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Research Article

Assessment of iron, folate and vitamin B12 status in children with infantile tremor syndrome

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ABSTRACT

Background: Infantile tremor syndrome (ITS) is a clinical syndrome of infants and young children characterized by acute or gradual onset with mental and psychomotor changes, pigmentary disturbances of hair and skin, pallor and tremors.
Methods: The study was conducted on 50 children of age group 6 – 24 months with clinical diagnosis of infantile tremor syndrome. The demographic profile and relevant information of individual patient were collected by using structured proforma and an informed consent was taken for enrolling the children into the study. Serum ferritin, folate and vitamin B12 levels were estimated to assess iron, folic acid and vitamin B12 status by electrochemiluminiscence (ECL) method.
Results: Significantly higher numbers of patients (68%) were exclusively breastfed. All children had dark skin pigmentation and regression (82%)/delayed (18%) developmental milestones; while most of children had palmer pallor (98%), hypopigmented hair (92%) and majority of the patients (52%) had tremors. Significant number of patients had vitamin B12 deficiency (P=0.005) whereas none of the child was found to be having folate and ferritin deficiency. There was significant association between vitamin B12 deficiency with severity of anemia (P=0.011) and thrombocytopenia (P=0.002).
Conclusions: Vitamin B12 deficiency was present in 70% of children with ITS while none of them had iron or folate deficiency.

Keywords: ITS, Vitamin B12 deficiency, Folate deficiency, Ferritin deficiency

INTRODUCTION

Infantile tremor syndrome (ITS) is a clinical syndrome of infants and young children characterized by acute or gradual onset with mental and psychomotor changes, pigmentary disturbances of hair and skin, pallor and tremors.[1]

Various theories has been postulated about etiopathogenesis of ITS including nutritional deficiency, infections, toxins and enzyme defects but none has been substantiated so far.[1-4]

Although the mechanisms underlying the effect of maternal folate status on neural tube development are not well understood, the shared metabolism between folate and vitamin B_{12} suggests that deficiencies in one vitamin may alter the metabolism of the other. This is perhaps related to the roles that vitamin B_{12} plays in myelination, or in the synthesis of methionine from homocysteine in combination with folic acid. This review was conducted to examine the evidence linking deficiencies in maternal and infant folate and/or vitamin $B_{12}$with infant cognitive and motor development iency.

Need of study

There are limited studies on the association of hematopoietic factor deficiency in patients with infantile tremor syndrome. Hence, we conducted this prospective study with the primary objective to assess serum ferritin, folate and vitamin B_{12} concentrations in these children. Secondary objective was to correlate the hematopoietic factor status with clinicoepidemiological profile of these patients.

METHODS

It was a prospective study on 50 children with clinical diagnosis of ITS aged 6monyh to 2year, admitted in Bal Chikitsalaya, RNT Medical College, Udaipur (Rajasthan) from May 2014 to Dec 2014. Those patients who had anemia, psychomotor retardation, tremors due to any other explainable cause or on haematinics or received blood transfusion in past 3 months before admission were excluded from the study. Details of personal, socio-demographic profile, medical history and examination were recorded on a structured Proforma.

Two ml of peripheral venous blood sample was taken in an EDTA vial for determination of complete blood count, 2ml in plain vial for C reactive protein (CRP) and 3 ml in another plain vial for serum ferritin, folate and vitamin B_{12} estimation.

Laboratory analysis

Serum ferritin, folate and vitamin B_{12} were estimated by electrochemiluminiscence (ECL) method using VIT B12 600, FOL III 618 and FERRITIN 381 ELECSYS kits for COBASe411 analyzer, Roche diagnostics GmBH Germany distributed by Roche diagnostics GmBH, Sandhofer Strasse 116 Manheim. Deficiencies were labeled when serum ferritin concentration was <12ng/ml, or <30ng/ml if the CRP was positive, serum folate concentration <10nmol/L (4 ng/ml) and serum vitamin B_{12} concentration <150pmol/L (203 pg/ml).[5-8]

Ethical issues

A written informed consent was taken from either of the parents. The protocol was reviewed and approved by the Clearance from Institutional Ethics Committee.

