Hyperphenylalaninemia without phenylketonuria and BH4 deficiency: DNAJC12 deficiency

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Hyperphenylalaninemia (HPA) is known to be caused by deficiencies of phenylalanine hydroxylase or its cofactor tetrahydrobiopterin.

- DNAJC12 is a co-chaperone responsible for the proper folding of the phenylalanine hydroxylase enzyme together with the 70kDa heat shock protein (HSP70).

- Mutations in DNAJC12 were recently identified as a BH4-responsive cause of hyperphenylalaninemia (HPA).

- All patients with exclusion of PAH and BH4 deficiencies should be evaluated for DNAJC12 deficiency.

- We report on a 7-year-old girl with HPA due to a homozygous splice site mutation in DNAJC12 gene.
Case:

- A 7-year-old girl was called to the outpatient clinic because of the detection of hyperphenylalaninemia in the newborn screening of her little sister. Newborn screening was not done because she was born in Syria.

- She had no complaints but math performance was bad. Neuromotor development was normal. Physical examination was normal except obesity.

- Phenylalanine: 479 µmol/L, tyrosine: 75 µmol/L and phenylalanine/tyrosine: 6.38 were detected. To exclude the BH4 metabolism defects, the BH4 loading test was performed. Phenylalanine concentration decreased by 30.6% 24h after BH4 administration.

- There was no mutation in phenylalanine hydroxylase (PAH) gene. When we searched for other causes of HPA, homozygous c.158-2A>T(p-)
variant was detected in intron 2 in DNAJC12 gene.

- She was treated with sapropterin dihydrochloride, a synthetic BH4 analog, at a dose of 10 mg/kg/day. Phenylalanine concentration dropped to 109 µmol/L within one week. She is currently clinically asymptomatic.
Conclusion:

- DNAJC12 deficiency is a recently identified cause of hyperphenylalaninemia.

- The phenotypic spectrum ranges from mild autistic features to severe intellectual disability or parkinsonism. In untreated cases, it can cause permanent neurological damage.

- Early diagnosis and treatment with sapropterin dihydrochloride and neurotransmitter precursors can be beneficial in patients.

- DNAJC12 genotyping is recommended in all patients in which deficiencies of PAH and BH4 are genetically excluded.

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