DOI: 10.4274/terh.galenos.2021.27122
J Tepecik Educ Res Hosp 2022;32(3):488-91

CASE REPORT / OLGU SUNUMU

Fragile-X-associated Tremor/Ataxia Syndrome (FXTAS) in a Female with FMR1 Premutation: Case Report

FMR1 Premutasyonu Olan Kadında Frajil-X-ilişkili Tremor/Ataksi Sendromu (FXTAS): Olgu Sunumu

Özgül Ocak[1], Fatma Sılan[2]

[1]Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Neurology, Çanakkale, Turkey
[2]Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Medical Genetics, Çanakkale, Turkey

Cite as: Ocak Ö, Sılan F. Fragile-X-associated Tremor/Ataxia Syndrome (FXTAS) in a Female with FMR1 Premutation: Case Report. J Tepecik Educ Res Hosp 2022;32(3):488-91

Abstract

People carrying a fragile-X-mental retardation 1 (FMR1) expansion between 55 and 200 cytosine-guanine-guanine (CGG) repeats are at increased risk of the fragile-X-associated tremor/ataxia syndrome (FXTAS). FXTAS clinical findings are late-onset psychological disorders, cerebellar gait ataxia, cognitive decline, and cerebellar intentional tremor. About 8% of female and 75% of male FMR1 premutation carriers develop FXTAS. Due to the protective effect of the second X chromosome, FXTAS have rarely been observed in women extremely rare. We describe a sixty-eight-year-old female carrier of the FMR1 premutation who presented with symptoms of tremor and gait ataxia and whose son has mental retardation with fragile-X syndrome. Mild global brain atrophy and white-matter lesions were observed in the magnetic resonance imaging images. Genetic analysis confirmed the premutation with a number of 90 CGG repeats. FXTAS is a neurodegenerative disease with a premutation of the *FMR1* gene. Female patients with gait ataxia and tremor should be referred for a genetic test with family members.

Keywords: Fragile-X-associated tremor/ataxia syndrome, female, FMR1 premutation

Öz

Frajil-X-mental retardasyon 1 (FMR1) genini 55 - 200 sitozin-guanin-guanin (CGG) tekrarı ile taşıyan kişiler, frajil-X ile ilişkili tremor/ataksi sendromu (FXTAS) için yüksek risk altındadır. FXTAS klinik bulguları, geç başlangıçlı psikolojik bozukluklar, serebellar yürüyüş ataksisi, bilişsel gerileme ve serebellar intansiyonel tremordur. FMR1 premutasyon taşıyıcı kadınların yaklaşık %8'i ve erkeklerin %75'i FXTAS geliştirir. İkinci X kromozomunun koruyucu etkisi nedeniyle, FXTAS kadınlarda son derece nadir gözlenmiştir. Tremor ve yürüme ataksisi semptomları ile başvuran, oğlunda frajil-X sendromuna bağlı mental retardasyon olan altmış sekiz yaşında FMR1 premutasyon taşıyıcısı kadın olgu sunulmaktadır. Manyetik rezonans görüntülerinde hafif global beyin atrofisi ve beyaz cevher lezyonları mevcuttu. Genetik analiz, premutasyonu 90 CGG tekrar sayısı ile doğruladı. FXTAS, *FMR1* geninin premutasyonu ile nörodejeneratif bir hastalıktır. Yürüme ataksisi ve tremoru olan kadın hastalar, aile üyeleriyle birlikte genetik test için sevk edilmelidir.

Anahtar Kelimeler: Frajil-X-ilişkili tremor/ataksi sendromu, kadın, FMR1 premutasyonu

Address for Correspondence/Yazışma Adresi: Özgül Ocak MD, Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Neurology, Çanakkale, Turkey
Phone: +90 286 263 59 50 **E-mail:** dr_ozgul@hotmail.com
ORCID ID: orcid.org/0000-0001-8276-0174

Received/Geliş tarihi: 29.01.2021
Accepted/Kabul tarihi: 24.06.2021

Introduction

Individuals who carry premutation alleles [55-200 cytosine-guanine-guanine (CGG) repeats] of the fragile-X-mental retardation 1 *(FMR1)* gene are caused by the phenotypic characteristic of fragile-X-associated tremor/ataxia syndrome (FXTAS)[1]. Premutation carriers have an increased risk of psychological diseases, primary ovarian insufficiency (POI), sleep problems, fibromyalgia, thyroid disorders, parkinsonism, ataxia, neuropathic findings, tremor, cognitive disorders, anxiety, depression, obsessive-compulsiveness, and muscle pain[2].

