

CLINICAL PROFILE AND VITAMIN B12 STATUS OF CHILDREN WITH INFANTILE TREMOR SYNDROME- A CROSS-SECTIONAL STUDY

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Abstract

Background: Infantile Tremor Syndrome (ITS) was first described in 1957 and we are still in search of its etiology. Various etiological factors like infectious, metabolic, and nutritional have been hypothesized but none is conclusive. It is believed to be because of Vitamin B12 deficiency by most of the researchers, however, this association has not been consistently found. We carried out this study to evaluate the clinical profile of children with ITS and to evaluate the status of Vitamin B12 in ITS patients and their mothers. **Methods:** This cross-sectional study was carried out at the Department of Paediatrics of a tertiary health care hospital affiliated with the medical college of Central Gujarat, India. Infants and children between the age of 4 months to 5 years who presented with signs and symptoms of infantile tremor syndrome were included in the study. Patient and maternal details were collected in predesigned proforma. parameters evaluated were serum vitamin B12 levels of the patient and mother, CBC and RBC indices, and peripheral smear examination. **Results:** Out of 50 ITS patients 50% were of 4-12 months of age, 42% were of 12-18 months of age, The median age of presentation was 12 months, with IQR for the presentation was 9-15 months. Out of 50 patients, 37(74%) were exclusively breastfed, and only 13(26%) were started with complementary feeds. Peripheral blood smear examinations have been done in all patients, which inferred that out of 50 patients, 70% had microcytic anemia picture out of, 12% had macrocytic anemia and 18% had dimorphic anemia. 50% were having lower vitamin B12 levels (<200ng/mL). **Conclusion:** In our study, ITS patients presented with anemia, tremor, pigmentation, developmental delay, and microcephaly. The majority of the children(82%) were not receiving an age-appropriate diet. In the hematological profile, 18% and 12% had dimorphic and macrocytic anemia respectively while the rest 70% had microcytic anemia. We found Vitamin B12 deficiency in 50% of the children and 14% of mothers.

INTRODUCTION

Infantile tremor syndrome is defined by tremors, pallor, developmental regression, skin pigmentation, and brown scanty scalp hair.^[1] Clinically, three phases of ITS have been described, The pre-tremor phase, the tremor phase, and the post-tremor phase. The pre-tremor phase has been described by neuromotor regression, pallor, and tremulous voice. The tremor phase appears with sudden onset of tremors involving various parts of the body mainly the extremities of hands and feet. The tremor decreases or disappears in sleep. (1) Though this condition is well recognized since more than 50 years and lots of

research has been done to find its etiology, but none is conclusive. Though vitamin B12 deficiency has been accepted by most of researchers, the causal association is not consistently found. Occurrence of ITS cases in particular rural geographical areas of Indian subcontinent cannot be explained just on basis of vitamin B12 deficiency which is found more universally in rural and urban population in all socioeconomic strata and this may point towards possibility of genetic predisposition. We planned this study to evaluate sociodemographic, clinical profile and status of vitamin B12 of such children and their mothers. This data may help to either support or refute

causative role of vitamin B12 in ITS cases and give direction for further research.

MATERIAL & METHODS

This cross-sectional study was carried out over a period of 12 months from January 2022 to December 2022 at the Department of Paediatrics, of the tertiary health hospital affiliated with a medical college of central Gujarat India after taking permission from institutional ethics committee. We decided to enrol a total of around 50 patients and this was a convenient sample based on the hospital data, no formal statistical tests were applied. No formal statistical tests were applied. The children were screened after obtaining written consent of the parents, enrolled if they met inclusion criteria of infants and children (4 months to 5 years) with clinical signs and symptoms of infantile tremor syndrome. Patients with other haematological and neurological disorders were excluded. All necessary details were entered in predesigned proforma. All admitted patients of infantile tremor syndrome were subjected to necessary history taking, dietary history, detailed developmental history, anthropometry, socioeconomic history, and physical examination along with the details regarding the past history of treatment, vitamin B12 supplements, and previous blood transfusion taken. WHO criteria for severe acute malnutrition: Weight for height: <-3SD or less, MUAC: <11.5cm, Visible severe wasting, Bilateral pedal edema. WHO criteria for MAM: Weight for height: between -2SD to -3SD. MUAC: between 11.5cm to 12.5cm. (18) WHO criteria for head circumference for age was taken to diagnose microcephaly considering head circumference for age less than -3SD considered as microcephaly. (19) Basic maternal history, along with details regarding the history of diet, Vitamin B12 supplements, and obstetrics history was taken. About 2 ml of venous blood was collected in plain and EDTA vacuette for patient sampling. 2ml of venous blood was drawn from the mother in a plain vacuette for serum B12 level. The parameters measured were: Serum B12 levels of the Patient and Mothers. Patient's Hemoglobin, Platelet count, and Total count. RBC indices, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Peripheral smear examination. Carbonylmetalloimmunoassay (CMIA) method was used for B12 level assessment, Sysmex 5 cell counter analyzer was used for the hemogram and CBC indices. Serum ferritin levels were measured using the

