Caspian Journal of Neurological Sciences
"Caspian J Neurol Sci"
Journal Homepage: http://cjns.gums.ac.ir

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

Shahin Koohmanaee[1], Fatemeh Kharaee[1], Reza Bayat[1], Maryam Shahrokhi[2], Afagh Hassanzadeh Rad[1], Saber Najafi Chakoosari[3], Setila Dalili[1*], Mahsa Karambin[1,4]

1. Pediatric Diseases Research Center, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
2. Department of Clinical Pharmacy, Faculty of Pharmacy, Guilan University of Medical Sciences, Rasht, Iran.
3. Student Research Committee, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
4. Research and Evaluation and Health Systems Management, Fanshawe College, London, Ontario, Canada.

Use your device to scan and read the article online

Citation Koohmanaee Sh, Kharaee F, Bayat R, Shahrokhi M, Hassanzadeh Rad A, Najafi Chakoosari S, et al. Early Onset of Fragile XAssociated Tremor and Ataxia Syndrome: A Case Report From Iran. Caspian J Neurol Sci. 2021; 7(3):180-183. https://doi.org/10.32598/CJNS.7.25.8

Running Title Early Onset of FXTAS

https://doi.org/10.32598/CJNS.7.25.8

Article info:
Received: 15 Feb 2020
First Revision: 20 Feb 2020
Accepted: 22 Oct 2020
Published: 01 Jul 2021

ABSTRACT

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

* **Corresponding Author:**
Setila Dalili
Address: *Pediatric Diseases Research Center, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran.*
Tel: *+98 (911) 1411463,* ***Fax:*** *+98 (13) 33369061*
E-mail: *setiladalili1346@yahoo.com*

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.

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.

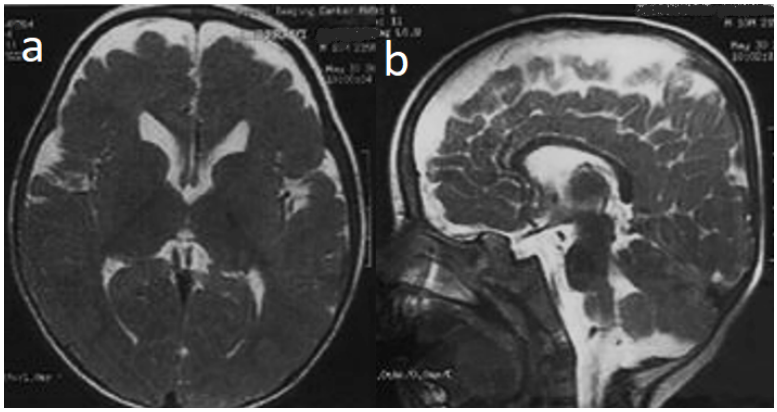
Case Presentation

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, pone, 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 µlU/mL, reference 0.35-5.0 µlU/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 triplet repeat primed PCR showed 99 CGG repeats in 5 untranslated regions of the FMR1 gene. Normal karyotype and CGH array was reported, too. Based on the results, the final diagnosis was the premutation in the FMR1 gene with early onset of FXTAS.

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 dysregulation 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].



CJNS

Figure 1. Axial (a) and sagittal (b) view of brain MRI of a child with the early onset of FXTAS (widening of subarachnoid space, sulci, and interhemispheric fissure)

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.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization: Setila Dalili; Methodology: Shahin Koohmanaee, Fatemeh Kharaee, Reza Bayat, Maryam Shahrokhi, Afagh Hassanzadeh Rad, Saber Najafi Chakoosari, 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.

References

[1] Hagerman R, Hagerman P. Advances in clinical and molecular understanding of the FMR1 premutation and fragile X-associated tremor/ataxia syndrome. Lancet Neurol. 2013; 12(8):786-98. [DOI:10.1016/S1474-4422(13)70125-X]

[2] Hall D, Todorova-Koteva K, Pandya S, Bernard B, Ouyang B, Walsh M, et al. Neurological and endocrine phenotypes of fragile X carrier women. Clin Genet. 2016; 89(1):60-7. [DOI:10.1111/cge.12646] [PMID] [PMCID]

[3] Shelton AL, Wang JY, Fourie E, Tassone F, Chen A, Frizzi L, et al. Middle cerebellar peduncle width-a novel MRI biomarker for fxtas? Front Neurosci. 2018; 12:379. [DOI:10.3389/fnins.2018.00379] [PMID] [PMCID]

