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Case Report

Paediatrics Section

Phenytoin Intake in Mothers Resulting in Early Onset Infantile Tremor Syndrome in Children: A Report of Two Cases

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ABSTRACT

Infantile Tremor Syndrome (ITS) is a complex neurological syndrome that affects exclusively breastfed infants, typically seen between 9 to 12 months of age. However, in the present case, it started at the ages of three months and four months, respectively. ITS is characterised by the presence of megaloblastic anaemia-like features, developmental regression, and the onset of tremors. Here, authors report two cases of ITS, whereby megaloblastic anaemia was present because of drug (phenytoin) intake in mothers. Phenytoin intake in mothers leads to low serum vitamin B12 levels in both the mother as well as the baby. Early onset of ITS in progeny has very rarely reported in the literature. Exclusive breastfeeding is generally considered nutritionally sufficient for infants below six months of age, and the onset of ITS is typically associated with the improper introduction of weaning foods beyond six months. However, in the present cases, although the babies were exclusively breastfed, they developed nutritional deficiencies that manifested as early onset ITS. Phenytoin intake and the associated vitamin B12 deficiency in the mothers are proposed as the causes of this presentation. Such an early presentation is also associated with severe pneumonia and was found to be fatal in one of the two reported causes. The authors would like to make a pertinent point that if pregnant mothers are taking any drugs that can lead to vitamin B12 deficiency, they should ideally be checked with relevant investigations and receive supplements if required, to prevent potentially fatal outcomes in their children.

Keywords: Drug intake, Infancy, Pregnant female, Vitamin B12 deficiency

CASE REPORT

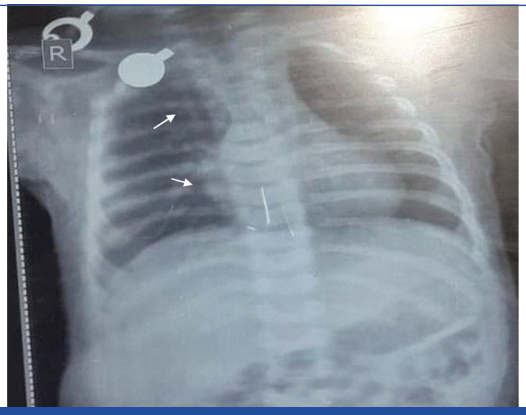
Case 1

A three-month-old female child presented to the paediatric emergency department with complaints of tremors for the past 15 days. She experienced 18-20 episodes per day, each lasting for around 10 seconds. Additionally, she had a fever, cough, and difficulty breathing for the last three days. The fever was undocumented and not associated with any rash, bladder or bowel complaints, ear discharge, or any other complaints. Cough and difficulty breathing had progressively increased for the past three days. The baby was a firstborn child in a non consanguineous marriage, with no history of previous hospitalisation for similar complaints. The mother had been on phenytoin for epilepsy for the past five years. No other relevant antenatal history was noted, and there was no history of chronic illness or congenital diseases in the family.

On examination, the child was febrile (axillary temperature: 102.3°F), inattentive to surroundings, lacked a social smile, appeared listless, had pallor, hyperpigmented knuckles, and scanty brown hair [Table/Fig-1], along with coarse tremors of the tongue and all four limbs, which are characteristic of nutritional tremor syndrome. The vital parameters were as follows: heart rate: 152 bpm; respiratory rate: 57/min; SpO_2: 98% on oxygen. Systemic examination revealed chest retractions, along with crepitations on auscultation. Other systemic findings were within normal limits. A chest X-ray suggested consolidation [Table/Fig-2]. A complete haemogram showed a haemoglobin level of 9.4 gm%. The Mean Corpuscular Volume (MCV) was 100.4 fL, Mean Corpuscular Haemoglobin (MCH) was 32.4 pg, and the Red Cell Distribution Width (RDW) was high at 67.6 fL, suggesting a dimorphic picture on the peripheral smear [Table/Fig-3,4]. Serum B12 levels of the baby were 151.2 pg/mL,

[Table/Fig-1]: Case 1: Child with Infantile Tremor Syndrome (ITS) showing apathetic look, sparse hypopigmented hair, and skin hyperpigmentation.

