

Case Series of Infantile Tremor Syndrome in Tertiary Care Paediatric Centre from Southern India

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ABSTRACT

Introduction: Infantile tremor syndrome (ITS) is characterized by anaemia, skin depigmentation, tremors and developmental delay. The lack of sufficient literature on ITS and its conflicting association with vitamin B12 deficiency made us present this article.

Objective: The objective of this study is to describe demographic, clinical and laboratory profile and outcome of ITS.

Methods: This is a retrospective chart review of all children presenting with typical features of ITS attending a tertiary paediatric centre in southern India between January 2014 and January 2017. All children with pallor, skin depigmentation and developmental delay, with/without tremors, were included. Anaemia, developmental delay and tremors secondary to non-nutritional causes like metabolic causes were excluded.

Results: Of 70 children, 66 were exclusively breastfed and 46 mothers were vegetarians. Mean age of presentation was 13.2 months. Developmental delay was noted in 64, regression in 6 and tremors in 40. Vitamin B₁₂ levels were low in 62 cases.

Conclusion: ITS should be considered in children <3 years with anaemia, developmental delay/regression and skin depigmentation, with/without tremors. ITS can be seen in < 3 months of age and in high socio-economic status.

KEYWORDS: infantile tremor syndrome, breastfeeding, vegetarian diet, vitamin B12, weaning

INTRODUCTION

Infantile tremor syndrome (ITS) is a clinical condition characterized by tremors, anaemia, skin depigmentation and developmental delay in children between age 5 months and 3 years [1, 2]. It is most commonly reported from Indian subcontinent, Southeast Asian countries and Africa. Exact

incidence is not known. In India, it accounts for 0.2–2% paediatric hospital admissions [3–6]. Currently no data are available on prevalence of ITS. ITS is not only associated with vitamin B12 deficiency, but it is also described in other micronutrient deficiencies and in non-vegan families. Recent review concluded that ITS is nutritional deficiency syndrome with

laboratory evidence of vitamin B12 deficiency [6]. However, Rajesh Gupta et al. reported only 2 of 12 children had low vitamin B12 level. Since number of patients in above studies are <50 in number, cause for ITS is not clear [7]. In view of paucity of sufficient literature and conflicting result in association with vitamin B12 deficiency in available literature, we planned for this study.

In all patients, detailed history, including birth history and diet history of child and mother, was taken and physical examination was carried out. Nutritional status was classified according to Indian academy of paediatrics [8]. A complete haematological work up (haemoglobin, total leukocyte count, platelet count, MCV, MCHC, MCH, peripheral blood film) using automated five-part differential haematology cell counter from Mindray 5200 BC (China) was carried out before the administration of any form of haematinics. Vitamin B12 level was done for all children. Vitamin B12 was measured by chemiluminescence method. Normal range of serum vitamin B12 is 200–800 pg/ml. The cut off value to consider vitamin B12 deficiency was taken as <200 pg/ml. Chest radiograph, urine examination, blood cultures were done in cases associated with lower respiratory tract infection, urinary tract infection or sepsis. CT/MRI scan of brain and metabolic work up was done as and when relevant. Institutional ethical clearance was taken.

RESULTS

The total number of cases seen during this period was 70. The mean age of presentation was 13.2 months (standard deviation of 5.6), ranging from 3 months to 30 months; three were less than 6 months. There were 38 males and 32 females, 24 were from urban areas and 46 were from rural areas. Nine children belonged to upper class, 2 to upper middle, 42 to lower middle and 17 to upper lower socio-economic status according to modified Kuppaswamy socio-economic classification. Two babies were preterm with low birth weight. History of birth asphyxia was present in three children. One child had a history of neonatal meningitis. Clinical features are mentioned in Table 1. Three children had convulsions, four had lower respiratory tract infection and three children had acute gastroenteritis.

All children were exclusively breastfed till the time of admission, except in four children, in addition to breastfeeding, ragi porridge was started but in insufficient amounts. Only 14 mothers were non-vegetarians. There was grade I malnutrition in 32, grade II in 13 and grade III in 10 as per IAP classification of malnutrition. All patients were haemodynamically stable at the time of admission except one child, who was in septic shock. All had pallor and knuckle depigmentation (Fig. 1). Other nutritional deficiency findings (vitamin A deficiency, cheilitis) were present in 10.

