Infantile tremor syndrome: Role of Vitamin B12 revisited

Rajesh Gupta1, Jagdish Mandliya2, Pavan Sonker3, Vandana Patil2, Manish Agrawal4, Ashish Pathak2,5
1Department of Pediatrics, Chirayu Medical College, Bhopal, Departments of 2Pediatrics and 3Biochemistry, R. D. Gardi Medical College, Ujjain, Madhya Pradesh, 4Department of Pathology, Chandulal Chandraker Memorial Medical College, Durg, Chhattisgarh, India, 5Department of Public Health Sciences, Global Health (IHCAR), Karolinska Institutet, Stockholm, Sweden

Address for correspondence: Dr. Rajesh Gupta, Department of Pediatrics, II Floor, Chirayu Medical College and Hospital, Bhopal - 462 030, Madhya Pradesh, India. E-mail: drrajesh93@gmail.com

ABSTRACT

Objective: To study the role of Vitamin B12 as an etiological factor in patients of infantile tremor syndrome (ITS).

Methods: Twelve consecutive admissions of children diagnosed clinically as ITS were assessed. Assessment was done using a predefined pro forma to document patient demographic factors, general examination, systemic examination as well as relevant hematological and biochemical investigations.

Results: Out of the 12 cases of ITS, 6 were males and 6 were females. Two cases had serum B12 levels below reference values, five had levels in low normal range, and remaining five had normal values.

Conclusions: Role of Vitamin B12 deficiency as an etiological factor in the patients of ITS is inconclusive.

Key words: Development, infantile tremor syndrome, nutrition, Vitamin B12

Introduction

The infantile tremor syndrome (ITS) is a clinical state characterized by tremors, anemia, pigmentedary skin disease, regression of mental development, and hypotonia of muscles in a plump-looking child.[1] Earlier published research had documented causal association of ITS with Vitamin B12 deficiency among B12-deficient mothers and their exclusively breast-fed babies.[2] However, decreased serum level of Vitamin B12 and the therapeutic, clinical, and hematological responses following administration of B12 have inconsistent response in patients of ITS.[2] Kaul et al. suggested that Vitamin B12 deficiency might be an important factor in the biochemical process resulting in ITS.[3] Sachdev et al. have reported macrocytic anemia in 58 out of 80 cases of ITS.[4] Pohowalla et al. did not notice megaloblastic anemia in their study.[5] In another study, megaloblastic bone marrow was found in one-fourth of cases, but none of the cases had shown any clinical improvement after 15 days of the treatment with Vitamin B12.[6] In another study, Vitamin B12 was administered intramuscularly in doses of either 50 or 100 µg in 17 cases of ITS. The tremors disappeared in 1–2 weeks in all the cases those received 100 µg/day of Vitamin B12, while in cases that received 50 µg/day of Vitamin B12, the tremors disappeared within 4 days to 1 month. In those patients where Vitamin B12 was not administered, the tremors continued throughout the 2–3 weeks period of hospitalization.[7]

In a case report of association of ITS with central pontine myelinolysis, the serum Vitamin B12 levels were within normal limits.[8] However, Goraya and Kaur observed low...
Vitamin B12 levels in 8 out of 16 ITS cases. In resource-rich countries, Vitamin B12 deficiency has been documented in infants with abnormal movements. Emery et al. reported below-normal serum Vitamin B12 levels in two infants presenting with delayed developmental milestones and tremors. Furthermore, Ozer has described two cases with cobalamin deficiency that developed tremors after giving injection cyanocobalamin. The tremors were reported to regress spontaneously within 3–6 weeks. Thus, the definite role of Vitamin B12 in the etiology of ITS is still uncertain. This communication is based on a study to find out the proportion of cases of ITS in the tremor phase having Vitamin B12 deficiency.

