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Case Report / Olgu Sunumu

Different Clinical Faces of the Same Gene Mutation: Fragile X Mental Retardation 1 Disorders

Aynı Gendeki Mutasyonların Farklı Yüzleri, FMR1 İlişkili Hastalıklar

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Abstract

The *fragile X mental retardation 1* gene located on the X-chromosome plays a role in protein synthesis of the same name (fragile X mental retardation protein). The normal allele of this gene has 5-40 CGG repeats, wherein >200 repeats of the same trinucleotide are called full mutations and 55-200 repeats are called premutations. These mutations cause different clinical pictures, which sometimes overlap each other, such as fragile X syndrome, fragile X-associated tremor/ataxia syndrome (FXTAS), fragile X-associated primary ovarian insufficiency (FXPOI), autism spectrum disorders, and attention deficit hyperactivity syndrome. These phenotypes, which make up different faces of mutations in the same gene, are grouped under the term fragile X-related diseases. The disease is more common in men; however, asymptomatic women are also affected. Therefore, careful evaluation of other family members, as well as patients, is important especially for early recognition and management of neuropsychiatric symptoms. This article aimed to emphasize the importance of evaluating family members to manage genetic diseases among the family by focusing on a 19-year-old female patient who presented with neuropsychiatric findings and FXTAS and FXPOI phenotypes.

Keywords: *FMR1* gene, fragile X syndrome, FMR1 disorders

Öz

X kromozomu üzerinde bulunan *frajil X mental retardasyon 1* geni, aynı adlı proteinin sentezinde rol alır. Bu genin normal alleli 5-40 CGG tekrarına sahipken, aynı trinükleotidin 200'den fazla tekrarı tam mutasyon, 55-200 tekrarı ise premutasyon olarak adlandırılır. Bu mutasyonlar frajil X sendromu, frajil X-ilişkili tremor/ataksi sendromu (FXTAS), frajil X ilişkili primer ovaryan yetmezlik (FXPOY), otizm spektrum bozuklukları (OSB), dikkat eksikliği hiperaktivite sendromu gibi kimi zaman birbiriyle örtüşen farklı klinik tablolara yol açar. Aynı gendeki mutasyonların farklı yüzlerini oluşturan bu fenotipler, frajil X ilişkili hastalıklar terimi altında toplanabilir. Hastalık erkeklerde daha sık görülse de, asemptomatik kadınların da etkilendiği bilinmektedir. Bu yüzden hastalar kadar diğer aile bireylerinin de dikkatle değerlendirilmesi, özellikle nöropsikiyatrik semptomların erken tanınması ve yönetimi bakımından önemlidir. Bu yazıda nöropsikiyatrik bulgularla başvuran 19 yaşında bir kadın olgu ve aynı aile bireylerindeki FXTAS, FXPOY fenotipleri konu edinilerek genetik hastalıkların yönetiminde aile bireylerine yönelik değerlendirmenin önemine vurgu yapılması amaçlanmıştır.

Anahtar Kelimeler: *FMR1* geni, frajil X sendromu, FMR1 ilişkili hastalıklar

Introduction

Fragile X syndrome (FXS) is one of the single-gene diseases that cause the most common neuropsychiatric symptoms. An increased number of CGG repeats are found in the *fragile X mental retardation* gene 1 (FMR1) on the long arm of the X chromosome. Those with 45-54 repeats, which should be 6-44 in normal individuals, are defined as patients with "gray zone", and those with 55-200 repeats are defined as patients with "premutation". In cases with CGG trinucleotide repeats >200, there is a full mutation (1).

FMR1 transcription is disrupted from the early stages of life in the presence of a full mutation, and the production of the fragile X mental retardation protein (FMRP), which is required for neurological development, is significantly reduced or completely stopped. Almost all men with full mutations are symptomatic; however, the inactivation rate of the X chromosome is determinant in women (2).

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These genetic underpinnings result in a rich variety of symptoms varying in the age of onset, severity, and combinations. Clinical conditions in which different entities, such as Fragile X tremor ataxia syndrome (FXTAS), Fragile X-associated premature ovarian insufficiency (FXPOI), autism spectrum disorders (ASD), and attention deficit and hyperactivity syndrome, are found together in various degrees are addressed under FMR1 disorders (2).

In this article, a 19-year-old female patient who presented with neuropsychiatric complaints and whose genetic diagnosis was confirmed is presented. The presence of FMR1 disorders, which appeared with three different clinical pictures in three generations, was revealed in her family members. We believe that increasing awareness of clinical features that are sometimes disconnected from each other or in the form of faint clues will be decisive in terms of early detection of patients and handling them with a multidisciplinary approach.

Case Report

A 19-year-old female patient with mental and motor developmental retardation was admitted to the neurological outpatient clinic with complaints of balance disorder and involuntary movements in the upper extremities.

