Phenylalanine Hydroxylase Deficiency and Citrin Deficiency in a Chinese Infant

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To the Editor: Tandem mass spectrometry (MS/MS)-based expanded newborn screening was first introduced in Pediatric Endocrinology/Genetics of Xin Hua Hospital in 2003. The screening is expected to detect genetic disorders leading to a secondary increase in blood phenylalanine (Phe) in newborns.[1]

We reported a rare case in a Chinese infant with hyperphenylalaninemia (HPA) caused by phenylalanine hydroxylase (PAH) deficiency and neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD). This constellation of two different metabolic pathway defects in one patient has not been reported previously.

A 2-month-old Chinese infant boy was referred to Department of Pediatric Endocrinology/Genetics of Xin Hua Hospital for mild HPA (Phe 150 mmol/L) detected by newborn screening. He had persistent jaundice. The MS/MS analysis showed high blood Phe (220 mmol/L), citrulline (Cit) (168 mmol/L), methionine, and arginine levels, but normal Phe/tyrosine (Tyr). Gas chromatography-mass spectrometry showed elevated 4-hydroxyphenylpyruvic acid and 4-hydroxyphenyllactic acid in urine. The biochemical investigation revealed hyperbilirubinemia, high alpha-fetoprotein, and abnormal liver function. He had normal urinary pterins and dihydropteridine reductase activity.

The patient was first diagnosed with NICCD and placed on a lactose-free formula containing medium-chain triglycerides at 2.5 months of age. However, biochemical marks and Cit level gradually returned to normal but elevated Phe (125–220 μmol/L) and Phe/Tyr (3.78–5.33) levels were noted since 8 months of age. Gene mutation analysis showed that this patient carries both known compound heterozygous mutations c.851del4/c.1638ins23 in *SLC25A13* gene and mutations C.158G >A (p.R53H)/c. 728G >A (p.R243Q) in *PAH* gene. So he suffered from both PAH and citrin deficiencies.

Urine pterin and dihydropteridine reductase activity analysis should be routinely performed to rule out BH4 deficiency. MS/MS analysis should be done to detect other genetic disorders leading to a secondary blood Phe increase in newborns with HPA according to the consensus.[2]

PAH deficiency and NICCD are different autosomal recessive inborn errors. The PAH catalyzes the conversion of Phe to Tyr and its deficiency results in HPA [Figure 1a]. Citrin deficiency caused by SLC25A13 mutation is another disorder of the urea cycle [Figure 1b]. Cit is transported out from mitochondrion and bound to aspartate by argininosuccinate synthase, and aspartate is provided by the mitochondrial transporter citrin.[3] A newborn with citrin deficiency can manifest intrahepatic cholestasis and has elevated Cit and other amino acids (secondary to liver lesion).

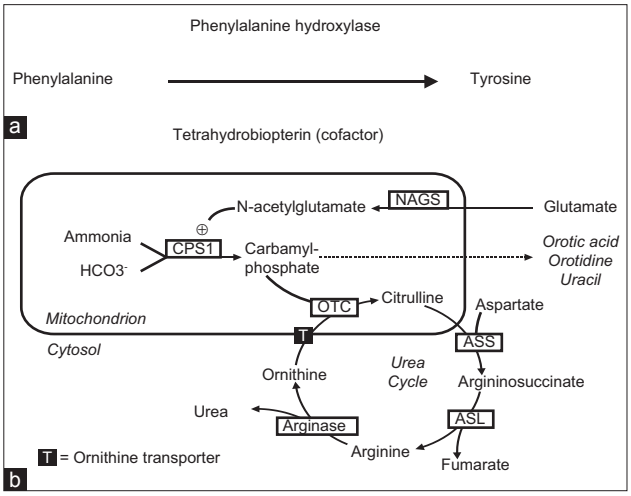

Figure 1: Metabolic pathways – (a) Metabolic pathway of phenylalanine; (b) Pathway of urea cycle.

The mutations p.R243Q and p.R53H in *PAH* gene produce <10% and 80% of the normal PAH activity, respectively.[4] Our patient with both mutations had mild HPA without treatment. He also carries two most common mutations c.851del4/c.1638ins23 in *SLC25A13* gene in China.[5]

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This rare case provided two important points for pediatric physicians: (1) Citrin deficiency that can lead to secondary high Phe levels should be ruled out for HPA by MS/MS analysis, and (2) if the blood Phe and Phe/Tyr are persistently elevated when Cit level returns to normal after treatment in an NICCD patient, she/he may also have PAH deficiency, and a gene mutation analysis is recommended to confirm the diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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