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TO STUDY CLINICAL AND HEMATOLOGICAL PROFILE AND ITS COMPARISON WITH NEUROIMAGING PROFILE IN PATIENTS OF INFANTILE TREMOR SYNDROME IN A RURAL BASED TERTIARY CARE CENTRE

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Abstract

Introduction: Infantile tremor syndrome (ITS) is characterized by gradual onset of mental and psychomotor changes, pigmentary disturbances in hairs and skin, pallor, tremors and neuroregression in malnourished children aged between 5 months and 3 years. It is a well-known entity, but the exact etiopathogenesis is still not known. We aimed to determine clinical, haematological and neuroimaging profile in patients admitted with infantile tremor syndrome.

Material & Methods: This prospective cross-sectional study was conducted in Department of Pediatrics, IMCHRC, Indore on 18 children in age group of 6 months to 5 years admitted with the diagnosis of ITS. Clinical, haematological and radiological profile parameters were analysed. Statistical analysis was done.

Results: Mean age was 12.21±3.69 months. M:F ratio was 1.25:1. 14(77.7%) had height less than -3SD & 17(94.4%) has weight <-3SD. 13(72.2%) of children belonged to lower socioeconomic status and 15(83.3%) were exclusively breastfed. SAM was reported in 2(11.1%) children. 17(77.7%) reported Vit B12 deficiency. Progressive paleness [16(88.9%)], developmental delay [11(61.1%)] and developmental regression [10(55.5%)] were the most common complaints. 66.7% had tremors at presentation. In MRI findings, the major findings were poor myelination with thinning of corpus callosum [3(16.7%)] and uniform thinning of corpus callosum with subtle hypomyelination in bilateral frontal lobes [2(11.1%)]. In majority of children [6(33.33%)] tremor disappeared in 11-15 days after starting treatment.

Conclusion: ITS should be considered as a differential diagnosis in an infant on exclusive breast feeding with vegetarian mother and poor weaning practices presenting with neuroregression, tremor and malnutrition with skin changes.

Keywords: Infantile tremor syndrome, Vit B12 deficiency, MRI brain, nutrition

INTRODUCTION

ITS is a clinical disorder associated with mental and psychomotor changes, pigmentary disturbances of hair and skin, pallor, tremors and neuroregression.[1] It is usually seen in

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malnourished children aged between 5 months and 3 years.[2] It was first reported in the Indian subcontinent[3] and it accounts for 0.2 to 2% of pediatric hospital admissions.[4]

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.[3] Most of studies done have observed low vitamin B12 levels.[5] ITS is strongly related to maternal vegetarian diet and delayed initiation of complementary feeds and has a clear association with adverse developmental consequences.[6] Depigmentation of substantia nigra may lead to tremors.[6] The tremors have been reported to regress spontaneously within 3-6 weeks.[2]

Most of cases of ITS occur in exclusively breast-fed infants. Commonly weaning has never been initiated because of lack of appropriate guidance.[7,8] 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.[9]

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).

In paucity of studies done to determine the exact etiopathogenesis, the present study was planned to study clinical and hematological profile and its comparison with neuroimaging profile in patients of infantile tremor syndrome.

MATERIAL AND METHODS

After approval from the institutional ethical committee, this prospective cross-sectional study was conducted in Department of Pediatrics, Index Medical College Hospital & Research Center, Indore on 18 children in age group of 6 months to 5 years who are admitted in the tertiary care hospital with the diagnosis of ITS. All infants with features suggestive of ITS in outdoor/indoor patient department were included after taking an informed written consent from the parent/guardian.

Inclusion criteria

- Age group of 6 months to 5 years of age;
- Parental consent for treatment and neuroimaging; and
- Clinical features suggestive of ITS.

Exclusion criteria

- Age<6 months and >5 years; and
- Congenital malformation of brain
- No parental consent.

Methodology

Detailed history of the presenting symptoms, dietary history, demographic details and clinical findings were noted down. Investigations including complete hemogram,

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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

Data was entered on a pre-structured Performa using Microsoft excel. Data was analysed using SPSS version 25.0 for windows. Mean and standard deviation (±SD) were used to describe quantitative data meeting normal distribution.

RESULTS

The mean age of study participants was 12.21±3.69 months. Majority of children were under age of 15 months [15(83.3%)]. A higher male preponderance was seen with M:F ratio of 1.25:1. Majority of patients [14(77.77%)] had height less than -3SD whereas 4(22.23%) had height between -3SD to -2SD. 17(94.4%) has weight <-3SD whereas only one patient (5.6%) had weight in range of -2SD to -3SD. For educational qualification. majority of mothers [17(94.4%)] were undergraduate and belonged to lower socio-economic status i.e., Class 4 and 5 [13(72.2%)] (Table 1).

Progressive paleness [16(88.9%)], developmental delay [11(61.1%)] and developmental regression [10(55.5%)] were the most common complaints. Majority of admitted children were exclusively breastfed [15(83.3%)] at time of presentation and complimentary feed was started only 3(16.67%) children.