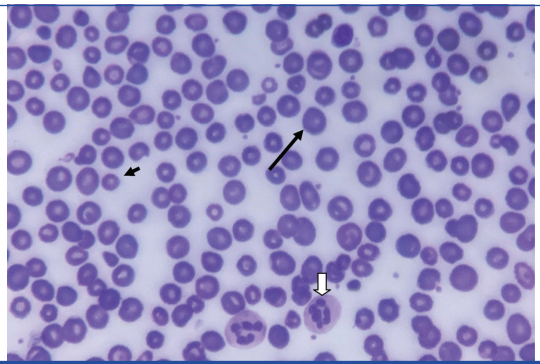
which is below normal for age. Serum homocysteine (59 µmol/L) and methylmalonic acid levels (0.62 µmol/L) were found to be elevated. Since the child was exclusively breastfed, the serum B12 levels of the mother were also evaluated, and came out to be low 135.7 pg/mL.



[Table/Fig-2]: Case 1- Chest X-ray suggestive of consolidation in right middle and upper lobes (arrows).

Test	Case 1	Case 2	Normal value
Haemoglobin (gm%)	9.4	5.2	11.0-16.0
Total Leukocyte count (/mm^3)	5800	3000	4000-10000
Platelet count (/mm^3)	3.1 lacs	73,000	1 lakh-3 lakh
Mean Corpuscular Volume (MCV) (fL)	100.4	114.2	80-100
Mean Corpuscular Haemoglobin (MCH) (pg)	32.4	34.4	27-34
Mean Corpuscular Haemoglobin Concentration (MCHC) (gm/dL)	32.3	39.1	32-36
RDW-Standard Deviation (SD) (fL)	67.6	87.2	35-56
RDW-Coefficient of Variation (CV) (%)	18.1	20.8	11-16
Peripheral blood film	Dimorphic picture	Macrocytic picture	Normocytic normochromic picture
Serum vitamin B12 levels			
Serum Vitamin B12 levels of child (pg/mL)	151.2	149.3	239-931
Serum Vitamin B12 levels of the mother (pg/mL)	135.7	162.0	239-931
Serum calcium levels (mg/dL)	8.3	7.2	8.5-10.5

[Table/Fig-3]: Complete haemogram of child.



[Table/Fig-4]: Peripheral blood film depicting dimorphic picture {Macrocytes (arrow) and Microcytes (small arrow)} and Hypersegmented neutrophils (white arrow) {Leishmann stain at 100x magnification}.

The differential diagnosis included nutritional anaemia (B12 deficiency/folate deficiency), pernicious anaemia (unlikely because of the age of presentation and absence of other clinical features like glossitis), and aplastic anaemia (leukocyte and platelet counts were normal). Raised methylmalonic acid and homocysteine levels were suggestive of vitamin B12 deficiency. The clinical features of fever with cough and respiratory distress, along with crepitations on auscultation and chest X-ray findings, were in favour of lobar pneumonia. Another differential diagnosis considered was acute bronchiolitis; however, the X-ray findings did not correlate with bronchiolitis).

The child was managed on the lines of pneumonia with intravenous Amoxiclav (150 mg twice a day) for five days and an injection of vitamin B12 (500 µg intramuscularly once a week). The child was discharged in a clinically stable condition, receiving 500 µg of vitamin B12 weekly for the first two months. The mother was also given a single intramuscular dose of 1000 µg of vitamin B12. Cough and respiratory distress settled after seven days of antibiotics, and the tremors resolved within two months of initiating vitamin B12 treatment. Vitamin B12 levels normalised (1020 pg/mL) after three months of follow-up.

Case 2

A four-month-old female child presented to the paediatric emergency department with complaints of cough for the past 10 days and difficulty breathing for the past three days. The parents had noticed tremors around one month ago; however, they did not seek medical advice at that time. The tremors had progressively increased from 7-8 episodes per day one month back to around 20 episodes per day at the time of presentation, with each episode lasting 15-20 seconds. The mother had been on phenytoin since the age of 15 for epilepsy, which she continued during pregnancy and lactation. The birth history was uneventful, and there was no history of previous hospitalisations.

