Original Research Article

Clinical Profile, Serum Vitamin B12 Levels and Outcome of Children with Infantile Tremor Syndrome (ITS) and Correlation with Maternal Serum Vitamin B12 Levels

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Abstract

Background: Infantile tremor syndrome (ITS) is a tetrad of mental and motor changes, pigmentary disturbances of skin and hair, pallor and tremors. It was first described in 1957 by Dikshit from Hyderabad who named it as Nutritional dystrophy and Anaemia. Usually, cortical atrophy and calcification takes time to develop and ITS has been reported as early as 3 to 6 months of age. **Objective:** To compare vitamin B12 levels of ITS patients with non-ITS healthy infants of similar age group. **Methodology:** This study was a prospective study, conducted at department of paediatrics, medical college & S.S.G hospital, Vadodara, Gujarat over the period of 2 years. Children between the age 6 months to 2 years, admitted with their mothers in department of paediatrics diagnosed as ITS clinically based upon clinical features like pallor, delayed milestones, skin pigmentation, hair changes and with/without tremors. 30 controls were also taken in same age group with history of appropriate complementary feeding with normal development and no or mild anaemia and no malnutrition or PEM I/II. **Results:** Majority of the subjects had fever (86.7%) has a major clinical symptoms followed by Cough (80%) and delayed development milestone in 567% of the subjects. In the present study 56.7% of the children were exclusively breastfed and 43.3% had inadequate complimentary feeding practices. The levels of vitamin B 12 was compared with the case and control group, among the study group 93.3% of the subjects had low Vitamin B 12 level and in the control group 13.3% had low Vitamin B 12 levels. The Association between study subjects and vitamin B12 levels was found to be statistically significant. Among the case subjects with ITS only 2 children subjects had normal vitamin B12 and 28 had low vitamin B 12 levels. On comparing with vitamin B 12 levels of mother it was found that 83.45 of the subjects had low Vitamin B12 Levels and the association was also found to be statistically significant. **Conclusion:** mothers having strict vegetarian diet making themselves prone to vit B12 deficiency leading to low vit B12 serum levels in their exclusive breastfed or inadequately weaned infants. Upon supplementation of vit B12 general condition including tremors, pigmentary changes, anaemia improves as well as mental motor quotient improves. However, they were still lagging behind their normal counterparts, more so in mental scale.

Keywords: Vitamin B 12, Tremors, Exclusive Breast Fed, Infantile Tremor Syndrome.

Introduction

Infantile tremor syndrome (ITS) is a tetrad of mental and motor changes, pigmentary disturbances of skin and hair, pallor and tremors[1]. It was first described in 1957 by Dikshit from Hyderabad who named it as Nutritional dystrophy and Anemia[2]. Later, in 1960 Pohowalla studied and described complete and clear clinical presentation in 61 infants and named it as "Meningo encephalitic syndrome"[3].Subsequently it was reported from various parts of the country.

Until 1988 it was believed that it occurs only in India but various cases were reported from all the world having resemblance with ITS in infants of vegetarian mothers[4].

Different researchers have given various names like syndrome of tremors, mental regression and anaemia in infants and young children[5], nutritional tremor syndrome. To establish the etiology many studies have been done in this area like biochemical profile, bone marrow examination, csf examination, X-ray skull, brain biopsy. MRI study of brain in 6 ITS patients was done at department of paediatrics of medical college Baroda which was suggestive of cortical atrophy and basal ganglia calcification[6].

Usually, cortical atrophy and calcification takes time to develop and ITS has been reported as early as 3 to 6 months of age. This made us think that the insult may be starting during in utero period[7]. Various hypotheses have been postulated like nutritional deficiency of various trace elements, viral infection, degenerative process, heavy metal deposition in basal ganglia etc.

It was Jadhav et al[8] from CMC Vellore, who first thought it to be due to vitamin B12 deficiency. Vitamin B12 deficiency in mother during pregnancy and puerperium leads to vit B12 deficiency in mother's milk, so in foetus and new-borns.

This study was carried out with the objectives to evaluate the correlation of serum vitamin B12 levels of children with ITS and their mothers and also to compare vitamin B12 levels of ITS patients with non-ITS healthy infants of similar age group. In this study we also tried to check the effect of vitamin B12 supplementation on developmental outcome.

Objective

To compare vitamin B12 levels of ITS patients with non-ITS healthy infants of similar age group.

Methods

Setting

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This study was a prospective study, conducted at department of paediatrics, medical college & S.S.G hospital, Vadodara, Gujarat over the period of 2 years.

Subject Eligibility

Children between the age 6 months to 2 years, admitted with their mothers in department of paediatrics diagnosed as ITS clinically based upon clinical features like pallor, delayed milestones, skin pigmentation, hair changes and with/without tremors. 30 controls were also taken in same age group with history of appropriate complementary feeding with normal development and no or mild anaemia and no malnutrition or PEM I/II.

