CASE REPORT

Reversible Cerebral Atrophy in Infantile Tremor Syndrome

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Background: We report changes in MRI brain of children with Infantile Tremor Syndrome (ITS) at the onset of illness and following treatment. **Case characteristics**: Three children with infantile tremor syndrome were assessed for changes in brain neuroimaging at admission and at follow-up visit. On MRI, all children had mild to severe diffuse cerebral atrophy, which reverted back to normal on follow-up visits. **Outcome**: Children with infantile tremor syndrome have reversible diffuse cerebral atrophy on neuroimaging.

Key words: *Management, Outcome, Tremors*.

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Infantile Tremor Syndrome (ITS) is a clinical state characterized by tremors, anemia, pigmentary skin disease, regression of mental development, and hypotonia of muscles [1]. Studies suggest that the most probable etiology of ITS is nutritional deficiencies [1]. Despite predominance of neurological symptoms, very few studies have documented neuroanatomical and/or neurophysiologic changes in ITS [2]. Reduced brain substance has been documented in children with ITS [3]. In contrast several studies in children with Protein Energy Malnutrition (PEM) have documented cerebral atrophy [4,5] and its reversibility after treatment [5].

We report three cases of ITS diagnosed clinically based on above definition with MRI findings described at diagnosis and on follow-up after 6-18 months. All patients were treated with WHO protocol for management of undernutrition with or without propranolol to control tremors. Developmental Quotient (DQ) of all cases was assessed using Developmental Screening Test (DST). Written informed consent was obtained from parents of all the children.

CASE REPORT

Case 1

A 10-month-old exclusively breastfed female child was admitted with the complaints of abnormal rhythmic jerky movements of both hands, feet, tongue and head nodding for 6 days prior to admission. Movements were suggestive of coarse resting tremors. Child was having moderate wasting and normal height for age. Head circumference was below –2 SD for age and sex. Developmentally, child was able to sit without support, had a palmar grip, and was able to tell monosyllables before the onset of disease (DQ 92±5). At admission, she was not able to sit without support and only cooing was present (DQ 44±5). Blood investigations suggested predominantly microcytic hypochromic anemia with normal serum levels of albumin and Vitamin B_{12}. MRI brain suggested mild diffuse cerebral atrophy (***Fig*.1a** and **1b**). Nutritional rehabilitation was continued at home after 5 days of admission. Follow-up of the patient was done after 17 months when she had normal development for her age (DQ 84±5). Anthropometrically she had normal weight for age, and length. Head circumference was still below -2 SD. MRI scan of brain showed improvement in cerebral atrophy with no sulcal prominence or ventricular enlargement (***Fig*.1c** and **1d**).

Case 2

An 8-month-old exclusively breastfed female child admitted with abnormal rhythmic movements of tongue and upper extremities and tremulous cry, along with loose motions for two days. She was having normal weight for height and mild stunting with head circumference <-2SD. She had normal development before illness (DQ 90±5) with regression of milestones during tremors (DQ 74±5). Child was mostly remaining in a flexed posture with fisting of the palms. Tremors used to increase on crying but disappeared on sleep. She stayed in hospital for 11 days and was treated with oral rehydration solution, Zinc sulfate, Vitamin B_{12} and Folic acid. Propranolol was given to control tremors. Blood investigations suggested normocytic hypochromic anemia with normal serum levels of albumin and Vitamin B_{12}. MRI brain was suggestive of mild diffuse cerebral atrophy (***Fig*. 2a** and

2b), which showed reversal of atrophy on follow up after 15 months (***Fig.* 2 c** and **2d**) with normal development (DQ 100±5).

***Case* 3**

A 13-month-old female with inadequate complementary feeding was admitted with complaints of not able to sit for about 6 weeks, cough for 4 days and abnormal cry, head nodding and rhythmic movements in extremities for one day. Severe pallor was present along with knuckle hyper-pigmentation. Child was having severe wasting, mild stunting and head circumference <-1SD (DQ 25±5). Blood investigations showed moderate polychromasia, mild anisopoikilocytosis, mainly normocytes, tear drop cells, target cells with normal serum albumin and sub-normal serum vitamin B_{12} levels. MRI brain suggested diffuse cerebral atrophy with prominent CSF spaces including sulci and sylvian fissures of both hemispheres and enlarged lateral ventricles (***Fig.* 3a** and **3b**).On follow-up, child was again admitted at the age of 20 months. Anthropometrically she had normal weight for height with mild stunting and mid arm circumference 14 cm. Head circumference was <-1SD with normal development (DQ 78±5). MRI brain showed reversal of atrophy and it revealed minimal residual prominence of sylvian fissures (***Fig.* 3c** and **3d**).

