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Original Research Article

Study of clinical, haematological and radiological profile of children admitted with infantile tremor syndrome to a tertiary care teaching hospital in Northern India

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ABSTRACT

Background: Infantile tremor syndrome (ITS) is characterized by gradual onset of mental and psychomotor changes, pigmentary disturbances in hairs and skin, pallor, tremors and neuroregression. The aim of study was to determine clinical, haematological and radiological spectrum of children admitted with infantile tremor syndrome.
Methods: It was a prospective cross-sectional study done in age group of 6 months to 5 years conducted in department of pediatrics of a tertiary care medical college with duration of 18 months. Clinical, haematological and radiological profile parameters of 36 children admitted during study period with ITS were recorded as per prepared performa and analysed. Microsoft excel was used in creating database while data was analysed by using Statistical Package for Social Sciences (SPSS) version 23.0.
Results: Total 36 children were enrolled in study. Mean age was 12.33±3.89 months and mostly were male (55.6%). Most (72.2%) of children belonged to lower socioeconomic status and (83.3%) were exclusively breastfed. Only 11.1% had severe acute malnutrition (SAM). 77.77% had vitamin B12 levels below normal. Progressive paleness (88.9%), delayed development (61.1%) and developmental regression (58.3%) were most common complaints reported. 63.9% had tremors at presentation. In MRI findings, poor myelination with thinning of corpus callosum (16.7%) and uniform thinning of corpus callosum with subtle hypomyelination in bilateral frontal lobes (8.3%) were major findings. In majority of children tremor disappeared in 11-15 days (30.6%) after starting treatment.
Conclusions: ITS should to be considered as a differential diagnosis in an infant on exclusive breast feeding with vegetarian mother with poor weaning practices presenting with neuroregression, tremor and malnutrition with skin changes.

Keywords: Breastfeeding, Neuroregression, Tremor, Myelination, Northern India

INTRODUCTION

Neuroregression seen in an infant is usually challenging to investigate and treat.[1]

Before keeping possibility of inherited metabolic conditions as etiology, we must always rule out nutritional deficiencies like vitamin-B12 and protein energy malnutrition (PEM); infections like tuberculosis, human immunodeficiency virus and environmental toxins like lead exposure etc.[2]

ITS is a clinical disorder associated with mental and psychomotor changes, pigmentary disturbances of hair and skin, pallor, tremors and neuroregression. It is usually seen in malnourished children aged between 5 months and 3 years.[3] It was first reported in the Indian subcontinent, however similar cases now are being reported from all over

world.[4] It accounts for 0.2 to 2% of pediatric hospital admissions.[5]

The causation of ITS is still under evaluation. Malnutrition, vitamins and mineral deficiency (e.g., Mg, Zn, vitamin B12, iron), infections, toxins, degenerative brain diseases, enzyme defects (e.g., tyrosine) all have been postulated as etiology of ITS.[4] Most of studies done have observed low vitamin B12 levels.[6]

ITS is strongly related to maternal vegetarian diet and delayed initiation of complementary feeds and has a clear association with adverse developmental consequences.[7] Tyrosine metabolism defect might lead to interference in melanin pigment production leading to pigmentary disturbances of hair/skin.

Depigmentation of substantia nigra may lead to tremors.[7] Reduced brain substance has been documented in children with infantile tremor syndrome. The tremors have been reported to regress spontaneously within 3-6 weeks.[3]

Most of 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.[8] Even when weaning has been started, foods of animal origin including top milk are missing from the diet or given in insufficient quantity.[9]

Certain questions are still unanswered and needs to be explored and researched like variable types of anaemia, male preponderance, presence of tremors only in some undernourished children, uncertain role of vitamin B12 and relation with delayed complementary feeding.

Nutrient deficiencies like vitamin B12, zinc, magnesium have been found to be associated with ITS. Radiologically cortical atrophy and prominence of subarachnoid space and ventricular system along with thinning of corpus callosum are commonest findings in CT/ MRI of brain.[11]

In an infant with neuro-regression and absence of tremors along with skin findings, we may not keep possibility of ITS. These days term neurocutaneous infantile B12 (NIB) is used which aptly describes key clinical features, provides clue to underlying etiology and leads to prompt treatment of this condition.[2]

Thus there is a need to change from ITS/pre-ITS to neurocutaneous infantile vitamin B12 to label these children. Treatment still focuses on providing appropriate nutritional support with vitamin B12 therapy and supplementation of other vitamins and minerals (iron, calcium, magnesium, zinc, selenium, chromium).

The aim of the study was to conduct clinical, haematological and neuro imaging profile in patients with infantile tremor syndrome amongst patients reporting to a tertiary care hospital.

METHODS

This study was conducted at department of pediatrics in Dr. Rajendra Prasad Government Medical College Tanda, a tertiary care medical college in Northern India for a duration of 18 months (January 2018 to August 2019). It was a prospective cross sectional study.

After approval of institute ethical committee and fulfilling inclusion criterias, children in age group of 6 months to 5 years presenting with features suggestive of ITS in outdoor/indoor patient department were included.

