Infantile tremor syndrome: A review and critical appraisal of its etiology

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ABSTRACT

Infantile tremor syndrome (ITS) is defined by the tetrad of pallor, developmental delay/regression, skin pigmentation, and brown scanty scalp hair. Involuntary movements in the form of tremors supervene in the natural course of the illness in a significant number of cases. The disorder occurs in exclusively breast-fed infants of vegetarian mothers belonging to economically deprived sections of society. Most of the children eventually recover but are frequently left with long-term cognitive and language neurodeficits. ITS continues to be seen in clinical practice, but there has been no consensus on its causation. Last comprehensive review was published in 1987 describing the ITS as a syndrome of unknown or multiple etiologies. Several important papers have been published since then. This review attempts to provide comprehensive and up-to-date information on the subject incorporating recently published studies. In the end, the issue of etiology is objectively re-examined in the light of available evidence some of which has been published in recent years.

Key words: Etiology, infantile tremor syndrome, vitamin B₁₂ deficiency

Introduction

Dikshit from Hyderabad, in 1957, reported a case series of 25 infants with constellation of symptoms and signs characterized by pallor, skin hyperpigmentation, and regression of neurodevelopment.[1] The infants were exclusively breast-fed by strictly vegetarian mothers belonging to the lower middle class. Moderate to severe anemia with tendency to macrocytosis was present in all. Bone marrow examination in one such case revealed megaloblastic change. The infants were treated with liver extract alone or in combination with “B complex factor” or vitamin B₁₂. The response was uniformly good in all the cases and began as early as 3rd or 4th day. The author called this condition “Nutritional Dystrophy with Anemia.”

Soon several reports emanated from other parts of the country describing cases with similar symptomatology thus confirming clinical existence of this disorder across the country. More than 30 papers were published between 1957 and 1979.[2] The research interest in ITS began to decline in the early 80s with publication of fewer and fewer reports in the following years. The subject was last comprehensively reviewed in 1987,[2] describing ITS to be a disorder without any established etiology. A number of important papers have been published since then. This review attempts to provide comprehensive and up-to-date information on the infantile tremor syndrome (ITS) to the academic and practicing clinicians and also to critically analyze the issue of its etiology.

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Literature Search

For the purpose of this review, we searched Medline and Google Scholar for identifying studies on ITS. Additional studies were identified from the references of the retrieved articles as well as from the pediatric textbooks published from India. Finally, hand search of the Indian Pediatrics and the Indian Journal of Pediatrics was done to complete the search process.

Synonyms

The disorder has been reported under various other names, namely, nutritional dystrophy and anemia,⁷ infantile meningoencephalitic syndrome,⁵ vitamin B₁₂ deficiency in Indian infants,⁶ megaloblastic anemia of infancy and vitamin B₁₂,⁵⁰ syndrome of tremors in infants,¹⁰ syndrome of tremors, mental regression and anemia,¹¹ and tremors, mental and physical retardation, light colored hairs and anemia in malnourished children.⁷ Since, the tremors are the dominant recognizable feature of this disorder and affect children below 2 years of age, the term infantile tremor syndrome or ITS gained popularity.¹³

Epidemiology

Incidence and prevalence

Exact incidence of ITS is not known but hospital statistics has revealed 0.77%–2.5% of the pediatric ward admissions to be due to this disorder.¹¹,¹⁶–¹⁸ The syndrome has been reported from Punjab, Himachal Pradesh, Jammu and Kashmir, Uttar Pradesh, Bihar, West Bengal, Madhya Pradesh, Tamil Nadu, Andhra Pradesh, Karnataka, Rajasthan, Gujarat, Maharashtra, New Delhi, and Chandigarh. Cases of ITS are generally encountered throughout the year.¹⁷ Some authors have found more cases of ITS during summer¹³,¹⁴,¹⁶,¹⁷ and winter/rainy seasons.⁴¹

Age and gender

ITS commonly affects infants between 6 and 24 months of age though infants younger or older than this (age range 40 days to 36 months) have been reported. There is male preponderance in the majority of the studies.¹¹

Socioeconomic status

Most of the infants with ITS come from poor families.

