International Journal of Contemporary Pediatrics
Nazish et al. Int J Contemp Pediatr. 2023 Nov;10(11):1721-1725
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

Case Report

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20233159

Infantile tremor syndrome: a case report

Nazish[1], M. Arif[1], M. Yasir Zubair[2]*

[1]Department of Pediatrics, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India
[2]Department of Community Medicine, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

Received: 02 October 2023
Revised: 10 October 2023
Accepted: 11 October 2023

***Correspondence:**
Dr. M. Yasir Zubair,
E-mail: yasmuhsin@gmail.com

ABSTRACT

Infantile tremor syndrome (ITS) is a rare but significant clinical condition characterized by a tetrad of pallor, developmental delay or regression, skin pigmentation abnormalities, and sparse brown scalp hair, often accompanied by involuntary tremors. ITS primarily affects children aged 5 months to 3 years, with a higher prevalence in males, especially in regions like the Indian subcontinent, Southeast Asia, and Africa. The exact cause of ITS remains uncertain, but a strong association with vitamin B12 deficiency has been observed in numerous studies. Malnutrition, including deficiencies of zinc, magnesium, iron, calcium, and hypoalbuminemia, is common among affected infants, who often come from lower socioeconomic backgrounds with vegetarian mothers lacking animal food in their diets. In this case report, an 8-month-old female child presented with progressive tremors, poor feeding, and developmental delay. The child had been exclusively breastfed by a vegetarian mother and lacked proper complementary feeding. Clinical examination revealed pallor, hypopigmented hair, hyperpigmented knuckles, and generalized hypotonia. Laboratory tests confirmed vitamin B12 deficiency, anemia and other nutritional deficiencies. Neuroimaging showed cerebral atrophy. Treatment involved addressing the nutritional deficiencies, primarily through vitamin B12 supplementation, iron, magnesium, calcium, and a protein-rich diet. Tremors were managed with propranolol and phenobarbitone. Within a month of treatment, the child exhibited significant improvement in tremors, developmental milestones, and overall well-being. This case emphasizes the importance of considering ITS in infants with specific clinical features and highlights the role of healthcare providers in educating parents about proper nutrition during pregnancy and infancy. Early diagnosis and management, including nutritional interventions and symptom control, can lead to substantial improvements in affected children's health and development. Further research is necessary to better understand the etiology and optimal management strategies for ITS.

Keywords: Infantile tremor syndrome, Nutritional insufficiency, Micronutrient deficiency, Vitamin B12 deficiency, Reversible cerebral atrophy

INTRODUCTION

Infantile tremor syndrome (ITS) is defined by the tetrad of pallor, developmental delay/regression, skin pigmentation, and brown scanty scalp hair. Involuntary movements in the form of tremors supervene in the natural course of the illness in a significant number of cases. The definition has evolved and currently it is defined as 'a clinical state characterized by tremors, anemia, pigmentary changes, delay or regression of developmental milestones, and hypotonia of muscles'.[1]

Epidemiology

Age

Age is between 5 months to 3 years (ranges from 40 days to 36 months).[2]

Gender

Male preponderance is reported.[2]

Place distribution

It is most commonly reported from Indian subcontinent, Southeast Asian countries and Africa. In India this syndrome has been reported from Punjab, Himachal Pradesh, Jammu and Kashmir, New Delhi, Chandigarh, Uttar Pradesh, Bihar, Rajasthan, Gujarat, West Bengal, Madhya Pradesh, Maharashtra, Andhra Pradesh, Karnataka and Tamil Nadu. Currently, this entity has been reported sporadically from various parts of the country.

Seasonal variation

No seasonal variation has been seen generally, however in a study conducted as early as1969, it was found that 52% of all cases presented in from May to July.[3]

Burden

In India, it accounts for 0.2–2% paediatric hospital admissions.[4]

Causes

Exact cause is not known. Etiology has remained a subject of intense research and ambiguity exists till date. Few observations which have been made in studies are listed below.[5-9]

1-Most of the studies found association with vitamin B12 deficiency.

2-Infants with ITS are mostly malnourished. Deficiencies of zinc, magnesium iron, calcium have been noted along with hypoalbuminemia and fatty liver changes. Most of the infants belong to poor families and lower socioeconomic status.

3-Mothers of infants with ITS are vegetarian in their dietary habits devoid of animal foods including milk and their nutritional status is also poor with multiple nutritional deficiencies. ITS occurs in exclusively breast-fed infants of vegetarian mothers in whom proper weaning was not initiated.

The debate regarding the etiology of ITS usually revolves around the role of vitamin B12 deficiency. Substantial amount of literature offers strong epidemiological, clinical, and laboratory data supporting vitamin B12 deficiency as a contributing etiology of ITS.

Clinical features of ITS

In majority of the cases ITS is triggered by some febrile illness. Megaloblastic anemia has been a consistent finding.