Inclusion criteria

Patients with following group were included (a) age group of 6 months to 5 years of age; and (b) parental consent for treatment and neuroimaging; and (c) clinical features suggestive of ITS.

Exclusion criteria

Patients with following group were excluded (a) age<6 months and >5 years; and (b) no parental consent.

Detailed history of the presenting symptoms, demographic details and clinical findings were noted down. Investigations including complete haemogram, peripheral smear, RBC indices, vitamin B12 levels, magnesium (Mg) levels were done. Neuroimaging in the form of MRI/CT was done at admission before starting any treatment.

Statistical analysis

Microsoft excel was used in creating database while data were analyzed using SPSS version 23.0 for windows. Mean and standard deviation (±SD) were used to describe quantitative data meeting normal distribution.

RESULTS

The mean age of study participants was 12.33±3.89 months. Majority of children were under age of 15 months (83.4%). Male children (55.6%) outnumbered the females. Majority of mothers (94.4%) were undergraduate and (75%) belonged to lower socio-economic status (class 4 and 5) (Table 1).

Progressive paleness (88.9%), developmental regression (75.0%) and poor weight gain (8.3%) were main complaints at admission. Majority of admitted children were exclusively breastfed (83.3%) at time of presentation and complimentary feed was started only in few (16.7%). Majority of children were having moderate pallor (66.7%). Hyperpigmented knuckles and hypopigmented hairs were seen in 94.4% each while chubby looks was present in 97.2%. Hepatomegaly was present in 44%, splenomegaly in 22% of admitted children. Only 4 (11.1%) children had severe acute malnutrition (SAM). 69.4% children showed tremor at presentation (Table 2).

The mean haemoglobin pre-treatment was observed to be 6.2 g/dl with the range from 3.8-8.5 g/dl. Severe anaemia (Hb<6 g/dl) was seen in all 25 patients. The mean MCV was observed to be 97.47 fl. Above normal MCV (normal MCV=80-95 fl) was seen in 30 patients (83.3%). Mean vitamin B12 level was 82.22 pg/ml with minimum vitamin B12 level being 52.96 pg/ml and maximum vitamin B12 level being 111.48 pg/ml. Below normal vitamin B12 levels (normal range=200-500 pg/ml) were seen in all children. Magnesium levels were found to be in normal range in all children. In PBF picture, majority of children were having dimorphic anaemia (77.8%) followed by macrocytic anaemia (22.2%). The peripheral smear also revealed hypersegmented neutrophils, macrocytes and tear drop cells. Majority of children (41.7%) had normal reports on neuroimaging, followed by poor myelination with thinning of corpus callosum (16.7%) and uniform thinning of corpus callosum with subtle hypomyelination in bilateral frontal lobes (8.3%). Tremors disappeared within 15 days in 44.5% of patients.

Table 1: Socio-demographic characteristics of study participants.

Variables	Category	N (%)
Age (in months)	≤10	15 (41.7)
	11-15	15 (41.7)
	16-20	4 (11.1)
	>20	2 (5.6)
Gender	Male	20 (55.6)
	Female	16 (44.4)
Mothers education	High school	20 (55.6)
	Intermediate	14 (38.9)
	Graduation	2 (5.6)
Socio-economic status	Class 3	9 (25)
	Class 4	26 (72.2)
	Class 5	1 (2.8)

Table 2: Clinical history and features of study participants.

Variables	Category	N (%)
Chief complaint at admission	Progressive paleness	32 (88.9)
	Delayed development	9 (25)
	Developmental regression	27 (75)
	Poor weight gain	3 (8.3)
	Others	8 (2.2)
Feeding history	Exclusive breastfed	30 (83.3)
	Partially breastfed	6 (16.7)
Nutritional status	SAM	4 (11.1)
	Normal	32 (88.9)
Tremor at presentation	Yes	25 (69.4)
	No	11 (30.6)
Clinical features	Moderate pallor	24 (66.7)
	Severe pallor	12 (33.3)
	Hyperpigmented knuckles	34 (94.4)
	Hypopigmented hairs	34 (94.4)
	Chubby looks	35 (97.2)
	Other positive G.P.E (frontal bossing)	4 (11.1)
	Hepatomegaly	16 (44)
	Splenomegaly	8 (22)

Table 3: Haematological profile of enrolled children (before treatment).

Parameters	Before treatment
Heamoglobin (g%)	6.21±2.39
MCV (fl)	97.47±7.38
Vitamin B12 levels (pg/ml)	82.22±29.26
Magnesium	2.22±0.105

Table 4: Distribution on basis of peripheral blood film (PBF) at time of admission.

PBF		n=36	%
Dimorphic anaemia (n=28) (77.8%)	Macrocytes	28	100.0
	Ovalocytes	20	71.4
	Tear drop cells	17	60.7
	Hypersegmented neutrophils	17	60.7
Macrocytic anaemia (n=8) (22.2%)	Anisocytosis	6	75.0
	Ovalocytes	6	75.0
	Macrocytes	8	100.0
	Hypersegmented neutrophils	2	25.0

Table 5: Radiological profile of children (CT/MRI before treatment).