Maternal diet and nutritional status

Mothers of the infants with ITS are mostly vegetarian and their diet devoid of animal foods including milk, resulting to a large extent from poverty and ignorance. Only rarely, has the vegetarianism been a matter of personal choice. Occasionally, mothers have been reported to have underlying pernicious anemia.¹⁰ Maternal health in many studies has been stated to be poor with multiple nutritional deficiencies,⁶,⁸,¹²,¹⁴,¹⁶ while others have provided no information on maternal diet and nutritional health.⁷,¹⁰,¹¹,¹³,¹⁷

Infant feeding

Almost all the cases of ITS occur in exclusively breast-fed infants. Commonly weaning has never been initiated because of lack of appropriate guidance. Equally common is weaning failure due to anorexia, refusal to solid foods, and spitting.¹¹,⁵,¹⁶,¹⁹ Even when weaning has been started, foods of animal origin including top milk are missing from the diet⁵,¹⁸ or given in insufficient quantity.¹²,¹⁴,¹⁹

Clinical Manifestations

Nutritional status of the infants

The presence of pallor, skin and hair changes, and dull apathetic look that the infants with ITS exhibit is quite reminiscent of kwashiorkor. In a typical scenario, affected infants look plump with preserved subcutaneous fat.¹¹,⁸,¹⁰,¹¹,¹³ Others have reported failure to thrive and wasted or marasmic look.⁴,⁵,¹⁰,¹²,¹⁵,²⁰ In any case, growth parameters are normal at birth and for the first 5–6 months of age. Later growth faltering occurs due to inadequate feeding caused by continued exclusive breastfeeding. Refusal to solid foods, anorexia, and intercurrent infections further aggravate the nutritional imbalance. In addition to anemia, infants with ITS frequently manifest multiple micronutrient deficiencies in the form of angular chelitis, stomatitis, and glossitis,¹¹,⁶,¹³,¹⁴,¹⁷ Rickets,¹¹,¹³,¹⁷,¹⁹ scurvy,¹⁹ and edema¹²,¹⁶,¹¹–¹⁵ have also been reported as has been Vitamin A deficiency.¹²,²⁰ Not surprisingly, most of the researchers do agree that infants with ITS are malnourished.

Pallor

Almost all infants with ITS look pale. The pallor is mostly due to anemia which is likely nutritional in origin.²¹

Skin and hair changes

Skin and hair changes are present in almost all the infants with ITS.²¹ Skin shows darkening or hyperpigmentation of dorsa of hands and feet which may be especially accentuated at the knuckles causing so-called \"knuckle pigmentation.\" Others may show diffuse honeycomb or reticulate pattern of hyperpigmentation affecting trunk as well as limbs [Figure 1]. Scalp hair displays variable depigmentation and appears rough and lusterless. Hair growth is sparse [Figure 2], and they are easily pluckible. Eyebrows may be similarly affected.²¹,²²

Neurodevelopment

Infants with ITS are born without any prenatal or perinatal complications and display normal neurodevelopment till the first 4–6 months of age.¹¹,⁸,⁹,²² Developmental slowing then sets in, and is followed by developmental regression, if
corrective measures are not instituted. The infant gradually becomes less active and withdrawn with loss of interest in surroundings. His/her interaction with parents and others decreases. Somnolence and lethargy supervenes but seldom do these infants lapse into coma.[22] Intercurrent illness may trigger rapid downhill course at any time during the course of illness.[1,4,5,8,22] Seizures are uncommon and may occur any time during the course of the disease.[5,13,22]

**Tremors**

Tremors are one of the most characteristic features of ITS allowing instant recognition of the syndrome by the experienced clinicians. Tremors are generally absent early in the course of illness, the pre-ITS stage.[2] Tremors tend to be coarse and have jerky (myoclonus-like) character. Onset is usually focal from one of the upper extremities with rapid progression to generalized involvement. Sudden onset of generalized tremors is not uncommon.[10,11,13] Even when generalized, tremors have asymmetric and multifocal appearance. Involvement of facial, labial, lingual, and laryngeal musculature is an unmistakable sign of ITS. Laryngeal involvement renders a distinctive tremulous character to the vocalization/cry in these infants which has been likened to the bleating of a goat.[1,6,10,11,13] Tremors may be intermittent initially, brought out only by crying, excitement, or physical stimuli. Later tremors become constant throughout the day but disappearing in sleep.[1,10,12,15,20] In severe cases, tremors may persist during sleep though at reduced intensity.[10,11,14,15] Tremors at times have been triggered or made worse by vitamin B12 treatment.[1,10,22,23] Other involuntary movement such as chorea or myoclonus have been described, often coexisting with tremors.[11,13,22]

**Neurological status**

Infants with ITS appear dull and apathetic showing little interest in the surroundings. They lie listlessly, becoming irritable when handled. Expressionless face, vacant stare, and open mouth with drooling are characteristic.[2,22] Spontaneous movements may be reduced (hypokinesia).[13] Swallowing dysfunction is sometimes present contributing to feeding difficulties. Majority of the infants have hypotonia with retained or exaggerated tendon reflexes. Hypertonia and extrapyramidal rigidity are less common.[2,22] No sensory deficits have been reported.