Data Collection

Clinic Profile: A detail history of presenting complaints, socio-economic status, diet, development was taken as per the set proforma. Maternal diet history was also recorded. Complete general and systemic examination of the children along with dietary details and developmental history were obtained.

Investigations: Haemoglobin estimation, total counts, differential count, peripheral smear, peripheral smear for malarial parasite, urine examination and other required investigation were done. Complete hemogram including RBC indices were obtained using venous blood collected in EDTA vacuities by fully automated cell counter at a standard laboratory. Serum levels of vitamin B12 estimation was done in all 30 patients and their mothers as well as all 30 controls using the kit named IMMULITE vitamin B12 which functions on the principle of competitive immune assay.

Treatment directed towards acute complications as well as towards the nutritional deficiencies and anaemia. Vitamin B complex, folic acid, iron, zinc, magnesium, vit-B12 were supplemented. To control tremors carbamazepine, benzodiazepine or propranolol etc were given. Associated conditions were treated adequately. Nutritional rehabilitation was started. Daily observation was done in wards for general improvement and disappearance of tremors.

Developmental assessment of all the children with ITS assessed using "Abridged Bayley's Scales of Infant Development" on admission.[9]

Follow up: After discharge patients were called for monthly follow-up till 6 months and observed for tremors, general activity, interaction, weight gain, skin pigmentation, anaemia. Development was re-assessed at 3 & 6 months interval after discharge using same developmental scale.

Results

A total of 30 study subjects were evaluated for the said objective in our study.

Majority of the subjects had fever (86.7%) has a major clinical symptoms followed by Cough (80%) and delayed development milestone in 567% of the subjects.

In the present study 56.7% of the children were exclusively breastfed and 43.3% had inadequate complimentary feeding practices.

The levels of vitamin B 12 were compared with the case and control group, among the study group 93.3% of the subjects had low Vitamin B 12 level and in the control group 13.3% had low Vitamin B 12 levels. The Association between study subjects and vitamin B12 levels was found to be statistically significant.

Among the case subjects with ITS only 2 children subjects had normal vitamin B12 and 28 had low vitamin On comparing with vitamin B 12 levels of mother it was found that 83.45 of the subjects had low Vitamin B12 Levels and the association was also found to be statistically significant.

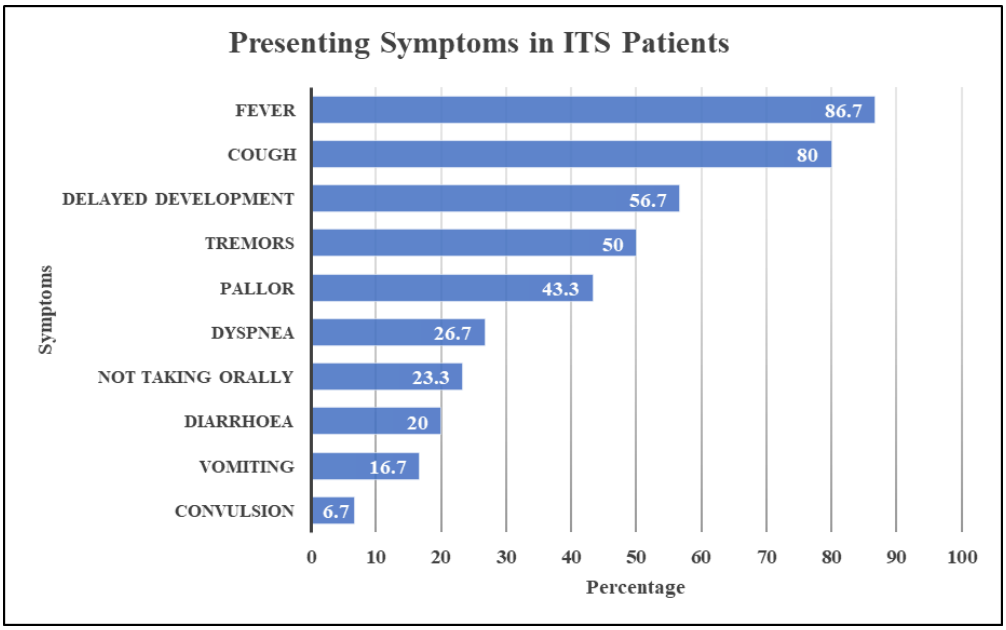

Fig. 1: Distribution of study subjects based on presenting symptoms

Table 1: Diet of ITS Patients

Diet	No of cases(n=30)	%
Exclusive BF	17	56.7
Inadequate CF	13	43.3
Adequate CF	0	0

Table 2: Serum vitamin B12 levels in ITS patients and in controls

Vit B12	Low	Normal
No of cases(n=30)	28(93.3%)	2(6.7%)
No of controls(n=30)	4(13.3%)	26(86.7%)
P<0.00001		

