

Infantile tremor syndrome: current perspectives

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Abstract: Infantile Tremor Syndrome (ITS) is a self-limiting clinical state characterized by tremors, anemia, pigmentary skin disease, regression of mental development, and hypotonia of muscles in a plump looking child. Tremors are coarse in character, decreased or disappeared in sleep and resolves within 4–6 weeks in its natural course. Various etiological factors as infectious, metabolic, nutritional have been hypothesized but none is conclusive. Consensus is developing on the role of Vitamin B12 deficiency in children with ITS but is still debatable. Empirical management of ITS children has been tried in the absence of exact etiology considering child as undernourished. Nutritional management includes supplementation of Iron, Calcium, Magnesium, Vitamin B12 and other multivitamins. Tremors can be managed with administration of propranolol most commonly or phenobarbitone, phenytoin, and carbamazepine.

Keywords: tremors, infantile tremor syndrome, undernutrition, vitamin B12

Introduction

Infantile Tremor Syndrome (ITS) is a clinical state characterized by tremors, anemia, pigmentary skin disease, regression of mental development, and hypotonia of muscles.¹ ITS cases have been reported predominantly from the Indian subcontinent. ITS is a self-limiting clinical disorder in infants and young children.² 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. This review focuses on the evolution of the current understanding of this benign but unsolved mystery.

Method

A comprehensive literature search has been made through online search from Pubmed and Google Scholar. Much of the material, which was unavailable online was retrieved physically from central library of Post Graduate Institute of Medical Education and Research, Chandigarh, India and by directly requesting authors.

Nomenclature

ITS was first described by Dikshit AK who named it as “Nutritional dystrophy and anemia”.³

Later on this entity was frequently reported with various names as “Infantile meningo-encephalitic syndrome”,⁴ “Vitamin B 12 deficiency syndrome”,⁵ “Syndrome of tremors in infants”,⁶ “The syndrome of tremors, mental regression and anemia in infants and young children”.⁷ The current nomenclature of infantile tremor syndrome seems to be misnomer as this entity has been seen even beyond infantile age and the syndrome can present without tremors in early stage.

Age group

Sachdev et al reported 102 cases of ITS, having an age range of 5 months to 2 years, with fifty percent of cases belonging to the age group of 12–18 months.⁷ Bajpai et al reported 134 cases between age of 5 and 25 months in a study done over a period of 8 years.⁸ Ramakumar et al reported 107 ITS cases and found maximum number of cases belonged to the age group of 6–18 months.⁹ The study reported only 3 cases in 0–6 months age group and another 3 cases beyond 24 months of age.⁹ In a more recently reported study, Goraya et al reported 21 cases of ITS between the age group 6–27 months of age.¹⁰ The same author has also reported 10 cases in the age group of 5–24 months.¹¹ Thus, most cases of ITS have been reported between six months to two years of age.

Gender

Most studies have reported a male preponderance among ITS cases. Boys are twice as commonly affected as girls.^{2,9,12} However, this ratio has not been consistently reported.^{7,10}

Socio-economic status

ITS has been postulated as the disease of poor socioeconomic status mostly having some grade of under-nutrition and primarily belonging to rural areas in India.^{7,13} However, under-nutrition alone cannot explain the etiology of ITS. It is argued that children of similar age group and with identical socio-ecological background are seen in the nutrition clinics and/or wards but do not present with the clinical picture of ITS.¹⁴ Socio-economic status seems important in the evolution of ITS, but the exact role has not been deciphered.

Geographic distribution

This syndrome is largely indigenous to Indian subcontinent.¹⁵ During 1960–1970's, ITS was reported from different regions of India ie Indore,⁴ Vellore,⁵ Jabalpur,⁶ Amritsar,⁷ and Lucknow.⁸ Even in recent time this entity has been reported discretely from various geographical locations in India.^{10,11,16} Few such cases have been reported in literature from South East Asia and Africa too.¹⁷ Cases similar to ITS have also been reported from North America¹⁸ and Italy¹⁹ and Iraqi Kurdistan.²⁰

Incidence

Incidence has been observed from 0.2%–2% of paediatric hospital admissions, although the exact data on incidence

is not available.¹⁶ Also in most geographical areas, the incidence is showing a decreasing trend, but still isolated cases are being reported from India.^{10,11,16}

