



Case Series

## Infantile tremor syndrome with megaloblastic anaemia – A case series

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### ABSTRACT

Infantile tremor syndrome (ITS) is a self-limiting clinical condition primarily affecting infants. It is characterised by a constellation of symptoms, including coarse tremors, often exacerbated by wakefulness and mitigated during sleep, anaemia, distinctive skin pigmentation changes, developmental regression and hypotonia in seemingly well-nourished infants. While a definitive aetiology remains elusive, various hypotheses have been proposed, including infectious, metabolic and nutritional factors. A growing body of evidence implicates Vitamin B12 deficiency as a significant contributor to ITS pathogenesis, though this association remains a subject of ongoing debate. In the absence of a conclusive diagnosis, empirical management often involves a multifaceted approach. Nutritional supplementation with iron, calcium, magnesium, Vitamin B12 and other essential micronutrients is a cornerstone of treatment. Pharmacotherapy, primarily with propranolol, may be employed to alleviate tremors, though other anticonvulsants such as phenobarbital, phenytoin and carbamazepine may be considered in refractory cases.

**Keywords:** Movement disorders, Neurology, Paediatrics, Vitamin B12

### INTRODUCTION

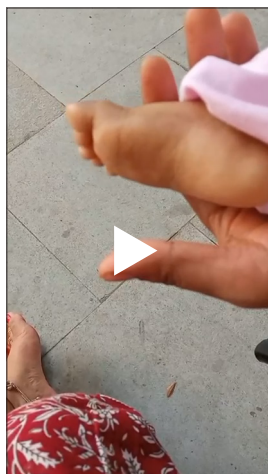
This case series presents infants who have exhibited a progressive decline characterised by tremors, feeding difficulties and developmental delay. A vegetarian mother had exclusively breastfed these infants and the absence of adequate complementary feeding exacerbated the nutritional deficiencies. Clinical evaluation revealed pallor, hypopigmentation of hair, hyperpigmentation of knuckles and generalised hypotonia. Laboratory investigations confirmed a diagnosis of Vitamin B12 deficiency anaemia, along with other nutritional deficits. Neuroimaging studies demonstrated cerebral atrophy, indicating the potential neurological sequelae of prolonged nutritional deprivation. The therapeutic approach focused on addressing the underlying nutritional deficiencies, primarily through supplementation with Vitamin B12, iron, magnesium and calcium, coupled with a protein-rich diet.

### CASE SERIES

#### Case 1

A 9-month-old female infant, a product of non-consanguineous marriage with spontaneous conception was born at term to a hypothyroid mother who is graduate, belongs to a strict vegetarian diet along with social economic background of lower middle class nuclear family,

presented with a complex clinical picture over the preceding month, she had experienced a concerning regression in her developmental milestones, indicating a decline in her neurocognitive function. This was further compounded by the onset of involuntary limb movements or jitteriness within the past week. In addition, a notable darkening of her skin pigmentation emerged, appearing suddenly over her body, despite a fair complexion trait in her family [Figure 1a-c]. Her birth history was unremarkable, with a normal vaginal delivery and a healthy neonatal period. Antenatal ultrasounds, while largely unremarkable, did identify a choroid plexus cyst. In the second trimester, a follow-up post-natal scan was found to be normal. The presentational anthropometry was length - 64 cm (-3 standard deviation [SD]), weight - 5.5 kg (-3 SD), occipito frontal circumference (head circumference) OFC 40 cm (-3 SD), indicating severe wasting with microcephaly. On physical examination, the infant appeared pale, and the most striking finding was the hyperpigmentation of her extremities and neck, along with tremor movements elicited at both wrists and ankles [Video1]. The central nervous system examination revealed generalised hypotonia. Despite the hypotonia, her reflexes were intact. The rest of the systemic examination was unremarkable.



