OBSERVATIONAL STUDY

Clinical, Laboratory and Neuroimaging Profile of Children with Infantile Tremor Syndrome at a Tertiary Care Center

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ABSTRACT

Introduction: Infantile tremor syndrome (ITS) is characterized by coarse tremors, anemia, pigmentary skin changes, regression of developmental milestones, muscle hypotonia and multiple micronutrient deficiencies. We studied clinical, laboratory and neuroimaging profile of children with ITS. **Material and methods:** This hospital-based prospective observational study was conducted in the Dept. of Pediatrics, SMS Medical College, Jaipur, Rajasthan. Fifty cases of pre-ITS or ITS, 4 months to 3 years of age, admitted in the department were included in the study and assessed at the time of admission in hospital and at follow-up after 3 months of discharge with detailed clinical, hematological and neuroimaging examination. **Results:** We noted a female preponderance. About 96% children were from rural background, 88% from poor socioeconomic status and 12% children were from lower middle socioeconomic status. Eighteen (36%) children presented with leukocytosis. Only 24 (48%) children had normal serum iron level, and 24 (48%) children had normal serum vitamin B12 at presentation. Six (12%) children had decreased level of serum folate (<3 ng/dL). All the parameters improved at follow-up after 3 months. Magnetic resonance imaging (MRI) brain was normal in 10% children, while MRI brain in 32 (64%) children revealed cortical atrophy. In 24 (92% of 26) follow-up MRI brain, 17 (70%) MRIs showed normal findings when compared with previous MRI done on admission but 7 MRIs out of 24 showed improvement on follow-up, compared to the MRI done on admission; however, changes in MRI were still seen and had not completely resolved. **Conclusions:** The encouraging results of nutritional rehabilitation suggest that supplementing mother with vitamin B12 during pregnancy or fortifying complementary feeds with vitamin B12 may be considered. As the infants with vitamin B12 deficiency show neuroregression and features similar to ITS and the fact that vitamin B12 is involved in evolution of DNA and myelinating changes, vitamin B12 deficiency may be implicated as etiology.

Keywords: Infantile tremor, MRI brain, nutrition

Infantile tremor syndrome (ITS) is marked by coarse tremors, anemia, pigmentary skin changes, regression of developmental milestones and muscle hypotonia, in a plump looking child. ITS usually affects infants aged 6-24 months, though infants younger or older than this have also been reported to be affected, with male preponderance in the majority of the studies. While the exact incidence of ITS is not known, hospital statistics indicate that around 0.77-2.5% of the pediatric ward admissions are attributed to this disorder. Besides anemia, infants with ITS often present with multiple micronutrient deficiencies in the form of angular cheilitis, stomatitis and glossitis. Rickets, scurvy, edema and vitamin A deficiency have also been reported. Most researchers agree that infants with ITS are malnourished.

Non-specific changes have been noted on neuroimaging in ITS patients in the form of cerebral atrophy. However, these changes are also noted in the cases of malnutrition and after certain viral infections of the central nervous system (CNS). Earlier, pneumoencephalography has been associated with signs of ventricular dilatation and cortical atrophy in patients with ITS. Cranial neuroimaging is an important component of investigations to determine the etiological correlation in the differential diagnosis of conditions associated with tremors. The present study describes clinical,

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laboratory and neuroimaging profile of children with ITS at a tertiary care center.

MATERIAL AND METHODS

This hospital-based prospective observational study was conducted in the Dept. of Pediatrics, SMS Medical College, Jaipur, Rajasthan, from June 2017 to May 2018, after requisite clearance from research review board of the institute. Sample size was calculated as 95% confidence level, Alpha Error of 0.05 assuming 53.33% tremors among the suspected cases of ITS, at an absolute allowable error in the tremors of the suspected cases of ITS. The required sample size was 50 cases of pre-ITS or ITS. All children >4 months and <3 years of age, presenting with tremors, skin pigmentary changes, anemia and mental developmental delay with brown scanty scalp hair admitted in the department were included in the study and assessed at the time of admission in hospital and at follow-up after 3 months of discharge with detailed clinical, hematological and neuroimaging examination. We supplemented all the nutrients including calcium, folic acid, vitamin B12, iron, multivitamin, zinc, phosphorus, magnesium, potassium and proper food supplementary advice was given at the time of discharge. At 3-month follow-up, 26 patients came to us again and we assessed them clinically, hematologically and developmentally and neurologically. We found that almost all cases of ITS/pre-ITS which were documented 3 months back, showed drastic improvement in all four domains. Developmental assessment was done at the CDC center in Sir Padampat Mother and Child Health Institute (SPMCHI), Jaipur using DASII (Developmental Assessment Scale for Indian Infants) method. Children with negative consent and those with other diagnoses, perinatal insult like hypoxic ischemic encephalopathy, neonatal jaundice, etc. and CNS infections like TORCH (Toxoplasmosis, Other agents, Rubella, Cytomegalovirus and Herpes simplex virus), tuberculous meningitis (TBM), pyomeningitis, etc., were excluded from the study. Data were analyzed statistically.