**Systemic findings**

Usually, there are no systemic symptoms and signs unless the course of illness has been complicated by intercurrent infections, usually of the gastrointestinal or respiratory tract.[7,10,11,13,17,20] Infections, in fact, may be one of the reasons to bring the child to medical attention.[4,13,20,15] Mild hepatomegaly with or without splenomegaly is frequently reported sign in ITS.[1,9,11,15,20] Congestive cardiac failure secondary to severe anemia may occur.

**Diagnosis**

A typical case of ITS is an exclusively breast-fed infant (of a strictly vegetarian mother) who presents with developmental regression and tremors. Often, the infant has been unwell for several weeks to months with progressive lethargy, failure to thrive, feeding difficulties, and developmental slowing. On examination, the child looks pale and has dull expressionless face, vacant stare, and drooling.[2,22] Skin shows generalized reticulate or diffuse dark pigmentation with peripheral accentuation over the hands and feet [Figure 1]. Scalp hair is brown and scanty [Figure 2]. The infant appears to be seized by constant and often distressing jerky involuntary movements affecting arms, legs, face, and tongue. Peculiar tremulous cry akin to bleating of a goat is generally audible from distance. When all these features are present, clinical diagnosis of ITS can be made beyond doubts.[2,22]

**Laboratory Investigations**

Laboratory investigations in the past have been undertaken to find out the etiology of this syndrome. The extent of investigations has been limited in most of the studies due to
lack of resources. Inferences made on the basis of insufficient laboratory data have contributed greatly to the controversy surrounding the etiology of ITS (vide infra).

Hematological
Mild to moderate anemia is almost always present in infants with ITS. This is, however, not universal finding as some infants display normal hemoglobin. Total leukocyte count is variable and may be affected by associated infectious illness. Leukopenia has sometimes been reported. Platelet counts are also variable. Rarely, pancytopenia is detected. While dimorphic peripheral smear has been reported by many authors, others have stressed the predominance of macrocytic morphology of the red blood cells. Bone marrow findings have varied from predominantly normoblastic through dimorphic to predominantly megaloblastic.

Biochemistry
Blood sugar, calcium, renal and liver function tests are mostly normal or do not point to specific etiology. Low serum albumin has been found in small number of infants with ITS in many studies. Deficiency of magnesium and zinc has been reported. Garewal et al. found iron deficiency in almost 50% of the infants with ITS. Examination of cerebrospinal fluid (CSF), urine, and stool has mostly been normal. Urinary amino acids in one study showed no abnormal pattern of excretion.

Low serum vitamin B12 is the laboratory diagnostic hallmark of vitamin B12 deficiency. Several studies including many published in recent years have shown unequivocal evidence of vitamin B12 deficiency in ITS. Only two studies have reported normal serum vitamin B12 levels in infants with ITS. Serum and red cell folate when measured have been normal. Mothers of the affected infants with ITS also have low vitamin B12 in serum as well as in the breast-milk. We found low maternal serum vitamin B12 to be a useful indirect measure of vitamin B12 deficiency in infants who have had normal serum vitamin B12 due to prior administration of vitamin B12.

Invasive investigations have been reported only in a few infants with ITS. Biopsies of skin, liver, muscle, nerve, and rectum have either been normal or have revealed only nonspecific changes of no etiological significance. Brain biopsy in one study has revealed no specific histopathological changes to suggest an etiology.

Neuroimaging
Initial studies with pneumoencephalography in the precomputed tomography/magnetic resonance imaging (CT/MRI) era showed decreased brain substance. These findings of cerebral atrophy but also showed delayed myelination in some cases. Subdural effusion and central pontine myelinolysis have been reported in one case each.

Electrophysiological studies
Electroencephalographic changes have only occasionally been reported and no definitive conclusions can be drawn. Nerve conduction studies, brainstem auditory evoked responses, and visual evoked response have not been reported.