The frequency of FXTAS syndrome increases with age. Seventy-five percent of males and 8% of females with FMR1 premutations show clinical symptoms after the age of 75[3]. The frequencies of psychiatric diseases, thyroid disorders, sleep problems, and fibromyalgia increase in women with FXTAS[4]. The clinical spectrum of FXTAS phenotype that may be explained by varying CGG repeat size and inactivation (lyonisation) ratios of the X chromosome in somatic cells[5].

FXTAS is generally observed in men, female patients with FXTAS are rarely reported. The most important reason for this is that the second X chromosome in women has a protective effect from this disease. Many people with FXTAS in the community are diagnosed only with fragile-X syndrome (FXS) after a grandchild has been diagnosed with FXS. Although FXTAS is common in the elderly, it is not well recognized and often misdiagnosed due to clinical variability.

Case Report

A sixty-eight-year-old female patient was admitted to the Neurology Department, with complaints of difficulty in walking, balance disorder, and tremors at the hands starting at age sixty-five-year old. In the family history, her son has mental retardation with FXS. Systemic examination findings of the patient were normal. In her neurological examination; she had bilateral dysmetria and dysdiadochokinesia, ataxic gait, and postural, resting tremor, and intention tremor with terminal dysmetria in both upper extremities. She was normal for neuropsychiatric functions. Hemogram, serum electrolytes, hepatic and kidney function tests, blood glucose, thyroid function tests, iron, iron-binding tests, vitamin B12 levels were in the normal range. No pathological findings were detected in the brainstem in axial fluid attenuated inversion recovery sequences of cranial magnetic resonance imaging (MRI) (Figure 1). Mild global brain atrophy and white-matter lesions were observed on MRI images (Figure 2).

DNA was isolated from the patient's venous blood and peripheral blood leukocytes. *FMR1* gene CGG repeat count was analyzed after polymerase chain reaction with an Applied Biosystems 3130 Genetic analyzer. It was determined that our case was the premutation carrier with a number of 90 repeats.

Informed consent was obtained regarding the publication of patient information.

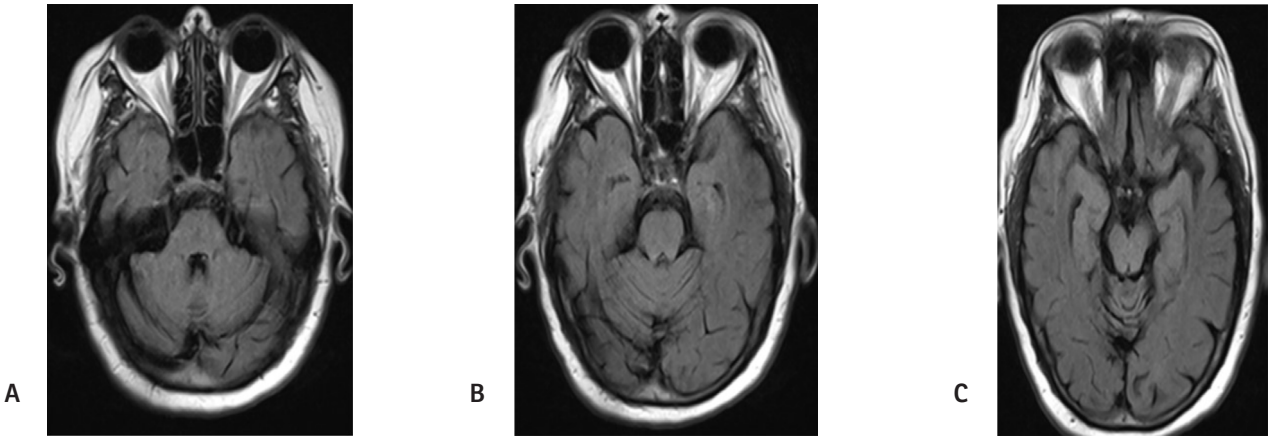

Figure 1. A-C) Magnetic resonance imaging MRI of the brain, axial fluid-attenuated inversion recover FLAIR sequences at normal brainstem