Seasonal variation

In a study of 67 infants with ITS admitted over a period of 4 years, majority (52%) of cases have been reported from May to July.²¹ However, some researchers found cases throughout the year with two peaks in May and November.^{22,23}

Feeding pattern

Children with ITS have been reported on breastfeeding alone, with poor complimentary feeds and are breast-fed by strict vegetarian mothers.^{7,9,24} Even if some mothers were taking a non-vegetarian diet, that was insufficient in quantity. Despite this the exact role of poor complimentary feeding and strict vegetarianism of mothers in the etiology of ITS has not been deciphered.^{7,9}

Etiology

Infections

ITS has been hypothesized to be associated with certain infections. Many children have been identified with some sort of infection preceding the onset of tremors like gastrointestinal disturbances, fever, respiratory tract infection, etc.⁷ Mishra et al made observations on brain biopsy of 19 ITS cases and found presence of inflammatory changes in meninges in six, astrocytosis in nine along with perivascular cuffing in three patients which lead to a possibility of a probable viral agent as the cause of ITS.¹⁴ They further suggested that in slow virus infections like Kuru or a prion in the Scrapie form (PrPSc).¹⁴ Scrapie astrocytic hyperplasia may be the only abnormality even in absence of any leucocytic infiltration but could not be proved.¹⁴

Metabolic factors

Depigmentation of hair and eyebrows in infants with ITS suggests defect in melanin production postulated to be resulting from transient enzyme deficiency in tyrosine metabolism. The involvement of substantia nigra might explain the involuntary movements and the parkinsonian appearance of these infants with a characteristic vacant stare, open mouth, expressionless face and tremors (Figure 1), but the exact anatomical site involved could not be confirmed in brain studies.²⁵ In another study in over 13 cases, biochemistry for serum Sodium, Potassium, Chloride, Blood urea, sugar, Aspartate Aminotransferase (AST or SGOT), Alanine



Figure 1 Showing a child with Infantile Tremor Syndrome (ITS).

Aminotransferase (ALT or SGPT) and liver biopsies done. No abnormalities were detected in these tests.¹²

Nutrition

Undernutrition has been accepted by most of the researchers as a cause of ITS^{13,26} but no specific macro or micro nutrient has been detected so far. Mathur et al have suggested the condition to be solely the result of Protein Energy Malnutrition (PEM).¹³ However, Mishra et al are not convinced with undernutrition as a cause of ITS and argue that children of similar age group and with identical ecological background are seen in the nutrition clinics and wards but do not present with the clinical picture of ITS.¹⁴

Bajpai et al noticed that although a few children could be labeled as overweight, a vast majority seemed to be within 75–100% of their expected weight, giving an impression of being well built unlike the usual physiognomy associated with low-income group patients.⁸ A study by the same author showed variable anthropometric findings in children with ITS.¹¹ The anthropometric analysis revealed that four patients had severe wasting, three had moderate wasting and one each had severe and moderate stunting out of the ten studied.¹¹ Garg et al estimated plasma proteins in 34 cases and found them to be low in 6 cases (18%) only.²⁷ Bajpai et al also estimated serum proteins and albumin in 77 cases and found them to be within normal limits in all except four cases.⁸ In a case-control study having 32 ITS cases, a comparison was done for serum Magnesium, Calcium and Zinc with undernourished children without tremors.²⁸ The study found significantly reduced levels of Magnesium in ITS cases without significant difference in the levels of Calcium and Zinc in both groups.²⁸ A case report has reported a fourteen-month-old male child with ITS and documented Zinc deficiency.²⁹ Further supportive literature for specific nutritional deficiencies is lacking.

