Left-Hand Motor Stereotypy in Vitamin B12 Deficiency: Expanding the Spectrum of Infantile Tremor Syndrome

Sir,

Infantile tremor syndrome (ITS) is a well-characterized neuro-cutaneous syndrome caused by vitamin B12 deficiency, occurring in children between 5 months and 3 years of age. It is characterized by a clinical tetrad of pallor, developmental regression with coarse tremors, hyperpigmentation of skin, and sparse brown hair.[1] Mothers of infants with ITS are vegetarian and, therefore, at a risk of vitamin B12 deficiency. Such infants have insufficient vitamin B12 stores at birth, which is further attenuated if not supplemented.[2] Apart from tremors, hypokinesia and mild rigidity, other movement disorders have not been described in this syndrome.[3] We present a case with motor stereotypy along with features of ITS, which includes pallor, neuroregression, and skin and hair changes, who responded to vitamin B12 supplementation.

A 15-month-old female child, second born offspring of nonconsanguineous marriage, was brought with complaints of abnormal repetitive motor stereotyped movement of the left upper limb (flexion of left upper limb reaching toward mouth) since 7 months of age. Parents observed that she had regression of developmental milestones from the 9 months of age along with irritability and sleep disturbances. She had also developed progressive pallor from the last 3 months. The child had been exclusively breastfed till 9 months of age, supplemented by inadequate complementary feeds subsequently. Milestones attained previously that were lost included loss of smile, interaction with parents and surroundings, sitting without support, and bisyllabic speech.

On examination, the child appeared dull and apathetic. She had sparse, hypopigmented hair, pallor and hyper-pigmented knuckles. Her weight was 6.5 kg and length 75 cm. Weight for length as per WHO growth charts fell below three standard deviations, suggesting severe acute malnutrition. She demonstrated repetitive abnormal flexion of the left upper limb with the hand reaching toward her mouth [Video 1]. Tone was decreased, and she was unable to sit or hold the neck. Remaining neurological and systemic examination was normal.

Evaluation revealed severe macrocytic anemia (Hb 5.8 gm/dL, mean corpuscular volume-112 fl; normal 80–95 fl). Peripheral blood smear showed macrocytic anemia along with thrombocytopenia. Vitamin B12 levels were 18 ng/mL (normal: 200–900 ng/mL). Tandem mass spectrometry for inborn errors of metabolism screening was normal. Magnetic resonance imaging of the brain showed mild cerebral atrophy. The patient was initiated on Vitamin B12 injections 1 mg intramuscularly, alternate day for 10 days, along with other micronutrient supplements. She was continued on oral vitamin B12 tablets at 30 µg/kg/day for 3 months. On follow-up at one month, she had improved. She was able to sit and had started playing with toys [Video 2]. Motor stereotypy improved substantially over 2 months of supplementation.

Movement disorders are uncommon among the protean neurological manifestations of vitamin B12 deficiency. Since the initial description of infantile tremor syndrome in 1957 by Dikshit *et al.*,[4] various movement disorders due to vitamin B12 deficiency have been described in both adults and children including those precipitated by B12 supplementation. The phenomenology ranges from hyperkinetic disorders like chorea,[5] ataxia,[5,6] tremor, myoclonus, dystonia[7] to hypokinetic disorders like parkinsonism.[8] These may be strikingly asymmetrical. So far, vitamin B12 deficiency presenting with stereotypy has not been described. Stereotypy may be primary or secondary to other neurological disorders. Secondary stereotypy occurs in association with autism spectrum disorders, intellectual disability, or sensory deprivation. Stereotypies have also been described in association with Wilson's disease and autoimmune encephalitis.