Table 3: Serum vitamin B12 of ITS cases and their mothers

S.vit B12		Mothers	
		Normal	Low
Baby	Normal	2(6.7%)	0
	Low	3(10%)	25(83.4%)

Normal: 200-900 pg/ml Low: <200 pg/ml

Discussion

The study comprised of 30 pairs of ITS patients with their mothers and 30 healthy children of same age group with similar baseline characteristics were taken as controls. Male to female ratio in our study was found to be 1.7:1. Bajpai et al[10] and Ramkumar[11]have reported the male:female ratio 2:1. Sachdev et al[5] reported ratio of 3:2. However, our study may not represent true incidence in the community as male admissions in our paediatric ward is as such higher.

During the study period male to female admission ratio was 1.5:1. Out of total 30 ITS patients 24 were from the age group of 7 months to 1 year which comprises of 80% of total cases. Bajpai et al[10] and Ramkumar[11] have reported maximum incidence between 6-12 months whereas Sachdev et al[7] reported maximum incidence between 12-18 months. Out of 30 cases of ITS 29 were from Hindu community and only 1 was from muslim community. However, all the 30 mothers of ITS cases were vegetarian (including muslim lady) and were consuming either no milk or very little amount of milk due to poverty.

We assumed that vegetarian diet in mothers give rise to deficiency of vitamin B12 in mothers as vegetarian diet other than milk does not contain vitamin B12, so in infants who were either exclusively on breastfeeding or had inadequate complimentary feeding will develop vitamin B12 deficiency. Wardinsky T.D. et al[12] demonstrated vitamin B12 deficiency in infants associated with low breast milk vitamin B12 concentrations. Renault F et al[13] observed neuropathy in vitamin B12 deficient breast-fed infants of vegetarian mothers. Honzik T et al[14] demonstrated metabolic complications and neurological manifestations of vitamin B12 deficiency in children of vegetarian mothers. Rural to urban ratio of cases was nearly 1:1. However, study done by Sachdev et al[5] found that 2/3rd of patients came from rural areas, Whereas Mathur et al[15] reported 3/4th patients from rural area indicating ITS is more common in rural population.

All the cases of ITS patients in present study were from lower socio-economic classes (III, IV, V) as per modified prasad classification. Ramkumar et al[11], Sachdev et al[5] & Mathur et al[15] had similar observations as found in our study. Most frequent complaint were fever & cough present in 86% & 80% patients respectively. Delayed development was present in 56.7% cases and 50% patients complained of tremors. Others complaints were vomiting, diarrhoea, dyspnoea, pallor, convulsions and not taking orally (Figure-1). Bajpai et al[12] observed tremors as presenting symptoms in 95.5% of the patients followed by fever in 52.2%, Ramkumar et al[11] observed that tremor was major presenting compliant, it was present in only 47.6% followed by fever in 46.7% of the cases. Hence fever, cough, diarrhoea were present as significant symptoms in all the studies including the present study, but it is difficult to correlate these to ITS as these are common and nonspecific symptoms in this age group.

Onset of tremors in all the patients who had tremors was sudden. Ramkumar et al[11] noted the similar observation. Out of 15 patients who were presented with tremors 12 (80%) presented with focal tremors and only 3 (20%) had generalised tremors. Out of 12 who had focal tremors 10 patients had only tongue tremors (table 1).

Majority of the ITS patients presented with bronchopneumonia and acute gastroenteritis, 40% and 30% respectively. Out of total 30 ITS patients, none of our patients had received adequate and appropriate complementary feeding, in fact 56.7% (n=17) were on exclusive breast feeding (Table-1). Similar observations were made by K.K Kaul[16], Sachdev[5].In our study, almost 60% cases had either no or mild malnutrition which suggests that even caloric requirements were met with, the diet must be deficit in one or more micronutrients. Study done by K.K.Kaul[16] found that 50% of his subjects are above the expected weight for age strengthening the above hypothesis.

On objective evaluation, delayed milestone, pallor, hair changes and pigmentation were present in almost all cases. Vacant look and chubby appearance were present in majority of patients. In pigmentary changes knuckle pigmentation was present in 70% (n=21) cases. Sachdev et al[[5]observed increased pigmentation in 40% of the cases whereas Ramkumar et al[11] reported in 88.8% of cases. However, other objective findings like hypertonia, hypotonia, hepatomegaly, splenomegaly was seen in very few cases. As described earlier pallor was seen in all cases (n=30) of which upon investigation severe anaemia was found in 53% (n=16) cases of which 8 patients required transfusion. Moderate and mild anaemia were seen in 5 and 7 cases respectively, whereas only 2 had normal haemoglobin levels. However, in mothers of these ITS patients 50% had normal haemoglobin levels and only 3 (10%) mothers had severe anaemia. Out of 30 cases, 17 cases showed normal MCV, 9 had low MCV where only 4 had high MCV. Anaemia was a constant feature described by other authors too. Jadhav et al[8] from vellore reported megaloblastic anaemia associated with ITS. Sachdev et al[5]observed macrocytic anaemia in 72.5% of cases whereas Ramkumar et al[11]found that majority of the cases has normocytic type.

