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Study of serum folate and ferritin levels in patients of infantile tremor syndrome

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ABSTRACT

Background: Infantile tremor syndrome (ITS) is a very common clinical entity. The etiology of ITS remains obscure. Various hypothesis has been proposed including vitamin B12 deficiency. But it remains to be seen whether there are other contributory factors also. So, this study was conducted to study serum folate levels, serum ferritin levels and type of anemia in patients with infantile tremor syndrome.

Methods: The study was a prospective study carried out in the inpatients of department of pediatrics, SSG hospital. Those patients who had clinical features of infantile tremor syndrome but had not received any hematinics or blood transfusion in the past were included in the study. A total of 40 patients were studied. These patients were studied according to the set proforma and were subjected to routine hematological investigations like complete blood count, peripheral smear, blood indices, CRP and serum ferritin and folate levels.

Results: Anemia of varying degree was present in all the patients. None of the patients showed low serum folate levels. Serum ferritin levels were low in 2 patients (5%).

Conclusions: Folic acid deficiency does not occur and play any role in the etiology of ITS. Iron deficiency is seen in a very small proportion of patients with ITS.

Keywords: Infantile tremor syndrome (ITS), Serum folate, Serum ferritin

INTRODUCTION

Infantile tremor syndrome is a clinical state comprising of tremors, delayed development, abnormal skin pigmentation and anemia affecting infants between 6 to 24 months of age. The disease has been reported not only from India but other countries like Afghanistan, Australia, Turkey, France, America, Italy etc also. Different researches have coined different terminologies for this clinical entity like nutritional dystrophy and anemia, Infantile Meningoencephalitic Syndrome, Syndrome of tremors in infants, Syndrome of tremors, mental regression and anemia in infants, Nutritional Tremor Syndrome, megaloblastic anemia of infancy,

Vitamin B12 deficiency in Indian infants, Infantile neuromotor pallor-pigmentation syndrome etc. ¹⁻⁸

Though the disease was described as early as 1957 from Hyderabad by Dikshit, the etiology of this disease still remains a mystery. Many studies have been done to find out the exact cause of this disease. Various hypothesis has been put forward like nutritional deficiency of various trace elements, viral infections, degenerative process, heavy metal deposition in basal ganglia etc. Jadhav from CMC, Vellore was first who thought it to be due to vitamin B12 deficiency. A study by Rimpi Singla found low vitamin B12 levels in patients with ITS and their mothers. However some studies didn't find a single

infant with ITS having megaloblastic anemia. Suraj Gupta supports the etiological cause to be due to iron deficiency anemia. Author was curious to know the status of folic acid and iron in patients of ITS. Is it folic acid deficiency or pure iron deficiency or vitamin B12 deficiency or combined deficiency. Hence this study was undertaken to know the serum folate and ferritin levels in patients with ITS which is a silent epidemic in the vicinity of vadodara.

The aim of the present study was to know the type of anemia and serum folate and ferritin levels in patients with infantile tremor syndrome.

METHODS

The study was a prospective study carried out in the inpatient department of pediatrics, SSGH. 40 patients were included in the study. Those patients who showed clinical features of ITS like tremors, hyperpigmentation of the skin, developmental delay or regression and anemia were enrolled in the study provided there was no past history of ingestion of hematinics or blood transfusion.

Admitted patients were studied as per set proforma and subjected to blood investigations like CBC with indices, peripheral smear, serum folate and serum ferritin levels. Serum C reactive protein was also assessed qualitatively using latex agglutination as serum ferritin behaves as acute phase reactant and infections are common presenting feature in patients with infantile tremor syndrome. Serum folate and ferritin levels were analyzed using Immulite 2000 Analyzer.

RESULTS

Total 40 cases were studied. 25 patients (62.5%) were males, while 15 patients (37.5%) were females. All the patients were in the age group of 6-18 months. These patients were predominantly vegetarian who did not eat

non-vegetarian diet or could not afford to do so.⁷ Patients (17.5%) of the patients came from urban domicile while 33 patients (82.5%) had a rural domicile.