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 21. Karl Pearson coefficient has been used for studying the correlation. Association of ITS with hematopoietic factor deficiency was found out by Chi-square test. A 'P' value of less than 0.05 was considered significant.

RESULTS

All the children under this study were from Hindu and most of them were below poverty line (64%), SC/ST (76%) families. Mothers of significant number of these patients were illiterate and housewives whereas fathers were either illiterate or literate up to primary standard and unskilled laborers (P<0.001) (Table 1).

Table 1: Sociodemographic profile of the study children.

Category	Number (%)	P value
Sex		
Male	30 (60)	0.157
Female	20 (40)	
Age (mo)		
6-12	25 (50)	<0.001
13-18	22 (44)	
19-24	3 (6)	
Caste		
ST	26 (52)	<0.001
SC	12 (24)	
OBC	7 (14)	
GEN	5 (10)	
Socioeconomic status		
Lower	50	
Poverty status		
APL	18 (36)	0.048
BPL	32 (64)	
Father occupation		
Semi professional	1 (2)	<0.001
Farmer	12 (24)	
Skilled	8 (16)	
Unskilled (laborer)	29 (58)	
Mother occupation		
Farmer	4 (8)	<0.001
Unskilled	2 (4)	
Unemployed(housewives)	44 (88)	
Father education		
Middle	6 (12)	<0.001
Primary	22 (44)	
Illiterate	22 (44)	
Mother education		
Secondary	2 (4)	
Middle	2 (4)	<0.001
Primary	19 (38)	
Illiterate	27 (54)	

APL-above poverty line, BPL-below poverty line

Significant numbers of these children were in age group 6-12 months and exclusively breastfed (Table 1, 2). Though boys were more than girls in numbers but this difference is not statistically significant. All patients with NTS had dark skin pigmentation. The other significantly common manifestations were hypopigmented hair (92%), palmer pallor (98%), apathetic look (76%) and regression of developmental milestone (82%) (P<0.001). Eighteen percent patients had delayed milestones; tremors (52%) and Hepatomegaly (62%) were also present in majority of

these children. Hepatomegaly was present in all children of 19-24 months age group. Significant number of patients had MUAC>11.5 cms; absence of pedal edema and visible wasting.

Table 2: Characteristics of the study children.

Category	Number (%)	P value
Feeding pattern		
EBF	34 (68)	<0.001
BF+TM	7 (14)	
BF+CF	9 (18)	
Clinical features of ITS		
Dark skin pigmentation	50 (100)	<0.001
Hypopigmented hair	46 (92)	<0.001
Palmer pallor	49 (98)	<0.001
Regressed milestone	41 (82)	<0.001
Delayed milestone	9 (18)	
Apathetic look	38 (76)	<0.001
Hepatomegaly	31 (62)	0.09
Tremor	26 (52)	0.777
Clinical features of SAM		
WT/HT < -3SD	21 (42)	0.258
MUAC < 11.5cm	17 (34)	0.024
Pedal edema	6 (12)	<0.001
Visible wasting	9 (18)	<0.001
Severity of anemia		<0.001
Mild anemia	2 (4)	
Moderate anemia	17 (34)	
Severe anemia	31 (62)	

EBF = exclusive breastfeeding, BF+TM = Breastfeeding and top milk, BF+CF = Breastfeeding and complementary feeding, MUAC = mid upper arm circumference, WT/HT = weight for height, 3SD = 3standard deviations.

Anemia was present in all patients which was severe in 62% (P<0.001) (Table 2). Vitamin B_{12} deficiency was present in significant number of patients (70%) but none of the patient had folate or ferritin deficiency (Table 3). Significant association of vitamin B_{12} deficiency was present with age 6 – 12 mo, exclusive breastfeeding, dark skin pigmentation, hypopigmented hair, apathetic look, hepatomegaly and dimorphic anemia (Table 4, 5). Out of total 35 vitamin b12 deficient patients in the study group 3 cardinal features of SAM i.e. MUAC <11.5cms, visible wasting and b/l pedal edema were absent in significant number whereas there was no significant association with Wt/Ht < or > -3SD.