General appearance

Typically affected infant appears plump with maintained subcutaneous fat, dull apathetic look, expressionless face, vacant stare, and appearance is quite reminiscent of kwashiorkor. Pallor is usually observed (due to nutritional deficiency anemia).

Skin and hair changes- knuckle pigmentation, reticulate or diffuse honeycomb pattern of hyperpigmentation of trunks and limbs. Hairs grow sparsely, are easily pluckable, lustreless and show variable depigmentation. The eyebrows can also be affected.

Signs of multiple vitamin and micronutrient deficiencies such as angular cheilitis, stomatitis, glossitis, rickets, scurvy as well as vitamin A deficiency are seen.

Developmental delay/regression is also seen- normal development till 4-6 months of age followed by developmental slowing and then developmental regression

Tremors are one of the characteristic finding of ITS. They are generally absent in early stage of disease. Later, tremors may manifest and have a jerky quality (myoclonus like). Facial muscles can also be affected by tremors leading to “tremulous vocalization and cry” which has been likened to the bleating of a goat.

CASE REPORT

An 8 months old female child was brought to the pediatric emergency of Jawaharlal Nehru Medical College by her parents. The family is strict vegetarian in its dietary pattern.

The chief complaints were progressive tremors involving both upper extremities and head and neck for last 2 weeks, poor feeding and decreased activity. Tremors were jerky and occurred only when the child was awake but initially they were present during sleep although of reduced intensity. There was no history of head trauma, loss of consciousness or fever, yellowish discoloration of body, recent drug intake or previous history of any abnormal movements.

On eliciting the developmental history, we found out that child had intermittent neck control. In Fine motor development bi-dextrous reach was not present, in social domain, social smile was present, baby recognized mother but did not recognize strangers and in language, intermittent cooing was present. The developmental age was 3 month in all domains and development quotient was 37.5%.

Dietary history

Child was on exclusive breastfeeding and the mother is known to be a strict vegetarian mother. There was no introduction of complementary feed till date. Reason for

non-introduction of complementary feed was lack of awareness.

Immunization history

Immunized at birth only. Reason given for incomplete immunization was again lack of awareness.

On examination

Her vitals were within normal range.

Anthropometry revealed weight of 7 kg, length of 66 cm, head circumference-41.5 cm, W/L: -0.48 SD, W/A: -1.06 SD, L/A: -1.17 SD, HC/A: -1.41 SD.

On general examination child looked chubby, plump and apathetic. Hairs were scanty, coarse and hypopigmented. Knuckles and toes were hyperpigmented. Moderate - severe pallor was present. CNS examination revealed a GCS of 14/15, coarse tremor of whole body and generalized hypotonia. Rest of the systemic examination did not reveal any significant finding.

Table 1: Biochemical profile of the patient.

Parameters	Values
Hemoglobin	7.7 g/dl
Total leucocyte count	12100/mm^3
Differential leucocyte count	N 15.3%, L 54.3%
Absolute neutrophil count	1850
Platelet	120000/mm^3
MCV	106 mm^3
MCH	34.2 pg
MCHC	32.2 g/dl
RDW	21.4%
Reticulocyte count	1%
Peripheral smear	Anisopoikilocytosis with microcytes and macro ovalocytes, hypersegmented neutrophils
Serum vitamin B12	150 pg/ml
Serum folic acid	11.75 ng/ml
Total serum protein	5.2 g/dl
Serum albumin	2.9 g/dl
Serum globulin	1.2 g/dl
A:G ratio	1.2:1
Thyroid profile	Normal
Serum sodium	142 meq/l
Serum potassium	3.5 meq/l
Stool for occult blood	Negative

Investigations

CBC revealed bi-cytopenia and high RDW. General blood picture showed anisopoikilocytosis comprising microcytes, ovalocytes, macrocytes and tear drop cells with platelet on the lower side and hypersegmented neutrophils. Reticulocyte count was low (1%). Serum vitamin b12 was found to be low (150 pg/ml). Total serum protein was low too.

CECT head showed atrophic changes in the form of prominent bilateral ventricles, cortical sulci and sylvian fissure of bilateral cerebral hemisphere (Figure 2).

Thyroid function test, LFT and RFT were normal. Bone marrow examination was not done.