The association of movement disorders with cobalamin deficiency has been explained by elevation of homocysteine

and methyl tetrahydrofolate levels due to impaired methylene tetrahydrofolate reductase (MTHFR) reaction that converts homocysteine to methionine. Homocysteine is a N-Methyl-d-aspartic acid (NMDA) glutamate receptor agonist via metabolites L-homocysteate and L-homocysteine sulphinate.[9] These activate basal ganglia causing dystonia through thalamocortical pathways. The basal ganglia are mitochondria-replete, and endothelial dysfunction due to elevated homocysteine levels may also promote mitochondrial dysfunction. Methyl malonic acid (MMA) levels are also elevated in cobalamin deficiency. MMA plays a role in the development of movement disorders as evidenced by the presence of extrapyramidal disorders and basal ganglia involvement in children with methyl malonic acidemia.[10] Hyperglycinemia secondary to cobalamin deficiency may also be a contributor, although these reports have not been consistent. The neuroanatomical localization for motor stereotypies involves the cortico-striatal-thalamo-cortical loop. Striatal dysfunction may be multifactorial in vitamin B12 deficiency and may have led to motor stereotypy in our patient.

Neurological features in children with ITS occur in three phases: Pre-tremor, tremor, and post-tremor. Pre-tremor phase involves developmental regression, tremulous cry, and pallor. In the tremor phase, coarse tremors develop involving various body parts. There may be rigidity although hypotonia is usual. In our case, the patient had motor stereotyped movements, but no tremors. The fact that three features of the classical ITS tetrad as well as motor stereotypy responded to vitamin B12 supplementation suggests that the neurological spectrum of this disorder may be expanded to include motor stereotypy.

Acknowledgements

We thank the patient and her parents for their co-operation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the parents have given their consent for patient's images and other clinical information to be reported in the journal. The parents understand that patient's name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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References

1. Goraya JS, Kaur S. Infantile tremor syndrome: A review and critical appraisal of its etiology. J Pediatr Neurosci 2016;11:298-304. doi:10.4103/1817-1745.199475.
2. Zengin E, Sarper N, Caki Kiliç S. Clinical manifestations of infants with nutritional vitamin B deficiency due to maternal dietary deficiency. Acta Paediatr Oslo Nor 1992 2009;98:98-102. doi:10.1111/j.1651-2227.2008.01059.x.
3. Goraya JS, Kaur S, Mehra B. Neurology of nutritional Vitamin B12 deficiency in infants: Case Series from India and literature review. J Child Neurol 2015;30:1831-7. doi:10.1177/0883073815583688.
4. Dikshit AK. Nutritional dystrophy with anemia. Indian J Child Health 1957;6:132-6.
5. Shyambabu C, Sinha S, Taly AB, Vijayan J, Kovoor JME. Serum vitamin B12 deficiency and hyperhomocystinemia: A reversible cause of acute chorea, cerebellar ataxia in an adult with cerebral ischemia. J Neurol Sci 2008;273:152-154. doi:10.1016/j.jns.2008.06.034.
6. Ahn T-B, Cho J-W, Jeon BS. Unusual neurological presentations of vitamin B(12) deficiency. Eur J Neurol 2004;11:339-341. doi:10.1111/j.1468-1331.2004.00778.x.
7. Pacchetti C, Cristina S, Nappi G. Reversible chorea and focal dystonia in vitamin B12 deficiency. N Engl J Med 2002;347:295. doi:10.1056/NEJM200207253470417.
8. Kumar S. Vitamin B12 deficiency presenting with an acute reversible extrapyramidal syndrome. Neurol India 2004; 52:507-509.
9. Müller T, Woitalla D, Hunsdiek A, Kuhn W. Elevated plasma levels of homocysteine in dystonia. Acta Neurol Scand 2000;101:388-90. doi:10.1034/j.1600-0404.2000.90339.x.
10. Higginbottom MC, Sweetman L, Nyhan WL. A syndrome of methylmalonic aciduria, homocystinuria, megaloblastic anemia and neurologic abnormalities in a vitamin B12-deficient breast-fed infant of a strict vegetarian. N Engl J Med 1978;299:317-323. doi:10.1056/NEJM197808172990701.

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Submitted: 29-Jan-2020 **Accepted:** 07-Feb-2020 **Published:** 07-Apr-2020

DOI: 10.4103/aian.AIAN_63_20