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Research Article

INFANTILE TREMOR SYNDROME IN CHILDREN AND MATERNAL VITAMIN B_{12} DEFICIENCY: A TIME FOR PRIMARY PROPHYLAXIS

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ABSTRACT

Objective: The aim of the study was to determine the percentage of Vitamin B_{12} deficiency in mothers of children suffering from infantile tremor syndrome (ITS). Other objectives were to determine the percentage of Vitamin B_{12} deficiency in children and to look for percentage of children having neurological changes in contrast enhanced computed tomography (CT) scan of brain.

Methods: Data of children between 1 and 60 months admitted between April 2019 and December 2019 with ITS in a tertiary care hospital were collected. Serum Vitamin B_{12} levels of both mother and child were determined. Vitamin B_{12} deficiency and insufficiency were defined as levels <200 pg/mL and 200–350 pg/mL, respectively. The primary outcome was percentage of mother with Vitamin B_{12} deficiency and the secondary outcomes were percentage of children with Vitamin B_{12} deficiency and percentage of children with cerebral atrophy on contrast-enhanced CT of brain.

Results: Forty-five children were enrolled in our study. Vitamin B_{12} deficiency was found in 29 (64.4%) children and 22 (55%) of their mothers. Cerebral atrophy in CT scan was found in 29 (70%) out of 41 children.

Conclusion: The most of the mothers of children with ITS are also Vitamin B_{12} deficient. ITS occurs in infants and toddler with underlying Vitamin B_{12} deficiency and causes early cerebral atrophy in children, which is crucial period of brain growth. Hence, screening and supplementing anemic pregnant women with vitamin B_{12} can be one of the primary prevention in India.

Keywords: Child, Deficiency, Mother, Tremors, Vitamin B_{12}.

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INTRODUCTION

Infantile tremor syndrome (ITS) is a nutritional deficiency disorder characterized by neurological, cutaneous, and hematological manifestation among infants and toddlers. It occurs in 0.77–2.5% of the pediatric hospital admission [1]. It starts with pre-tremor (prodrome – for 2–3 weeks) stage characterized by apathy, skin hyperpigmentation or reticular pattern, and regression of attained milestones, followed by tremor stage (3–4 weeks) which is characterized by tremors or involuntary movements that subsides on sleeping and is precipitated by crying or feeding. Tremor stage is followed by convalescent phase in which tremors get subsided and child's general wellbeing improves [2]. Although, etiology of ITS is still unknown, most of the previous studies reported its associated with Vitamin B_{12} deficiency [1,3,4]. It is reported in children with exclusive breast feeding (EBF) and delayed and improper complementary feeding [1,3-5]. Some Indian studies found it in apparently plum child [6], while some studies showed malnutrition in 60–75% of the children with ITS [4,5,7]. There have been various causes implicating to ITS such as infections, metabolic disorders, and under nutrition but yet no proven etiology of the disease has been found [3].

Vegetarian diet is very common in India. This along with poor feeding pattern due to lack of awareness and poverty leads to Vitamin B_{12} deficiency in infants and children. Vitamin B_{12} is vital for brain growth and myelination in first 2 years of life. Inadequate myelination due to Vitamin B_{12} deficiency during this period may lead to permanent neurological or cognitive problems later in life. Vitamin B_{12} deficiency in infancy and early childhood is mainly due to its deficiency in mothers and delayed initiation of complementary feeding [8]. There are only few studies which shows that ITS is associated with Vitamin B_{12} deficiency in their mother. Hence, we aimed to study the prevalence of Vitamin B_{12} deficiency in mothers of children with ITS. The objectives were to determine the Vitamin B_{12} deficiency in mother of children suffering from ITS. Other objectives were to determine percentage of Vitamin B_{12} deficiency in children and percentage of children having neurological changes in their computed tomography (CT) scan of head.