Majority of children [12(66.67%)] were having moderate pallor. Hyperpigmented knuckles and hypopigmented hairs were seen in 17 (94.4%) patients each while chubby looks were present in 88.9%. Hepatomegaly was present in 8(44.4%) splenomegaly in 4(22.2%) of admitted children. SAM was reported in only 2 (11.1%) children. 17(77.7%) reported Vit B12 deficiency. 66.7% children showed tremor at presentation.

The mean haemoglobin pre-treatment was observed to be 6.5 g/dl with the range from 3.9-8.6 g/dl. Severe anaemia (Hb<6 g/dl) was seen in all 12(66.7%) patients. The mean MCV was observed to be 97.34 fl. Above normal MCV (normal MCV=80-95 fl) was seen in 15 patients (83.3%). Mean vitamin B12 level was 82.25 pg/ml with minimum vitamin B12 level being 52.46 pg/ml and maximum vitamin B12 level being 111.38 pg/ml. Below normal vitaminB12 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 Peripheral blood film (PBF) picture, majority of children [14(77.8%)] were having dimorphic anaemia followed by macrocytic anaemia [4(22.2%)]. The peripheral smear also revealed hypersegmented neutrophils, macrocytes and tear drop cells.

In MRI findings, majority of children [8(44.4%)] had normal reports on neuroimaging, followed by poor myelination with thinning of corpus callosum [3(16.7%)] and uniform thinning of corpus callosum with subtle hypomyelination in bilateral frontal lobes [2(11.1%)]. In majority of children [6(33.33%)] tremor disappeared in 11-15 days after starting treatment.

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Variables	Category	N (%)
Age (in months)	≤10	8 (44.4%)
	15	7 (38.8%)
	16-20	2 (11.1%)
	>20	1 (5.6%)
Gender	Male	10 (55.6%)
	Female	8 (44.4%)
Height	<-3SD	14 (77.77%)
	-3SD to -2SD	4 (22.23%)
Weight	< -3SD	17 (94.4%)
	-2SD to -3SD	1 (5.6%)
Mothers' education	High school	10 (55.6%)
	Intermediate	7 (38.9%)
	Graduation	1 (5.6%)
Socio-economic status	Class 3	5 (27.8%)
	Class 4	12 (66.7%)
	Class 5	1 (5.5%)

Table 1: Socio-demographic characteristics of study participants

Variables	Category	N (%)
Chief complaint at admission	Progressive paleness	16 (88.9%)
	Delayed development	11 (61.1%)
	Developmental regression	10 (55.5%)
	Poor weight gain	2 (11.1%)
	Others	4 (22.2)
Feeding history	Exclusive breastfed	15 (83.3%)
	Partially breastfed	3 (16.7%)
Nutritional status	SAM	2 (11.1%)
	Normal	16 (88.9%)
Tremor at presentation	Yes	12 (66.7%)
	No	6 (33.3%)
Clinical features	Moderate pallor	12 (66.7%)
	Severe pallor	6 (33.3%)
	Hyperpigmented knuckles	17 (94.4%)
	Hypopigmented hairs	17 (94.4%)
	Chubby looks	16 (88.9%)
	Other positive G.P.E (frontal bossing)	2 (11.1%)
	Hepatomegaly	8 (44.4%)
	Splenomegaly	4 (22.2%)

Table 2: Clinical history and features of study participants

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Parameters	Before treatment
Heamoglobin (g%)	6.5±2.29
MCV (fl)	97.35±7.53
Vitamin B12 levels (pg/ml)	82.25±28.36
Magnesium	2.24±0.125

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

PBF		n=18	%
Dimorphic anaemia (n=14) (77.8%)	Macrocytes	14	100
	Ovalocytes	10	71.4
	Tear drop cells	8	57.1
	Hypersegmented neutrophils	9	64.3
Macrocytic anaemia (n=4) (22.2%)	Anisocytosis	3	75
	Ovalocytes	3	75
	Macrocytes	4	100
	Hypersegmented neutrophils	1	25

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

CT/MRI abnormality	Before treatment n=18	%
Within normal limit	8	44.4
Poor myelination with thinning of corpus callosum	3	16.7
Uniform thinning of corpus callosum with subtle hypomyelination in bilateral frontal lobes	2	11.1
Global atrophy of cortical and subcortical white matter of bilateral cerebral hemisphere with subdural hygroma	1	5.5
Global atrophy of cortical and subcortical white matter	1	5.5
Uniform thinning of corpus callosum with subtle hypomyelination changes in all lobes bilaterally	1	5.5
Thinning of corpus callosum with prominence of extraxial CSF spaces	1	5.5
Bilateral cerebral atrophy with loss of myelination in subcortical white matter and thinning of corpus callosum	1	5.5

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

Tremor disappearance in days	n=18	%
≤10	3	16.7%
15	5	27.8%
16-20	2	11.1%
>20	2	11.1%
Not applicable	6	33.3%

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

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DISCUSSION

Infantile tremor syndrome is a syndrome characterized by megaloblastic anemia, skin pigmentation, tremors, physical and mental regression. It has been reported in children between 5 months and 3 years of age with a male predominance. The exact incidence of ITS is not available. However, in various studies 0.87- 1.55 % hospital admissions were due to ITS.[10] The exact etiopathogenesis of this condition remains obscure. Studies suggest that the most probable etiology of infantile tremor syndrome is nutritional deficiencies including Vit B12 deficiency.