**Video 1:** Tremors noted in index case 1.

### Case 2

A 11-month-old male infant, a product of non-consanguineous marriage with spontaneous conception was born at term to a mother who is graduate, belongs to a strict vegetarian diet along with social economic background of lower middle class nuclear family, presented with a complex clinical picture over the preceding month, she had experienced a concerning regression in her developmental milestones, indicating a decline in her neurocognitive function. This was further compounded by the onset of involuntary limb movements or jitteriness, within the

past week. Her birth history was unremarkable, with a normal vaginal delivery and a healthy neonatal period. The antenatal ultrasound scans were found to be normal with no anomalies detected. The presentational anthropometry was normally appropriate for age. On physical examination, the infant appeared pale with severe hypotonia with poor axial tone along with intentional tremors elicited at both wrist and ankle. The central nervous system examination revealed generalised hypotonia. Despite the hypotonia, her reflexes were intact. The rest of the systemic examination was unremarkable [Figure 2].

### Case 3

A 6-month-old male infant, a product of non-consanguineous marriage with spontaneous conception was born at term to a mother who is graduate, belongs to a strict vegetarian diet along with social economic background of lower middle class nuclear family, presented with a complex clinical picture over the preceding month, she had experienced abnormal movement disorder by the onset of involuntary limb movements or jitteriness, within the past few weeks. Her birth history was unremarkable, with a normal vaginal delivery, and she was admitted for neonatal hyperbilirubinaemia during the neonatal period, which was managed with phototherapy and fluid therapy. The antenatal ultrasound scans were found to be normal with no anomalies. The presentational anthropometry was normally appropriate for age. On physical examination, the infant appeared pale and most striking finding was the severe hypotonia with slip sign on vertical suspension and u sign in horizontal suspension was noted and poor neck control along with tremor movements elicited at both wrist and ankle [Figure 3]. The central nervous system examination revealed

**Table 1:** Investigation reports of index case-1.

Test conducted	Reports	Normal range
HB/HCT	5.8/34.1	11–13 g/dL
TLC	7040	3000–10000
PLT	1.39 lakh	>1.5 lakhs
Reticulocyte count	1.74	<1
TIBC	285	<250
Vitamin B12 level	104 pg/mL	211–710 pg/mL
Serum homocysteine	97.99	-
Serum thyroid profile	Normal limits	-
HPLC	HbA-97.99	-
TMS/GCMS	Increased MMA levels	-

HB/HCT: Haemoglobin/haematocrit, TLC: Total leucocyte count, PLT: Platelet count, TIBC: Total iron-binding capacity, HPLC: High-performance liquid chromatography, TMS/GCMS: Tandem mass spectrometry/gas chromatography–mass spectrometry, MMA: Methylmalonic acid, HbA: Hemoglobin A



Figure 1: (a-c) Hyperpigmentation of index case 1.



Figure 2: Hyper pigmentation of case 2.

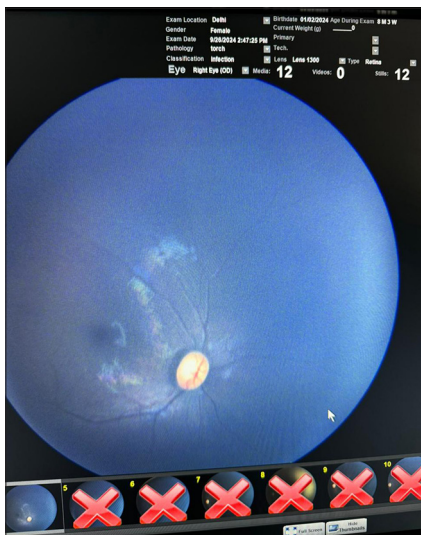


Figure 3: Fundoscopy through retcam-optic atrophy.

generalised hypotonia with delayed milestones. Despite the hypotonia, her reflexes were intact. The rest of the other systemic examination was unremarkable.