METHODS

The study was conducted from April 2019 to December 2019 in a tertiary care teaching hospital of Eastern Uttar Pradesh in India. It was a cross-sectional study. Informed consent was taken from all the participants. Inclusion criteria were: (a) Patients suffering from ITS, that is, having triad of tremors, anemia, and developmental delay or regression and (b) children aged 6–60 months and having their mothers in hospital. We excluded children with accompanying seizures, history of perinatal asphyxia, cerebral palsy, and bacterial or tubercular meningitis. Nutritional history of children included EBF (defined as children feeding exclusively on mother milk till 6 months of age) and timely initiation of complementary feeding (defined as complementary feeding started at 6–8 months of age) was taken in children. Dietary history in mother regarding vegetarian or non-vegetarian was taken. Clinical features of Vitamin B_{12} deficiency including anemia, hyperpigmentation of skin, irritability, hypotonia, involuntary movements, glossitis, developmental delay or regression, and bleeding spots were also looked in children. Detailed examination of development was done using Trivandrum developmental scale for children till 2 years of age and then by Vineland social maturity scale. Development delay was diagnosed when developmental quotient (DQ) was <70. DQ was calculated by formula: ×100 (Developmental age/Chronological age).

The World Health Organization (WHO) growth charts were used as reference for grading the anthropometric indices of children including

weight for age (W/A), height for age (H/A), weight for height (W/H), mid upper arm circumference (MUAC), and head circumference. Stunting, underweight and wasting was defined as mild, moderate, and severe, when H/A, W/A, and W/H were between -1 to -2 standard deviation (SD), −2−−3 SD, and -3 to -2 SD, respectively. Severe acute malnutrition (SAM) was defined as: (1) Weight for height/length (for children below 2 years) (W/H or W/L) <−3 SD and/or, (2) presence of bipedal edema and/or, and (3) MUAC below 11.5 cm. Edema was classified as mild (having edema only on feet), moderate (edema involving feet and lower limbs), and severe (generalized edema). In a child below 6 months of age, all the criteria were same except that MUAC was not included in the study. Head circumference <−2 SD and >2 SD was taken as microcephaly and macrocephaly, respectively.

Complete blood count, peripheral blood smear, serum Vitamin B_{12} (by ARCHITECT Plus Analyzer by Abbott Diagnostics which is a Chemiluminescent Microparticle Intrinsic Factor assay for the quantitative determination of vitamin B_{12}), and serum folate levels of child were investigated. Mothers of these children were also investigated for serum Vitamin B_{12} and folate levels. Contrast-enhanced CT of head of children was done to identify any structural abnormality associated with ITS.

Anemia was defined as hemoglobin (Hb) level <12 g/dL while severe anemia was defined as Hb level <7 g/dL. Mean corpuscle volume (MCV) of red blood cell >108 fl at birth and >100 fl at 0.5–5 years was taken as macrocytic [9]. Vitamin B_{12} levels were taken as deficient, insufficient, and sufficient, if the serum levels were <200 pg/ml, 200–350 pg/ml, and >350 pg/ml, respectively. All children were treated with injection Vitamin B_{12} (1000 µg) and folate (500 µg) on alternate days for 14 days, weekly for 4 weeks, and monthly for 6 months [10]. Mothers who were deficient were supplemented with oral Vitamin B_{12}. The children with SAM were given supplements according to the WHO protocol [11].

Statistical analysis

Data were entered on Microsoft Excel sheet and proportions were calculated. Means and standard deviation was calculated from Excel sheets functions.

RESULTS

Forty-five children were admitted in hospital during the study period and 2 (4.4%) children died. The median age of presentation was 10.5 month with male to female ratio of 0.87:1. Baseline characters of children are shown in Table 1. Anthropometric indices are given in Fig. 1.

Edema was seen in 19 (42.2%) children with mild, moderate, and severe edema in 44.4%, 37%, and 3.7%, respectively. Other involuntary movement seen was chorea which was present in 2/45 (4%) children.

