

# Clinicoaetiological Profile of Infantile Tremor Syndrome in a Tertiary Care Hospital, Punjab, India: An Observational Study

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## ABSTRACT

**Introduction:** Infantile Tremor Syndrome (ITS) is a condition that mainly affects infants aged 6-24 months. Although predominantly considered a disorder of vitamin B12 deficiency, there have been some reports of an association of other micronutrient deficiencies in ITS babies.

**Aim:** To assess the clinicoaetiological profile of cases of ITS admitted to the tertiary care centre.

**Materials and Methods:** This was a retrospective observational study conducted at Punjab Institute of Medical Sciences, Jalandhar, Punjab, India. All cases of ITS admitted to the Paediatric ward from April 2022 to March 2023 were enrolled. Their case records were studied for clinical signs and symptoms like presenting complaints, demographic profile, feeding history, history of tremors, and developmental milestones. Examination findings were studied for the degree of malnutrition, presence of anaemia, knuckle hyperpigmentation, sparse hypopigmented hair, other evidence of micronutrient deficiency, hepatosplenomegaly,

and any focal neurological deficit. Laboratory parameters, mainly blood counts, haemoglobin, Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin Concentration (MCHC), peripheral smear findings, vitamin D and B12 levels, and serum albumin, were analysed to ascertain the clinicoaetiological profile of ITS.

**Results:** A total of 19 cases were included in the study. All of them had sparse hypopigmented hair and anaemia. Thirteen (68.4%) had knuckle hyperpigmentation, 11 (58%) had tremors, and 16 (84.2%) had developmental delay/regression without any other underlying cause. Only 9 (47.4%) had laboratory evidence of vitamin B12 deficiency, while 14 (73.7%) had vitamin D deficiency. All the babies were discharged home, and tremors resolved in all of them after vitamin D, B12, and zinc therapy.

**Conclusion:** In addition to vitamin B12, Vitamin D deficiency was seen in most cases of ITS. Hence, all patients with ITS need to be evaluated and treated for vitamin B12 as well as vitamin D deficiency for optimal treatment of this disorder.

**Keywords:** Anaemia, B12 deficiency, Developmental delay, Vitamin D deficiency

## INTRODUCTION

Infantile tremor syndrome is characterised by pallor, skin hyperpigmentation, sparse brown hair, developmental regression or delay with or without tremors [1,2]. It usually affects babies between 6-24 months of age and accounts for 0.77-2.5% of ward admissions [2]. First reported in 1957, this neurocutaneous syndrome mainly affects babies who are exclusively breastfed beyond six months of life. Earlier, it was considered a mysterious disorder of unknown aetiology [3]. Presently, most authors have stressed that there is sufficient evidence to implicate vitamin B12 deficiency as the causative factor [3,4] and recovery of symptoms with vitamin B12 supplementation [3,5].

However, in these studies, babies with ITS were treated with oral supplements of zinc, calcium, and magnesium in addition to vitamin B12 [3,4]. Moreover, researchers also found inconclusive evidence of vitamin B12 deficiency in this disorder [6]. Ratageri VH et al., in their study found radiological evidence of vitamin C deficiency in the patients [7], while Gautam P et al., documented magnesium deficiency in these cases [8]. Agarwal R et al., also demonstrated low calcium, magnesium, and zinc levels in their patients admitted with ITS, and Vora RM et al., documented zinc deficiency in their case of ITS [9,10].

Hence, although vitamin B12 deficiency may be the major causative factor behind ITS, the role of associated micronutrient deficiencies cannot be neglected. Recently, Collins M and Young M have reported cases of neonatal tremors secondary to vitamin D deficiency [11]. Also, vitamin D deficiency has been implicated in worsening motor symptoms in patients with Parkinson's disease [12,13]. It has been found that the vitamin D receptor and 1 $\alpha$ -hydroxylase enzyme

responsible for the conversion of vitamin D to its active form are expressed in the Substantia nigra also [14]. So, inadequate vitamin D levels might lead to substantia nigra dysfunction and tremors. Likewise, systematic reviews by Homann CN et al., have suggested the role of vitamin D deficiency in the causation of hyperkinetic movement disorders, including essential tremor [15] and basal ganglia diseases [16]. Therefore, in addition to vitamin B12, vitamin D deficiency might have some role in ITS. As data regarding the role of vitamin D as an associated causative factor in ITS is scarce, this retrospective study was planned to know the clinicoaetiological profile of ITS patients admitted to our hospital.