DISCUSSION

We demonstrated reversibility of cerebral atrophy by MRI brain in cases of ITS, after nutritional rehabilitation. All three cases had various grades of cerebral atrophy on MRI during acute tremor phase of ITS. Bajpai, *et.al.* [3] observed a reduced brain substance with normal sized skull in majority of cases of ITS on Pneumoencephalo-graphy [3]. Other cross-sectional studies [2,6] have done CT/ MRI scan during tremor phase of ITS and demonstrated cerebral atrophy, but none of these studies did follow-up neuroimaging. Ozer EA, *et al.* [7] described two cases of tremors in infantile cobalamin deficiency and cerebral atrophy on CT scan [7]. However, cobalamin deficiency is not constantly present in all patients of ITS, as shown in our series in which only one child had sub-normal vitamin B_{12} levels.

Reversibility in cerebral atrophy has not been documented in reference to ITS. Previous studies have reported reversible cerebral shrinkage in Kwashiorkor on MRI of twelve children aged 6 to 37 months [5]. At 90 days, the cerebral changes had resolved in nine and improved substantially in the remainder. Improvement in brain size was apparent on day 30 of nutritional rehabilitation in the majority of Kwashiorkor patients. This improvement in brain size was attributed to fluid shifts between various compartments and to a lesser degree to fat or protein abnormalities in the brain. It is postulated that fluid moves out of intravascular spaces as a result of decreased colloid osmotic pressure, floods the subarachnoid spaces, dilates the ventricles, and widens the cisternal spaces and sulci. When nutrition is improved the plasma proteins rise, the extracellular fluid moves

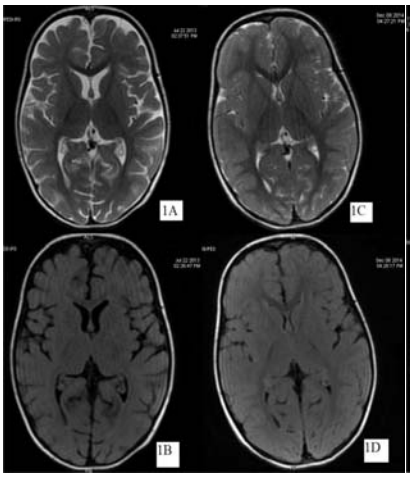

FIG.1

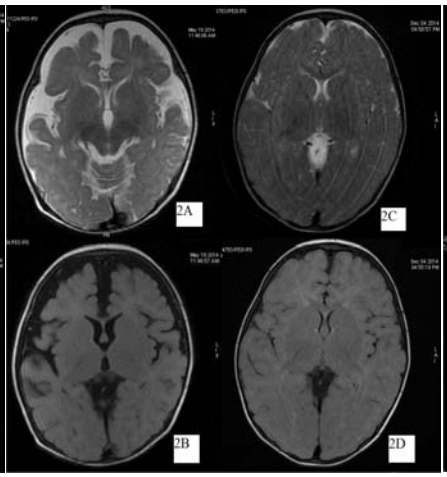

FIG.2

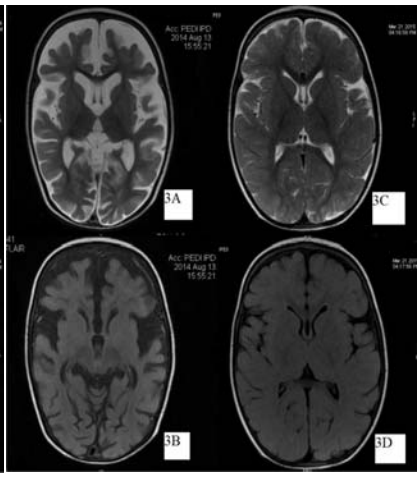

FIG.3

Fig 1-3. *Flair and T2W sequence of MRI brain in axial plane showing: mild cerebral atrophic changes (1A & 1B), moderate atrophic changes appearing as prominent sylvian fissure and CSF spaces in frontal region (2A & 2B), significant atrophic changes appearing as prominent sylvian fissure and CSF spaces in temporo-fronto-parietal region (3A & 3B). On follow up with same sequences of brain in axial plane is within normal limits (1C, 1D, 2C, 2D, 3C & 3D).*

back into the intravascular space [5]. In our case series, no patient had reduced levels of serum albumin on admission, therefore the above theory does not explain the reversible cerebral atrophy in our patients.

A 11-month-old infant with malnutrition, failure to thrive and marked cortical atrophy on brain CT has previously been described [8]. Improvement of the maternal-infant relationship, combined with appropriate nutrition, transformed the infant within 2 months into a normally developing baby with body weight and head circumference within the normal percentile range. A corresponding improvement was found in the brain CT [8].

All our cases on follow-up showed marked improvement in their anthropometric and developmental measures. The corresponding neuroimaging reversibility of cerebral atrophy suggests the role of dietary management along with social stimulation and support. Primarily ITS seems to be related to undernutrition [1] and is reversible with nutritional rehabilitation. Therefore, this series suggests a neuro-anatomical evidence of effectiveness of nutritional rehabilitation in management of ITS.

Contributors: RG, AP, JM: involved in the study concept, designing and manuscript writing; RG: did assessment of patients; PG: did radiological assessment; PV: did biochemical analysis. The final manuscript was approved by all authors.
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