Laboratory findings are given in Table 2. Mean Hb was 7.47±2.31 g/dL with mild, moderate, and severe anemia in 18 (40%), 20(44.4%), and 7 (15.5%) children, respectively. Mean MCV was 97.06±10.06 fL. Macrocytosis was found in 21 (45%) children while rest of the children had normal MCV. The mean total leukocyte count (TLC) was 9438.23±1.5321 cells/mm^3. Leucopenia (TLC <4400 cells/mm^3) was found in 19 (42.2%) and Leukocytosis (>13,000 cells/mm^3) was found in 7 (15.5%) children. The mean platelet count was 1.99 lacks±1.83 lacks/mm^3 with thrombocytopenia (platelet count <1.5 lacs/mm^3) in 19 (42.2%) and thrombocytosis (platelet count >4 lacs/mm^3) in 6 (15.5%) children. Mean reticulocyte count was 0.9±0.82 cells/µL.

On peripheral blood smear, 24 (53%) children showed dimorphic anemia, 7 (15.5%) children had macrocytic and 14 (31%) children had normocytic red blood cells. The mean serum Vitamin B_{12} levels of children were 274.36±431.9 pg/ml. Vitamin B_{12} deficiency, insufficiency, and sufficiency were found in 29 (64.4%), 7 (15.5%), and 9 (20 %) children, respectively. Mean serum folate levels were 19.85±7.61 ng/ml. All the children had normal folate levels. We were able get the Vitamin B_{12} levels in only 40 mothers because of monitory reasons and non-consent. Mean serum Vitamin B_{12} levels in the

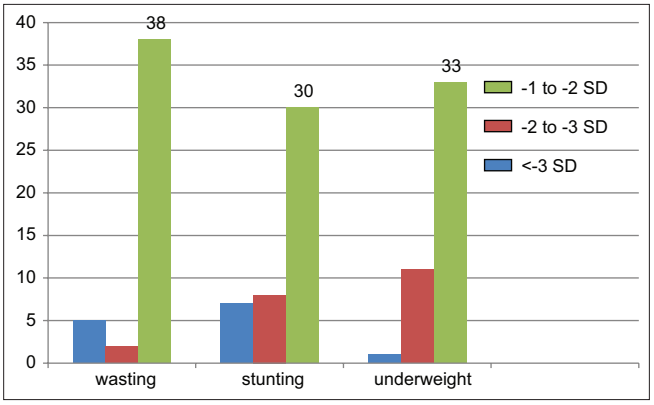

Fig. 1: Distribution of various anthropometric indices in children with infantile tremor syndrome

Table 1: Baseline characteristics of patients infantile tremor syndrome in children

Features	Values	
Age [Mean (SD)]	10.85 (3.81) months	
Weight [Mean (SD)]	6.4 (1.24) kg	
height/length [Mean (SD)]	66.88 (4.22) cm	
Mid upper arm circumference [Mean (SD)]	121.58 (18.19) mm	
Head circumference [Mean (SD)]	41.06 (1.7) cm	
Number of children with EBF [n (%)]	45 (100)	
Number of children with TICF [n (%)]	0 (0)	
Number of mother with vegetarian diet [n (%)]	45 (100)	
Number of children with severe wasting [n (%)]	24 (51)	
Number of children with severe stunting [n (%)]	38 (85)	
Number of children with severe underweight (W/A) [n (%)]	44 (96)	
Number of children with microcephaly [n (%)]	36 (80)	
Number of children with severe acute malnutrition [n (%)]	38 (84)	
Number of children with developmental delay or regression [n (%)]	37 (82)	
Number of children with skin hyperpigmentation [n (%)]	35 (78)	
Number of children with Edema [n (%)]		
Mild	8 (17)	19 (40)
Moderate	7 (15)	
Severe	4 (8)	
Number of children with Glossitis [n (%)]	34 (75)	
Number of children with chorea [n (%)]	2 (4)	