immunoturbidimetry method. All patients received appropriate treatment as per their clinical condition.

Statistical Analysis

The data were entered by using MS Office Excel in a password-protected file and data were checked for accuracy and consistency. Data analysis was done by using MedCalc software 20.018. Data collected from the study were analysed by applying appropriate statistical tests like CHI SQUARE TEST at a 95% confidence interval.

RESULTS

We observed that out of 50 ITS patients, the median age of presentation was 12 months, with IQR for the presentation was 9-15 months. The youngest patient was of 4 months of age and the eldest one was of 48 months of age. We found out of 50 patients 25(50%) were of 4-12 months of age, 21(42%) were of 12-18 months of age, and the rest 9(18%) were >18 months of age (table 1). We 41(82%) were not receiving age-appropriate feeding and only rest 9(18%) were receiving age-appropriate feeding. Distribution of most of them was within Panchmahal, Narmada, Chhota Udaipur, and Dahod areas of Gujarat. Out of 50 mothers, majority 43(86%) were on a vegetarian diet. Out of 50 mothers only 6 (12%) had a history of vitamin B12 supplementation. We observed microcephaly in 41 (82%) patients. Peripheral blood smear examinations have been done in all patients, which inferred that out of 50 patients, 70% had microcytic anemia picture, 12% had macrocytic anemia and 18% had dimorphic anemia. We found vitamin B12 to be deficient(<200ng/ml) only in 25 patients that is 50% of total patients. Out of 25 vitamin B12 deficient patients, 23(92%) were receiving inadequate feeding patterns according to age, and only 2(8%) were receiving age-appropriate feeding. While on the other side, out of 25 patients with normal vitamin B12 levels 7(28%) were receiving appropriate feeding and the rest 18(72%) were not receiving age-appropriate feeding. Out of 50 mothers only 7(14%) were found to be deficient. We observed that out of 25 B12 deficient patients 6 had maternal B12 deficiency and 19 B12 deficient patients did not have maternal B12 deficiency. On the other side 25 ITS patients with normal B12 level patients, 24 patients also had maternal B12 level normal, and only the remaining 1 had maternal B12 deficiency. The Chi-square test p-value is 0.13, which suggests no statistical significance

Table 1: Base line characteristics in ITS patients

Baseline Characteristics		N=50
Gender	Male	28/50(56%)
	Female	22/50 (44%)

Age	4-12 months	25/50(50%)
	12-18 months	21/50(42%)
	>18 months	4/50(8%)
Geographical Distribution	Rural	50/50(100%)
Socioeconomic Status	Lower middle socioeconomic class	01/50(2%)
	Upper lower socioeconomic class	49/50(98%)
Dietary Assessment	Not receiving age-appropriate feeding	41/50(82%)
	Receiving age-appropriate Feeding	9/50 (18%)
Maternal Diet Assessment	Vegetarian only	43/50(86%)
	Mixed	7/50(14%)
Presenting Illness	Acute respiratory illness	34/50 (68%)
	Acute gastrointestinal illness	9/50 (18%)
Clinical Features	Triad of pallor, tremor and pigmentation	50/50(100%)
Nutritional Status	Severe acute malnutrition	23/50(46%)
	Moderate acute malnutrition	07/50 (14%)
	Normal	20/50(40%)
Developmental Status	Global developmental delay	50/50(100%)
Head Circumference	Microcephaly	41/50(82%)
	Normal	9/50(18%)

DISCUSSION

In this study, we observed all the cases were from rural populations and among lower socioeconomic strata. It was observed that involvement of the age group between 9 to 15 months was common that too with infants and children not starting with age-appropriate feeding and having a lack of maternal supplementation. All patients, had a characteristic triad of pallor, pigmentation, and tremor on presentation. It was observed that head circumference is one of the major growth parameters affected in ITS, 82% of patients had microcephaly. 50% of our patients had vitamin B12 deficiency, and maternal vitamin B12 deficiency was also found in 14% of patients. Hematological parameters observed that 70% of patients had microcytic anemia and the rest had macrocytic or dimorphic anemia.