Table 3: Micronutrients deficiency status in ITS patients.

Micronutrient deficiency	Number (%)	p value
Vitamin B_{12}	35 (70)	
Folate	0	0.005
Ferritin	0	

Table 4: Distribution of baseline variables with relation to serum vitamin B_{12} deficiency in the study population.

Characteristics	Serum vitamin B_{12} <203pg/ml (n=35)	P value
Age (mo)		
6-12 (n=25)	18	
13-18 (n=22)	14	0.006
19-24 (n=3)	3	
Sex		
Male (n=30)	19	0.612
Female (n=20)	16	
Feeding patterns		
EBF (n=34)	22	
BF+TM (n=7)	6	0.001
BF+CF (n=9)	7	
Hair changes		
Hypopigmented hair (n=46)	31	
Normal hair (n=4)	4	<0.001
Dark skin pigmentation (n=50)	35	
Look		
Apathetic (n=38)	31	<0.001
Interactive (n=9)	3	
Irritable (n=3)	1	
Milestone		
Delayed (n=9)	5	<0.001
Regression (n=41)	30	
Tremors		
Present (n=26)	18	0.866
No tremor (n=24)	9	
Hepatomegaly		
Present (n=31)	25	0.011
No hepatomegaly (n=19)	10	

EBF= exclusive breastfeeding, BF+TM= Breastfeeding+ Top milk, BF+CF = Breastfeed+ complementary feeding.

Table 5: Distribution of baseline variables with relation to serum vitamin B_{12} deficiency in the study population.

Characteristics	Serum vitamin B_{12} < 203pg/ml (n=35)	P value
Severity of anemia		
Mild (n=2)	0	
Moderate (n=17)	10	0.011
Severe (n=31)	25	
Type of anemia		
Dimorphic (n=27)	24	
Macrocytic (n=6)	5	<0.001
Normocytic (n=11)	6	
Microcytic (n=6)	0	

Table 6: Association of serum vitamin B_{12} deficiency with features of SAM in the study population.

Characteristics	Serum vitamin B_{12} < 203pg/ml (n=35)	P value
Wt/Ht		
> -3SD	22	
< -3SD	13	0.128
MUAC(cms)		
> 11.5	24	0.028
< 11.5	11	
Visible wasting		
Absent	30	<0.001
present	5	
B/l pedal edema		
Absent	31	<0.001
Present	4	

DISCUSSION

ITS has been reported from various part of our country since last many decades and is not a rare entity in many parts of India. The incidence has been reported to be 1.42% to 1.73% by various workers.[9-11] All patients belonged to Hindu and lower socioeconomic status families, out of which 76% SC/ST and 64% were in BPL category. Bajpai et al, Sachdev et al and Garg et al also reported that all children in their study were from lower socioeconomic status.[10,12,13] Similarly Ramkumar et al and Arya et al also found that majority of their patients with ITS were from lower socioeconomic status.[9,14] Mothers of significant number of these patients were illiterate and housewives whereas fathers were either illiterate or literate up to primary standard and unskilled laborers. Udaipur district and nearby areas of other district of Rajasthan and M.P. who constituted our study population, have poor female literacy in rural areas (32.8%). The other remarkable demographic data of Udaipur district is that 55.85% families are SC/ST and below poverty line (48%).[15,16] In our study 6 -12 mo age group was significantly associated with ITS which is similar to previous studies but Sachdev et al reported that 13-18 mo was most affected group.[4,9,10,12,13,17,18] Mean age of our study population was 13.72 mo which is similar to study by Udani et al (13.9mo). Like previous studies there was slight preponderance of ITS in boys in our study also though the difference is not statistically significant.