#### Investigations and management

The infant was admitted as a case of generalised hypotonia with severe nutritional anaemia and microcephaly (under evaluation). The investigations in Table 1 revealed severe macrocytic hyperchromic anaemia on peripheral smear with lower Vitamin B12 levels, along with serum methylmalonic acid and homocysteine levels. Non-contrast computed tomography brain was done and was found to have cerebral atrophy. The baby was started on injection hydroxocobalamin 1000 mcg daily (14 days), followed by weekly injection and further on oral supplementation. The child responded well to treatment in the form of active limb movements with resolution of milestones and adequate weight gain during the hospital stay. On discharge follow-up, the neurological examination was normal with absent tremors and adequate weight gain.

#### DISCUSSION

Infantile tremor syndrome (ITS) is a clinical condition characterised by a constellation of symptoms including tremors, anaemia, skin pigmentation abnormalities, developmental regression and muscle weakness.<sup>[1]</sup> Primarily prevalent in the Indian subcontinent, ITS is a self-limiting disorder affecting infants and young children.<sup>[2]</sup> Despite decades of research, the precise aetiology of this enigmatic condition remains elusive. ITS is a self-limiting condition primarily affecting infants aged 5–36 months in the Indian subcontinent. Its characteristic features include coarse tremors, anaemia, skin pigmentation abnormalities and developmental regression, often observed in seemingly well-nourished infants. Despite decades of research, the underlying cause of ITS remains elusive, posing an enduring medical mystery.<sup>[3]</sup> There is literature stating that the incidence of ITS is

mostly observed during the winter/rainy seasons, and a higher incidence is noted in Karnataka.<sup>[4,5]</sup> The sex predominance of male gender, as well as socio-economic status, with mothers often vegetarian, are some other important factors for ITS.

### Clinical presentation

Variable clinical presentation from bizarre presentation of neuroregression to a typical scenario often appears malnutrition characteristic (severe acute malnutrition [SAM] with anaemia), hidden hunger (micronutrient deficiency). Tremors, mostly coarse characters (facial muscles and hands), are one of the most significant characteristic features of ITS. These tremors are typically absent during the early course of illness. The bleating of a goat's voice is another finding in these patients, which has been noticed.<sup>[5,6]</sup> Other movement disorders include myoclonus and chorea.<sup>[5]</sup> Systemic involvement may be noticed as hyperpigmentation of knuckles and flexors, along with some characteristic features of (SAM, moderate acute malnutrition). Congestive cardiac failure secondary to super-added thiamine deficiency has also been reported.<sup>[5]</sup> Bone marrow features are variable, from normoblastic to megaloblastic appearance. Successful treatment with Vitamin B12 alone has been observed, with a uniform pattern of response resulting in a dramatic improvement in symptoms, accompanied by rapid haematological and neurological recovery.<sup>[5]</sup> Supportive care in the form of intravenous fluids to treat and prevent dehydration, antibiotics for associated infections, and other medications to treat associated complications are commonly used during the acute phase. Tremors have been treated with propranolol, sedatives, carbamazepine and emetine, but their role in treatment requires evaluation through controlled studies.

### Treatment

Most often, ITS infants were symptomatically managed with multivitamins and a methylcobalamine regimen of 14 days (1000 mcg) followed by 1000 mcg/week for 6 weeks later on a monthly basis till symptoms disappear or anaemia is corrected. Recovery is gradually noticed in terms of clinical response (resolution of mental abilities, tremors and disappearance of hyperpigmentation). Refractory diseases require further genetic testing in terms of malabsorption syndromes (Imerslund-Grasbeck Syndrome [CUBAM defect], Hereditary Intrinsic Factor Deficiency).

### CONCLUSION

ITS is a condition caused by nutritional deficiencies, primarily characterised by its impact on the nervous system. Children with ITS also consistently show signs of megaloblastic anaemia. This syndrome is most often seen in families facing socioeconomic challenges, particularly where mothers follow a vegetarian diet lacking essential nutrients. Effective treatment for ITS involves multivitamin therapy, with a particular focus on Vitamin B12 supplementation, along with addressing any other nutritional deficits. Supportive care is also crucial for comprehensive management. Early diagnosis and treatment are vital to prevent long-term cognitive problems.

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