Case Report: Early Onset of Fragile X Associated Tremor and Ataxia Syndrome: A Case Report from Iran

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Background: Different alleles of Fragile X Mental Retardation1 (FMR1) gene with separate molecular etiologies cause Fragile X Syndrome (FXS) and Fragile X-associated Tremor and Ataxia Syndrome (FXTAS). Premutation alleles with 55 to 200 repeats in the FMR1 gene lead to FXTAS. It is carried by 1 in 209 women and 1 in 430 men. FXTAS commonly appears in 50- to 70-year-old adults.

Case Presentation: An 11 months old boy was referred to the hospital due to clinical presentations of productive cough seizure, mental disability, and ataxia. Magnetic Resonance Imaging (MRI), Electroencephalography (EEG), hematology, biochemistry, hormone, and genetic tests were done. Triplet repeat PCR (TP PCR) showed 99 CGG repeats as permutation alleles.

Conclusion: In this study, the authors reported the early onset of FXTAS in an 11 months old boy for the first time.

Keywords: Fragile X syndrome, Tremor, Ataxia

ABSTRACT

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Introduction

Fragile X Syndrome (FXS) and Fragile X-associated Tremor and Ataxia Syndrome (FXTAS) are two separate disorders with different molecular etiologies. Silencing of the FMR1 (FMRP translational regulator 1) gene followed by full mutation with more than 200 CGG repeats causes FXS which is on the X chromosome. However, premutation alleles with 55 to 200 repeats in the FMR1 gene cause FXTAS. They induce increased production of mRNA, which leads to a new function for them and consequently causes FXTAS as the most severe form [1, 2]. According to previous investigations, premutation alleles are commonly carried by 1 in 209 women and 1 in 430 men [3, 4]. It is assumed that the lower frequency of this syndrome in women can be due to the existence of one normal X chromosome, which has a protective role for presenting features [5]. Premutation disorders commonly occur in adults aged 50-70 years [6]. FXTAS causes progressive cognitive decline and multisystem involvement and may induce diverse symptoms such as Parkinsonism, peripheral neuropathy, lower limb proximal weakness, and autonomic dysfunction. Furthermore, there are some clinical characteristics such as dementia, emotional liability, and peripheral neuropathy, as well as white matter abnormalities and global brain atrophy that can be observed on magnetic resonance imaging [6, 7]. In this case report, investigators present a boy with premutation in the FMR1 gene with early onset of FXTAS from Talesh City, Iran.

Case Presentation

An 11 months old boy, the second child of non-consanguineous parents, was referred to the hospital due to productive cough, seizure, mental disability, and ataxia. The first child in the family was aborted due to a heart anomaly. Magnetic Resonance Imaging (MRI) and Electroencephalography (EEG) were done. EEG was normal. Multi-planar and multi-sequential images of 1.5 Tesla MRI revealed widening of cerebrospinal space (subarachnoid, sulci, and interhemispheric fissure, which may be due to physiologic dilatation of subarachnoid space). No evidence of hydrocephaly, mass occupying space, or midline shift was shown. The brain stem, pons, cerebellum, cerebellopontine angle, and both orbits and globes had normal appearance (Figure 1).

The organic acids in urine measured by gas chromatography-mass spectrometry showed a normal pattern with no evidence for metabolic diseases. Blood amino acids chromatography test showed normal amino acids level. Immunoassay tests showed high thyroid-stimulating hormone (3.53 µIU/mL, reference 0.35-5.0 µIU/mL) and total thyroxin (8.10 µg/dL, reference ranges were based on sex/age- 4.4-10.8 for male and 4.8-11.6 for female) levels. General biochemistry test showed increased alkaline phosphatase in the blood (1300.0 U/L, the reference range for child up to 15yr: 180-1200 U/L), blood urine nitrogen=12.1 mg/dL, creatinine=0.44). Hematology test results were WBC=10680 mil/cumm, RBC=4.53 mil/cumm, hemoglobin=11.9 g/dL, hematocrit=36.5%, mean corpuscular volume=80.6 fl, mean corpuscular hemoglobin=26.3 pg, mean corpuscular hemoglobin concentration=32.6%, platelets 215000 mil/cumm, red cell distribution width: 14.9%. Regarding the laboratory results and clinical examinations, the first diagnosis was FXS. Therefore, genetic counseling was done and trip-let repeat primed PCR showed 99 CGG repeats as permutation alleles in an 11 months old boy with the clinical presentations of mental disability, tremor, and ataxia.

Discussion

FXTAS is a neurodegenerative disorder with 55 to 200 repeats of CGG in the FMR1 gene that occurs in adulthood [8]. In patients with premutation alleles, there is dys-regulation of cytokines and chemokine. Increasing age in patients with premutation worsens the deregulation and induces a decreased immune system activity compared to controls without the premutation [9]. In early childhood, neural deficits can be developed, but as was mentioned, age can be associated with diverse deficits [10].

Highlights

- In this study, an unusual presentation of premature mutation of the FMR1 gene was reported.
- Triplet repeat PCR (TP PCR) showed 99 CGG repeats as permutation alleles in an 11 months old boy with the clinical presentations of mental disability, tremor, and ataxia.
According to the previous investigation, the frequency of CGG repeats was positively correlated with the inclusion in CNS neurons but negatively with the onset and the death age of patients with FXTAS [11]. A previous study showed that 60.6 years of age was the mean age of FXTAS onset and mentioned the occurrence of ataxia two years after tremor [12]. The first report of FXTAS with a manifestation of kinetic tremor, cerebellar gait ataxia, Parkinsonism, and executive dysfunction was reported in men aged more than 55 years [13].

Up to now, there is only one published report of a 36-year-old man as the youngest patient with FXTAS who had alcohol and methamphetamine abuses [14]. In another study by Hagerman and colleagues in 2004, five females as the carriers of permutation alleles were reported. All of them presented tremor and ataxia later in life. Only one of them had an intermittent tremor in her 30s [15]. Although it was mentioned that changes in cerebellar or front-motor tract white matter changes could occur in patients with FXTAS before detecting clinical features [16], in this study, for the first time, an 11 months old boy with tremor and ataxia was reported. Based on the high prevalence of consanguinity marriages and genetic disorders in Gilan Province, especially Talesh City [17], it seems that this unusual clinical presentation occurs due to these factors. As the child with this presentation was detected in this study and his sibling aborted due to heart anomaly, the family tended to perform whole-exome sequencing and had a repeated test. But because of the high cost, it may need more time. In case of further information about this patient, the authors will mention it as a letter to the editor.

Conclusion

Although FXTAS commonly occurs in older patients, in this study, the authors reported a rare presentation of tremor and ataxia caused by permutation in early childhood. Therefore, it seems that clinicians should consider this phenomenon in childhood as well as adulthood.

Ethical Considerations

Compliance with ethical guidelines

Written informed consent was obtained from the patient’s parents, and the study was approved by the Ethics Committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC.1399.564). All study procedures were done in compliance with the ethical guidelines of the Declaration of Helsinki, 2013.

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Authors’ contributions

Conceptualization: Setila Dalili; Methodology: Shahin Koohmanaee, Fatemeh Kharae, Reza Bayat, Maryam Shahrokhi, Afagh Hassanzadeh Rad, Saber Najafi Chakooari, and Setila Dalili; Investigation, writing the original and final draft, review, and editing: all authors; Supervision: Shahin Koohmanaee and Setila Dalili.

Conflict of interest

The authors declared no conflict of interest.
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