Most of the patients were brought to medical facility because of some form of febrile illnesses. Tremors, pallor and developmental delay were complained of in a lesser proportion of patients. Developmental delay and pallor though present for long period, patients seek medical attention only after onset of some acute illness.

Bronchopneumonia (57.5%), acute gastroenteritis (15%) and congestive cardiac failure (25%) were the most common associated morbidities. One of the most common etiological factor was exclusive breast feeding (67.5%) or inappropriate weaning (32.5%). 60% of the patients were weighing below 60% of weight for age.

Pallor (100%), pigmentary changes of the skin (100%), hair changes (100%) and developmental delay (97.5%) were the most common clinical signs. Tremors were seen in 7 patients (17.5%).

Anemia of varying degrees was present in all the patients. The table signifies the frequent occurrence of severe and moderate degrees of anemia in ITS patients. Blood transfusion was required in 20 patients (50%) (Table 1).

Table 1: Hemoglobin levels in patients with ITS.

Hb (g/dl)	No. of patients	Percentage (%)
< 7	21	52.5
7-9	14	35
9-11	5	12.5
>11	0	0

Macrocytic anemia was present in 25 patients (62.5%); normocytic anemia was seen in 13 patients (32.5%) and a microcytic anemia which was proved by serum ferritin levels to be iron deficiency anemia was seen in 2 patients (5%).

Table 2: Morphology of anemia in ITS patients.

Macrocytic		Normocytic		Microcytic	
Normochromic	Hypochromic	Normochromic	Hypochromic	Normochromic	Hypochromic
19	6	-	13	-	2

Peripheral smear showed a predominantly macrocytic with normocytic/hypochromic picture in 25 patients (62.5%), a dimorphic picture in 13 patients (32.5%) and a microcytic hypochromic picture in 2 patients (5%). (Table 2). Normal range of serum folate: 4-20 ng/ml. ¹¹ In the Table 3, a low serum folate level was not seen in any of the patient.

Table 3: Serum folate levels in its patients.

Serum folate	Number	%
<4 ηg/ml	0	0
4-20 ηg/ml	30	75
>20 ng/ml	10	25

Serum ferritin level in the study population

The gold standard for the diagnosis of iron deficiency is examination of stainable iron in the bone marrow. ¹² But this is an invasive procedure. In the present study, serum ferritin level was estimated to know the status of iron in patients with infantile tremor syndrome. However, since serum ferritin behaves as an acute phase reactant, serum CRP was used as a pointer of infection or inflammation.

Normal level of serum ferritin is $10-140 \mu g/l$. Out of 40 patients, only 2 patients were found to have serum ferritin levels less than $10 \mu g/l$ while in 13 patients' serum ferritin level was normal and elevated in 25 patients. Serum ferritin levels could be elevated in patients with vitamin B12 deficiency. From above we can assume that pure iron deficiency is not the cause of anaemia in most of patients of infantile tremor syndrome (Table 4).

Table 4: Serum ferritin level in patients of infantile tremor syndrome.

Serum ferritin (µg/l)	No. of patients
<10	2 (5%)
10-140	13 (32.5%)
>140	25 (62.5%)

However, in the presence of infection or inflammation, a serum ferritin level less than 25 $\mu g/l$ to 50 $\mu g/l$ can be a fairly good indicator of decreased iron stores. 11 There were 2 patients who had normal serum ferritin levels and their serum c-reactive protein was also positive. One patient had positive serum c-reactive protein with serum ferritin level of 15.1 $\mu g/l$. He could have had iron deficiency anemia as in the presence of inflammation, a serum ferritin level less than 25 $\mu g/l$ is suggestive of iron deficiency anemia.

Table 5: Status of serum ferritin level with reference to c-reactive protein (CRP).

Status Serum	Serum ferritin level		
ferritin level (μg/l)	<10	10-140	>140
Serum CRP +ve	0	2 (5%)	16 (40%)
Serum CRP -ve	2 (5%)	11 (27.5%)	9 (22.5%)

Table 6: Possibility of iron deficiency anemia in relation to serum ferritin levels.