Despite predominance of neurological symptoms, very few studies have documented neuroanatomical and/ or neurophysiological changes in infantile tremor syndrome.[11] Reduced brain substance has been documented in children with infantile tremor syndrome. Improvement in nutritional status, living condition and better weaning practices could explain the reducing incidence rates over the years. It has been primarily reported from India and South East Asia countries in Asia and Africa.[12]

In present study, majority of admitted children were under 15 months of age (83.3%). Similar results were reported by Bajaj M et al. Kumar et al. & Singla et al.[4,9,13] In our study majority of admitted children were males which is in concordance with study done earlier.[4,9]

Majority of admitted children had complaints of progressive paleness, developmental regression which is in concordance with studies reported earlier by Bajaj M et al. Kumar et al. & Singla et al.[4,9,13]

For educational qualification. majority of mothers were undergraduate and belonged to lower socio-economic status i.e., Class 4 and 5. Majority of admitted children were exclusively breastfed. This data on mothers' profile is concurrence to studies conducted earlier by Bajaj M et al. Kumar et al., Singla et al and Gehlot et al.[4,9,13,14]. This shows that although mothers had knowledge on importance of breastfeeding, they lacked knowledge of importance of timely introduction of complementary feeding and weaning.

Hyperpigmented knuckles, hypopigmented hairs, chubby looks were the most prominent features seen in more than 2/3rd children with 11.1% having severe acute malnutrition (SAM). Hepatomegaly and splenomegaly were seen in 44.4% and 22.2% children respectively. Similar results were reported by Bajaj M et al., Kumar et al., Singla et al. and Brahmabhatt et al. [4,9,13,15]

Moderate to severe anaemia (Hb<6 g/dl) was observed, similar levels of Hb were observed by Bajaj M et al. & Pohowalla et al.[4,16] Vitamin B12 levels were low in majority (77.7%) of enrolled children which was in concurrence with studies done by Bajaj M et al.[4] However, it was higher than as reported by Gorava et al.[17] Thus Vitamin B12 deficiency was found to be an important underlying factor for ITS in our study. This was in concurrence with studies done by Bajaj M et al. & Kumar A et al.[4,18] Magnesium levels were found to be in normal range in all children which was contradictory to various anecdotal studies done earlier by Chhaparwal et al. & Agarwal et al.[19,20]

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In Peripheral blood film (PBF) picture, majority of children [14(77.8%)] were having dimorphic anaemia followed by macrocytic anaemia [4(22.2%)]. The peripheral smear also revealed hypersegmented neutrophils, macrocytes and tear drop cells.

Peripheral smear revealed dimorphic anaemia (77.8%), macrocytic anaemia (22.2%), hypersegmented neutrophils similar to study done by Bajaj M et al & Holla et al.[4,21] Thus, we can conclude that iron deficiency co-exists with Vitamin B12 deficiency. Many children had frontal bossing as a clinical feature which is indirect evidence of associated other nutritional deficiencies like protein, Vitamin A, D, K and other micronutrients.

In our study,12 children had tremors at time of presentation. However, after treatment majority of children tremors disappeared within 15 days (6) which is comparable to studies done by Bajaj M et al., Brahmbhatt et al. Agarwal R & Holla et al.[4, 15, 20,21]

In our study, 44.4% (8) 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 (5.5%). These results were comparable to various other studies.[4, 9]

As in this syndrome, etiology could not be pinpointed, treatment comprised of symptomatic treatment of anaemia and nutritional deficiency 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. For severe tremors phenobarbitone (3-5 mg/kg/day) may be required to decrease the intensity.[21,22] The tremors subside slowly. Initially there is gradual reduction in the amplitude and severity, then the tremors become intermittent and finally stop. Propanolol and chlorpromazine are other drugs which can be used to control tremors.[23,24]

The etiology of ITS is still elusive. Vit. B12 deficiency has been found to be associated in many studies. It is usually seen in children who are exclusively breast-fed for prolonged periods by vegan mothers. The low levels of vitamin B12 and its transport protein Transcobalamine II (TC II) in the cerebrospinal fluid (CSF) may be responsible for the neurological features of this syndrome. Iron, Magnesium and zinc deficiency have also been postulated to cause ITS. It is usual to find direct or indirect evidence of associated other nutritional deficiencies like protein, vitamin A, D, K and other micronutrients. Other speculations for its etiology include viral encephalitis and degenerative processes.

We concluded a positive correlation between Vitamin B12 deficiency, maternal and infant diet, adverse developmental consequences and ITS syndrome. However, the sample size of our study was too small and 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 is associated with infantile tremor syndrome (ITS). ITS must be considered in an infant on exclusive breast feeding with mother

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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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Declarations

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