OBSERVATIONS AND RESULTS

Socio-demographic Profile

In our study, 44% (22) children were in 9-12 months age group, 30% (15) children were in 12-15 months age group and 26% (13) children were in 6-9 months age group. Forty-four percent (22) children were male and 56% (28) children were female. Ninety-six percent (48) children were from rural area and 4% (2) children were from urban area. Additionally, 96% (48) children were Hindu and 4% (2) were Muslim. Ninety-six percent (48) children were from vegetarian family and 4% (2) were from nonvegetarian family. Furthermore, 88% (44) children were from poor socioeconomic status and 12% (6) children were from lower middle socioeconomic status, according to Kuppuswamy's scale.

Clinical Profile of ITS/Pre-ITS Children on Admission

All children presented with pallor, hair color change and dark pigmentation of skin. Eighteen (36%) children presented with leukocytosis at the time of admission and at follow-up at 3 months, 2 (4%) children had leukocytosis (Table 1).

Twenty-five (50%) children presented with consolidation in chest X-ray at the time of admission and at follow-up at 3 months, none had consolidation. Ten (20%)

Table 1. Clinical Symptoms of ITS/Pre-ITS Children on Admission

Symptoms	No. of children	Percentage (%)
Pallor	50	100
Hair color change	50	100
Dark pigmentation of skin	50	100
Associated comorbid illness	47	94
Regressed milestone	40	80
Delayed milestone	10	20
Apathetic look	48	96

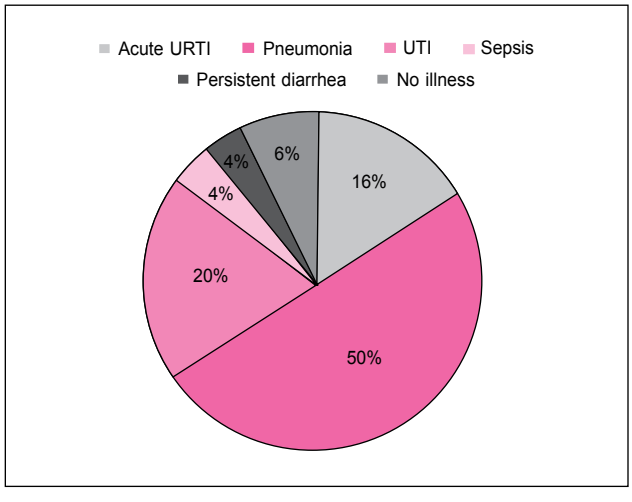

Figure 1. Associated comorbid illness in ITS and pre-ITS patients (n = 50).

children presented with nonsterile urine culture at the time of admission while all children had sterile urine culture at follow-up. Two (4%) children had nonsterile blood culture at the time of admission and at follow-up, all had sterile blood culture. Overall, 94% children had associated comorbid illness, like acute upper respiratory tract infection (URTI) (16%), pneumonia (50%), urinary tract infection (UTI) (20%), sepsis (4%) and persistent diarrhea (4%) (Fig. 1). All patients were developmentally delayed, in which 80% (40) patients were with regressed milestone and 20% (10) patients were with delayed milestone. In all, 96% (48) patients had apathetic look in our study. No children had normal weight at the time of admission and at 3-month follow-up, 38% children had normal body weight according to the World Health Organization (WHO) growth chart (Table 2).

Signs of ITS/Pre-ITS on Admission

Hundred percent children had developmental delay, wherein 10 (20%) patients were actually developmentally delayed since birth and 40 (80%) patients were developmentally regressed; they were normal at the time of birth to 3-4 months, and after that, they show development delay. Anemia and dark pigmentation of skin were present in 100% patients. Overall, 38% children presented without tremor and 62% presented with tremor (Table 3).

