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SCIENTIFIC LETTER

Pyruvate Dehydrogenase Complex Deficiency due to a De Novo Heterozygous Mutation in Exon 7 of *PDHA* 1 Gene Presenting as Isolated Severe Lactic Acidosis in an Infant

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To the Editor: A 45-d-old girl, 1st born to parents of non-consanguineous marriage presented with lethargy and poor feeding for 1 d. There was no fever, vomiting, loose stool or oliguria. She weighed 3.7 kg at birth and was exclusively breastfed. On examination, she weighed 3.8 kg, head circumference (HC)- 36 cm, was tachypneic (RR- 62/min) without hypoxia and drowsy but responding to painful stimuli. Other systems were normal. Investigations revealed normal blood counts, glucose, urea, creatinine, electrolytes, ammonia & creatine phosphokinase (CPK), negative C-reactive protein (CRP), no ketonuria and elevated liver enzymes (AST-80 U/L; ALT-122 U/L). Her blood pH was 7.03 with anion gap- 18 and lactate & pyruvate levels were high [9.9 mmol/L, peak (20 mmol/L) & 1 mmol/L respectively] with L:P ratio 9.9. Blood and urine cultures were sterile. USG abdomen showed mild hepatomegaly, MRI brain and ECHO were normal. Her plasma amino acids, acyl carnitine and urine organic acids were normal. She was diagnosed as Pyruvate Dehydrogenase Complex (PDHC) deficiency and treated with parenteral dextrose, sodium bicarbonate, carnitine (100 mg/kg/d), thiamine (50 mg/d) and peritoneal dialysis with bicarbonate based fluid, following which her metabolic acidosis improved (pH 7.4), lactate levels dropped to 1.7 mmol/L and was discharged home. Genetic testing revealed a de novo heterozygous missense variation c.685A > T [p.Met229Leu] in exon 7 of *PDHA1* gene, inherited in an X-linked manner. In silico analysis implied a potentially deleterious effect to protein function (Polyphen −2, SIFT, Mutation Taster). Gene testing of parents did not reveal any suggested absence of variants. At 1 y of age, she weighs 9 kg, HC-44 cm, has normal motor, personal & social, language and hearing milestones, continuing treatment with oral carnitine and thiamine.

PDHC converts pyruvate into acetyl coA in citric acid cycle and its deficiency leads to accumulation of pyruvate that gets converted into lactate [1], and manifests as severe lactic acidosis. PDHC deficiency can present at any age depending upon the activity level of PDHC enzymes [2]. Males with PDHC deficiency have severe form of the disease than females [2]. Our patient has a milder phenotype attributed to X-linked inheritance pattern. Sofou K et al. had reported that psychomotor delay improves with ketogenic diet [3]. Ketogenic diet has not been initiated in our case as she is developmentally normal, thriving well and has no further metabolic decompensations till date.

Compliance with Ethical Standards

Conflict of Interest None.

References

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