Methods

This cross-sectional study was done among patients admitted in Department of Pediatrics, R. D. Gardi Medical College, Ujjain, Madhya Pradesh, during the period of April 2013 to August 2014. A total of 12 cases were included in the study based on clinical definition of ITS. A written informed consent was taken from the parents of all studied participants. The Institutional Ethics Committee, R. D. Gardi Medical College, Ujjain, approved the study. A predesigned pro forma (questionnaire) was filled for all patients included in the study. The pro forma included complete patient profile, general examination, systemic examination, and hematological and biochemical investigations. Biochemical investigations were done in collaboration with the Department of Biochemistry and included serum Vitamin B12, folate, magnesium, phosphates, albumin, and globulin levels. Enhanced chemiluminescence immunoassay using Vitros ECI machine (Refurbished by Johnson & Johnson do Brasil Industria e Comercio de Produtos para Saude Ltda. Version 3 Year of refurbishment 2012) was used to assay serum Vitamin B12, folate, magnesium, phosphates, albumin, and globulin levels. The association of tremors with serum Vitamin B12 was assessed. Reference range for serum Vitamin B12 levels in the study was 239.0–931.0 pg/ml with reportable dynamic range <159.0 and >1000.0 pg/ml. The reference ranges observed for other biochemical parameters done are mentioned in Table 1. A complete blood count of each patient with peripheral smears and anemia typing was also done with the help of five-part analyzer. All patients received treatment as per the WHO guidelines for underweight children. Patients with documented B12 deficiency received intramuscular injection of Vitamin B12 1000 µg in divided dosage over three consecutive days followed by oral preparation.

Results

Table 1 shows the age, sex, findings of peripheral blood smear, serum Vitamin B12, serum folate, serum magnesium, and serum phosphate levels. Mothers of all participants are vegetarian and are from rural background. Only two cases (2/12, i.e., 16.6%) had serum B12 levels below reference values, five cases had levels in low normal range (<300.0 pg/ml), and rest five had normal values. Serum folate levels and serum magnesium levels in all the cases were normal. Serum phosphate level was below normal in six cases. The mean duration of tremors was 24 days in ITS patients in our study.

Discussion

Etiology of ITS was postulated to be multifactorial in the past, but recently a consensus is developing toward association with Vitamin B12 deficiency. This is because the chief component of the neurologic syndrome of cobalamin deficient infants is neurodevelopmental regression and involuntary movements which are also observed in ITS patients. In India, children diagnosed with ITS are most often exclusively breast-fed and their mothers are vegetarian, with little or no milk intake. These facts support the hypothesis of Vitamin B12 deficiency as an etiology factor. Indian researchers have studied the role of Vitamin B12 deficiency and type of anemia in ITS patients. Goraya observed 15 ITS patients out of which 13 were megaloblastic anemia in peripheral blood smears. In our study, only 3 ITS cases showed macrocytic picture on peripheral blood smear out of which 2 had below-normal serum Vitamin B12 levels. Bone marrow aspiration was not considered as the gold standard for the present study as serum Vitamin B12 levels could be done in our laboratory. Pohowalla et al., in their case series, did not notice megaloblastic anemia in any of the participants. In another study, megaloblastic bone marrow was found in 23% cases of whom 66% were put on Vitamin B12 in the dose of 100–200 µg/day, but none of them showed any clinical improvement after 15 days of treatment. We also treated our B12 deficient ITS patients with parenteral Vitamin B12 in the dose of 1000 µg in divided doses followed by oral therapy. There was no reduction in duration of tremors.

The association of tremors with serum Vitamin B12 was investigated in twenty patients by Bajpai et al. None of the infants with tremors had serum Vitamin B12 levels below normal (<100 µg/ml), 4 had between 100 and 280 µg/ml, while remaining 16 had a range of 180–900 µg/ml. Administration of parenteral Vitamin B12 failed to change the course and duration of tremors. However, the serum Vitamin B12 levels increased on weekly estimation.

Goraya observed 15 ITS patients out of which 13 were Vitamin B12 deficient, and role of Vitamin B12 deficiency in ITS was strongly emphasized. Other workers have recommended early treatment with Vitamin B12 for rapid reversal of neurological signs in ITS patients. However, the present study does not support the above conclusion.
The present study establishes that Vitamin B12 is not the sole factor behind tremors in ITS. The therapeutic role of Vitamin B12 is still a moot question. Additional studies using available technology are needed to search for a definitive etiology of ITS.

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Conflicts of interest

There are no conflicts of interest.

References

1. Gupta BD, Maheshwari RK, Miglani N. Infantile tremor syndrome. Indian J Pediatr 1978;45:221-8.
2. Goraya JS, Kaur S. Infantile tremor syndrome – Down but not out. Indian Pediatr 2015;52:249-50.
3. Kaul KK, Prasan N, Chowdhry RM. Some clinical observations and impressions on a syndrome of tremors in infants from India. J Pediatr 1963;63:1158-66.