TICF: Timely initiation of complementary feeding

Table 2: Laboratory findings of children with infantile tremor syndrome

Laboratory findings	Number (Percentage)
Macrocytic anemia (MCV>100 fL)	21 (45)
Moderate to severe anemia	27 (60)
Leukopenia	19 (42.2)
Thrombocytopenia	19 (42.2)
Cerebral atrophy on CT scan	29 (70)
Vitamin B_{12} deficiency and insufficiency in mothers	31 (77)
Vitamin B_{12} deficiency and insufficiency in child.	36 (80)

CT: Computed tomography, MCV: Mean corpuscle volume

mothers of were 245.88±63.13 pg/ml; with deficiency, insufficiency, and sufficiency in 22 (55%), 9 (22.5%), and 9 (22.5%) mothers, respectively. Mean serum folate levels of mothers were 8.73±5.2 ng/ml; with low folate levels in 10 (25%) mothers. Four children with normal Vitamin B_{12} levels had Vitamin B_{12} deficient mothers and two mothers with normal Vitamin B_{12} levels had child with low Vitamin B_{12} levels. CT scan of brain of the children was done only in 41 children with ITS. It showed cerebral atrophy, prominent ventricle, and normal scan in 29 (70.7%), 7 (17 %), and 5 (12%) children, respectively.

DISCUSSION

The most common age of presentation of children with ITS is 9–18 months with male preponderance in most of studies similar to our study [1,3-5]. Some studies have shown female preponderance also in their studies [12,13]. Vitamin B_{12} is found mainly in animal food, so inadequate complementary feeding may aggravate the Vitamin B_{12} deficiency in exclusively breast fed baby of deficient mothers. Almost all the studies showed exclusive breastfeeding along with delayed initiation of complementary feeding as universal finding similar to our study [1,3-5,7]. Vegetarian diet is deficient in Vitamin B_{12}. Studies showed that almost all mothers of children with ITS were vegetarian with little or no consumption of milk in their diet similar to our study [3,4,13-16]. The most of the children in our study were malnourished similar to findings in the previous studies [1,3,4,7]. This could be because of improper infant and young child feeding practices either due to unawareness or poverty. Minimum dietary diversity (defined as consumption of at least four food groups among: Cereals/roots/tubers, Vitamin A rich green vegetables and fruits, dairy, flesh/meat, legumes and nuts, eggs, etc.) is one of the important indicators which can prevent Vitamin B_{12} deficiency in early childhood.

General features of Vitamin B_{12} deficiency like dullness and apathy were found in all the children with ITS similar to the study done by Gorayal and Kaur, while study done by Gowda *et al*. found it in only 54.2% [1,4]. Hyperpigmentation of knuckles and skin and glossitis was found in almost three quarter of the children in our study. Several studies have shown 100% association of hyperpigmentation with ITS [5,7,17]. Pallor is universal finding in most of the studies similar to our study [1,4,18]. Study by Chaudhary *et al*. showed microcephaly in 84% of children with ITS similar to our study indicating involvement of brain structures in ITS [13]. This could be because of Vitamin B_{12} deficiency induced Myelination defects, while some studies found it in only quarter of their children [4,5]. Studies have shown developmental delay and regression in 80–100% children with ITS similar to our study [4-7]. Tremors were found in all the children in our study similar to study done by Garewal and Narang [18], while some other studies have found it in only 64 to74% of children [1,4]. The mean duration of pre-tremor stage and tremor stage was 19.8±15.7 days and 22±5.71 days, respectively. It was similar to the study done by Gupta *et al*. and Gowda *et al*. in which mean duration of tremor was 24 days and 35.5 days, respectively [4,13]. Tremors disappeared in all the children who survived with improvement in apathy and activity after treatment, similar to the study done by Gautam *et al*. [5].