Serum ferritin level (μg/l)	Presence of iron deficiency anaemia
<12	Certain
12-20	Highly likely
20-60	Possible
60-100	Rare
>100	Unlikely

The other patient with positive c-reactive protein had a serum ferritin of 75.3 μ g/l (Table 5).

As per Dr Usha Rusia, the possibility of iron deficiency anemia can be seen as in Table 6.¹⁵

From the above table, it is seen that 27 patients had serum ferritin level above 100 $\mu g/l$. Iron deficiency anemia is very unlikely in these patients. Four patients had serum ferritin level above 60 $\mu g/l$ which suggests that the possibility of iron deficiency anemia in these patients is rare. Six patients had serum ferritin level between 20-60 $\mu g/l$. However, c-reactive protein of all these 6 patients was negative. It possible that these patients could be having a coexisting iron deficiency anemia. One patient had serum ferritin 15.1 $\mu g/l$ whom we assume to have iron deficiency anemia as c-reactive protein of this patient was positive. Two patients had serum ferritin level less than 12 $\mu g/l$ who had confirmed iron deficiency anemia which was evident from their blood indices and peripheral smear also.

Table 7: Serum ferritin level in the present study.

Serum ferritin level (µg/l)	No. of patients
<12	2 (5%)
12-20	1 (2.5%)
20-60	6 (15%)
60-100	4 (10%)
>100	27 (67.5%)

Outcome

None of the patients in the study expired. On discharge, the patients showed improvement in weight, hemoglobin status, general condition and interest in surroundings.

DISCUSSION

In the present study, the male: female ratio was 1.6:1. This may not represent the true incidence of sex distribution as the admission of male patients outnumbers that of females in our hospital. Dr. Rimpi Singla9 found a male: female ratio of 1.7:1 in her study. Sachdeva observed a ratio of 3:2 while Bajpai and Ramakumar observed a ratio of 2:1.4.5,16

Maximum incidence in the study was seen in the age group of 7-12 months. Sachdeva reported maximum incidence between 12-18 months while Ramakumar and Bajpai observed maximum incidence between 6-12 months. Mathur reported maximum cases between 13-18 months. 4,16-18

In this study 27 patients (67.5%) were exclusively breast fed, 13 (32.5%) patients were inappropriately weaned while none was adequately weaned. The etiological role of delayed or inappropriate weaning has also been observed by Mathur18 and Sachdeva.⁴

The diet of the family was predominantly vegetarian. Rama kumar and Pandove in his study of 40 patients found 75% mothers to be vegetarian while 25% were non-vegetarian. Renault F from France observed neuropathy in two cobalamin deficient breast fed infants of vegetarian mothers. Smolka V demonstrated metabolic complications and neurological manifestations of vitamin B12 deficiency in children of vegetarian mothers.

In this study pallor was present in 40 patients (100%), pigmentary changes of the skin 40 patients (100%), hair changes 40 patients (100%), developmental delay 39 patients (97.5%), hepatomegaly 16 patients (40%), tone abnormalities 12 patients (30%), chubby look 10 patients (25%) and tremors were observed in 7 patients (17.5%). Mathur found tremors, light coloured hairs, delayed dentition, delayed mental and emotional development in all his 30 patients.¹⁸ Sachdeva found normal motor, mental and emotional development before the onset of disease.4 However, all his patients had mental retardation at the time of presentation. Ramakumar found tremors in 64 infants (59.1%), hyperpigmentation of the skin was found in 95 patients (88.8%), sparse, dry and light brown hair in 105 cases (98.1%), chubby appearance in 96.2% cases and developmental delay in 80.3% cases. 16 Mathur found tremors in all his 30 patients with variable involvement of limbs, faces and tongue.¹⁸ Arya found generalized tremors in 6 patients (66.6%) and focal tremors in 3 patients (33.4%) out of his 9 patients with a mean duration of tremors of 20 days.²¹ Ramakumar found generalized tremors in 14 patients and focal tremors in 50 patients out of 107 patients.¹⁶

Most of these patients presented to the hospital because of acute morbidities in the form of bronchopneumonia, acute gastroenteritis, congestive cardiac failure etc. Associated features like pallor, developmental delay and skin pigmentation though present did not alert the parents to seek medical care. Tremors were present in 7 patients (17.5%) only on presentation.