## MATERIALS AND METHODS

This was a retrospective observational study conducted at Punjab Institute of Medical Sciences, Jalandhar, Punjab, India, over a one-year period from April 2022 to March 2023, and data were analysed from July to August 2023. The study protocol was approved by the Institutional Research and Ethics Committee (vide letter no. PIMS/DP/Gen 163/6085). As it was a retrospective study, a consent waiver was granted by the Institutional Research and Ethics Committee.

**Inclusion criteria:** Case records of all children diagnosed and admitted with ITS were included. Babies with sparse hypopigmented hair, pallor, skin hyperpigmentation, and developmental delay or regression with or without tremors were diagnosed as ITS and were included in the study.

**Exclusion criteria:** Children with pre-existing neurological disorders such as cerebral palsy, global developmental delay, and a known history of seizures were excluded from the study.

**Data collection:** All cases of ITS admitted to the paediatrics ward over the last one year were enrolled. The patient records

were reviewed for age, feeding history, presenting illness, any developmental delay or regression, examination findings such as the presence of pallor, knuckle hyperpigmentation, tremors, and sparse hypopigmented hair. Weight for age was ascertained from World Health Organisation (WHO) growth charts to assess the degree of malnutrition [17]. Developmental milestones were assessed based on the Trivandrum Development screening chart as it is easy to use for junior residents on duty [18].

Laboratory investigations were reviewed for haemoglobin, platelet count, MCV, MCH, MCHC, peripheral smear, vitamin D, and B12 levels. Serum zinc levels were not taken into account as this investigation had not been done due to affordability issues. The incidence of anaemia, vitamin D, and vitamin B12 deficiency was determined to understand the role of these micronutrient deficiencies in the causation of ITS. Serum vitamin D levels <30 ng/mL were considered deficient, and levels more than 50 ng/mL were considered high [19]. Serum vitamin B12 levels between 160-950 pg/mL were taken as normal [20].

STATISTICAL ANALYSIS

The data collected on the proformas were transferred into an MS Excel database. The data were analysed using Statistical Package for Social Sciences (SPSS) for Windows, version 21. Categorical data were expressed as number (percentage), and continuous variables were expressed as median (interquartile range).

RESULTS

A total of 19 cases of ITS were admitted during the study period. The male to female ratio was 1.7:1, suggesting a slight male preponderance. Eighteen (94.7%) of them were between 9-18 months of age. Sixteen (84.2%) children were from rural areas. All of them were on milk only, with none being initiated on complementary diet. Sixteen (84.2%) were being exclusively breastfed beyond six months of age, and three (15.8%) were on top milk. Twelve (63.2%) had a history of delayed milestones, and 4 (21%) had regression of milestones [Table/Fig-1]. All these children had normal development until six months of age with an uneventful birth and antenatal history.

Variables	n (%)
Age (months)	
<9	0
9-18	18 (94.7)
>18	1 (5.3)
Gender	
Male	12 (63.2)
Female	7 (36.8)
Residence	
Rural	16 (84.2)
Semi-urban	3 (15.8)
Feeding	
Exclusive breastfeeding	16 (84.2)
Mixed feeding	3 (15.8)
Complementary feeding	0
Development	
Delay	12 (63.2)
Regression	4 (21)
Normal	3 (15.8)

[Table/Fig-1]: Baseline demographic variables of subjects.

Eleven (58%) cases had tremors at admission. In addition, 3 (15.8%) had acute diarrhoea, and 10 (52.6%) had Wheeze Associated Lower Respiratory Infection (WALRI). On examination, all 19 (100%) children had pallor and sparse brown hair. Knuckle hyperpigmentation was

seen in 13 (68.4%) children. The mean weight was 7.72±0.9 kg. Five (26.3%) children had Protein Energy Malnutrition (PEM) (weight for age -2 to -3SD) at the time of admission. The remaining 14 children had weight for age in the normal range (>-2SD). None of the children had severe malnutrition (weight for age <-3SD) [Table/Fig-2]. Other anthropometric parameters could not be compared as they were not consistently mentioned in case records.

