Study of clinical profile of infantile tremor syndrome and its correlation with serum Vitamin B12 level

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ABSTRACT

Objective: The objective of this study was to assess the clinical profile of infantile tremor syndrome (ITS) and to correlate serum Vitamin B12 level with ITS. **Materials and Methods:** This prospective study was done in the Department of Pediatrics of a Medical College of Kota. A total of 40 children, presenting with clinical features of ITS, were included in the study. A detailed history was taken. Investigations including complete blood count with blood indices (mean corpuscular volume, mean corpuscular hemoglobin [MCH], and MCH concentration), peripheral smear, and serum Vitamin B12 level were done in accordance with the WHO guidelines. Vitamin B12 deficiency was defined as serum Vitamin B12 concentration <150 pmol/L or 203 pg/mL. **Results:** All patients with ITS had pallor (100%) and skin hyperpigmentation (100%). Psychomotor changes in the form of apathy and/or developmental regression/stasis were found in 40 (100%) cases. Regression of developmental milestones was found in 26 (65%) and 10 (25%) patients had stasis of milestones. Tremor was present in 14 (35%) cases. Hepatomegaly was present in the majority 25 (62.5%) of these children, whereas splenomegaly was present in only 8 (20%) patients. Hypopigmented hair was found in only 12 (30%) cases. Twenty-five (62.5%) children were exclusively breastfed ($p<0.05$). Of the 40 cases, 26 (65%) presented in prodromal phase and 14 (35%) presented in the tremor phase. Among 26 patients of prodromal phase, 22 (84.62%) had Vitamin B12 deficiency while among 14 cases of tremor phase, 9 (64.28%) had Vitamin B12 deficiency. The majority of ITS children had macrocytic anemia (65%) followed by dimorphic anemia (25%). A significant number of ITS patients (21, 80.77%), having macrocytic anemia, had Vitamin B12 deficient. **Conclusion:** We conclude that children of ITS presented with anemia, skin hyperpigmentation, psychomotor changes, apathetic look, and developmental abnormality. The majority of children were on faulty feeding in the form of prolonged exclusive breastfeeding. Vitamin B12 deficiency was present in a significant number of patients with ITS.

Key words: *Exclusive breastfeeding, Infantile tremor syndrome, Vitamin B12 deficiency*

Infantile tremor syndrome (ITS) is a clinical condition of infancy and early childhood characterized by acute or insidious onset with mental and psychomotor changes, pigmentary changes of hair and skin, pallor, and tremors [1,2]. It has been primarily reported from Southeast Asia including India and other developing countries. ITS is seen in infants and children of 6–36 months of age group [1], but majority of the cases reported under 6–18 months of age group [3,4]. Many theories have been proposed by different research workers regarding the etiopathogenesis of ITS, but the etiology of ITS is still elusive [5]. Various nutrient deficiencies (e.g., Vitamin B12, magnesium, zinc, Vitamin C, etc.) have been found to be associated with ITS. Other theories showed an association of viral encephalitis and degenerative processes with ITS [1,6].

Among all proposed theories, the most widely accepted theory is nutritional theory or malnutrition theory. It is usually seen in children who are exclusively breastfed for prolonged periods by Vitamin B12 deficient vegetarian mother [6]. Vitamin B12 deficiency has been found to be associated with ITS in many studies with normal serum ferritin and folic acid level [1,5,7]. The low levels of Vitamin B12 and its transport protein Transcobalamin II in the cerebrospinal fluid (CSF) may be responsible for the neurological features of this syndrome [8]. Zinc and magnesium deficiency have also been postulated to cause ITS. Iron and folic acid level were normal in some studies [5,7]. It is usual to find direct or indirect evidence of malnutrition associated other micronutrients deficiencies such as Vitamin A, D, and Vitamin B complex [1,9,10].

Other factors for its etiology include viral encephalitis and degenerative processes. Seasonal incidence and cortical biopsy suggest that it might be due to meningoencephalitis. However, consistently normal CSF and failure to isolate any viral antigen do not support this hypothesis [6]. Metabolic or enzyme defect, a transient tyrosine metabolism defect, might lead to interference in melanin pigment production. Depigmentation of substantia nigra may explain tremors. Undeniable incidence of ITS is not known. In India, incidence is 0.2–2% of total pediatric hospital admissions (1–2% in the 1960s, 1.1% in 1975–77, and 0.2% in

the mid-1990s). Incidence rate of the disease was reduced over the years due to better weaning practices and improvement in nutritional status [11]. Therefore, this study was conducted to evaluate the clinical profile of ITS and to correlate the serum Vitamin B12 level with ITS.

