Homocystinuria Due to *MTHFR* Variant Presenting As Infantile Tremor Syndrome

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To the Editor: Infantile tremor syndrome (ITS) is characterized by tremors, anemia, skin depigmentation, and developmental delay [1]. We are reporting a case of homocystinuria presenting as ITS.

An 8-mo-old boy presented with developmental delay and tremors for 3 mo. The child was on exclusive breast-feeding till 6 mo of age, and later weaned on ragi malt. The mother was on vegetarian diet. The child attained partial neck control and social smile by 7 mo, and following upper respiratory tract infection, there was a loss of above milestones. On examination, microcephaly (head size: 39 cm, *z* score: −4.78), weight of 6.9 kg (*z* score: −2.31), hypopigmented hair, pallor, hypotonia, brisk deep-tendon reflexes and tremors involving hands and tongue, complete head lag, and no social smile were observed.

On investigation, hemoglobin was 8.5 g/dL, megaloblastic anemia on peripheral smear with normal total leukocyte and platelets counts. Serum vitamin B12 was low - 180.5 (normal: 211–911 pg/mL), homocysteine was high - 127.05 (3–50 micromol/L), and urine methylmalonic acid level was normal. MRI of brain showed cerebral atrophy. The child was treated with vitamin-B12 1000 µg intravenous daily for 14 d followed by intramuscular twice weekly and nutritional rehabilitations. Repeat serum homocysteine after 1 mo, 2 mo, and 3 mo were 88, 80, and 75 micromol/L, respectively. Hence, considered possibility of inherited homocystinuria and exome sequencing revealed compound heterozygous variant in *MTHFR* gene. The variant-1 was c.1129 C>T/p.R377C in exon 7 and variant-2 was c.767 T>A/p.I256N in exon 5. Later, the child was treated with pyridoxine, folic acid, betaine, and special formula diet. Clinical improvement was noted at 12 mo of age with complete attainment of head control and social smile.

The child had features of ITS, but despite treatment there was persistent homocysteinemia. Hence, after further evaluation, the child was diagnosed as *MTHFR* deficiency. Both the variants were described earlier [2, 3]. The pathogenic variants in *MTHFR* gene may cause secondary vitamin B12 deficiency [4]. To conclude, homocystinuria due to *MTHFR* deficiency should be considered when ITS is not improving, and persistent homocysteinemia as the treatment and prognosis are different.

Declarations

Conflict of Interest None.

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