Variables	n (%)
Presenting feature	
Diarrhoea	3 (15.8)
Lower respiratory infection	10 (52.6)
Tremors	11 (58)
Lethargy	3 (15.8)
Floppiness	1 (5.3)
Examination findings	
Pallor	19 (100)
Knuckle hyperpigmentation	13 (68.4)
Hepatosplenomegaly	2 (10.5)
Hepatomegaly	6 (31.6)
Sparse hypopigmented hair	19 (100)
Acrodermatitis enteropathica	3 (15.8)
Rickets	10 (52.6)
Weight for age	
>-2SD	14 (73.7)
-2 to -3SD	5 (26.3)
<-3SD	0

[Table/Fig-2]: Presenting features and examination findings in study subjects.  
SD: Standard deviation

All the children were anaemic at admission. Fourteen (73.7%) babies had severe anaemia (Haemoglobin <7 g/dL), and the remaining 5 (26.3%) had moderate anaemia (Haemoglobin 7-10 g/dL). The mean haemoglobin was 5.9±3.7 g/dL. The mean MCV, MCH, and MCHC were 74.2±29.6 fL, 29.3±10.6 pg, and 32±4.5 g/dL, respectively, suggesting a predominance of macrocytic anaemia. All the babies had normal serum calcium levels (Mean±SD 7.75±1.55 mg/dL) [Table/Fig-3].

Laboratory parameters	Value (mean±SD) n=19
Haemoglobin (g/dL)	5.9±3.7
Mean Corpuscular Haemoglobin (MCH) (pg)	29.3±10.6
Mean Corpuscular Volume (MCV) (fL)	74.2±29.6
Mean Corpuscular Haemoglobin concentration (MCHC) (g/dL)	32±4.5
Serum calcium (mg/dL)	7.75±1.55

[Table/Fig-3]: Laboratory parameters of children with Infantile Tremor Syndrome (ITS).

The peripheral blood smear showed a megaloblastic picture in 11 (57.9%), dimorphic in 5 (26.3%), and microcytic hypochromic in 3 (15.8%). The platelet count was moderately reduced (<1 lac/μL) in 7 (36.8%) children, suggesting bicytopenia of vitamin B12 deficiency. In the rest of the children, the platelet count was normal.

In the present study, vitamin D levels were low (<30 ng/mL) in 14 (73.7%) children, 4 (21.1%) had values in the low normal range (30-40 ng/mL), median (IQR): 10 (8-36 ng/mL). Only one child had normal vitamin D levels (88 ng/mL). Vitamin B12 levels were low in 9 (47.4%) children, median (IQR): 220 (62-520 pg/mL), 3 (15.8%) children had high vitamin B12 levels (>2000 ng/mL). Also, 7 (36.8%) children had normal vitamin B12 levels, but all of them except one had vitamin D deficiency [Table/Fig-4].

Serum albumin levels were normal in 17 (89.5%) children, only 2 (10.5%) patients had borderline low serum albumin levels (2 g/dL).

Parameter	Value median (Interquartile range)	Normal level	Low level	High level
Vitamin B12 levels	220 (62-520 pg/mL)	7 (36.8%)	9 (47.4%)	3 (15.8%)
Vitamin D levels	10 (8-36 ng/mL)	4 (21.1%)	14 (73.7%)	1 (5.2%)

**[Table/Fig-4]:** Comparison of vitamin B12 and vitamin D levels in ITS patients.  
ITS: Infantile tremor syndrome

Computed Tomography (CT) head was done only in four children- two had cortical atrophy, while the other two babies had both subdural effusion and cortical atrophy.

All the children received symptomatic treatment for co-existing illness, complementary feeding was initiated, and micronutrients (zinc, vitamin D, and B12) were supplemented. Ten (56.6%) children required packed red cell transfusion in view of severe anaemia. Eight children received drug therapy (carbamazepine/phenobarbitone) for persistent debilitating tremors interfering with feeding [Table/Fig-5].

Symptom	Treatment	n (%)
Severe anaemia	Packed red cell transfusion	10 (56.6)
Tremors	Carbamazepine	4 (21)
	Phenobarbitone	3 (15.8)
	Phenobarbitone+carbamazepine	1 (0.05)
	No treatment	3 (15.8)

**[Table/Fig-5]:** Additional treatment needed for symptom control in ITS subjects.  
ITS: Infantile tremor syndrome

DISCUSSION

ITS is a clinically well known but aetiologically mysterious entity. Until 1987, it was considered to be a syndrome of unknown or multiple aetiologies [1,2]. Later on, it was found that there was enough evidence to prove that it is a nutritional deficiency disorder [2,3]. Many researchers now believe that this disorder is mainly caused by vitamin B12 deficiency [2-5]. However, Gupta R et al., found normal vitamin B12 levels in their patients [6]. Likewise, there have been reports of vitamin C [7], magnesium [8,9], and zinc [9,10] deficiency in patients with ITS. However, vitamin D deficiency has not been studied as an associated causative factor in ITS. There have been reports of the role of vitamin D deficiency in neonatal tremors [11], Parkinson's disease [12-14], essential tremor [15], as well as basal ganglia diseases [16]. Hence, present study assessed the role of vitamin D along with vitamin B12 deficiency in cases of ITS.