CT/MRI abnormality	Before treatment n=36	%
Within normal limit	15	41.7
Poor myelination with thinning of corpus callosum	6	16.7
Uniform thinning of corpus callosum with subtle hypomyelination in bilateral frontal lobes	3	8.3
Global atrophy of cortical and subcortical white matter of bilateral cerebral hemisphere with subdural hygroma	2	5.7
Global atrophy of cortical and subcortical white matter	1	2.8
Uniform thinning of corpus callosum with subtle hypomyelination changes in all lobes bilaterally	2	5.7
Thinning of corpus callosum with prominence of extraxial CSF spaces	1	2.8
Cerebral atrophy primarily involving bilateral frontal lobes	2	5.6
Bilateral cerebral atrophy with loss of myelination in subcortical white matter and thinning of corpus callosum	1	2.8
Bilateral deep and subcortical white matter hyperintensities and hypo intensities in frontal and temporal lobe	1	2.8
Hypomyelination in B/L frontal, parietal, temporal, frontal and occipital lobes	1	2.8
Global atrophy of cortical and subcortical white matter with generalized hypomyelination	1	2.8

Table 6: Distribution of patients of the basis of tremor disappearance.

Tremor disappearance in days	n=36	%
≤10	5	13.9
11-15	11	30.6
16-20	5	13.9
>20	4	11.1
Not applicable	11	30.6

DISCUSSION

In present study, majority of admitted children were under 15 months of age (83.3%). Similar results were reported by Kumar et al and Singla et al.[11,12] In our study majority of admitted children were males which is in concordance with study done earlier.[11] Majority of admitted children had complaints of progressive paleness, developmental regression which is in concordance with studies reported earlier by Kumar et al and Singla et al.[11,12]

Majority of mothers were high school pass and had lower socioeconomic status class 4. Majority of admitted children were exclusively breastfed. This data on mothers profile is similar to studies conducted earlier by Kumar et al, Gehlot et al and Singla et al.[11-13]

This shows that mothers know importance of breastfeeding and lacked knowledge of importance of timely introduction of complementary feeding. Hyperpigmented knuckles, hypopigmented hairs, chubby looks were seen in more than 2/3rd children with 11.1% having severe acute malnutrition. Hepatomegaly was present in 44%, splenomegaly in 22%.

The results were similar to various studies done by Brahmabhatt et al, Kumar et al and Singla et al.[11,12,14] Moderate to severe anaemia (Hb<6 g/dl) was observed,

similar levels of Hb were observed by Pohowalla et al.[15] Vitamin B12 levels were low in majority (76%) of enrolled children which is higher than reported by Gorava et al.[16] Thus B12 deficiency was an important underlying factor for ITS in our study. Magnesium levels were found to be in normal range in all children which is contradictory to various studies done earlier by Chhaparwal et al and Agarwal et al.[17,18]

Peripheral smear revealed dimorphic anaemia (77.8%), macrocytic anaemia (22.2%), hypersegmented neutrophils similar to study done by Holla et al.[19] Thus we can conclude that iron deficiency co-exists with B12 deficiency. Many children had frontal bossing as a feature which is indirect evidence of associated other nutritional deficiencies like protein, vitamin A, D, K and other micronutrients. In our study, 69.4% children had tremors at presentation. In majority of children tremors disappeared within 15 days (44.5%) which is comparable to studies done by Brahmbhatt et al and Holla et al and Prasad et al.[14,19]

About half of children had neuroimaging within normal limit. It was followed by poor myelination with thinning of corpus callosum (16.7%) and uniform thinning of corpus callosum with subtle hypomyelination in bilateral frontal lobes (8.3%). These results were comparable to various other studies.[11] As in this syndrome, etiology could not be pinpointed, treatment comprised of treatment of anaemia as per etiology. Patients who were vitamin B12 deficient were given 250-500 µg intramuscular daily for 7 days, biweekly for 3 months and then monthly for 3 months. Multivitamins, iron, zinc, vitamin C, magnesium, calcium along with recommended diet under nutrition counsellor in age-appropriate doses were given as suggested in the literature

Limitation

The sample size was too small. The nature of study was cross-sectional, so causation could not be commented upon. Follow-up with radiological and hematologic investigations of these children could have resulted in a clear overview of their profile over a period of time.

CONCLUSION

Our study highlighted that vitamin B12 deficiency associated with ITS. ITS must be considered in an infant on exclusive breast feeding with mother on vegan diet presenting with neuroregression, tremor, developmental delay and malnutrition with skin changes. Primarily ITS seems to be related to undernutrition and is reversible with nutritional rehabilitation. ITS is strongly related to maternal and infant diet and has a clear association with adverse developmental consequences. This deficiency disease is eminently preventable by injectable vitamin B12 and nutritional supplementation, food fortification or dietary modification and awareness of parents, otherwise it can lead to profound implications on long term cognitive functions in children.

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