All of the 50 patients had tremor, pigmentation, and pallor on receiving, 34(68%) presented with acute respiratory illness, and 9(18%) presented with acute gastrointestinal illness. According to Gowda *et al.* they have studied 70 ITS patients, 40 patients (57%) were presented with a classical triad of tremor, pigmentation, and pallor, however, all of them were having pallor and pigmentation but few of them lacked tremors on presentation and presented in pretremor stage.^[11]

We observed 41(82%) patients were having microcephaly. According to Chaudhary H. *et al.* Out of 92 patients they assessed, 53(58%) had microcephaly.^[12]

All patients' hematological parameters were evaluated, on peripheral smear examination out of 50 patients 35(70%) had microcytic anemia, 6 (12%) had macrocytic anemia and the rest 9(18%) had dimorphic anemia. According to Goraya *et al.* out of 21 patients, 12(66%) showed macrocytic anemia.^[1] According to Rajesh *et al.* out of 12 cases enrolled 3(25%) showed macrocytosis. Which was nearly similar to our study. Though

many studies found the prominent occurrence of macrocytic anemia, but our findings suggest the dominance of microcytic anemia in ITS patients.^[2]

In our study, we found out that among a total of 50 patients 25/50(50%) were vitamin B12 deficient. According to Jatinder's Goraya *et al.* study, among 16 ITS patients 8(50%) were having low vitamin B12 levels. Six of the 8 infants with normal serum vitamin B12 levels had received vitamin B12 before referral.^[1] According to rajeshgupta *et al.* study, out of 12 cases, 2(16.6%) were having lower serum vitamin B12 levels, and the rest 10 have normal serum vitamin B12 levels.^[2] According to Jadhav *et al.* and Srikantia *et al.*, vitamin B12 deficiency found in 100% and 87.5% of patients respectively.^[8,9] This difference among B12 status among ITS patients depends upon various factors including patient already received B12 supplementation or blood transfusion before drawing B12 sample, however to avoid this fallacy in our study we excluded individuals who already received B12 supplement. OPD basis intake of oral multivitamins remedies also a factor affecting a B12 level.

All 50 patients' feeding patterns had been assessed, and The Diet history of both groups has been compared. Out of 25 B12 deficient patients, 23(92%) not receiving age-appropriate feeding, Out of 25 ITS patients with normal B12 levels, 7(28%) were receiving feeding appropriate for age. While 18(72%) were not receiving age-appropriate feeding. According to Jain *et al.* out of 40 patients, they have studied 25(62.5%) were breastfed. The majority of patients 22 of 6-12 months were exclusively breastfed, 8(20%) out of 40 were started with inadequate complementary feeding in form of top milk and 7(17.5%) out of 20 were on adequate complementary feeds.^[3]

The limitations of the study include data from a single center, Investigations like calcium, magnesium, zinc, and folate levels were not carried

out and Neuroimaging was not routinely performed in all patients.

Conclusion: In our study, ITS children presented with anemia, tremor, pigmentation, developmental delay, and microcephaly. The majority of patients were from low socioeconomic class and from rural populations. The majority of children did not have an age-appropriate dietary intake. In the hematological profile, 18% and 12% had dimorphic and macrocytic anemia respectively while 70% had microcytic anemia. We found vitamin B12 deficiency in 50% of the ITS children. Maternal vitamin B12 deficiency was found in 14% of the cases.