MATERIALS AND METHODS

This was a one year, cross sectional study, conducted in Department of Pediatrics, Government Medical College and Associated Group of Hospitals, Kota, between December 2015 and November 2016. Children presented with pallor, skin hyperpigmentation, and psychomotor changes including apathy and/or developmental abnormalities were considered as prodromal stage of ITS and children presented with tremors with clinical features of prodromal stage were considered as tremor stage of ITS. Children presented with other comorbid neurological conditions, neurodegenerative disorder, preexisting cerebral palsy, mental retardation, developmental delay, post-meningitis, encephalitis, and/or meningoencephalitis sequel were excluded from the study.

Sample size calculation was done by the formula: $Z_{1-@/2}^{2}$ p $(1-p)/d^2$ [12]. A total of 40 children were included in the study. This study was conducted after getting approval from the institutional ethics committee and informed consent was obtained from the parents or legal guardians. A detailed history was taken including presenting features, past history, family history, birth history, developmental milestones, and dietary history. Skin hyperpigmentation at terminal phalanges, hands, wrist, elbow, ankle, knee, and any other parts of the body was noted. Hair color was recorded. Hair changes in ITS cases were hypopigmentation, sparse, and lusterless. Pallor was looked at palpebral conjunctiva, tongue, nails, and palmer creases. Type of tremor was noted as generalized or local. Investigations including complete blood count (CBC) with blood indices (mean corpuscular volume, mean corpuscular hemoglobin [MCH], and MCH concentration), peripheral blood smear, and serum Vitamin B12 level were done of every case. Peripheral venous blood sample was taken in an ethylenediaminetetraacetate vial (2 ml) for the determination of CBC and 3 ml of blood was taken in a plain vial for the estimation of serum Vitamin B12 level. Serum Vitamin B12 level was estimated by electrochemiluminescence method. Serum Vitamin B12 levels in this study were defined as low <200 pg/ml [13].

Statistical analyses were performed using the SPSS Windows, version 21. Association of different aspects of ITS with serum Vitamin B12 (cobalamin) level was calculated by Chi-square test. $p<0.05$ was considered statistically significant.

RESULTS

A total of 40 children clinically diagnosed as ITS, according to the inclusion criteria, and were enrolled for the study. Maximum numbers of the children (77.5%, 31) were in the age group of 6–12 months followed by 20% (8) in 13–18 months and only 2.5% (1) of cases in 19–24 months age group. Among 40 children, 28 were male (70%) and 12 were female (30%) and male-to-female ratio was 2.3:1. The mean age of affected children was 10.8 months.

All patients with ITS had pallor (100%) and skin hyperpigmentation (100%). Psychomotor changes in the form of apathy and/or developmental regression/stasis were found in 100% of cases. Apathy was found in all cases. Developmental abnormality was found in 90% of the children. Regression of developmental milestones was found in 26 (65%) ($p<0.05$) and 10 (25%) patient had stasis of milestones. Tremor was present in 15 (37.5%) cases among which 9 (22.5%) had generalized tremor and rest 6 (15%) patients had localized tremor. Hepatomegaly was present in 25 (62.5%) of these children, whereas splenomegaly was present in only 8 (20%) patients. Hypopigmented hair was found in only 12 (30%) cases.

Twenty-five (62.5%) children were exclusively breastfed. Majority of the patients 22 (71%) of 6–12 months were exclusively breastfed. Top feeding in the form of diluted cow or goat milk was given in 8 (20%) cases. Faulty feeding was found in 33 (82.5%) cases (Table 1). Exclusive breastfeeding pattern was significantly associated with ITS ($p<0.05$).

Of 40 cases, 26 (65%) cases presented in prodromal phase and 14 (35%) presented in the tremor phase. Of 26 patients with prodromal phase, 22 (84.62%) had Vitamin B12 deficiency, whereas 9 (64.28%) cases of tremor phase had Vitamin B12 deficiency. Rest of the children had normal or increased Vitamin B12 level (Table 2).

Majority of the ITS children had macrocytic anemia 26 (65%) followed by dimorphic anemia 10 (25%). Of the remaining four cases, 2 (5%) patients had microcytic and 2 (5%) had normocytic anemia. Twenty-six (65%) ITS patients had macrocytic anemia and out of them, 21 (80.77%) cases were Vitamin B12 deficient also ($p<0.05$).

