



ORIGINAL RESEARCH PAPER

Paediatrics

TO STUDY OF ASSOCIATION OF CLINICAL PROFILE WITH SERUM VITAMIN B12 AND FOLATE LEVEL IN CHILDREN WITH INFANTILE TREMOR SYNDROME

KEY WORDS: ITS, B12, Folate level, Clinical profile.

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ABSTRACT	Background- We planned the present study with objective of to find out correlation in vitamin B ₁₂ and folate levels with clinical profile in children with ITS
	Methods- This Hospital based cross sectional observational study was conducted in, Sir Padampat Mother and Child Health Institute (SPMCHI), SMS Medical College, Jaipur.
	Results- Vitamin B ₁₂ and folate were reduced in children with generalized tremors, psychomotor retardation, delayed milestones, presence of hepatomegaly and splenomegaly.
	Conclusion- All children with Infantile Tremor Syndrome should be screened for vitamin B ₁₂ and folate levels, high risk children should be supplemented B ₁₂ and folic acid.

INTRODUCTION

ITS is commonly found in age of 6 to 24 months though also present in younger for older children with majority in male preponderance. Most of the infants with ITS come from poor families and almost all the cases of ITS occur in exclusively breast fed infants. Mothers of the infants with ITS is more common in babies whom mothers are vegetarian and have pernicious anemia. babies with delayed weaning, lack of animal origin milk had higher chance of ITS.³

Other etiologies hypothesized were central nervous system (CNS) infection to being a spectrum of Protein energy malnutrition (PEM) or degenerative CNS disease. However, few hypothesis remains debated⁴⁻⁵ Capute AJ, et al Germany have described a similar illness in breastfed infants of vegetarian mothers⁷ The role of vitamin B₁₂ and cobalamine and folate in the neurodevelopment of a child during infancy is being studied and cobalamine deficiency can present with varied neurological manifestations described in ITS⁹ The role of vitamin B₁₂ and folate in children with ITS remains largely debated. The newer and complete range of biomarkers of vitamin B₁₂ deficiency, including blood counts, peripheral smears, B₁₂ levels, folate level have not been systematically evaluated in children with ITS. Published literature and research work on ITS is available for the last six decades, but still no conclusive etiology for the syndrome has been ascertained.⁸

Hence we planned the present study with objective of to find out correlation in vitamin B₁₂ and folate levels with clinical profile in children with ITS.

MATERIALS AND METHODS

STUDY PLACE:- This study was conducted in, Sir Padampat Mother and Child Health Institute (SPMCHI), SMS Medical College, Jaipur.

STUDY DESIGN:- Hospital based cross sectional observational study

DURATION OF STUDY:- June 2019 to May 2020 after approval of Research Review Board (RRB)

SAMPLE SIZE: Sample size was calculated with 95% confidence level and alpha error 0.05, assuming 80% power of study and has vitamin B12 <200 and folate <5 in 80% of cases, as per reference article¹⁰ within absolute error of 12% required sample size was 45 cases of ITS.

STUDY SUBJECTS: All children > 6 months to < 2 years presenting with symptoms of ITS admitted in SPMCHI, SMS Medical College Jaipur were enrolled for study after applying inclusion and exclusion criteria.

INCLUSION CRITERIA

- (A) Children presenting with following clinical features of ITS
1. Tremors – localized/generalized,
 2. Hair and knuckle pigmentation
 3. Pallor
 4. Delayed Milestones / Psychomotor Retardation,
 5. Organomegaly
- (B) Parents given written consent for participation in study

EXCLUSION CRITERIA

1. Known neurological illness
2. Tremors due to any other explainable cause
3. On vitamin B₁₂ and folate therapy
4. Received blood transfusion in past 3 months before admission
5. Refusal for participation in study

RESULTS

Table 1. Association between clinical profile and Serum Vitamin B₁₂ levels and folate