REFERENCES

1. Goraya J, Kaur S. Infantile tremor syndrome: A review and critical appraisal of its etiology. *Journal of Pediatric Neurosciences*. 2016;11(4):298.
2. Gupta R, Rawat A, Singh P, Gupta J, Pathak A. Infantile tremor syndrome: current perspectives. *Research and Reports in Tropical Medicine*. 2019 Jul;Volume 10:103–8.
3. Garewal G, Narang A, Das KC. Infantile Tremor Syndrome: A Vitamin B12 Deficiency Syndrome in Infants. *Journal of Tropical Pediatrics*. 1988 Aug 1;34(4):174–8.
4. Sharma N, Gautam P, Chaudhary S, Kaushal A. Infantile tremor syndrome in modern times. *Journal of Pediatric Neurosciences*. 2017;12(3):232.
5. Jain JK, Sharma G, Bhatt D, Bairwa AL, Meena IL. STUDY OF CLINICAL PROFILE OF INFANTILE TREMOR SYNDROME AND ITS CORRELATION WITH SERUM VITAMIN B12 LEVEL. *Indian Journal of Child Health*. 2019 Jul 31;6(7):345–8.
6. Sachdev KK, Manchanda SS, Lal H. The syndrome of tremors, mental regression and anaemia in infants and young children: a study of 102 cases. *Indian Pediatrics* [Internet]. 1965 Jul 1 [cited 2023 Apr 10];2(7):239–51. Available from: <https://pubmed.ncbi.nlm.nih.gov/5834538/>
7. Pohowalla JN, Kaul KK, Bhandari NR, *et al.* Infantile “meningo-encephalitic” syndrome. *The Indian Journal of Pediatrics*. 1960;27(2).
8. Jadhav M, Webb JKG, Vaishnav S, Baker SJ. VITAMIN-B12 DEFICIENCY IN INDIAN INFANTS. *The Lancet*. 1962 Nov;280(7262):903–7.
9. Srikantia SG, Reddy V. Megaloblastic anaemia of infancy and vitamin B12. *British Journal of Haematology* [Internet]. 1967 Nov 1 [cited 2023 Apr 10];13(6):949–53. Available from: <https://pubmed.ncbi.nlm.nih.gov/6075449/>
10. Rogerson D. Vegan diets: practical advice for athletes and exercisers. *Journal of the International Society of Sports Nutrition* [Internet]. 2017 Sep 13;14(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5598028/>
11. 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. *Journal of Tropical Pediatrics*. 2017 Jul 27;64(4):284–8.
12. Lee YP, Loh CH, Hwang MJ, *et al.* Vitamin B12 deficiency and anemia in 140 Taiwanese female lacto-vegetarians. *Journal of the Formosan Medical Association*. 2021;120(11).
13. Rashid S, Meier V, Patrick H. Review of Vitamin B12 deficiency in pregnancy: a diagnosis not to miss as veganism and vegetarianism become more prevalent. *European Journal of Haematology*. 2021 Feb 2;
14. Bansal PG, Toteja GS, Bhatia N, Vikram NK, Siddhu A. Impact of weekly iron folic acid supplementation with and without vitamin B12 on anaemic adolescent girls: a randomised clinical trial. *European Journal of Clinical Nutrition*. 2015 Dec 23;70(6):730–7.
15. Strand TA, Ulak M, Chandyo RK, Kvestad I, Hysing M, Shrestha M, *et al.* The effect of vitamin B12 supplementation in Nepalese infants on growth and development: study protocol for a randomized controlled trial. *Trials* [Internet]. 2017 Apr 21 [cited 2023 Apr 10];18(1):187. Available from: <https://pubmed.ncbi.nlm.nih.gov/28431557/>
16. Samson JC, Karuppanan U, Ganesan H, Velusamy S, Thangara P. Vitamin B12 deficiency, its prevalence and haematological manifestations - A study in a tertiary care hospital. *Indian Journal of Pathology and Oncology* [Internet]. 2020 Dec 15 [cited 2023 Apr 10];5(2):230–6. Available from: <https://www.ijpo.co.in/article-details/6423>
17. Chaudhary H, Verma S, Bhatia P, Vaidya PC, Singhi P, Sankhyani N. Infantile Tremor Syndrome or a Neurocutaneous Infantile B12 Deficiency (NIB) Syndrome? *The Indian Journal of Pediatrics*. 2020 Jan 27;87(3):179–84.
18. Kebede F. Severe Acute Malnutrition (SAM) associated mortality rate of children attending HIV/AIDS care in North West Ethiopia, 2009–2019. *SAGE Open Medicine*. 2022 Jan;10:205031212210813.
19. Passemard S, Kaindl AM, Verloes A. Microcephaly. In: *Handbook of Clinical Neurology*. 2013.