In present study serum levels of vitamin B12 found to be low in 28 cases of ITS, whereas only 2 had normal vitamin B12 levels of which one patient had history of taking some tablets regularly for a week before admission which may be hematinics, that might have changed serum vitamin B12 levels to normal (table-2). In spite of having low level of serum vitamin B12 in 28 patients only 4 patients had high MCV hence, we conclude blood indices is not a good screening tool in detecting serum vitamin B12 deficiency in ITS patients. In our study, it was found that out of all(n=30) mothers of ITS patients' vitamin B12 levels found low in 25 (83.3 %) mothers and normal levels were found in 5 (16.7%) mothers.

All the mothers who had low vitamin B12 levels, had low vitamin B12 levels in their children also. However, there were 3 cases where mothers had normal vitamin B12 levels but babies' levels were low. All of these babies were either exclusively breastfed or inadequately weaned. Jadhav et al[8]also found that serum vitamin B12 levels were low in ITS patients and their mothers. Hamza Karabiber et al[17] reported cases with similar clinical picture, cases were exclusively breastfed and no complimentary feed was stared had low serum vitamin B12 level. Grattan Smith PJ from Australia[18] reported 3 infants with vitamin B12 deficiency and were exclusively breastfed and their mothers were vegetarian. Renault F[13]reported neuropathy in 2 patient with low vitamin B12 levels and exclusively breastfed by vegetarian mothers. Lovblad K[19] reported severe brain atrophy with retarded myelination in a child presented with severe psychomotor retardation and low vitamin B12. Honzik T[14] reported similar MRI finding in 2 infants who were purely breastfed and had psychomotor retardation and low serum vitamin B12 levels. Table-3 shown maternal S.vitamin B12 levels correlates well with babies S.vitamin B12 levels.

One should pick up the morbidity of vit B12 deficiency in mothers, so her children who usually nurture on breastfeeding for initial few months could escape from ITS disease. More studies require to support this hypothesis. If it is proved so one should not hesitate to supplement Vit B12 like iron to adolescent girls or like folic acid to pregnant women if not contraindicated. In our study, general

condition improved in majority 76%(n=23) of children. Mean duration of stay was 18 days. Weight gain noted in 80% (n=24) patients. They started smiling, interacting and taking food well orally. Only 1 child expired because of meningitis and septicaemia.

Developmental status of ITS patients- developmental assessment of all the ITS patients was done by Abridged BSID scale. Although developmental delay was complained of 17 (56.6%) patients, on examination it was found in all 30 (100%) patients. Patients were called regularly for follow-up after discharge. But out of 30 patients 22 came for regular follow up. Developmental assessment was also done on follow up at 3rd and 6th month after discharge using the same scales. Developmental Quotient (D.Q.) was compared in all these 22 patients. Chronological age of the child on admission has been taken to calculate D.Q. The improvement in mental and motor quotients was significant even at 3 months of follow up with p value of < 0.001. But, when on follow-up, D.Q. score was calculated and compared using actual chronological age (added 3 and 6 months), the result was statistically not significant and p value was >0.1. At 6 months of follow up also these patients were much behind than normal children of that age. All the children failed to perform optimally on motor and mental scales in spite of nutritional recovery, disappearance of the tremors and improvement in general activity.

K.K. Kaul[16] observed that in series of 123 patients, of which 23 were followed up for 10 years, 18 had subnormal intelligence (IQ- 46 to 95).

Von Schenck V. et al[20] reported that cognitive and language development remained seriously retarded at the age of 2 years in his patients. These findings were supported by Goraya J.S[21].

General Condition on follow-up: Improvement noted in the general condition in form of disappearance of tremors, decrease in skin pigmentation, and improvement in anaemia as well as PEM status.

Conclusion

ITS occurs almost equally in male and female most commonly in age group of 7-12 months of age with mothers having strict vegetarian diet making themselves prone to Vit B12 deficiency leading to low vit B12 serum levels in their exclusive breastfed or inadequately weaned infants in whom deficiency manifested as tetrad of symptoms comprises of mental & motor changes, pigmentary changes of skin and hairs, pallor and tremors which is named as “Infantile Tremor Syndrome”. Upon supplementation of vit B12 general condition including tremors, pigmentary changes, anaemia improves as well as mental motor quotient improves. However, they were still lagging behind their normal counterparts, more so in mental scale.

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