Anemia was present in all the cases. 52.5% patients had severe anemia. Bajpai found 87.5% (117/134) of his patients to be anemic. Ramakumar and Pandove found 98/101 of his patients to have Hb <10 g/dl. Hb varied from 2 g/dl to 11.5 g/dl, the average being 6.8 g/dl. Sharda8 had all his patients with Hb <11 g/dl.

Macrocytic anemia was present in 25 patients (62.5%); normocytic anemia was seen in 13 patients (32.5%) and a microcytic anemia which was proved by serum ferritin levels to be iron deficiency anemia was seen in 2 patients (5%). Ramakumar observed macrocytic anemia in 29.6% cases, normocytic anemia in 69.1% cases and microcytic anemia in 1.2% of cases. The red blood cells were normochromic in 43.2% cases and hypochromic in 56.7% cases. Mathur18 found microcytic hypochromic anemia in 26 patients (86%) while normocytic hypochromic was seen in 4 out of 30 patients (13.3%). Mahajan reported

dimorphic hypochromic anemia.²² Bone marrow aspiration also showed variable picture of megaloblastic, dimorphic and normoblastic erythropoeisis. Sachdeva found a normoblastic bone marrow in 83.8% of cases and megaloblastic in the remaining 15.2% cases.⁴ Srikantia found a mean Hb 7.1 g/dl with a range of 4.5-11 g/dl and megaloblastic hematopoeisis in most patients.^{6,9} A predominantly normoblastic bone marrow was found by Pohowalla, Kaul, Bajpai and Arya.^{2,3,17,21} However Jadhav found a megaloblastic bone marrow in all his patients.⁷

None of the patients had low serum folate levels. Out of 40 patients, only 2 patients were found to have serum ferritin levels less than 10 μ g/l while in 13 patients' serum ferritin level was normal and elevated in 25 patients. Though serum ferritin behaves as an acute phase reactant and as most of the patients with ITS presented with infections, still the possibility of iron deficiency anemia was seen in less than 9 patients (22.5%)

Many workers like Jadhav, Srikantia, Ingle, Deshpande and Garewal found a good response to vitamin B12 alone and they believed vitamin B12 deficiency to play a major role in the etiology of infantile tremor syndrome. 7.6,23,24 Ramakumar found a good response of folic acid supplementation. 16 Bajpai found normal serum vitamin B12 levels in all his cases. 17 Rimpi Singla found serum vitamin b12 levels to be low in 93.3% patients of infantile tremor syndrome and 83.4% of their mothers also. 6

The normal serum folate levels found in the study suggests that the macrocytic/normocytic anemia seen in these patients may be solely due to vitamin B12 deficiency.

The present study did not show a single patient with folic acid deficiency.

CONCLUSION

Unlike vitamin B12 deficiency, folate deficiency is not the cause of anaemia in patients with infantile tremor syndrome. Folic acid deficiency does not exist in patients with infantile tremor syndrome. Similarly, pure iron deficiency is not commonly found in present study. The occurrence of iron deficiency anaemia might be a possibility in one fourth number of cases which may coexist with B12 deficiency. However, iron deficiency anaemia is as such common in the age group of 7-24 months. Hence it would be wiser to do blood indices/serum ferritin/ transferrin receptor assay for confirmation of iron deficiency anaemia. Wherever lab facility is not available, it would be better to give iron supplementation along with vitamin B12 to patients with infantile tremor syndrome.

From above it is concluded that 95% cases of anaemia occurring in patients with infantile tremor syndrome is

non-microcytic type and it might be due to vitamin B12 deficiency and not due to folic acid deficiency.

Supplementation of vitamin B12 is must. Folic acid supplementation is not required and iron supplementation may help to improve haemoglobin status in some cases.

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Institutional Ethics Committee

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