Vitamin B12 was thought to be associated with ITS and studies have generated evidence in favor as well as against its role in ITS. Initially, Jadhav had described this entity as Vitamin B12 deficiency syndrome.⁵ Sachdev et al reported a megaloblastic bone marrow only in 11 cases out of 68 bone marrow aspirates in children with ITS however, macrocytic anemia was present in two-thirds of cases (58 out of 80).⁷ Pohowalla et al did not report megaloblastic anemia in any of the cases.⁴ Agarwal and Katiyar also found megaloblastic bone marrow only in 23% cases, of whom 66% were put on Vitamin B12 in the dose of 100–200 $\mu\text{g}/\text{day}$ but none of them showed any clinical improvement after 15 days of treatment.³⁰ At places where investigation facilities were lacking, researchers have prompted Vitamin B12's role by managing ITS cases with therapeutic doses of Vitamin B12. Deshpande and Ingle administered Vitamin B12 intramuscularly in 50–100 $\mu\text{g}/\text{dose}$ in 17 cases of ITS.²⁴ The tremors disappeared in 1–2 weeks in all the cases where the dose of B12 was 100 $\mu\text{g}/\text{day}$ while in cases who received 50 $\mu\text{g}/\text{day}$ Vitamin B12, the tremors disappeared between 4 days to 1 month.²⁴ The cases in whom no Vitamin B12 was given, the tremors continued throughout the period of hospitalization, which varied from 2 to 3 weeks.²⁴ In more recent studies, role of Vitamin B12 has also been studied and some studies support its etiology in ITS.^{31,32} Goraya observed 15 ITS patients out of which 13 were Vitamin B12 deficient, and role of Vitamin B12 deficiency in ITS was strongly emphasized by the authors.³¹ On the other hand the same author in another study found two cases with serum B12 levels below reference values, five had levels in low normal range, and remaining five had normal values out of the 12 cases of ITS.³³ Thus, the role of Vitamin B12 deficiency as an etiological factor in the patients of ITS is inconclusive.

Clinical features

Three stages of ITS have been described on the basis of history, physical examination and follow up: pre-tremor phase, tremor phase and post-tremor phase. Pre-tremor phase characterized largely by a neuromotor regression, pallor and sometimes a tremulous voice.⁸ Tremor phase appeared with sudden onset of tremors involving various parts of the body mainly extremities of hands and feet.⁸ Tremors are coarse in character, decreased or disappeared in sleep.⁷ Though the limb muscles are usually flabby to feel, however, there is presence of extrapyramidal type of rigidity on passive movements.⁷ Overall impression of children diagnosed with ITS can be described as a clinical state characterized by tremors in the form of rhythmic, coarse, twitching of the angles of eye, mouth, eyelids, and tongue

with a tremulous cry resembling the bleating of a lamb, tossing movement of the head, wriggling movements of the trunk and coarse rhythmic continuous rapid movements of varying but usually of low amplitude in the extremities, most marked in the distal parts especially the fingers along with anemia, pigmentation over extremities, regression of mental development and hypotonia of muscles in a plump looking child (Figure 1).^{4,15} ITS is mostly triggered by some febrile illness.^{4,15} Anemia has been a prominent feature in ITS.^{5,9,13,21} Researchers have found a wide clinical spectrum and subtypes of anemia as megaloblastic,⁵ normocytic⁹ or microcytic hypochromic.^{13,21} Infants have been reported with glossitis, angular cheilitis, edema, rickets¹⁰ and scurvy.³⁴

Neuroimaging

In modern era of newer imaging technology, on cranial neuroimaging non-specific cerebral atrophy of different grades has been observed in 10 studied cases except one and cerebellar atrophy in one case of ITS. Reduced thickness of corpus callosum was observed in six patients and prominence of Sylvian sulcus in nine.¹¹ Similar findings of corpus callosum and Sylvian fissure along with non-specific cerebral atrophy are reported in a more recent study.³³ In another such study, the MRI findings were primary hypomyelination, cerebral atrophy, dilatation of ventricular system and extracerebral spaces.³⁵ Cerebral atrophy was present in 8 out of 10 cases, while dilatation of ventricles and prominence of extracerebral CSF spaces was the next common finding. Thinning of the corpus callosum was seen in three cases.³⁵ Such non specific diffuse cerebral atrophy on neuroimaging was observed by other researchers too.^{10,26,33} A single case has also been reported with subdural effusion in ITS.³⁶ One case report has reported three cases which on MRI scans had mild to severe diffuse cerebral atrophy, reverted back to normal on follow-up visit scans done after 6 months to one year after nutritional rehabilitation.¹

Treatment

Empirical management of ITS children has been tried in the absence of exact etiology considering child as undernourished. Nutritional management has been implemented as per standard guidelines for management of severe acute malnutrition.^{2,11} Iron, calcium, magnesium, Vitamin B12 along with multivitamins have been supplemented.^{2,37} Tremors have been observed to diminish considerably after administration of propranolol² although phenobarbitone,²

phenytoin² and carbamazepine³⁸ have also been tried occasionally. Associated infections and secondary complications must be treated and parents to be counselled and reassured explaining prognosis.