[4] Tassone F, Iong KP, Tong TH, Lo J, Gane LW, Berry-Kravis E, et al. FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States. Genome Med. 2012; 4(12):100. [DOI:10.1186/gm401] [PMID] [PMCID]

[5] Ram S, Devapriya IA, Fenton G, Mcvay L, Nguyen DV, Tassone F, et al. Axonal neuropathy in female carriers of the fragile X premutation with fragile x-associated tremor ataxia syndrome. Muscle Nerve. 2015; 52(2):234-9. [DOI:10.1002/mus.24515] [PMID] [PMCID]

[6] Jacquemont S, Hagerman RJ, Leehey M, Grigsby J, Zhang L, Brunberg JA, et al. Fragile X premutation tremor/ataxia syndrome: Molecular, clinical, and neuroimaging correlates. Am J Hum Genet. 2003; 72(4):869-78. [DOI:10.1086/374321] [PMID] [PMCID]

[7] Brown SS, Stanfield AC. Fragile X premutation carriers: A systematic review of neuroimaging findings. J Neurol Sci. 2015; 352(1-2):19-28. [DOI:10.1016/j.jns.2015.03.031] [PMID]

[8] Kong HE, Lim J, Zhang F, Huang L, Gu Y, Nelson DL, et al. Metabolic pathways modulate the neuronal toxicity associated with fragile X-associated tremor/ataxia syndrome. Hum Mol Genet. 2019; 28(6):980-91. [DOI:10.1093/hmg/ddy410] [PMID] [PMCID]

[9] Careaga M, Rose D, Tassone F, Berman RF, Hagerman R, Ashwood P. Immune dysregulation as a cause of autoinflammation in fragile X premutation carriers: Link between FMRI CGG repeat number and decreased cytokine responses. PLoS One. 2014; 9(4):e94475. [DOI:10.1371/journal.pone.0094475] [PMID] [PMCID]

[10] Gallego PK, Burris JL, Rivera SM. Visual motion processing deficits in infants with the fragile X premutation. J Neurodev Disord. 2014; 6(1):29. [DOI:10.1186/1866-1955-6-29] [PMID] [PMCID]

[11] Greco CM, Tassone F, Garcia-Arocena D, Tartaglia N, Coffey SM, Vartanian TK, et al. Clinical and neuropathologic findings in a woman with the FMR1 premutation and multiple sclerosis. Arch Neurol. 2008; 65(8):1114-6. [DOI:10.1001/archneur.65.8.1114] [PMID]

[12] Leehey MA, Berry-Kravis E, Min SJ, Hall DA, Rice CD, Zhang L, et al. Progression of tremor and ataxia in male carriers of the FMR1 premutation. Mov Disord. 2007; 22(2):203-6. [DOI:10.1002/mds.21252] [PMID]

[13] Debrey SM, Leehey MA, Klepitskaya O, Filley CM, Shah RC, Kluger B, et al. Clinical phenotype of adult fragile X gray zone allele carriers: A case series. Cerebellum. 2016; 15(5):623-31. [DOI:10.1007/s12311-016-0809-6] [PMID]

[14] Hagerman PJ, Hagerman RJ. Fragile X-associated tremor/ataxia syndrome. Ann N Y Acad Sci. 2015; 1338(1):58-70. [DOI:10.1111/nyas.12693] [PMID] [PMCID]

[15] Hagerman RJ, Leavitt BR, Farzin F, Jacquemont S, Greco CM, Brunberg JA, et al. Fragile-X-associated tremor/ataxia syndrome (FXTAS) in females with the FMR1 premutation. Am J Hum Genet. 2004; 74(5):1051-6. [DOI:10.1086/420700] [PMID] [PMCID]

[16] Shickman R, Famula J, Tassone F, Leehey M, Ferrer E, Rivera SM, et al. Age- and CGG repeat-related slowing of manual movement in fragile X carriers: A prodrome of fragile X-associated tremor ataxia syndrome? Mov Disord. 2018; 33(4):628-36. [DOI:10.1002/mds.27314] [PMID] [PMCID]

[17] Behnam B, Zakeri M. Genetics and genomic medicine in Iran. Mol Genet Genomic Med. 2019; 7(2):e00606. [DOI:10.1002/mgg3.606] [PMID] [PMCID]