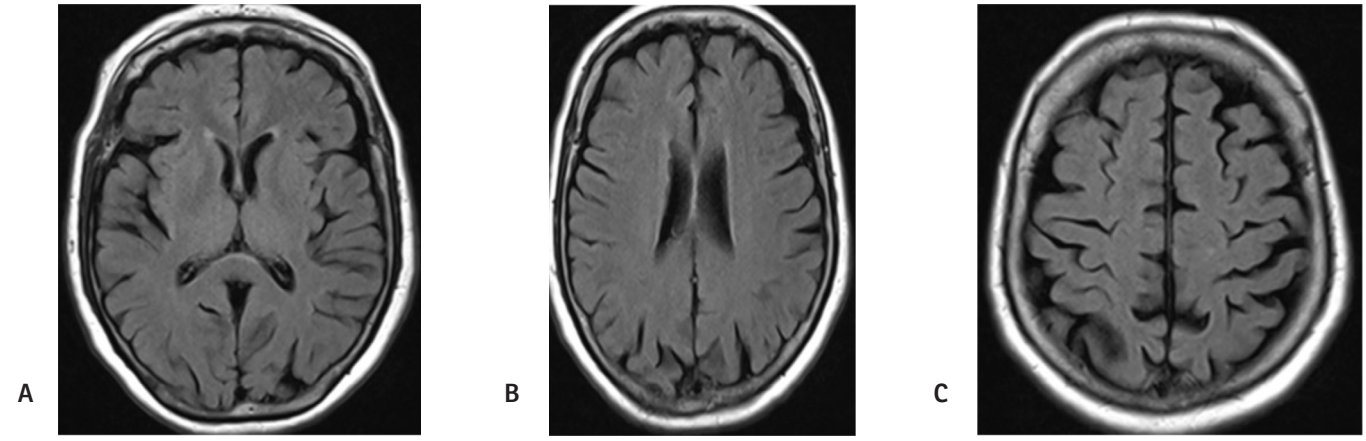

Figure 2. A-C) Magnetic resonance imaging (MRI) of the brain, axial fluid-attenuated inversion recover FLAIR sequences at MRI cerebral white matter lesions, MRI white matter lesions in the splenium of the corpus callosum and generalized brain atrophy

Discussion

FXTAS was first described in 2001. This disease causes cerebellar ataxia and intention tremors in people who are carriers of premutation (55 to 200 CGG repeats)[6]. In a study, it was revealed that the prevalence of a premutation was 1:209 females and 1:430 males[7].

A study showed that the frequency of tremor is lower in women with premutation, as well as muscle pain and sensory loss are observed more frequently[8]. Tremor and ataxia are usually observed in men with premutation. Women with FXTAS have less cognitive dysfunction than men, but female cases with dementia have been reported[9].

FXTAS is divided into three categories as "definite," "probable," and "possible," which are used in the clinical diagnosis of FXTAS (Table 1)[10]. In this study, definitive FXTAS was diagnosed with the detection of major clinical and radiological findings and confirmed with a genetic test that showed premutations. Her first-degree relatives were also invited for genetic counseling and tests. The family tree chart is shown in Figure 3.

