Infantile Tremor Syndrome – A Tale of 50 Years

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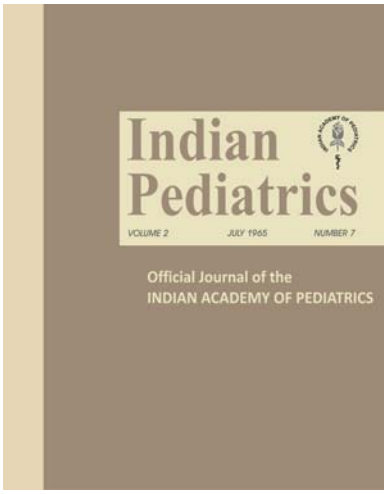
We continue with the second stop of our journey, the July issue of *Indian Pediatrics* in 1965. This comprised of 41 pages with seven articles that had three research papers (the syndrome of tremors, mental regression and anemia; neonatal blood pressure recording; and effects of long acting sulfonamides), a review on tremors, a case series (diaphragmatic disorders), book reviews and current literature. Out of all these, we chose to review the syndrome, since although it is a common and easily recognizable entity, our understanding is just marginally more than it was 50 years ago.



THE PAST

The study published in this issue was conducted over three years by Sachdev, *et al*. [1] at Amritsar Medical College in collaboration with the University of Oregan Medical School. Children presenting with tremors, mental regression and anemia were enrolled, evaluated and managed according to hospital protocol. The final study population comprised of 102 children aged 5 to 24 months (50% between 12-18 months) with a boy-girl ratio of 3:2, and belonging to the lowest socio-economic strata (mostly rural). All children were exclusively breastfed. Majority (62.7%) had history of preceding febrile illnesses. All the children had anemia and mental changes, with dystrophic hair and skin pigmentation patterns seen in 70% and 40%, respectively. Most children had weights 20% to 50% below expected with 11.7% displaying marasmus. The term mental regression was used to denote the mental and developmental status. The former (apathy and listlessness) was insidious, preceding tremors by weeks to months. An initially normal development followed by stagnation was seen in 85%, and early onset delay in the rest. A tremulous cry (described as 'bleating of a goat') was noted in 43%. All children developed tremors that were coarse, rhythmic, rapid, predominantly generalized (involving face, trunk and/or extremities), initially intermittent and gradually became continuous. Tone was variable; mild hypotonia in 39.3%, marked hypotonia in 4.9% and rigidity in 55.8%. Hyperreflexia was seen in 43%. Apart from hepatomegaly (in almost 50%), there were no other salient systemic findings.

The degree of anemia varied with mild (hemoglobin levels 7-9 g/dL) in 38%, moderate (5-7 g/dL) in 28%, and severe (3-5 g/dL) in 22%. A macrocytic hypochromic picture was observed in 47.5%, macrocytic normochromic in 25% and microcytic hypochromic in 27.5%. Bone marrow aspiration was done in two-thirds; majority displayed normoblastic reaction with 16.2% showing megaloblastic marrow. Fatty liver changes were seen in 12 out of 18 liver biopsies. A protein rich diet was given to all, and empirical treatment to 100 children who were divided into select groups (inclusion criteria unspecified) according to modality. These included daily administration of: (*i*) vitamin B_{12} (5 µg oral or 100 µg intramuscular) in 16 and 28 children, respectively; (*ii*) pyridoxine (10 mg) in 18 children; (*iii*) acetazolamide (125 mg) in 15 children; (*iv*) multiple therapy (liver extract, vitamin B complex, vitamin C and iron) in 15 children; and (*v*) phenobarbitone and antibiotics in 8 children. Majority (62.7%) remained symptomatic, however a clinical response (disappearance of tremors by 2 weeks) was observed in 5/8 (62.5%) of children receiving phenobarbitone, 7/15 (46.6%) receiving multiple therapy, 3/16 (18.8%) receiving B_{12} orally and 12/28 (42.8%) receiving B_{12} parenterally.

Historical background and past knowledge: The described syndrome was first reported in Indian medical literature as 'Nutritional dystrophy and anemia' by Dikshit, *et al.* [2] in 1957. Subsequently, it was reported from all over India under various names: 'infantile

meningo-encephalitic syndrome' by Pohowalla, *et al.* in 1960, 'vitamin B_{12} deficiency – a clinical syndrome' by Jadhav, *et al*. in 1962, and 'infantile syndrome of tremors in infants' by Kaul, *et al*. in 1963. The term 'infantile tremor syndrome' was introduced by Bajpai, *et al*. [3] in 1965, and is still in use, despite the fact that the phenotype is neither restrictive to infants nor to tremors.

Till the 1970s, studies aimed at describing the clinical manifestations. Subsequently, focus shifted to ascertaining etiology and therapy. Most affected children were aged between 6 and18 months, were predominantly males, belonged to lower socio-economic strata, and were exclusively breastfed by predominantly vegetarian mothers. The illness showed seasonal variation and the clinical course could be delineated into pre-tremor (prodromal), tremor (classical) and post-tremor (recovery) phases. Besides routine investigations, many others were performed ranging from biopsies (liver, brain, nerve and rectal) to pneumo-encephalograms, but were found inconclusive. Various etiological hypotheses were proposed with arguments both in favor and against. These included vitamin B_{12} deficiency (typical peripheral smear and bone marrow findings and response to therapy *versus* absence of hematological picture and response), multiple nutritional deficiencies (exclusively breastfed beyond the recommended period, typical hair and skin features associated with malnutrition *versus* absence of overt malnutrition in most cases, variable response to therapeutic nutrition and inability to pinpoint a specific deficiency), defects in tyrosine metabolism (hair and skin changes suggesting interference in melanin synthesis and aminoaciduria *versus* absence of these changes in some), and a probable viral infection (seasonal variation, preceding febrile illness with respiratory or gastrointestinal symptoms, self-limiting course, non-specific structural changes, cerebral atrophy and ventricular dilatation on neuroimaging and non-specific inflammatory changes on brain biopsy *versus* consistently negative viral studies). Short-term neurodevelopment outcomes were evaluated in a few cohorts and variable recovery was seen, ranging from partial to complete.

THE PRESENT

For reasons unknown, infantile tremor syndrome still remains confined to the Indian subcontinent. Though there is lack of community-based data, numbers of hospital-based admissions appear to be decreasing. Surprisingly, even now etiopathogenesis remains obscure. It appears that vitamin B_{12} deficiency has some causal association. The evidence is epidemiological (B_{12} deficient diets of mothers and infants), clinical, laboratory-based (decreased serum levels, abnormal deoxyuridine suppression tests) and therapeutic (clinical and hematological response) [4]. However, the reason for variability in hematological phenotype and response to B_{12} therapy is unclear. It has been suggested that the studies disproving deficiency as a cause were based only on blood picture, and not on vitamin B_{12} assay. Genetic predisposition is yet to be explored. Treatment still focuses on providing appropriate nutritional support with vitamin B_{12} therapy and supplementation of other vitamins and minerals (iron, calcium, magnesium, zinc, selenium, chromium). Since scurvy has also been reported in a few cases, vitamin C supplementation has also been advocated [5]. The drugs used now-a-days for persistent tremors are propranolol and carbamazepine. Long-term neuro-developmental outcomes need to be ascertained. It may be speculated that children in whom therapy is initiated late may already have suffered irreversible brain damage resulting in poorer prognosis. There is a strong need to rekindle interest in this mysterius disease [6], especially since advanced molecular and genetic technologies are now available.

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