She was able to sit without support at the age of 2 years, walked at the age of 3, started to talk at the age of 5, and completed her basic education by undergoing special inclusive education. Her medical records revealed many hospital admissions due to recurrent otitis media, which was treated with antibiotherapy. Additionally, at 16 years old, she was examined in our gynecology and obstetrics outpatient clinic for menstrual irregularity and hirsutism, and diagnosed with polycystic ovary syndrome (PCOS) due to results of elevated serum free testosterone (8 ng/dl), endometrial thickening (16 mm) in the pelvic ultrasonography, and bilateral antral follicle count of >18. Additionally, she was admitted to the orthopedics outpatient clinic due to pes planus, joint hyperlaxity, scoliosis, and osteopenia. Clomipramine (10 mg/day) and carbamazepine (400 mg/day) were started with the diagnosis of obsessive-compulsive disorder and impulse control disorder at 12 years old, and has been changed to risperidone (2 mg/day) and sertraline (50 mg/day) during follow-up.

Her mother developed menopause at 25 years and diagnosed with FXPOI, due to results of follicle-stimulating hormone level of 56 mIU/Ml, decreased number of bilateral ovarian antral follicles (1-2 units) in the pelvic ultrasonography, and 99 CGG repeats in an allele in the *FMR1* gene in the genetic analysis which is in the premutation range. Her mother's uncle had been hospitalized with progressive imbalance and tremors, which started when he was 55 years old. While his cranial magnetic resonance imaging (MRI) revealed mild cerebral atrophy, symmetrically located T2 hyperintense lesions on the middle cerebellar peduncles, 108 CGG repeats in the *FMR1* gene in his genetic test was detected which is in the premutation range. Thus he was diagnosed with FXTAS.

During examination, the patient was fully oriented, avoided eye contact, and occasionally showed aggression and impaired impulse control. Hyperlaxity was observed in the joints (wrist, fingers, and elbows) of the patient, whose emotional instability and expression disorder was remarkable. Additionally, no features were found in her neurological examination, except gait ataxia and choreiform movements in the oromandibular region and bilateral upper extemities.

Cranial MRI and biochemistry tests of patient requested based on history and family history, were found to be normal. The genetic examination of the patient studied with triplet primed polymerase chain reaction resulted as, in addition to an allele with 33 CGG repeats in the *FMR1* gene, the presence of a mosaic allele with 178 and 200 repeats was detected. Thus, the patient had full mutation mosaicism and premutation, and the patient's genetic family tree was extracted (Figure 1). Subsequently, multidisciplinary follow-up of the patient and family members with genetic counseling were planned.

Discussion

The FMRP is a protein that plays a role in the nervous system development and is encoded by the *FMR1* gene located on the X chromosome (2). Males with >200 CGG trinucleotide repeat in the *FMR1* gene present with mental retardation, whereas FMR1 related disorders with different phenotypes occur in male and female members of the same family, depending on gender and number of repeats. This diversity of phenotypes may make it difficult to treat the common pathogenesis as distinct clinical presentations. The questioning of the family's medical history by clinicians plays a key role in viewing the whole picture. The variety and severity of symptoms and findings are related to the *FMR1* gene mutation as a "full mutation", presence of mosaicism, gender of the patient, and affected tissue distribution (3). Without a clear family history during admission, patient diagnosis is mainly based on suspicion. Therefore, deepening the anamnesis and family history is important.

Craniofacial features such as macrocephaly, elongated face, wide forehead, high arched palate, prominent ears, and other features such as strabismus, joint hyperlaxity, pes planus, scoliosis, recurrent otitis media, mitral valve prolapse, aortic dilatation, which can come together in different severity and combinations, are important clues and can occur in both men and women. In addition to these findings, PCOS can be seen in women and macroorchidism in men (1,2).

Barad et al. (4) defined the incidence of PCOS increased in a group of patients with CGG repeat mutations in the *FMR1* gene, and osteopenia could develop due to hypoestrogenism in these cases. In our patient, diagnoses of PCOS and osteopenia were compatible with this finding. Additionally, the presence of pes planus, scoliosis, and recurrent otitis media attacks in our patient's history drew attention. Considering all these features, which seem disconnected and different from each other, together are considered as an important clue in terms of the diagnostic approach.

Cognitive, behavioral, and emotional characteristics are as important as physical characteristics in terms of FXS and other FMR1 related disorders, which are the most common causes of hereditary cognitive disorders, and both patients and family members should be considered for the diagnoses of ASD, ADHD, and other neuropsychiatric features. Psychiatric diseases, developmental delay, and intellectual disorders occur in different individuals with different severity. Hyperactivity, impulsivity, stereotypical movements, impaired speech fluency, and social anxiety disorder are among the common features (5).