Treatment and Therapeutic Response
In the absence of agreement on etiology, treatment of ITS has remained controversial and suboptimal at best. Many authors have treated ITS infants symptomatically with various combinations of dietary modification, multivitamins, and mineral supplements and reported gradual recovery over weeks to months irrespective of the treatments. Others have reported successful treatment with dietary modification along with the treatment of anemia with folic acid, vitamin B12, and iron, indicating that dietary deficiency of some kind was likely responsible for the manifestations of the syndrome.

Successful treatment with vitamin B12 alone resulting in dramatic improvement in symptoms has been consistently reported by many authors. Dikshit administered liver extract alone or in combination with B complex factor or B12 to the infants with ITS and observed rapid hematological and neurological recovery. Similar response to the treatment was obtained by Jadhav et al. with oral vitamin B12 in doses as low as 0.1 µg/day. Srikantia and Reddy successfully used a novel method of treating infants with ITS through augmenting the vitamin B12 content of breast-milk by giving a single intramuscular dose of 50 µg vitamin B12 to the mothers. Similarly, encouraging results have been described by Deshpande and Ingle and in many recent studies. In all these studies, patients were treated with vitamin B12 alone and a uniform pattern of response was observed. Initial change was observed within 48–72 h of treatment in the form of improved general activity and responsiveness. The infants became more active, playful, and social smile returned. Appetite improved and the aversion to weaning food disappeared. The infants started accepting the same food which was once refused or spit. The lost developmental milestones began to return. Tremors also started to disappear within a week in most of the infants and were gone by 3–4 weeks in all. In some cases, tremors appeared first after treatment with vitamin B12 had been started. Hematological recovery was also observed within 5–7 days. Skin pigmentation resolved in about 2–4 weeks. The hair changes were slow to occur, generally taking several months to years for complete recovery.

On the other hand, certain authors have reported results to the contrary and observed that tremors did not disappear faster in those who were given vitamin B12 than those who were...
not, prompting these authors to negate vitamin $B_{12}$ deficiency as the cause of ITS.\cite{10,11,13}

Supportive care in the form of intravenous fluids to treat and prevent dehydration, antibiotics for associated infections, and other medications to treat associated complications are commonly used during acute phase. Tremors have been treated with propranolol,\cite{35} sedatives,\cite{7,28} carbamazepine,\cite{30} and emetine,\cite{21} but the role of these treatments is difficult to assess in the absence of controlled trials.

**Prognosis**

Although most of the infants ultimately recover, neurodevelopmental deficits, especially in cognitive and language skills, often persist in the long-term.\cite{13,5,7,12,22,36} Mortality in ITS is very rare and has resulted from the inter-current infections.\cite{10,11,13,36}

**Etiological Considerations**

Etiology of the disorder has remained a subject of intense research and controversy. The role of infectious, nutritional, toxic, or metabolic agents in the etiology of ITS has been speculated.\cite{2} Authors of many recent publications\cite{18,26,31,32} and Indian textbooks of pediatrics continue to regard ITS as a disorder of unknown etiology.\cite{15,30} In the absence of agreement on its etiology, treatment of ITS has remained suboptimal at best. In the following paragraphs, we critically appraise the issue of etiology of ITS and also explore the reasons for controversy.

**Infections**

Pohowalla *et al.*\cite{17} called this entity as infantile meningoencephalitis, but no virus or other microbial agent has ever been isolated. Investigations, such as CSF analysis\cite{7,10,12,15,17,20,28} brain biopsy,\cite{29} and more recently neuroimaging,\cite{31} have not pointed to any infectious agent(s).

**Toxic/Metabolic**

No evidence is available to implicate any known or unknown toxic substance in the causation of ITS, and this hypothesis has therefore largely been discarded. One study reported aminoaciduria in ITS but found no specific abnormalities.\cite{27} From a clinical point of view, hereditary disorders of cobalamin metabolism can have similar clinical presentation. However, detailed investigations for inborn errors of metabolism have not been carried out in any of the studies. Lack of family history, clinical course of the disease with ultimate recovery, and no relapse of symptoms also do not favor genetic or neurometabolic etiology.

**Unknown or Multiple Etiologies**

Many authors believe that ITS is a disorder of self-limited nature and resulted from some yet unidentified causative factor(s).\cite{10,14,17,27}

**Nutritional deficiency**

It is beyond any reasonable doubt that infants with ITS are malnourished, a fact that is agreed on by almost all the researchers.\cite{1,3,6,8,9,11,12,15,16,20} Of all the specific nutrients, deficiencies of zinc and magnesium have been found in ITS,\cite{24,26} but the clinical picture associated with these deficiencies bears no resemblance to that of ITS. These deficiencies are therefore likely incidental to the malnutrition that is observed in ITS rather than being causative. Similarly, hypalbuminemia, hypocalcemia, iron deficiency, and fatty liver change in ITS are part of the malnutrition spectrum.

