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Letter to the Editor

Hypothermic reaction after infection in an infant with pyruvate dehydrogenase complex deficiency

Pyruvate dehydrogenase complex (PDC) deficiency is a rare genetic mitochondrial disorder that impairs the activity of PDC, the rate-limiting enzyme in aerobic glucose oxidation, thereby being integral to cellular energetics.[1] Defects in PCD activity may also decrease the availability of acetyl-CoA for the tricarboxylic acid cycle, resulting in lactic acidosis and cellular energy failure, which is indicated by progressive neurological and neuromuscular deterioration.[2] Reviews of molecular genetics reported that most patients with PDC deficiency lack the PDC-E1 alpha component, encoded by the *PDHA1* gene located on the Xp22.1–22.2 chromosome. Female patients often harbor frameshift mutations, which result in shorter life spans than missense mutations.[2]

Our female patient was born with a weight of 2468 g (−1.2 SD). Brain MRI revealed severe bilateral and third ventriculomegaly and periventricular leukomalacia, which indicated dysgenesis of the cortex and cerebral atrophy. She presented with lactic acidosis, and her serum lactic acid and pyruvic acid levels were 65.0 and 7.24 mg/dl, respectively. Genetic mutational analysis of the *PDHA1* gene revealed a de novo heterozygous frameshift mutation, namely c.1039_1045del, p.E347fsX15 (Fig. 1).

After diagnosis, she was treated with thiamine (vitamin B1), ketogenic therapy, and dichloroacetate. However, she exhibited growth failure and delayed psychomotor development.

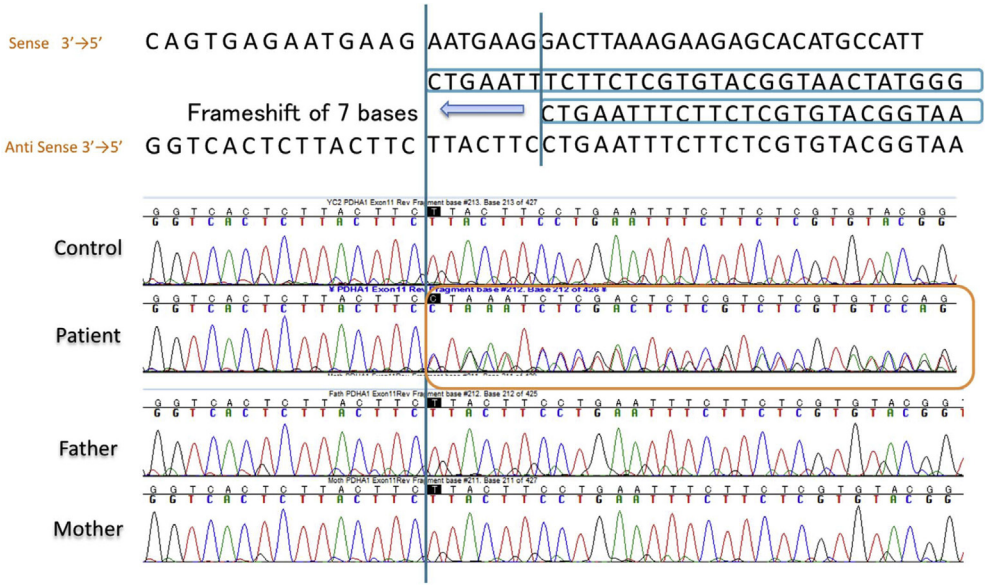

Figure 1 Sequence analysis of the *PDHA1* gene reveals the de novo frameshift mutation p.E347fsX15.

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At 28 months of age, she visited our hospital because of severe hypothermia of 33.0 °C. Blood sample analysis revealed a mild increase in her white blood cell count to 19,500/mm^3 and a C-reactive protein concentration of 3.87 mg/dl. During the hypothermic period, her serum interleukin-6 (IL-6) level was extremely high at 287 pg/ml (normal range is less than 4.0 pg/ml), and her tumor necrosis factor (TNF)-alpha level was 1.48 pg/ml (normal range is less than 4.0 pg/ml). She was successfully treated with ceftriaxone, and her serum C-reactive protein levels belatedly increased after infection at the same time that her body temperature normalized.

After this episode, she was frequently admitted because of hypothermia caused by bacterial infection. Analysis of her immunoglobulin, thyroid, or adrenal function did not reveal abnormalities. Finally, daily treatment with oral trimethoprim-sulfamethoxazole effectively prevented frequent infection.

The fever response is executed by integrated physiological and neuronal circuitry, and it confers a survival benefit during infection. The fever response after infection is caused by various immune factors such as the pyrogenic cytokines IL-6 and TNF-alpha produced by pathogen-associated immune cells such as dendritic cells and macrophages.[3] Excessive IL-6 production was confirmed in our infant, meaning that an immune response occurred. These infectious mediators or regulators of thermogenesis are essential for recovery from infectious events, and thus, such antipyretic reactions to infectious events may be correlated with increased mortality or negative outcomes in patients with mitochondrial disease.

Induction of fever incurs a high metabolic cost such that a 1 °C rise in body temperature requires a 10%—12.5% increase in the metabolic rate.[3] In addition, brain temperature is reported as hypothermic in patients with mitochondrial diseases because of malfunction of oxidative phosphorylation and poor neural response after physiologic stimulation.[4] These reports indicate that the hypothermic reaction might incur a metabolic cost and promote cell survival given that less mitochondrial function is needed at lower temperatures in patients with mitochondrial diseases.

In conclusion, we experienced a case of severe hypothermic reaction during an infectious state in a patient with PDC deficiency. Analysis of mitochondrial function and body temperature may provide better knowledge for managing life-threatening events in patients with mitochondrial diseases.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2019.04.005.

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