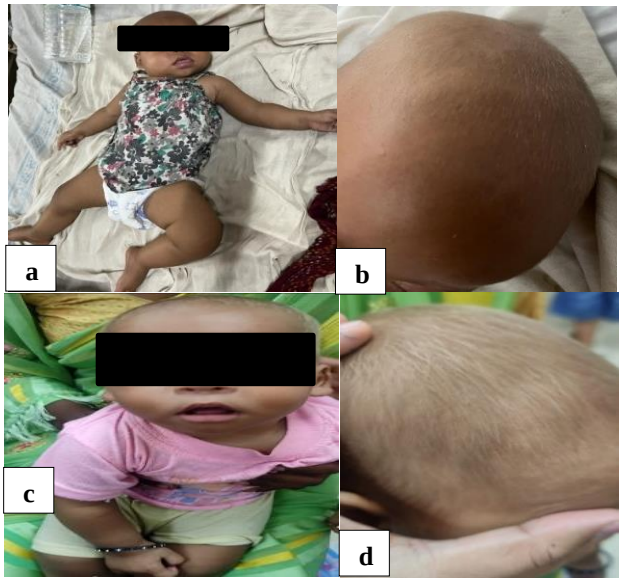

Figure 1: General appearance of patient (a) and (b) at the time of presentation, (c) and (d) one month after the treatment.

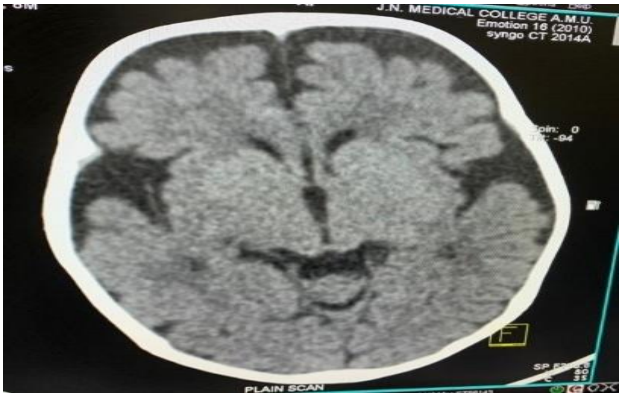

Figure 2: CECT brain shows bilateral cerebral hemisphere atrophy with ex vacuo dilatation of ventricles.

Based on history, clinical and radiological findings, a diagnosis of infantile tremor syndrome with vitamin B12 deficiency anemia with global developmental delay with generalized cerebral atrophy with hypo-proteinemia was made. Child was started on tablet propranolol and injection phenobarbitone for tremors (this was later switched to oral). Vitamin B12 was supplemented in the form of

injection methyl-cobalamine which was later switched to oral preparation. Folate, iron, multivitamin and nutritional supplements in the form of protein rich diet along with proper complementary feeding were also started. Child began to show improvement by day 3- tremors gradually reduced, child became cheerful and was discharged after 5 days.

At 1 month follow up, the child's general condition changed from one of apathy to joy, tremors disappeared, hair growth and texture improved although hairs were still hypopigmented. Developmentally child was now able to sit with support, had developed bi-dextrous reach, recognizes strangers. No substantial progress in language was observed.

DISCUSSION

ITS poses a diagnostic challenge due to its infrequency (rarity). This case highlights the importance of considering ITS in the differential diagnosis of infants presenting with tremors, anemia, sparse coarse hypopigmented scalp hairs, hyperpigmentation of the skin and developmental delays or regression, especially in regions with a high prevalence of malnutrition.

Tremors are acute in onset and coarse in nature and involve the distal limbs, head face, and tongue. They appear at the late stages of the disease. They are intermittent initially but become continuous over a course of few days. They are brought on by stress, infection, and disappear during sleep.[2-4] Tremors are mostly due to structural and functional alterations of the extrapyramidal system.[11] Developmental delay or regression is noted at around 4-6 months of age.[2] The disorder is often accompanied by multiple vitamins and nutrient deficiencies.

Our child presented with complaints of tremors that were gradually progressing. On examination, the child was plump with pallor, thin sparse hypopigmented hair, and hyperpigmented knuckles. Developmental history also revealed developmental delay. Most often, this syndrome is associated with children who are exclusively breastfed for an extended period and do not receive timely supplemental nutrition and moms who are strict vegetarians.[10] Our patient was exclusively breastfed by a vegetarian mother even at the age of 8 months. In infantile tremor syndrome, anemia is seen with the red cell morphology being macrocytic or dimorphic.[11] In our case also the complete blood picture revealed MCV of 106 μm^3, general blood picture revealed anisopoikilocytosis comprising microcytes, ovalocytes, macrocytes, and teardrop cells with platelet on the lower side and hypersegmented neutrophils. The reticulocyte count was low. The serum vitamin B12 level is reported to be low in most cases.[12,13] Our case also has a similar finding with vitamin B12 of 150 pg/ml. Low vitamin B12 levels in breast milk can occur when the mother has a vitamin B12 deficiency and if the child is on exclusive breastfeeding, it can lead to vitamin B12 deficiency in the child as well. The neuroimaging finding in cases of infantile tremor syndrome reveals cortical atrophy with involvement of the subarachnoid space, ventricular prominence, and myelinolysis of the pontine region.[13] In most cases, cerebral atrophy gets reversed with timely treatment which should include nutritional intervention. In our child also CECT head showed atrophic changes in the form of prominent bilateral ventricles, cortical sulci, and Sylvian fissures of the bilateral cerebral hemisphere.