Haematological results in children with ITS are shown in Table 2. Serum vitamin B12 levels of babies were analysed in 66 of 70; it was found to be low in 62, normal in 4. Vitamin B12 levels were low in all children without tremors. Serum vitamin B12 levels were performed in nine mothers and in all it was low. Chest radiograph was suggestive of pneumonia in four children. CT scan of brain was done in 11 children; four were normal and the other seven had features of cerebral atrophy.

All children received vitamin B12 injection intravenously for 14 days, with folic acid and iron supplementation given in case of iron-deficiency anaemia. Antibiotics were given as and when indicated. Three

Table 1. Clinical findings in children with ITS

Clinical findings	Number of cases (70)
Developmental delay	64 (91.0%)
Regression	06 (8.5%)
Tremors	40 (64.2%)
Predominantly breastfed	66 (94.2%)
Mothers vegetarian diet	46 (65.7%)
Protein energy malnutrition	55 (78.0%)
Pallor	70 (100%)
Knuckle pigmentation	70 (100%)
Hypopigmented and sparse hair	53 (75.0%)
Pedal oedema	02 (02.8%)
Lethargy/apathy	38 (54.2%)
Hypertonia	29 (41.4%)
Hypotonia	13 (18.5%)
Hepatomegaly	02 (02.8%)
Microcephaly	20 (28.5%)
Maternal anaemia	40 (57.1%)

children required blood transfusion. For all children, diet advice and infant stimulation was given. Forty children had tremors and 20 of them received propranolol. The mean duration for control of tremors in our cases was 35.3 days. One child expired because of septic shock, despite good supportive care



Fig. 1. Clinical photo showing hypopigmented sparse hair, knuckle pigmentation and apathy.

with mechanical ventilation, inotropes and antibiotics. Remaining children improved with treatment.

DISCUSSION

In the present study, equal sex distribution was found. Some studies reported that boys are more commonly affected than girls, while few studies showed equal sex distribution in occurrence of ITS [9, 10]. Present study found 82.8% babies were between 6 and 18 months of age. Bajpai et al. found 94.1% and Sachdev et al. found 89.2% children between 6 and 18 months [11, 12]. The youngest child in our study was 3 months. This was the earliest presentation described in the literature and could be explained by underlying maternal nutritional deficiency. The reason for this age of presentation may be improper introduction of complementary food and predominant breastfeeding; large number of malnourished individuals were also seen in this age group.

Earlier studies reported ITS mainly in low socioeconomic class. However in this study, nine belong to upper class. This may be because of lack of awareness of timely introduction of complementary food.

Most of the children had grade 1 malnutrition, and none of the children were marasmic, on the contrary, they appeared plump; only two children had pitting pedal oedema, and evidence of other vitamin

Table 2. Laboratory findings in children with ITS

Laboratory findings	Number of cases (70)
Haemoglobin (Hb < 11 mg/dl)	70 (100%)
Leucopenia (TLC < 4000/mm ³)	22 (31.4%)
Thrombocytopenia (Platelet count <1,50,000/mm ³)	26 (37.1%)
High MCV (>100 fl)	40 (57.1%)
High MCH (>32 pg)	42 (60.0%)
High MCHC (>36 g/dl)	16 (34.2%)
Macrocytic anaemia	45 (64.2%)
Microcytic anaemia	06 (8.50%)
Dimorphic anaemia	05 (7.10%)
Normocytic normochromic anaemia	14 (20.0%)
Low child serum Vit B ₁₂ (<200 pg/ml) (n=66)	62 (93.9%)
Low maternal Vit B ₁₂ (<200 pg/ml) (n=9)	09 (100%)
Cerebral atrophy (n=11)	07 (63.6%)

deficiency was present in 10 cases. Similar changes have been consistently reported by others [13].

In this study, neurological and haematological manifestations were present in all children. In the present study, tremors were seen in 40 cases. Before onset of tremors, seven had preceding illness, either respiratory tract infection or gastroenteritis. The preceding or accompanying illness may precipitate the nutritional deficiency and lead to acute manifestation of ITS. Any occurrence of systemic illness could initiate a reaction, resulting in functional disturbance of motor activity and manifested as tremors [11]. In one case, tremor developed following DPT vaccine. Usually these children are listless, apathic and disinterested in surroundings. Hypertonia was present in 29 cases, and exaggerated deep tendon reflexes were present in 29 cases. In the literature, hypotonia is most commonly described, but in the present study, hypertonia is more commonly seen than hypotonia; this may be because of development of spastic quadriplegia as a late presentation, and microcephaly was observed in all these cases.