On examination, the child had severe pallor, scanty hair, skin hyperpigmentation, and coarse tremors [Table/Fig-5]. The child had a fever (temperature: 103°F), tachycardia (heart rate: 164 beats/min), and tachypnoea (respiratory rate: 57/min). Systemic examination findings indicated nasal flaring, accompanied by severe subcostal and intercostal retractions. Clinical and radiological features were suggestive of severe pneumonia [Table/Fig-6]. A complete haemogram revealed a macrocytic picture with an MCV of 114.2 fL, haemoglobin of 5.2 gm%, and TLC of 3000 cells/mm^3, with lymphocytic predominance (79% lymphocytes) [Table/Fig-3]. The child was exclusively breastfed. Suspecting vitamin B12 deficiency, further history was extracted, which revealed that the mother had been taking phenytoin for the last 13 years without any folic acid or B12 supplementation. The mother also exhibited pallor and

[Table/Fig-5]: Case 2- Child with nutritional tremor syndrome having sparse hair, pallor, and hyperpigmented knuckles.

[Table/Fig-6]: Case 2- Chest X-ray suggestive of consolidation in right lung (arrow).

hyperpigmented knuckles [Table/Fig-7]. Serum B12 levels were low in both the child (149.3 pg/mL) and the mother (162 pg/mL). Serum homocysteine and methylmalonic acid levels in the child (serum homocysteine: 64 µmol/L, serum MMA: 0.51 µmol/L) were more than the normal reference ranges. Differential diagnosis of vitamin B12 deficiency anaemia and folate deficiency anaemia were considered, and based on laboratory parameters, a diagnosis of vitamin B12 deficiency was made. The child was managed with one unit of packed red blood cell transfusion, parenteral antibiotics (i.v. Amoxycillin 200 mg twice daily), and intramuscular vitamin B12 (500 µg per day). However, the child developed respiratory failure with cardiorespiratory shock on day 3 of admission, and despite the best possible efforts, could not be saved.

[Table/Fig-7]: Hyperpigmented knuckles- seen in the hands of a mother on Phenytoin- suggesting Vitamin B12 deficiency.

DISCUSSION

The ITS has been described as a clinical syndrome presenting in exclusively breastfed children >six months of age, characterised by apathy, irritability, developmental delay, feed refusal, tremors, and failure to thrive. If untreated, it can even lead to coma and death [1-4]. As per the literature reviewed, ITS has earlier been reported in exclusively breastfed infants beyond six months due to improper introduction of weaning foods, resulting in multiple micronutrient deficiencies [5-7]. Although, a case has been reported in infants younger than six months [8]. Some authors have reported cases of phenytoin-induced megaloblastic anaemia in women of reproductive age group [9,10]. Reports have also indicated that ITS secondary to nutritional vitamin B12 deficiency in breastfeeding infants have also been reported [11]. Vitamin B12 deficiency in infancy is associated with severe neurological manifestations in some cases [12,13]. However, megaloblastic anaemia in mothers on antiepileptic drugs, resulting in early neurological manifestations in infants, has rarely been reported. Furthermore, existing public health programs have focused on the development of neural tube defects in foetuses with the use of antiepileptic drugs such as phenytoin during pregnancy. However, due importance has not been given to the postnatal consequences of phenytoin use in mothers during the antenatal period and lactation. Infants of such mothers may present with severe manifestations of B12 deficiency in early infancy, usually associated with serious infective complications, which can be life-threatening [4].

A plausible explanation for this presentation is that the child may not have received complete immunisation by that time, leading to the development of serious and sometimes fatal infections. Authors have reported two cases of early and severe presentation of megaloblastic anaemia in infancy, one of which was associated with severe respiratory illness at presentation and landed in respiratory failure and death. Such mortality is preventable by the administration of B12 supplements to both mother and child [14]. This further highlights the importance of early identification and prevention of the condition. Comprehensive research is required on this topic to identify more such cases and establish a causal relationship between phenytoin use in the mother and severe B12 deficiency in the child.

CONCLUSION(S)

It is hereby concluded that phenytoin intake in mothers during the antenatal and postnatal periods can result in severe vitamin B12 deficiency in the baby, which may go undetected until the child develops manifestations like apathy and tremors. The child may also experience severe infective complications. Hence, early identification is essential to prevent the development of nutritional tremor syndrome in such babies by supplementing vitamin B12, along with iron and folic acid, for both the mother as well as the child.

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