



REVERSIBLE NEURODEVELOPMENTAL SYNDROME IN EARLY INFANCY: INSIGHTS FROM 18 CASES OF INFANTILE TREMOR SYNDROME

Paediatrics

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ABSTRACT

Background: Infantile Tremor Syndrome (ITS) remains a public health concern in resource-limited settings, often associated with exclusive breastfeeding and maternal strict vegetarianism. Despite its classical presentation, diagnostic uncertainty and non-evidence-based interventions persist. **Methods:** This retrospective observational study analyzed 18 children diagnosed with ITS over a 6-month period (November 2024 to April 2025) at a tertiary care teaching hospital in rural India. Demographic data, clinical features, laboratory findings, treatment received, and outcomes were recorded. Diagnosis was based on clinical features consistent with descriptions in standard pediatric references and previously published Indian case series. **Results:** The median age of presentation was 9 months (range: 7–14 months), with a male predominance (10:8). All children had a history of exclusive breastfeeding, and their mothers followed strict vegetarian diets with complete avoidance of dairy products. Common features included tremors (100%), pallor (100%), developmental delay (94%), hypotonia (100%), and apathy (61%). Seizures occurred in 3 children. Dimorphic anemia was seen in 89%, and B12 levels were normal in 8 children despite classical symptoms. All children were treated with oral vitamin B12, folic acid, and other micronutrients; 6 received parenteral B12 initially. No transfusions were administered at our tertiary care hospital, though 4 children had received transfusions before referral. Clinical improvement, assessed by resolution of tremors and developmental progress, was evident in most by 1 month. Three children had residual deficits at 3 months. No relapses were observed. **Conclusion:** ITS is a reversible yet often inappropriately treated due to limited awareness in rural India. Oral therapy is effective in most cases. Maternal nutritional screening during antenatal care and awareness against unnecessary anticonvulsants like phenobarbitone are urgently needed. Routine antenatal screening of maternal B12 levels and dietary counseling should be integrated into national maternal health programs.

KEYWORDS

Infantile Tremor Syndrome, Vitamin B12 deficiency, Pediatric Neurodevelopment, Nutritional encephalopathy, Vegetarianism, Reversible disorders

INTRODUCTION

Infantile Tremor Syndrome (ITS) is a unique neurodevelopmental disorder predominantly observed in exclusively breastfed infants aged 6 to 24 months, often born to vegetarian mothers in low- and middle-income countries, particularly India [1,2]. Characterized by tremors, developmental regression or delay, pallor, pigmentation changes, and apathy, ITS reflects a reversible yet under-recognized nutritional encephalopathy [3,4]. The estimated prevalence ranges from 0.2% to 2% in certain pediatric outpatient populations in India.

Despite several published case series and reviews, ITS continues to pose diagnostic and therapeutic dilemmas. The pathogenesis remains debated, with hypotheses centering around vitamin B12 deficiency, although not all cases show reduced serum levels [5,6]. Functional or cellular B12 deficiency, possibly due to impaired absorption or transport, may explain this discrepancy [11]. The disorder is frequently misdiagnosed, and non-evidence-based interventions such as prolonged anticonvulsant use are still practiced [8,9]

This study reports our tertiary care hospital's 6-month experience managing 18 consecutive cases of ITS, highlighting clinical patterns, treatment responses, and policy-relevant insights in a rural Indian setting.

METHODS

Diagnosis was based on clinical features consistent with descriptions in standard pediatric references and previously published Indian case series.

This retrospective observational study was conducted at a tertiary care teaching hospital in rural India from November 2024 to April 2025. The hospital serves primarily underserved rural communities and includes a Pediatric Intensive Care Unit (PICU).

All children aged 6 to 18 months diagnosed clinically with ITS based on classical features (tremors, pallor, developmental delay/regression, hypotonia, and hyperpigmentation) were included. Alternate causes of encephalopathy such as hypothyroidism, neurodegenerative diseases, and infectious encephalitis were ruled out.

Data on demographics, feeding and maternal dietary history, clinical presentation, neurological findings, investigations, imaging (if any), treatment, and follow-up were extracted from case records. Follow-up data were also gathered from outpatient records and telephonic communication.

Hemoglobin, MCV, peripheral smear, LDH, and serum B12 levels were reviewed. MRI and CSF analysis were performed for children presenting with seizures. Micronutrient levels (zinc, folate) were not routinely measured but were supplemented empirically.