DISCUSSION

In the present study, all cases of ITS had pallor which was similar to the study done by Garg and Srivastava [14] and

Table 1: Feeding pattern in relation to age group

Feeding pattern	6–12 months n=31 (%)	13–18 months n=8 (%)	19–24 months n=1 (%)	Total n=40 (%)	p value
EBF	22 (71)	3 (7.5)	0 (0)	25 (62.5)	0.001
BF+TF	6 (20)	2 (5)	0 (0)	8 (20)	0.065
BF+CF	3 (9)	3 (7.5)	1 (2.5)	7 (17.5)	0.12

EBF: Exclusive breastfeeding, BF: Breastfeeding, TF: Top feeding, CF: Complementary feeding

Table 2: Serum Vitamin B12 status in relation to phase of ITS

Phase of ITS	Vitamin B12 (%)	
	Deficiency	Normal or increased
Prodromal (n=26)	22 (84.62)	4 (15.38)
Tremor (n=14)	9 (64.28)	5 (35.72)
Total (n=40)	31 (77.5)	9 (22.5)

ITS: Infantile tremor syndrome

Jadhav *et al*. [7]. In this study, skin hyperpigmentation, psychomotor changes and apathetic look, and developmental abnormality were reported in the majority of cases as reported in the earlier studies by Sachdev *et al.* [15]. Ramakumar and Pandove [4] reported hair changes in 98.1%, dark skin in 88.8%, and delayed milestone in 80.3% of cases as observed in our study. Significant developmental abnormality was also observed by Jadhav *et al*. [7] and Srikantia and Reddy [5]. Apart from the known features of ITS, significant incidence of hepatomegaly, splenomegaly, and tremor was noted as observed in other studies [3,16,17].

Vitamin B12 is water-soluble vitamin required for hematopoiesis, myelination of central nervous system, and for psychomotor development. Deficiency of Vitamin B12 can occur due to poor dietary intake in children with faulty feeding, prolong exclusive breastfeeding by Vitamin B12-deficient mother. Vitamin B12 deficiency impairs DNA maturation during hematopoiesis which leads to ineffective erythropoiesis and macrocytic anemia. Vitamin B12 deficiency also impairs psychomotor development and myelination of nervous system which leads to developmental abnormality and tremors.

As malnutrition is commonly associated with ITS, fatty infiltration of liver can lead to hepatomegaly. Lower respiratory tract infection and malaria can present with splenomegaly. In this study, majority of children were on faulty feeding in the form of prolonged exclusive breastfeeding without proper complementary feeding and diluted cow or goat milk. In such children, there were deficiencies of Vitamin B12, multiple macro- and micro-nutrients which lead to manifestations in the form of anemia, skin hyperpigmentation, tremor, and psychomotor changes. Similar result was observed in the previous studies [3,18,19].

In the present study, 31 (77.5%) children had low serum Vitamin B12 level. About 84.62% of cases of prodromal stage were found Vitamin B12 deficient, while 64.28% of cases of tremor stage were found Vitamin B12 deficient. Similarly, Jadhav *et al*. and Srikantia and Reddy reported low serum Vitamin B12 level in 100% and 87.5% of patients of ITS, respectively [5,7]. The most common type of anemia diagnosed by peripheral smear was macrocytic 26 (65%) followed by dimorphic 10 (25%) in our study. Of 26 cases of macrocytic anemia, 21 (80.77%) cases had Vitamin B12 deficiency.

Vitamin B12 deficiency impairs DNA maturation during hematopoiesis which leads to ineffective erythropoiesis and large size red blood cell production seen as macrocyte in peripheral blood smear. Similar results were shown by other studies also [3,15]. Of 40 cases of ITS, 9 (22.5%) children had normal or increased Vitamin B12 level in our study. Various possible causative factors other than Vitamin B12 deficiency have been postulated such as malnutrition, vitamin, and mineral deficiency (e.g. Mg and Zn), infections, toxins, degenerative brain disease, and enzyme defects (tyrosine) [20]. The study was limited by its small sample size. Other investigations suggestive of Vitamin B12 deficiency such as the urinary methylmalonic acid (MMA) level, serum homocysteine levels, and serum MMA were not done in our study.

CONCLUSION

We conclude that all children of ITS presented with anemia, skin hyperpigmentation, psychomotor changes, apathetic look, and developmental abnormality. Majority of children were on faulty feeding in the form of prolonged exclusive breastfeeding without proper complementary feeding. Vitamin B12 deficiency was present in a significant number of patients with ITS. A significant number of ITS patients had macrocytic anemia and out of them, most of the cases were Vitamin B12 deficient also. This study provides a unique hospital-based biochemically defined estimate of Vitamin B12 deficiency as a strong causal relationship with ITS.

AUTHORS' CONTRIBUTIONS

Data collection was done by Dr. Dhaval Bhatt and Dr. Ishwar Lal Meena. Analysis and manuscript preparation were done by Dr. Gopikishan Sharma and Dr. Jitendra Kumar Jain. All research works had been done under the guidance of Dr. A. L. Bairwa.

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