Anemia is very common in Vitamin B_{12} deficiency. Vitamin B_{12} is a cofactor for enzyme methionine synthase which converts homocysteine to methionine. In Vitamin B_{12} deficiency, this process is defective and thus pyrimidine bases of DNA are not formed. This slows down DNA synthesis and leads to megaloblastic anemia. Defective maturation of nucleus occurs in all the three cells lines of blood causing breakdown of these cells in marrow itself and thus leads to anemia, leucopenia, and thrombocytopenia. Anemia (Hb <12 g/dL) was present in 80–100% of children with ITS in several studies, similar to our study [1,4-7,15]. Studies have showed macrocytosis in 40–50% of children similar to our study [4,10,13]. Since most of the children were malnourished, concomitant iron deficiency in them leads to dimorphic anemia in peripheral blood smear. It was seen in more than half of the children similar to the previous studies [7,14], while study done by Gowda *et al*. found it in only 7.5% children [4,7,14]. Leucopenia and thrombocytopenia were found in around half of the children in our study while the previous studies showed it in one-third of the children [4,15].

Vitamin B_{12} is also a cofactor for enzyme methymalonyl-CoA mutase which converts methymalonyl-CoA to Succinyl-CoA. In Vitamin B12 deficiency this reaction does not occur, leading to accumulation of methymalonic acid (MMA). Elevated levels of MMA and homocysteine lead to myelin damage and defective myelination. This could be the reason for neurological features in ITS. Several studies have found Vitamin B_{12} deficiency in 52–93% of children similar to our study [4-6,12,18]. This finding was further strengthened by finding of cerebral atrophy in 70% of these children. The previous studies have found cerebral atrophy on CT scan in 54–63% children [4,12] while it was universal finding in study done by Gehlot *et al*. [16].

Child's early nutritional status depends on maternal transfer of nutrients during fetal period and early feeding practices. Both were found inadequate in our study. We found Vitamin B_{12} deficiency and insufficiency in 2/3rd of the mother. It was similar to studies done by Gorayal *et al*. and Chaudhary *et al*.; while, study done by Gowda *et al*. found it in all the mothers [4,14,15]. Some babies with normal Vitamin B_{12} levels also had Vitamin B_{12} deficient mothers and some mothers with sufficient B_{12} levels had deficient babies. This indicates either the test that we did would have given some false negative results or there could have been other associated factors leading to ITS in their babies.

The treatment in the form of high dose injection Vitamin B_{12} (1000 μg) and folate (500 μg) on alternate days for 2 weeks, weekly for 1 month, and monthly for 6 months was given. Mothers who were found deficient were also advised for oral high dose Vitamin B_{12} supplementation for 2 months. Oral propranolol was given for severe tremors, and gradually tapered once the tremors decreased. The children who were malnourished were also given supplements like magnesium sulfate, potassium chloride, multivitamin syrup, iron syrup, Vitamin A (single dose), and zinc according to the WHO guidelines for the management of SAM. Most of the children showed improvement in general condition within 3–7 days. In four children, tremors increased initially while on treatment which gradually improved after 4–5 days.

Strength of the study was that these children were kept under treatment in hospital for at least 14 days or till all medical complications were cured which helped us to understand their course of disease better. Limitation of the study was inability to do urine methylmelonic acid test for Vitamin B_{12} deficiency which is more specific for its diagnosis, because of unavailability of this test in our center. This could be the reason for not detecting Vitamin B_{12} deficiency in some of the typical cases. Magnetic resonance imaging is a better for detecting structural changes in the central nervous system involvement but could not be done because of financial issues.

CONCLUSION

About 2/3rd of the mothers of children with ITS were either Vitamin B_{12} deficient or insufficient. Vitamin B_{12} deficiency is also found in around 2/3rd of the children with ITS. Vitamin B_{12} insufficiency was also found in both children and mother. Developmental delay, microcephaly, and cerebral atrophy were evidence of severe neurological involvement at admission. Long-term follow-up may be required to demonstrate the neurological consequences later in life. Screening of pregnant women with anemia and appropriate Vitamin B_{12} supplementation might have a beneficial role in reducing ITS and associated neurological consequences in their off springs.

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AUTHORS' CONTRIBUTION

MM and AKM conceptualized and designed study. MM, NM, and SKS collected the data. MM, AKM, NM, and MVS analyzed the data. MM, AKM, and SKS prepared the manuscript. Final proofreading was done by all.

CONFLICT OF INTEREST

None.

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