Prognosis

ITS is a self-limiting entity and resolves within 4–6 weeks in its natural course.²¹ A follow up study by Kaul et al 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 IQ. A total of 7 children out of 23 had speech defect i.e. dyslalia.³⁹

Discussion

ITS has been reported from Indian subcontinent as a self-limiting entity most commonly reported in 5 months to 3 years age group and is clinically characterized by coarse tremors, anemia, skin pigmentation and mental regression in a plump looking child. Even after decades of research the mystery of its etiology has to be resolved.⁴⁰

In recent times, Vitamin B12 has been shown to be strongly associated with ITS¹⁰ and there have been suggestions even to discard the syndrome status for this disorder, and rename it as “nutritional vitamin B12 deficiency in infants”.⁴¹ This was primarily because of some similar reported cases from western world.⁴¹ An assessment of Iron, Folate and Vitamin B12 status in 50 ITS children revealed Vitamin B12 deficiency in 70% children while none had Iron or Folate deficiency.⁴² Vitamin B12 deficiency may be emphasized due to the fact that mothers of ITS children are vegetarian and their complementary feeds are also delayed.^{7,9} This fact is also supported by a case report from Czech republic describing two cases of metabolic complications and neurologic manifestation of Vitamin B12 deficiency in children of vegetarian mothers in the form of psychomotoric retardation, apathy, muscular hypotonia, abnormal movements which disappeared after B12 supplements and the development of the children improved but they continued to have generalized hypotonia.⁴³

In contrast to above case report, another case report reviewed two cases with signs of Vitamin B12 deficiency who developed tremors after giving 1st dose of B12 which disappeared during sleep.⁴⁴ The tremors appear to be similar to that seen in ITS. This case report observed abnormal levels of homocysteine in the blood with explanation that several cofactors, derived from vitamin B12, are necessary for the conversion of homocysteine to methionine and methylmalonyl-CoA to

succinyl-CoA and in the absence of these cofactors, abnormal levels of homocysteine are found in the blood and excessive methylmalonic acid is excreted in the urine.⁴⁴ Methylmalonic aciduria and homocystinuria have been demonstrated in Vitamin B12-deficient patients in past too⁴⁵ but in previous case report⁴⁴ tremors developed after treatment with Vitamin B12. Such neurologic symptoms which appeared after treatment, have been reported to regress spontaneously within 3–6 weeks.⁴⁶ But it is still unknown that how cobalamin deficiency causes neurologic problems, which is another debatable matter regarding the role of Vitamin B12 in ITS. Age distribution of ITS is also not completely overlapping with the appearance of symptoms and signs of Vitamin B12 deficiency, which usually presents between the age of 2 to 12 months.⁴⁵

Brain structural changes on neuroimaging^{11,26} correlates with the findings of cerebral atrophy in infants with protein energy malnutrition⁴⁷ which reverses over a period.^{1,48} This fact does have phenomenal support to nutritional etiology in cases of ITS even though any specific element still needs to be discovered and researched.

Conclusion

Efforts have been made with limited success in Indian subcontinent to identify exact etiological agent for ITS. It seems that there is a missing link in the chain that can help researchers to fully explain the etiology of this entity. Certain questions are still unanswered and needed to be explored and researched like, variable types of anemia, male preponderance, presence of tremors only in some undernourished children, uncertain role of Vitamin B12 and relation with delayed complementary feeding. The authors have expectations that the exact etiology of this entity can be researched with newer tools, technologies, research collaborations, and enthusiasm of researchers.

What is known already

- ITS has a nutritional etiology

Unsolved questions

- Why there are variable types of anemia?
- Why there is male preponderance?
- Why there is presence of tremors only in some undernourished children?
- Why there is uncertain role of Vitamin B12?
- What is the relation with delayed complementary feeding?

Author contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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