The etiology of infantile tremor syndrome has been a subject of debate and discussion. It has been postulated as multifactorial in the past including infections, degenerative processes, and nutritional deficiencies such as iron, magnesium, and zinc but no consensus has been reached till date. In recent times, hypothesis of vitamin B12 has gained grounds.[2] Other factors which favor vitamin B12 as an etiology are frequent association with macrocytic anemia, hyperpigmentation, lack of complementary feeding, low vitamin B12 levels in children and mothers, and a strict vegetarian diet.

Symptomatic relief from vitamin B12 supplementation further consolidate the causal relationship. In the absence of a clear cause, vitamin B12 supplementation along with iron, magnesium and calcium is the cornerstone of treatment.

In some circumstances, further medications are needed to manage tremors, such as propranolol (0.5-1 mg/kg/day), phenobarbitone (3-5 mg/kg/day), and carbamazepine (10-20 mg/kg/day).

In our case, treatment consisted of the correction of vitamin B12 deficiency via injection of cobalamine 1000 mcg intramuscularly once daily initially which was later switched to oral (500 mcg once daily), and correction of coexisting hypo-proteinemia through the introduction of complementary feeding. Tremors were managed with propranolol (0.5 mg/kg/day in three divided doses) and phenobarbitone (3 mg/kg/day in two divide doses) which were tapered off within 2 weeks in the follow-up as the child improved. Vitamin B12, iron and multivitamin supplementation was continued until the correction of anemia. The child showed gradual and marked improvement.

CONCLUSION

ITS needs to be considered in a young child presenting with pallor, malnutrition, developmental delay, tremors, and skin and hair changes. ITS is a serious ailment that can lead to significant neurodevelopmental impairments and behavioural abnormalities. Management should focus on correcting nutritional deficiencies, primarily vitamin B12, and providing appropriate nutritional counselling to parents/caregivers. This case report underscores the importance of early diagnosis and management when it's reversible, as well as the role of healthcare providers in educating families about proper nutrition during

pregnancy and about infant and young child feeding practices. Further research is needed to better understand the etiology and optimal management scheme for ITS.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Gupta R, Pathak A, Mandliya J, Gehlot P, Sonker P. Reversible cerebral atrophy in infantile tremor syndrome. Indian Pediatr. 2016;53:727-9.
2. Goraya JS, Kaur S. Infantile tremor syndrome: A review and critical appraisal of its etiology. J Pediatr Neurosci. 2016;11(4):298-304.
3. Garg BK, Srivastava JR. Infantile tremor syndrome. Indian J Pediatr. 1969;36(257):213-8.
4. Holla RG, Prasad AN. Infantile Tremor Syndrome. Med J Armed Forces India. 2010;66(2):186-7.
5. Gowda VK, Kolli V, Benakappa A, Srinivasan VM, Shivappa SK, Benakappa N. Case Series of Infantile Tremor Syndrome in Tertiary Care Paediatric Centre from Southern India. J Trop Pediatr. 2018;64(4):284-8.
6. Sirolia V, Arya S. Study of clinical profile and estimation of Vitamin B12 level in infantile and pre-infantile tremor syndrome. J Evol Med Dent Sci. 2014;3:10134-7.
7. Goraya JS, Kaur S. Infantile tremor syndrome – Down but not out. Indian Pediatr. 2015;52:249-50.
8. Agarwal R, Singh RN, Gupta BD, Agarwal DK, Arora AK. Serum magnesium, calcium, zinc in infantile tremor syndrome. Indian Pediatr. 1993;30:374-6.
9. Kaul KK, Prasan N, Chowdhry RM. Some clinical observations and impressions on a syndrome of tremors in infants from India. J Pediatr. 1963;63:1158-66.
10. Gupta BD, Maheshwari RK, Miglani N. Infantile tremorsyndrome. Indian J Pediatr. 1978;45:221-8.
11. Gupte S. Infantile tremor syndrome (ITS). Indian J Paediat. 2007;74:88.
12. Gowda VK, Kolli V, Benakappa A, Srinivasan VM, Shivappa SK, Benakappa N. Case Series of Infantile Tremor Syndrome in Tertiary Care Paediatric Centre from Southern India. J Trop Pediatr. 2018;64(4):284-8.
13. Ukkali S, Arif A, Hussain AA, Rajgoli E, Saifuddin S. A case report of an infantile tremor syndrome in a 9months old girl with severe nutritional deficiencies. IOSR J Dent Med Sci. 2017;4:105-8.

Cite this article as: Nazish, Arif M, Zubair MY. Infantile tremor syndrome: a case report. Int J Contemp Pediatr 2023;10:1721-5.