Hematological Profile

None of the children presented with hemoglobin (Hb) level >11 g/dL at the time of admission and at follow-up at 3 months, 53.85% children had Hb level >11 g/dL. Two (4%) children had normochromic, normocytic peripheral blood film (PBF) at the time of admission and at follow-up, 54% children had normochromic, normocytic PBF. Twenty-four (48%) children presented with normal serum iron level at the time of admission and at follow-up, 92% children had normal serum iron level. Only 72% children presented with normal total iron-binding capacity (TIBC) level at the time of admission and at follow-up, 100% children had normal TIBC level.

Serum vitamin B12 levels at the time of admission and after follow-up are depicted in Table 4.

Six (12%) children revealed decreased level of serum folate <3 ng/dL. On follow-up after 3 months, 100% children had normal serum folate level.

Neuroimaging Profile

Eighty-two percent children had normal cranial USG at the time of admission and at 3 months follow-up, 100% children had normal cranial USG.

In our study, 5 (10%) children had normal MRI of brain. Thirty-two (64%) children had cortical atrophy at the time of admission, 10 (20%) children presented with ventricular dilatation and thinning of corpus callosum was revealed in 6 (12%) MRI of brain. Prominence of sylvian sulcus was seen in 12 (24%) children, diffuse dilatation of sulci was seen in 19 (38%) children and generalized atrophy of grey matter was seen in 4 (8%); remaining miscellaneous changes like cerebellar atrophy, delayed myelination (hyperintensities in cortical areas) were seen in 4 (8%) children at the time of admission (Table 5).

Two out of 26 attendants refused for repeat MRI of brain on follow-up. In 24 (92% of 26) follow-up MRI brain, 17 (70%) MRI showed normal finding on follow-up and 7 showed improvement in MRI changes that were noted previously on admission but had not completely resolved till date of follow-up.

In our study, motor quotient at 50% pass level (according to DASII developmental scale) was 37.46 ± 5.89 and at

Table 2. Weight for Age (According to WHO Growth Chart)

Weight for age (according to WHO growth chart)	Before treatment (n = 50)		Follow-up (n = 26)	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
Mean weight or more	0	0	10	38.46
B/w Mean & 1 SD	3	6	14	53.85
B/w 1 SD & 2 SD	7	14	2	7.69
B/w 2 SD & 3 SD	12	24		
B/w > 3 SD	28	56		
Total	**50**	**100.00**	**26**	**100.00**

3-month follow-up, motor quotient at 50% pass level was 71.38 ± 5.72. The difference between before and after treatment value was found to be statistically significant. The mental quotient at 50% pass level was 38.52 ± 4.61 and at follow-up, mental quotient at 50% pass level (according to DASII developmental scale) was 73.23 ± 5.50. The difference between before and after treatment value was again statistically significant.

Table 3. Signs of ITS/Pre-ITS on Admission

Sign	No. of children	Percentage (%)
Tremors absent	19	38
Tremors present	31	62
Developmental delay	10	20
Developmental regression	40	80
Anemia	50	100
Dark skin pigmentation	50	100

Table 4. Serum Vitamin B12 Levels at the Time of Admission and at Follow-up

Serum vitamin B12 (pg/dL)	Before treatment (n = 50)		Follow-up (n = 26)	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
<211	26	52	0	00
211-911	24	48	26	100
>911	0	0	0	0
Total	**50**	**100.00**	**26**	**100.00**

DISCUSSION

In our study, 44% children presented in 9-12 months age group, 44% children were male and 56% children were female. All children had abnormal weight. In a study conducted by Parsawala et al, most of the patients (93.3%) were found to have some degree of protein energy malnutrition (PEM), with maximum having Grade II. No child had Hb level >11 g/dL at the time of admission and at follow-up, Hb levels improved in 53.85% children. Only 24 (48%) children had normal serum iron level at the time of admission and at follow-up, 92.31% children had normal serum iron level. Overall, 72% children had normal TIBC level at the time of admission while all children had normal TIBC level at follow-up. Twenty-four (48%) children had normal serum vitamin B12 at the time of admission and at follow-up, 100% children had normal level. Six (12%) children had decreased level of serum folate <3 ng/dL, which improved at follow-up in all children.

In our study, MRI brain was normal in 10% children, while in 32 (64%) children, it revealed cortical atrophy. Mathur et al have suggested that these anatomical changes might be attributed to PEM. A case report of ITS reported computerized tomography (CT) scan of the brain showing cerebral atrophy with thinning of corpus callosum. A study on patients with essential tremors (ETs) noted that high resolution proton density and T2-weighted MRI images among 12 patients and 15 controls did not show any structural abnormalities of the brain. Various degrees of cerebral atrophy have been evaluated in children having CNS manifestations of PEM.