**Vitamin B$_{12}$ deficiency**

Most of the controversy concerning the etiology of ITS has centered on the role of vitamin B$_{12}$ deficiency in the disorder. There, now, exists a large body of literature which provides robust epidemiological, clinical, and laboratory evidence in favor of vitamin B$_{12}$ deficiency as the cause of ITS.

Epidemiologically, mothers of infants with ITS are vegetarian in their dietary habits and therefore are at risk of vitamin B$_{12}$ deficiency. Studies have repeatedly confirmed low vitamin B$_{12}$ in the maternal serum\cite{5,6,15} and in the breast-milk.\cite{8,9} Infants born to these mothers have suboptimal vitamin B$_{12}$ stores at birth which get further depleted during infancy in the absence of external supplementation.\cite{19} From a clinical viewpoint too, the clinical symptoms and signs of ITS are similar to those of nutritional vitamin B$_{12}$ deficiency in infants.\cite{40,41}

Much of the controversy surrounding the role of vitamin B$_{12}$ deficiency in the etiology of ITS has resulted from the interpretation of the laboratory findings as they pertain to vitamin B$_{12}$ deficiency. Many studies excluded vitamin B$_{12}$ deficiency in ITS solely on the basis of lack of macrocytosis in peripheral blood and megaloblastic erythropoiesis in the bone marrow, and serum vitamin B$_{12}$ was not measured.\cite{13,14,15,17,27} Incidentally, these studies were conducted in general hospitals or other places with no access to vitamin B$_{12}$ testing. It is well known that neurological manifestations of vitamin B$_{12}$ deficiency can occur in the absence of concomitant hematological changes, the so-called hematological-neurological dissociation.\cite{19,9} Estimation of serum vitamin B$_{12}$ is therefore necessary to diagnose or exclude vitamin B$_{12}$ deficiency. In cases with borderline or functional vitamin B$_{12}$ deficiency, serum homocysteine levels, methylmalonic acid, and holotranscobalamin are more sensitive measures of vitamin B$_{12}$ deficiency.\cite{42}

On the other hand, wherever attempts have been made to determine serum vitamin B$_{12}$ in ITS, low serum levels of
vitamin $B_{12}$ have consistently been found.$^{1,4,8,9}$ JadHAV et al., in 1962, were the first to demonstrate low serum vitamin $B_{12}$ in infants with ITS, a finding later corroborated by Srikanta and Reddy in 1967.$^{10}$ Several years later in 1988, Garewal et al.$^{11}$ in their elegant study demonstrated low serum vitamin $B_{12}$ in 20/23 (87%) of the infants with ITS. Twenty of 23 infants had megaloblastic erythropoiesis. In 10 patients including three with normoblastic erythropoiesis, cellular evidence of vitamin $B_{12}$ deficiency was revealed by the deoxyuridine suppression test performed on the bone marrow cultures. Levels of vitamin $B_{12}$ and its transporter protein transcobalamin II in CSF were reduced suggesting the causal role of vitamin $B_{12}$ deficiency in ITS.

With the easy availability of laboratory testing of vitamin $B_{12}$ testing now, several recent studies have reaffirmed vitamin $B_{12}$ deficiency in ITS. Jain et al.$^{12}$ described vitamin $B_{12}$ deficiency in infants who had presented with developmental delay or regression, pallor, and knuckle pigmentation. They were exclusively breastfed by vegetarian mothers. Low serum vitamin $B_{12}$ was found both in infants as well as their mothers. Sirolia and Arya$^{13}$ found low vitamin $B_{12}$ in 80% of their infants with ITS. We recently reported low serum vitamin $B_{12}$ in 12 of the 21 infants with ITS.$^{22}$ Of the 9 infants with normal levels, 7 had received vitamin $B_{12}$ before referral but they had other evidence of vitamin $B_{12}$ deficiency in the form of macrocytosis and low maternal serum vitamin $B_{12}$.