Table 1: Hematological and biochemical investigations results of infantile tremor syndrome cases

| Patient | Age (months) | Sex | Peripheral smear findings | Serum B12(a) (pg/ml) | Serum folate(b) (ng/ml) | Serum magnesium(c) (mg/dl) | Serum phosphate(d) (mg/dl) |
|---------|--------------|-----|----------------------------|----------------------|-------------------------|---------------------------|---------------------------|
| 1       | 10           | Male| Normocytic normochromic RBC's | 738                  | >20                     | 2.6                       | 6.8                       |
| 2       | 10           | Female| Predominantly microcytic, hypochromic elliptocytes and pencil cells | 585                  | >20                     | 1.7                       | 3.6                       |
| 3       | 24           | Male| Microcytic, normochromic anemia | 296                  | 13.7                    | 2.5                       | 5.9                       |
| 4       | 11           | Female| Anisocytosis, target cells | 653                  | >20                     | 2.4                       | 4.3                       |
| 5       | 15           | Male| Predominantly macrocytic, anisopoikilocytosis | <159               | 19                      | 2.6                       | 4.1                       |
| 6       | 5            | Male| Normocytic, mild hypochromia, and anisocytosis | 256                  | 7.2                     | 2.4                       | 5.1                       |
| 7       | 7            | Female| Mainly microcytic hypochromic, normochromic, few polychromatotic macrocytes | 204                 | >20                     | 1.9                       | 5.9                       |
| 8       | 8            | Female| Normocytic, mild hypochromic | 253                  | >20                     | 2.4                       | 4.0                       |
| 9       | 8            | Female| Mainly normocytic, normochromic, mild lymphocytosis | 297                 | >20                     | 2.6                       | 4.5                       |
| 10      | 9            | Male| Anisopoikilocytosis, dimorphic blood picture, polychromasia, target cells, nRBCs present | 407                 | >20                     | 2.4                       | 5.2                       |
| 11      | 13           | Female| Moderate polychromasia, mild anisopoikilocytosis, mainly normocytes, tear drop cells and target cells present | 174                 | 12.7                    | 2.2                       | 3.7                       |
| 12      | 8            | Female| Anisopoikilocytosis, macrocytes and microcytes, dimorphic cells, thrombocytopenia | 200                 | >20                     | 2.3                       | 3.7                       |

Normal reference values: a Serum vitamin B12: 200.0-835.0 (pg/ml), b Serum folate: 5.0-21.0 (ng/ml), c Serum magnesium: 1.7-2.3 (mg/dl), d Serum phosphate: 4.5-6.7 (mg/dl). nRBC's: Nucleated red blood cells, ITS: Infantile tremor syndrome
4. Sachdev KK, Manchanda SS, Lal H. The syndrome of tremors, mental regression and anaemia in infants and young children: A study of 102 cases. Indian Pediatr 1965;2:239-51.
5. Pohowalla JN, Kaul KK, Bhandari NR, Singh SD. Infantile meningo-encephalitic syndrome. Indian J Pediatr 1960;27:49-54.
6. Agrawal SP, Katiyar GP. Infantile tremor syndrome. Pediatr Clin 1972;7:203.
7. Deshpande TV, Ingle VN. Tremor syndrome in children. Indian Pediatr 1969;6:550-6.
8. Datta K, Datta S, Dutta I. Rare association of central pontine myelinolysis with infantile tremor syndrome. Ann Indian Acad Neurol 2012;15:48-50.
9. Emery ES, Homans AC, Colletti RB. Vitamin B12 deficiency: A cause of abnormal movements in infants. Pediatrics 1997;99:255-6.
10. Ozer EA, Turker M, Bakiler AR, Yaprak I, Ozturk C. Involuntary movements in infantile cobalamin deficiency appearing after treatment. Pediatr Neurol 2001;25:81-3.
11. Ashworth A, Khanum S, Jackson A, Schofield C. General principles for routine care (the 10 steps). In: Guidelines for the Inpatient Treatment of Severely Malnourished Children. New Delhi: World Health Organization; 2003. p. 10-20.
12. Bajpai PC, Misra PK, Tandon PN. Further observations on infantile tremor syndrome. Indian Pediatr 1968;5:297-307.
13. Dalal NJ, Udani PM, Parekh JG. Megaloblastic anaemias in infancy and childhood. Indian Pediatr 1969;6:255-62.
14. Goraya JS. Acute movement disorders in children: Experience from a developing country. J Child Neurol 2015;30:406-11.