In our study major features of ITS described in literature were present in significant number of patients, tremor (52%) and hepatomegaly (62%) were also present in majority but not in significant number, perhaps due to presentation of some patients in pre-tremor stage. The previous studies reported these clinical features in varying percentage of patients i.e. skin pigmentation (0%-100%), hypopigmented hair (33.33%-100%), apathy (12.65%-100%), pallor (10%-100%) and tremors (59%100%). Most of studies reported regression of milestones (6.5%-100%) although delayed milestone (30.4%-80.3%) were also reported in some studies.[3,4,9,10,12-14,18-20]

Most of the workers have found vitamin B_{12} deficiency in children with ITS but to the best of our knowledge and thorough web search ours is the first planned study to assess iron (serum ferritin) and folate status along with vitamin B_{12} in children with ITS.[3,4,21]

In our study all the ITS patients were anemic but none of them had low levels of folate or ferritin which are commonly responsible for anemia in children. This could be due to routine iron folic acid supplementation to pregnant and lactating mother and presence of subclinical infection which can increase serum ferritin as an acute phase reactant.[22] Vitamin B_{12} deficiency is well recognized in exclusively breastfed infants of vitamin B_{12} deficient mothers.[3,23] Concentration of vitamin B_{12} in breast milk reflect maternal vitamin B_{12} stores, and maternal vitamin B_{12} stores are depleted in up to one-third of rural Indian women.[24,25] A study in rural Karnataka by SR Pasricha, et al also found that concentrations of ferritin and vitamin B_{12} were decreased in toddlers who continued to receive breast milk.[26] Folate concentrations in breast milk are generally high and independent of maternal stores thus, prolonged breastfeeding in most of our patients might be protective from folate deficiency.[27,28] The adverse neurological outcome in the form of apathy, tremors, delayed and/or regression of milestones in these patients can be attributed to vitamin B_{12} deficiency.[29] Chandra, et al reported folic acid deficiency in 54.3% and vitamin B_{12} deficiency in 65.7% of anemic children in age group less than 2 yrs and breastfed, admitted in kalavati saran children hospital, new Delhi.[30] However, they found no significant difference in these deficiencies between breastfed children of less than 2 yrs and non-breastfed children of more than 2 yrs. We also found vitamin B_{12} deficiency in similar percent of ITS patients but in significantly more number of patients in age group 6 – 12 mo and exclusively breastfed (P value 0.006 and 0.001 respectively). Various other investigators have also documented vitamin b12 deficiency in 33.8% to100% of ITS patients. (Udani et al, Srikantia et al, Jadhav et al, Smith G et al). In our study occurrence of vitamin B_{12} deficiency was significantly higher in boys, low socioeconomic status families, those who had hypopigmented hair, apathetic look, regression of milestones, hepatomegaly, severe and dimorphic anemia. Out of four cardinal features of SAM i.e. MUAC<11.5 cms, visible wasting and b/l pedal edema were absent in significant number of these patients. Similarly vitamin B_{12} deficiency was also less in those patients who had above features of SAM concomitantly. No significant association of presence or absence of Wt/Ht <-3SD with ITS or vitamin B_{12} was found. We found no such study to correlate vitamin b12 deficiency with various features of ITS and ITS with SAM.

The results of our study should be considered within its strengths and limitations. This study strengthens the hypothesis that vitamin B_{12} deficiency is responsible for ITS. The measurement of holotranscobalamin and metabolites such as homocysteine and methylmalonic acid in urine or serum are more sensitive indicators than serum vitamin B_{12}. Pre-analytic haemolysis of blood samples might also be a factor for higher folate values. The measurement of breast milk micronutrient contents might have also strengthened the results. Absence of a comparative group is also another setback of the study. Finally, we recruited only a small sample size to understand the prevalence and determinants of micronutrient deficiency in this group of children.

CONCLUSION

In conclusion, serum vitamin B_{12} deficiency were present in significant number of patients with ITS and none of them had iron and folate def. Our findings provide a framework for the development of strategies to improve vitamin B_{12} status in this specific population and to disseminate knowledge regarding timely introduction of adequate complementary feeding. In national nutritional anemia prophylaxis program vitamin B_{12} supplementation should also be given along with iron and folic acid to prevent hematological as well as non-hematological manifestations of vitamin B_{12} deficiency.

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