In present study, the subjects were predominantly males, mean age of onset was around 9-18 months, suggesting inadequate complementary feeding as an underlying cause. Many previous studies have also found a similar demographic profile in their patients [21,22]. The majority of the children belonged to a rural background and were exclusively breastfed. This signifies the importance of educating the mothers about breastfeeding and weaning practices, particularly in rural areas. Most of the children presented with co-morbid infections, particularly respiratory and gastrointestinal, implying decreased immunity due to micronutrient deficiencies, as also found by Gautam P et al., [8].

All the children had anaemia and sparse depigmented hair. Most of them had developmental delay or developmental regression. Vitamin B12 levels were significantly reduced (p-value <0.05) in these children. Many children had low serum vitamin B12 levels (47.4%), and the majority of those with normal levels also had a dimorphic or megaloblastic picture in their peripheral smears (84%). This might be due to borderline or functional vitamin B12 deficiency. This was similar to the findings of Goraya JS et al., and Chaudhary H et al., who documented low vitamin B12 levels in 57% and 42% of cases of ITS, respectively [4,23,24].

In present study, 73.7% of cases had low vitamin D levels, and many of them (47.4%) had low vitamin D levels despite normal or high

vitamin B12 levels. Vitamin D deficiency has already been shown to be associated with neonatal tremors, even with normal serum calcium [11]. It was postulated that calcium levels may be normal with early vitamin D deficiency, and neuronal excitability in these cases is the result of calcium deficiency at the intracellular level [11]. In their systematic reviews, Homann CN et al., also suggested the role of low vitamin D levels in essential tremor [15] and basal ganglia diseases [16]. Likewise, recent studies in adults have documented low vitamin D levels in patients with Parkinson's disease, which is another disorder marked by tremors [12,13]. Therefore, in addition to vitamin B12, vitamin D deficiency might also contribute to tremors in cases of ITS.

In their review article, Goraya JS and Kaur S also recommended supplementation with all micronutrients, not just vitamin B12, for the management of ITS cases [2]. Likewise, editorial comments by Kamate M suggest that 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 breastfeeding (beyond six months of age) without weaning foods can predispose a child to multiple micronutrient deficiencies along with vitamin B12 [25,26]. Similarly, in the latest randomised controlled trial by Kesavan S et al., cases of ITS received oral multivitamin supplements in addition to vitamin B12 [5].

Hence, vitamin D levels also need to be estimated and deficiency corrected in cases of ITS. To the best of our knowledge, this was the only study analysing the role of vitamin D alongside vitamin B12 deficiency in ITS. Many studies have earlier substantiated the role of vitamin B12 [2,4,9], vitamin C [7], and zinc [9,10] deficiency, but none have studied vitamin D levels earlier. As vitamin D deficiency is easily preventable and treatable, vitamin D levels should be measured in all cases of ITS, and supplements given to the deficient ones.

Limitation(s)

The sample size was small, and magnesium and zinc levels was not assessed in patients. Moreover, authors could not comment on the presence of stunting and microcephaly in these patients as it was a retrospective study, and data on length and head circumference were not available in all case records.

CONCLUSION(S)

In conclusion, ITS is a micronutrient deficiency disorder that can cause developmental regression and tremors in babies who are not started on complementary feeding well in time. In addition to vitamin B12, vitamin D deficiency may also be an important aetiological factor in the causation of ITS. Its management should focus on investigation and treatment for micronutrient deficiencies, including vitamin B12 and D. Multicentric trials with larger sample sizes, including investigation for all micronutrient deficiencies, are needed to substantiate present study findings.

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**Authors' contribution:** AB designed the hypothesis, enrolled the subjects and conducted analysis under the guidance of HSB. Both AB and HSB wrote the discussion and conclusion. Both AB and HSB approved the final manuscript.

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