Two studies in this regard deserve special mention. Kaul et al.$^{23}$ measured serum vitamin $B_{12}$ in 5 infants with ITS. Three (60%) infants had low serum vitamin $B_{12}$ (<100 µg/ml). Serum vitamin $B_{12}$ was also measured in 4 mothers and 2 (50%) of them had low serum vitamin $B_{12}$. In another study by these authors,$^{41}$ which appears to be an updated version of the previous study,$^{23}$ low serum vitamin $B_{12}$ was documented in 3 (27%) of the 11 infants and 7 (100%) of the 7 mothers. The authors concluded that vitamin $B_{12}$ deficiency was not present! No explanation for low maternal serum vitamin $B_{12}$ was offered. Bajpai et al.$^{11}$ measured serum $B_{12}$ in 20 of the 134 infants with ITS and none had low serum vitamin $B_{12}$. This is the only study reported to have normal levels of serum vitamin $B_{12}$ in ITS, although only a small number (15%) of children were tested in this series, and serum vitamin $B_{12}$ values for individual infants were not mentioned.

Assessment of response to treatment with vitamin $B_{12}$ has also not been without disagreement largely because different studies chose different criteria to assess the therapeutic response. Some studies chose disappearance of tremors as the indicator of positive response and found that tremors did not abate faster in children who were treated with vitamin $B_{12}$ than those who were not.$^{10,11,13,14,23}$ On the other hand, studies reporting good response to treatment with vitamin $B_{12}$ found entirely a different pattern of response following treatment with vitamin $B_{12}$. Improvement in general activity and responsiveness appeared within 48–72 h of treatment followed by return of social smile and oral intake. Lost developmental milestones were regained. The tremors tended to abate by the end of 1st week and were generally gone by 3–4 weeks in the majority.$^{1,4,8,9}$ This pattern of therapeutic response to vitamin $B_{12}$ in ITS is similar to that reported in the infants with vitamin $B_{12}$ deficiency.$^{40}$

Interestingly, infants with megaloblastic anemia due to vitamin $B_{12}$ deficiency have been reported to have symptoms and signs consistent with ITS$^{44,49}$ but these studies apparently escaped attention of ITS researchers. Mittal and Agarwal$^{43}$ described 52 young children (mean age 14.9 months) with megaloblastic anemia. Pallor was present in 96% while 77% had skin hyperpigmentation, 67% developmental delay, and 43% hypotonia. Tremors were noted in 8%. Kumar et al.$^{48}$ retrospectively studied the incidence of ITS in children with megaloblastic anemia due to vitamin $B_{12}$ deficiency and found that 16 (48.4%) out of 33 children with megaloblastic anemia due to vitamin $B_{12}$ deficiency had clinical features consistent with ITS. A Study by Chandra et al.$^{47}$ is also very significant in this regard. Authors described 51 children with nutritional megaloblastic anemia caused by deficiency of vitamin $B_{12}$ and/or folic acid. Four had tremors at presentation while 6 additional children developed tremors following treatment with vitamin $B_{12}$. Tremors were initially seen in the hands and feet and became generalized in 5. Three cases developed tremors of the tongue, and tremulous cry was noted in 2. The tremors subsided during sleep. The tremors eventually resolved in 5–11 days. The mean age of the children who developed tremors was 15.8 months.

It is now easy to understand that infants with vitamin $B_{12}$ deficiency can have predominantly hematological (megaloblastic anemia) or predominantly neurological (ITS) manifestations.$^{19}$ Quite often both coexist in the same patient. Uncommonly infants manifest with purely hematological manifestations in the absence of concomitant neurological manifestations and rarely vice versa may be true. This dissociation between neurological and hematological features is a well-known phenomenon in vitamin $B_{12}$ deficiency in adults. At the same time, it must be, however, born in mind that clinically apparent deficiency of vitamin $B_{12}$ deficiency is like the proverbial “tip of the iceberg” representing an extreme form of vitamin $B_{12}$ deficiency in infants, with a large number of asymptomatic or minimally symptomatic infants remaining undiagnosed. Appropriate screening methods need to be devised to detect these infants in presymptomatic phase.

To conclude, ITS is a nutritional deficiency syndrome presenting predominantly with neurological manifestations. A variable number of these children has concomitant hematological findings consistent with megaloblastic anemia. Laboratory evidence of vitamin $B_{12}$ deficiency is found whenever adequate investigations are undertaken. Treatment with vitamin $B_{12}$ produces results in rapid amelioration of symptoms. Treatment of other associated nutritional deficiencies and correction of feeding practices is necessary for comprehensive management of these infants. Since long-term cognitive and language impairments can occur, early diagnosis and treatment are necessary.
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Conflicts of interest
There are no conflicts of interest.

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