Clinical profile	Serum Vitamin B ₁₂	p-value	Serum folate	p-value

Tremor	Generalized	177.09±93.85	0.003	20.64±7.13	0.143
	Localized	69.75±52.47		15.96±6.55	
Pallor	Yes	77.29±64.05	0.038	16.28±6.77	0.045
	No	176.00±53.74		20.83±3.49	
Delayed milestone	Present	81.48±58.57	0.982	15.56±7.44	0.124
	Absent	81.92±76.60		17.63±5.62	
Psychomotor Retardation	Yes	88.32±60.12	0.553	16.14±6.57	0.762
	No	76.36±71.74		16.76±6.93	
Hepatomegaly	Yes	70.99±55.31	0.383	16.78±6.31	0.269
	No	88.81±72.95		16.28±7.04	
Splenomegaly	Yes	51.22±38.04	0.001	17.74±4.65	0.595
	No	87.29±69.25		16.25±7.04	

Most of the children presented with localized tremors (88.9%). The mean serum B₁₂ level was higher in children with generalized tremors (117.09 pg/ml) as compared to children with localized tremors (69.75 pg/ml). Mean serum folate level was higher in children with generalized tremor (20.64 ng/ml) as compared to children with localized tremors (15.96 ng/ml). Most children had pallor (95.5%). The mean of vitamin B₁₂ were higher in children without pallor (176.00) as compared to children with pallor (77.29). The mean of serum folate were higher in children without pallor (20.83) as compared to children with pallor (16.28). Most of the children had delayed milestones (55.6%). Mean serum B₁₂ level was higher in children without delayed milestones (81.92 pg/ml) as compared to children with delayed milestones (81.48 pg/ml). The mean serum folate level was higher in children without delayed milestones (17.63 ng/ml) as compared to children with delayed milestones (15.56 ng/ml). Majority of the children did not have psychomotor retardation (55.6%). Mean serum B₁₂ level was higher in children with psychomotor retardation (88.32 pg/ml) as compared to children without psychomotor retardation (76.36 pg/ml). Mean serum folate level was higher in children without psychomotor retardation (16.76 ng/ml) as compared to children with psychomotor retardation (16.14 ng/ml). Around 40% of the children had hepatomegaly. The mean serum B₁₂ level was higher in children without hepatomegaly (88.8 pg/ml) as compared to children with hepatomegaly (70.99 pg/ml). Mean serum folate level was higher in children without hepatomegaly (16.28 ng/ml) as compared to children with hepatomegaly (16.78 ng/ml). About 15.6% of the children had splenomegaly. The mean serum B₁₂ level was higher in children without splenomegaly (87.29 pg/ml) as compared to children with splenomegaly (51.22 pg/ml). Mean serum folate level was higher in children with splenomegaly (17.74 ng/ml) as compared to children without splenomegaly (16.25 ng/ml).

DISCUSSION

Most of the children had localized tremors (88.9%) and 11.1% children had generalized tremors. The mean serum B₁₂ level was higher in children with generalized tremors (117.09 pg/ml) as compared to children with localized tremors (69.75 pg/ml). This difference in B₁₂ level in relation to tremors was statistically significant. Mean serum folate level (20.64 ng/ml) was higher in children with generalized tremor as compared to children with localized tremors (15.96 ng/ml) (Table No. 20). This difference in folate level was however statistically not significant. Similar to our study Garewal G et al.⁸ and Ratageri

VH et al.⁸ observed that all cases presented with tremors had lower vitamin B₁₂ level. In contrast to our study Rajpoot S K et al.¹⁰ found that 52% of patients had tremors.

Vitamin B₁₂ deficiency causes increase glycine level in blood which leads tremor in ITS (Zanus Cet al.)¹¹

Majority of (95.5%) the children had pallor. Mean of vitamin B₁₂ level (176.00 pg/ml) were higher in children without pallor as compared to children with pallor (77.29 pg/ml). This difference in vitamin B₁₂ level in relation to pallor was statistically significant. The mean of serum folate level (20.83 ng/ml) were higher in children without pallor as compared to children with pallor (16.28 ng/ml) (Table No. 22). This difference in serum folate level in relation to pallor was statistically significant. Similar to our study Garewal G. et al.⁸, Ratageri VH et al.⁹, Siroli V et al.¹² and Rajpoot S K et al.¹⁰ observed that most of children had pallor. In contrast to our study Parsawala KM et al.¹³ found 83% children have pallor. Vitamin B₁₂ with folate is necessary for the formation and maturation of red blood cells and the synthesis of deoxyribonucleic acid (DNA) which is the genetic material of cells. In deficiency of vitamin B₁₂ and folate causes macrocytic anemia and child present with pallor (Lorry E. Johnson)¹⁴.