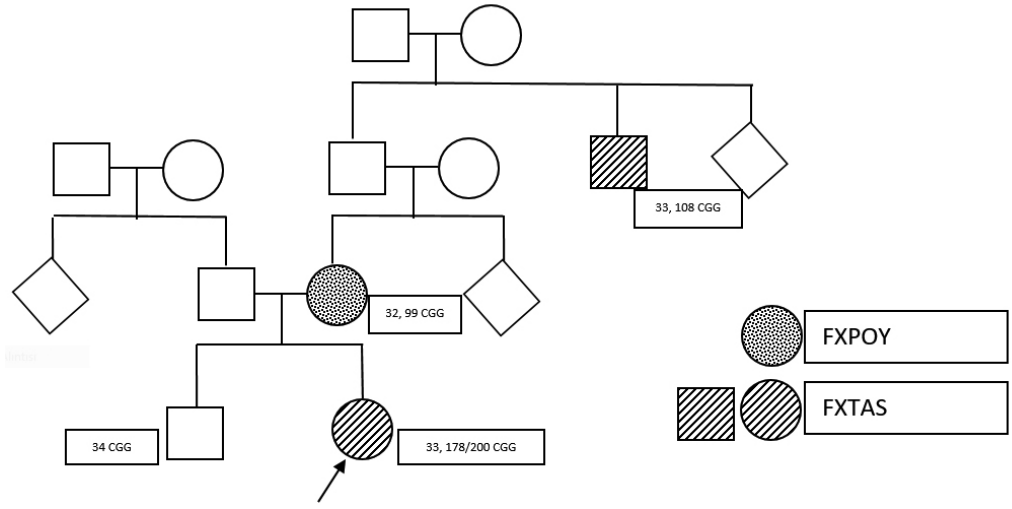

Figure 1. Our patient was indicated with an arrow, and 33 CGG repeats were detected in one allele and 178 and 200 in the other allele in the *FMR1* gene. The patient showed premutation and full mutation mosaicism. Her mother had 32 CGG repeats in one allele and 99 CGG repeats in the other allele and was followed up with FXPOI diagnosis. The genetic analysis of her mother's uncle was not performed in our hospital, and the result of the genetic examination performed with the triplet primed method in the external center was added to the family tree. Molecular FMR1 analysis of the patient and the patient's mother was performed using FastFrax FMR1 Sizing Kits (The Biofactory Pte Ltd, Singapore). TP-PCR was performed for "sizing" analysis. TP-PCR was performed according to the manufacturer's instructions using 100 ng of genomic DNA per patient. The resulting amplicons were run through a 50-cm capillary loaded with POP-7 polymer on the ABI 3500 DNA analyzer (Applied Biosystems) after undergoing various treatments according to the manufacturer's recommendations. Capillary electrophoresis results were analyzed using PeakScanner™ 2 software (Applied Biosystems). The number of CGG repeats was determined following the manufacturer's instructions
FMR1: Fragile X mental retardation gene, FXPOI: Fragile X-associated primary ovarian insufficiency, TP-PCR: Triplet primed polymerase chain reaction

In the literature, a separate title has been defined under the name of fragile X-related neuropsychiatric diseases (FXRND) in premutation carrier patients. This disorder begins at a relatively early age and has a diverse spectrum of neuropsychiatric symptoms, most commonly anxiety disorders (5). In patients with neuropsychiatric complaints, reviewing their family's medical history and assessing specific clinical manifestations of FXPOI, FXTAS, and FXRND is important. Detection of these specific phenotypes or symptoms in family members will be decisive in accurate and early diagnosis, with appropriate genetic studies and multidisciplinary follow-up.

Ethics

Informed Consent: Informed consent was obtained from all patients included in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A., B.Ö., F.G.U., Concept: B.A., B.Ö., F.G.U., Design: B.A., B.Ö., F.G.U., Data Collection or Processing: B.A., B.Ö., F.G.U., Analysis or Interpretation: B.A., F.G.U., Literature Search: B.A., F.G.U., Writing: B.A.

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

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References

1. Quartier A, Poquet H, Gilbert-Dussardier B, et al. Intragenic FMR1 disease-causing variants: a significant mutational mechanism leading to Fragile-X syndrome. Eur J Hum Genet 2017;25:423-431.
2. Rajaratnam A, Shergill J, Salcedo-Arellano M, et al. Fragile X syndrome and fragile X-associated disorders. F1000Res 2017;6:2112.
3. Ciaccio C, Fontana L, Milani D, et al. Fragile X syndrome: a review of clinical and molecular diagnoses. Ital J Pediatr 2017;43:39.
4. Barad DH, Weghofer A, Goyal A, Gleicher N. Further refinement in defining the effect of heterozygous-abnormal CGG counts on the FMR1 (fragile X) gene: definition of a distinct subgroup of PCOS patients, based on norma/low genotype. Fertil Steril 2009;92:S105.
5. Seritan AL, Ortigas M, Seritan S, Bourgeois JA, Hagerman RJ. Psychiatric Disorders Associated with FXTAS. Curr Psychiatry Rev 2013;9:59-64.