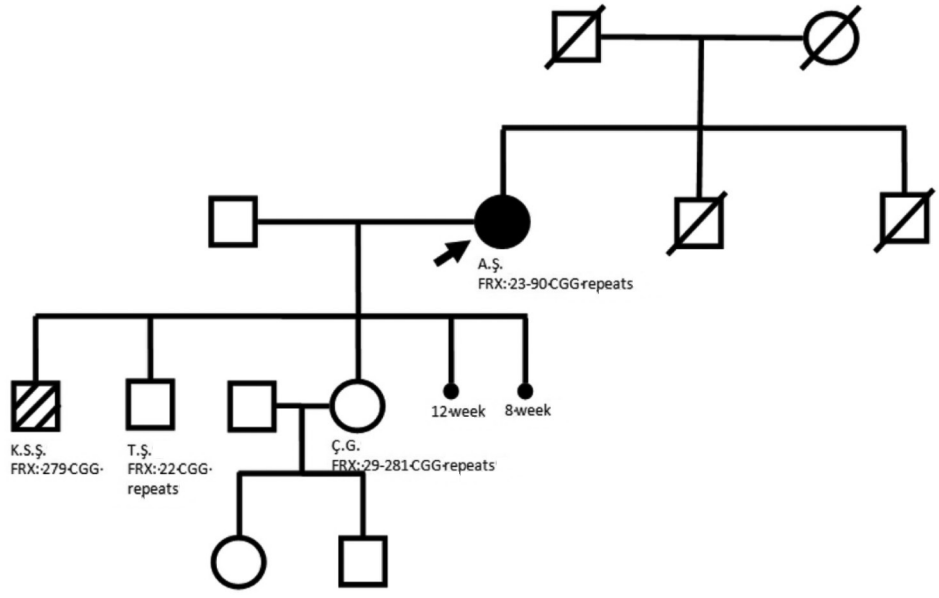

Figure 3. Family tree chart of the case

Table 1. FXTAS diagnostic criteria in FMR1 premutation carriers[10]

Diagnostic Categories	
Definite	Presence of one major radiological sign plus one major clinical symptom
Probable	Presence of either one major radiological sign plus one minor clinical symptom or has the two major clinical symptoms
Possible	Presence of one minor radiological sign plus one major clinical symptom
Symptom types	
Radiological	
Major	MRI white matter lesions in middle cerebral peduncles and brain stem
Minor	MRI white matter lesions in cerebral white matter
Minor	Moderate to severe generalized athropy
Clinical	
Major	Intention tremor
Major	Gait ataxia
Minor	Parkinsonism
Minor	Moderate to severe short-term memory deficiency
Minor	Executive function deficit

FXTAS: Fragile-X-associated tremor/ataxia syndrome, FMR1: Fragile-X-mental retardation 1, MRI: Magnetic resonance imaging

FXS, POI and FXTAS diseases are observed because of *FMR1* gene mutation. POI and FXTAS diseases are observed with the premutation of the FMR1 gene. These two diseases are common in the general population and thus are an important cause of morbidity. Although FXTAS is common in the elderly, it is not well recognized and often misdiagnosed due to clinical variability. The correct diagnosis of this disease is important not only for the patient, but also for family members to obtain information about the disease risks.

FXTAS is a neurodegenerative disease that is very rarely reported in women with premutation. As in this study, female patients with gait ataxia and tremor should be referred for a genetic test and counseled.

Ethics

Informed Consent: Informed consent was obtained regarding the publication of patient information.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.O., Concept: Ö.O., F.S., Design: Ö.O., F.S., Data Collection or Processing: F.S., Analysis or Interpretation: Ö.O., F.S., Literature Search: Ö.O., F.S., Writing: Ö.O., F.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Hagerman RJ, Hagerman P. Fragile X-associated tremor/ataxia syndrome - features, mechanisms and management. Nat Rev Neurol 2016;12:403-12.
2. Merino S, Ibarluzea N, Maortua H, et al. Associated Clinical Disorders Diagnosed by Medical Specialists in 188 FMR1 Premutation Carriers Found in the Last 25 Years in the Spanish Basque Country: A Retrospective Study. Genes (Basel) 2016;7:90.
3. Jacquemont S, Hagerman RJ, Leehey MA, et al. Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. JAMA 2004;291:460-9.
4. Hall D, Todorova-Koteva K, Pandya S, et al. Neurological and endocrine phenotypes of fragile X carrier women. Clin Genet 2016;89:60-7.
5. Hall DA, Robertson-Dick EE, O'Keefe JA, Hadd AG, Zhou L, Berry-Kravis E. X-inactivation in the clinical phenotype of fragile X premutation carrier sisters. Neurol Genet 2016;2:e45.
6. Hagerman RJ, Leehey M, Heinrichs W, et al. Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X. Neurology 2001;57:127-30.
7. Tassone F, Iong KP, Tong TH, et al. FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States. Genome Med 2012;4:100.
8. Coffey SM, Cook K, Tartaglia N, et al. Expanded clinical phenotype of women with the FMR1 premutation. Am J Med Genet A 2008;146A:1009-16.
9. Karmon Y, Gadoth N. Fragile X associated tremor/ataxia syndrome (FXTAS) with dementia in a female harbouring FMR1 premutation. J Neurol Neurosurg Psychiatry 2008;79:738-9.
10. Leehey MA. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. J Investig Med 2009;57:830-6.