Most of the children had delayed milestones (55.6%). Mean serum B₁₂ level was higher in children without delayed milestones (81.92 pg/ml) as compared to children with delayed milestones (81.48 pg/ml) (Table No. 10). The mean serum folate level (17.63 ng/ml) was higher in children without delayed milestones as compared to children with delayed milestones (15.56 ng/ml) (Table No. 23). Both the differences viz in B₁₂ as well as folate level in relation to delayed milestones was however statistically not significant. Compare with our study Siroli V et al.¹² and Rajpoot KS et al.¹⁰ found similar presentation. In contrast our study Garewal G. et al.⁸ and Ratageri VH et al.¹⁵ observed that clinically, all of them presented with regression of milestones.

Vitamin B₁₂ deficiency causes delayed myelination or demyelination of nerves; alteration in the S-adenosylmethionine (SAM): S adenosyl homocysteine (SAH) ratio; imbalance of neurotrophic and neurotoxic cytokines; and/or accumulation of lactate in brain cells. These changes leads developmental delay in ITS (Dror DK et al. Nutr Rev)¹⁶.

Majority of the children did not have psychomotor retardation (55.6%). Mean serum B₁₂ level was higher in children with psychomotor retardation (88.32 pg/ml) as compared to children without psychomotor retardation (76.36 pg/ml) (Table No. 11). Mean serum folate level (16.76 ng/ml) was higher in children without psychomotor retardation as compared to children with psychomotor retardation (16.14 ng/ml) (Table No. 24). Both the observed differences in relation to psychomotor retardation were however statistically not significant. Kaul et al.¹⁷ in a study done in 23 patients for up to 10 years period, 18 children were found mentally subnormal 2 to 10 years after onset of this disease, rest 5 also were in lower normal range of Intelligence Quotient (IQ). A total of 7 children out of 23 had speech defect i.e. dyslalia. Garewal G. et al.⁸ and Ratageri VH et al.¹⁵ observed that clinically, all of them presented with subnormal developmental quotient.

Around 40% of the children had hepatomegaly. The mean serum B₁₂ level (88.8 pg/ml) was higher in children without hepatomegaly as compared to children with hepatomegaly (70.99 pg/ml) (Table No. 12). This difference in B₁₂ level in relation to hepatomegaly also not found to be statistically significant. Mean serum folate level (16.78 ng/ml) was higher in children with hepatomegaly as compared to children without hepatomegaly (16.28 ng/ml) (Table No. 25). This difference in folate level in was however statistically not

significant. Compared with our study Siroliya V et al.¹² found similar result.

About 15.6% of the children had splenomegaly. The mean serum B₁₂ level was higher in children without splenomegaly (87.29 pg/ml) as compared to children with splenomegaly (51.22 pg/ml) (Table No.13). However this difference in B₁₂ level in relation to splenomegaly was found to be statistically significant. Mean serum folate level was higher in children with splenomegaly (17.74 ng/ml) as compared to children without splenomegaly (16.25 ng/ml) (Table No.26). This difference in folate level in was however not found to be statistically significant. Siroliya V et al.¹² found that splenomegaly observed in 6 (20%) cases.

CONCLUSION

Vitamin B₁₂ and folate were reduced in children with generalized tremors, psychomotor retardation, delayed milestones, presence of hepatomegaly and splenomegaly. All children with Infantile Tremor Syndrome should be screened for vitamin B₁₂ and folate levels, high risk children should be supplemented B₁₂ and folic acid.

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