lactic acidemia, and/ or metabolic acidosis are common. We describe the clinical presentation and mutation analysis of a patient with persistent lactic acidosis and delayed neurological development due to *E3BP* deficiency.

CASE

Fourteen-year-old girl was admitted due to intractable seizures. She was the second child of healthy parents who were first-degree cousins. His younger sister died at the age of two for unknown reasons. Her neonatal period was unremarkable. At nine months of age, she was admitted with developmental delay. Her seizures started at one year old. Her weight was 21 kg (3.P), length 135 cm (3.P) and head circumference 52 cm. She had hyperreflexia, spasticity, and hypertonicity and was sitting without support but could not walk independently. At the time of admission , she had lactic acidosis, with a blood lactate level of 4,84 mmol/L. Urine organic acid showed lactic acid 1401mmol/molkr (35-131), and pyruvic acid 526 mmol/molkr (3,5-17,3). Brain magnetic resonance imaging (MRI) at 14 years revealed diffusion-restriction in bilateral putamen (Figure I). MRI spectroscopy findings are compatible with mitochondrial disease due to lactate peaks in several voxels at the level of the right putamen.

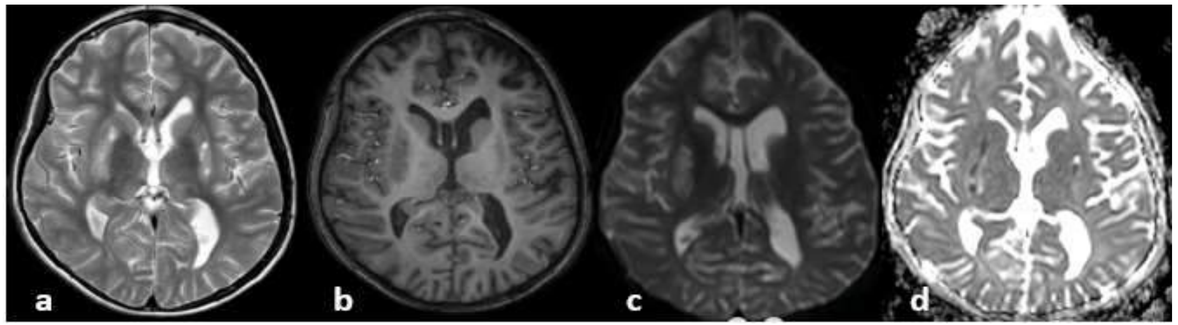

Figure I. Cranial Magnetic resonance images. Hyperintense bilateral and symmetrical lesions in the globus pallidus and putamina, on T2 weighted images, hypointense on T1. **a**-axial T2, **b**-axial T1, **c**-axial DWI, **d**-axial ADC

A homozygous pathogenic mutation c.1336C>T (p.Arg446Ter) was found in *PDHX* gene (*Pyruvate dehydrogenase E3-binding protein deficiency*, OMIM#245349). The patient was started on a ketogenic diet, continued levetiracetam treatment for seizures, and a mitochondrial cocktail.

CONCLUSION

PDCD is a mitochondrial disorder that leads to decreased ATP production and energy deficit. Mutations in the *E3BP* gene are increasingly recognized as a cause of PDCD. The most typical cranial imaging findings in *E3BP* deficiency have been the absence or thinning of the corpus callosum and necrotic lesions of the basal ganglia.

The varied clinical presentation of PDC deficiency, as with many other genetic mitochondrial disorders, often delays the achievement of a rapid diagnosis. Patients can be suspected of PDCD based on clinical signs/symptoms and biochemical data, namely elevated plasma lactate and pyruvate levels. The ketogenic diet provides a direct source of acetyl-CoA, leading to the improvement of some symptoms at PDCD. We herein present a sporadic case of PDH deficiency, a delayed diagnosis, and identification of the specific gene mutation that caused dysfunction of the *PDHX* gene with clinical exome sequencing.

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