



Evidence-Based Treatment of Infantile Tremor Syndrome

Mahesh Kamate¹

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Infantile tremor syndrome (ITS), more appropriately described as Neurocutaneous syndrome associated with Infantile vitamin B-12 deficiency (as tremor is not always seen in all cases), is an important eminently treatable condition seen in children less than 2 y of age. It usually presents as developmental delay/ regression of milestones, hyperpigmentation of skin especially over knuckles, palmar creases, hypopigmentation of hair and with or without tremors [1]. Out of many proposed causes of this condition like deficiency of zinc, vitamin B-12, iron, magnesium *etc.*, based on the available literature, nutritional deficiency of vitamin B-12 due to prolonged periods of exclusive breastfeeding by a mother who is herself deficient in vitamin B-12, seems to have the maximum evidence [1, 2]. But, there are no good quality studies to support the fact that vitamin B-12 deficiency alone causes it and not any other micronutrient deficiency or a combination of other micronutrient deficiencies. The paper by Kesavan et al. in this issue of the journal, provides some good quality evidence regarding the role of vitamin B-12 deficiency in the causation and treatment of Infantile tremor syndrome [3].

In the study by Kesavan et al., though the authors have concluded that treatment with vitamin B-12 alone was non-inferior to vitamin B-12 with multivitamin supplements, it is important to note that in this study, after one week, even those on only vitamin B-12 injections were also given multivitamin supplements. So, though ITS is caused by vitamin B-12 deficiency, there can be associated micronutrient deficiencies like iron, vitamin D, and vitamin B complex in any given case of ITS as prolonged breast feeding (beyond 6 mo of age) without weaning foods can predispose a child to multiple micronutrient deficiencies along with vitamin B-12. So, on a case-to-case basis, the decision to

supplement micronutrients needs to be taken based on the clinical findings and laboratory reports. As the authors have themselves mentioned in the paper, supplementation of vitamin B-12 in a child with ITS can stimulate hematopoiesis and many other repair mechanisms in the body. Hence there is a need for supplementation of other micronutrients (iron, folic acid) in addition to vitamin B-12. The child in question needs to be holistically managed including dietary counseling of parents, supplementing calories, proteins, micronutrients, advising physiotherapy, speech therapy and other allied therapies.

Another important finding from this study is the improvement that is seen in children within one week of vitamin B-12 administration, which is appreciated both by parents and clinicians alike. This can be extremely useful in clinical practice. In a suspected case of ITS, if we do not get improvement in one week's time, then alternative diagnoses need to be considered.

Though ITS has been reported from India in the last six decades, the exact treatment of this condition is not clear from the published literature. The dose of vitamin B-12, the route of administration, duration and the form of vitamin B-12 to be used have been different in different studies. As the gastro-intestinal tract is normal in children with ITS unlike pernicious anemia and the symptoms are due to dietary vitamin B-12 deficiency (not due to a genetic defect), is there always a need for parenteral vitamin B-12 therapy [4]? Can't we supplement vitamin B-12 orally instead of parenterally? Can we use injection methylcobalamin instead of hydroxocobalamin? Even the dose and duration of vitamin B-12 therapy is not very clear. These are some questions that need to be answered in future studies which can be multicentric and study large number of subjects.

Few children develop new onset myoclonus/tremors or notice worsening of the pre-existing tremor/myoclonus, a few days after injectable vitamin B-12. While the exact pathogenesis of this is not clear as the EEG is normal here, it is proposed to be due to an imbalance of excitatory vs. inhibitory activity or to a dysfunction along fibre tracts, during recovery from myelin degradation [5]. It is important to

✉ Mahesh Kamate
drmaheshkamate@gmail.com

¹ Department of Pediatric Neurology, Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research University, Belagavi, Karnataka 590010, India

counsel the parents about this possibility before treatment. It would be interesting to know if this can be avoided by oral vitamin B-12 supplementation instead of injectable form.

To conclude, while it is becoming clear that vitamin B-12 deficiency is the cause of infantile tremor syndrome, there are many unanswered questions in the treatment of this condition.

Declarations

Conflict of Interest None.

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