All children were treated with oral vitamin B12, folic acid, multivitamins, calcium, zinc, magnesium sulfate, and prophylactic vitamin D. Six children received three intramuscular B12 injections on alternate days before transitioning to oral therapy. Iron was started 14 days after initiating B12.

Ethical clearance was obtained from the Institutional Ethics Committee. Data were anonymized for confidentiality.

RESULTS

Eighteen children met the inclusion criteria. Median age at presentation was 9 months (range: 7–14 months); 13 were below 1 year. There was a male predominance (10 boys). All were exclusively breastfed; maternal history revealed strict vegetarianism with complete dairy avoidance [6,7].

Despite signs of micronutrient deficiency, all had weights above the 3rd percentile for age based on WHO growth standards [19]. Nutritional supplementation followed standard protocols for moderate acute malnutrition (SAM) excluding therapeutic feeds.

Clinical Features:

Table 1: Clinical Features

Clinical Feature	Number of Cases (n=18)	Percentage (%)
Tremors	18	100
Pallor	18	100
Hypotonia	18	100

Developmental delay	17	94
Apathy	11	61
Seizures	3	17
Regression of milestones	6	33
Facial nerve palsy	2	11
Head circumference	4	22

MRI and CSF were normal in seizure cases. Head circumference was subnormal in 4 children.

Neurological exam showed sluggish reflexes in all. Six children had infections; three required PICU support with high-flow nasal cannula (HFNC).

Laboratory Findings:

Table 2: Laboratory Findings With Summary Statistics

Laboratory Parameter	Range	Mean	Median	Mode	n (%) Abnormal
Hemoglobin (g/dL)	5.1 – 8.9	6.9	6.8	5.0	18 (100%)
MCV (fL)	83.0 – 123.5	101.3	100.5	107.0	18 (100%)
Serum B12 (pg/mL)	224.8 – 555.5	327.7	286.4	224.0	10 (56%) Low
LDH (U/L)	9044.0 – 16895.0	12938.7	13664.0	9044.0	18 (100%)
Peripheral Smear	—	—	—	—	16 (89%) Dimorphic

Treatment And Outcomes:

- All received oral vitamin B12 and micronutrient therapy
- Six received IM B12 prior to oral switch [10]
- No transfusions at our tertiary care hospital (4 had prior transfusions) [8]
- Neurostimulation guidance was provided

Clinical improvement, measured by tremor resolution, developmental catch-up, and caregiver-reported activity, was seen within 1 month in most children. Tremors resolved in all but 3 (resolved by 3 months). Three children had residual motor or speech delays at follow-up [16]. No relapses or readmissions occurred.

DISCUSSION

This study reinforces the classical yet under-recognized features of ITS. The universal presence of tremors, pallor, and hypotonia aligns with earlier findings [4]. The unexpectedly normal serum B12 in 8 children supports theories of functional/cellular deficiency [11].

The maternal dietary patterns, particularly strict vegetarianism with dairy avoidance emerged as a significant contributor, underlining the need for antenatal nutritional counseling [6,7,14]. Maternal B12 supplementation may serve as a preventive intervention [12,13].

All children responded well to oral vitamin B12, challenging the necessity of routine parental therapy [10]. Where used, IM B12 showed no added benefit in outcomes.

Avoidance of unnecessary transfusions and anticonvulsants further exemplifies rational management [8,9]. Sepsis in a subset of children underscores the importance of multisystem vigilance [15].

At 3 months, 3 children had mild residual deficits, highlighting the need for early recognition and neurodevelopmental support [16].

Limitations:

- Single-center retrospective design [18]
- Small sample size
- Absence of formal developmental scores
- Incomplete micronutrient level data

CONCLUSION

Routine antenatal screening of maternal B12 levels and dietary counseling should be integrated into national maternal health programs.

ITS is a reversible neurodevelopmental disorder predominantly affecting infants in vegetarian households. Our experience shows oral vitamin B12 and micronutrient therapy as effective in most cases.

Public health policies should incorporate antenatal dietary screening, maternal B12 supplementation, and discourage non-evidence-based interventions. Early diagnosis and rational therapy can significantly improve outcomes. Our findings support the development of standardized clinical protocols and public health strategies to address this preventable condition [17].

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