Table 5. MRI Brain at Presentation and Follow-up Visit

MRI	Before treatment (n = 50)		Follow-up (n = 26)	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
Normal	5	10	17	70
Cortical atrophy	32	64		
Ventricular dilatation	10	20		
Thinning of corpus callosum	6	12		
Subdural effusion	6	12		
Prominence of sylvian sulcus	12	24		
Diffuse dilatation of sulci	19	38		
Generalized atrophy of grey matter	4	8		
Miscellaneous	4	8		

A study conducted by Kumar et al found cerebral atrophy in 7 patients of ITS (53.8%), subdural hygroma in 2 patients while rest of the 4 patients were normal. In a study by Gehlot et al, among ITS cases with severe wasting, 3 out of 4 had cerebral atrophy.

All 3 children with moderate wasting had signs of cerebral atrophy. There was evidence of cerebral atrophy in all children with stunting and also in children with normal height for age and sex. Six out of 10 patients had mild-to-moderate ventricular dilatation and most patients (9/10) had sylvian sulcus prominence. Ventricular dilatation and prominence of sylvian sulcus were correlated with the grades of cerebral atrophy in all patients.

In our study, 10 (20%) children presented with ventricular dilatation, 6 (12%) children each presented with thinning of corpus callosum and subdural effusion at the time of admission. After 3 months, 26 children came for follow-up. Two out of 26 attendants refused for repeat MRI of brain on follow-up. In 24 (92% of 26) follow-up MRI brain, 17 (70%) MRIs showed normal findings as compared to previous MRI done on admission, but 7 MRIs out of 24 showed improvement on follow-up as compared to previous MRI done at admission, but changes in MRI of brain were still seen and had not completely resolved.

A study conducted by Gehlot et al noted that on cranial neuroimaging, there was non-specific cerebral atrophy of different grades in all cases except one while cerebellar atrophy was noted in 1 case of ITS. Corpus callosum thickness was reduced in 6 patients while 9 had prominence of sylvian sulcus.

Motor quotient and mental quotient at 50% pass level difference between before and after treatment was found statistically significant.

In a case series of childhood head tremors, MRI showed no abnormal findings. Hypomyelination disorders are associated with evidence of cerebral and cerebellar atrophy and little or no myelin in the cerebral white matter on MRI scans of most adolescents and adults. The infantile form of Pelizaeus-Merzbacher disease (PMD) that presents with head tremors, is associated with mild-to-moderate brain atrophy. There is little MRI data on the patients clinically diagnosed as ITS.

A study conducted by Gupta et al found that MRI changes in ITS/pre-ITS patients showed improvement after nutritional rehabilitation on follow-up even 2 months later. As persisting neurodisability is a concern, it should be prevented rather than treated.

FUTURE RECOMMENDATIONS

The encouraging results of nutritional rehabilitation suggest that supplementing the mother with vitamin B12 during pregnancy or fortifying complementary feeds with vitamin B12 may be considered because vitamin B12 seems to be the etiological factor in ITS as per studies. As the infants with vitamin B12 deficiency show neuroregression and features similar to ITS and the fact that vitamin B12 is involved in evolution of DNA and myelinating changes, vitamin B12 deficiency may be implicated as the possible etiology.

In infants, vitamin B12 deficiency is tied to demyelination and brain atrophy. Therefore, retardation of myelination of the brain in infants results in delay in acquiring cognitive skills and regression of cognitive skills. The most common neuroimaging finding in all studies correlate with cortical atrophy.

Some reports specifically indicate demyelinating changes. While neurological injury is classically described as irreversible, patients of stroke and other injuries usually recover with gliosis or porencephalic cyst, and patients of ITS show complete recovery. The cortical atrophy heal or recover without scarring.

Patients of ITS tend to have persisting neurodisability - their IQ is on lower side in comparison with others of the same age, while some may attain normal development few months after treatment. The degree of improvement may be associated with the time of presentation. As the brain is still a developing organ and myelination continues, till 2 years of age, early intervention results in less damage to the brain and there are lesser odds of neurodisability. Early diagnosis and treatment are essential.

CONCLUSION

Our finding of complete resolution of MRI findings of cortical atrophy, ventricular dilatation, demyelination, increased subarachnoid space, etc., would suggest the possibility of near complete reversibility of the neurological abnormalities and support recommendation of vigorous attempts for rehabilitation of the patients.

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