In the present study, serum vitamin B12 levels were low in 93.9% of cases. Only four children had normal vitamin B12 level, and one had evidence of vitamin B12 deficiency such as macrocytosis and peripheral smear suggestive of megaloblastic anaemia and low maternal serum vitamin B12. Other three children had iron-deficiency anaemia. The findings of earlier authors were anaemia in ITS may be due to vitamin B12 deficiency or iron deficiency alone or dual deficiency or folate deficiency may be present. In G. Garewal et al.'s study, in addition to vitamin B12 deficiency, folate and iron deficiency was found [14].

The aetiology of ITS is still elusive. Aetiological possibilities are nutritional, viral infections and degenerative hypothesis, but none have been conclusively proven [1]; nutritional theory is the most accepted. Recent review concluded that ITS is because of vitamin B12 deficiency [6]. However, Rajesh Gupta et al. reported only 2 of 12 children had low vitamin B12 level [7]. In this study, all children had evidence of vitamin B12 deficiency, except three children. Epidemiologically, ITS occurs in exclusively breastfed infants of vegan mothers, pointing to vitamin B12 deficiency [15], which showed similarity with the present study. Skin depigmentation seen in ITS is also a

well-known sign of vitamin B12 deficiency [16]. It is usual to find other associated nutritional deficiencies like protein, vitamin A, D, C and B-complex and other micronutrients [1, 17–19]. In this study, other nutritional deficiency findings were present in 10.

Management of ITS being largely empirical, it includes vitamin B12, folic acid, iron, calcium, zinc, magnesium and high protein diet [20]. All our cases received vitamin B12, folic acid and iron (in case of iron deficiency anaemia) apart from dietary advice. Three children required blood transfusion because of severe anaemia. Infant stimulation is also important to reduce long-term neurodevelopmental sequelae. For management of tremors, many drugs have been tried, including phenobarbitone, chlorpromazine, carbamazepine and propranolol [9, 21]. Patients in the present study were treated with propranolol and favourable response was obtained. The mean duration of tremor control in our cases was 35.3 days with range from 7 to 75 days. Other studies reported mean duration of tremors control being 50.5 days with a range from 3 to 225 days. All of them responded well both haematologically and neurologically except one child who expired because of septic shock. One child developed infantile spasms during recovery.

Skin depigmentation and hair colour changes take months to clear. Children in pretremor stage improved gradually, showing interest in surroundings, apathy decreases and mental dullness takes months to years to come back to normal. In the present series of cases, it took 8–12 months. This therapeutic response favours a vital role of vitamin B12 deficiency in causation of this syndrome.

Based on above findings, we considered vitamin B12 deficiency is a possible aetiology for ITS. We suggest *in vivo* experiments in mice/primates using magnetic resonance spectroscopy to clearly identify major aetiological factors. Inadequate calories because of improper introduction of complementary foods, poor dietary habits, predominant breastfeeding, mothers living on diet devoid of animal products are likely cause for low vitamin B₁₂ levels. Improvement in nutritional status, living conditions and better weaning practices could explain the reducing rates of ITS over the years. We recommend fortified foods with vitamin B12 for vegan mothers. It is necessary to check vitamin B12 levels in mothers if clinically

suspected in last trimester and to supplement accordingly to prevent ITS in babies and to improve weaning practices. Study limitation is that this is a retrospective case review. However, this is the largest number of cases reported.

CONCLUSION

ITS needs to be considered in any child <3 years presenting with anaemia, developmental delay/regression, skin depigmentation and sparse hair, with or without tremors. ITS should be excluded in any child presenting with neuroregression, as it is a treatable condition to prevent long-term neurodevelopmental sequelae. This study adds that ITS can be seen in <3 months of age, in high socio-economic status and it can mimic neurodegenerative diseases.

ACKNOWLEDGEMENTS

We acknowledge department of pathology for analysis of complete blood count and peripheral smear.

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