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Ocular Manifestations of Fragile X Syndrome – A Case Study and Literature Review

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Abstract

Fragile X syndrome (FXS) is a common X-linked genetic disorder acquired most commonly by a >200 CGG repeat expansion in the fragile X mental retardation 1 gene (*FMR1*). Phenotypic manifestations of fragile X syndrome can vary greatly from patient to patient and characteristic features can be absent in early life. Previous literature has described FXS to be associated with a variety of ophthalmologic findings, most frequently with strabismus. We describe three siblings that were diagnosed with FXS, each with various FXS-associated presentations. Two of our patients had ophthalmologic findings including strabismus, lagophthalmos and ptosis. Our study demonstrates ocular findings previously reported with FXS. Patients with FXS are an at-risk population for a variety of ophthalmologic disorders that are reversible if corrected early in life and should benefit from ophthalmologic examinations.

Keywords: *fragile X syndrome; FMR1 gene;CGG repeat; trinucleotide repeat expansion; ocular manifestations; strabismus*

Introduction

Fragile X syndrome (FXS; OMIM 300624) is the leading cause of inherited intellectual disability and autism and is caused by an alteration of the *FMR1* gene on chromosome Xq27.3 [1]. The prevalence has been estimated at 1.4 per 10,000 for males and 0.9 per 10,000 for females [2]. In FXS, most of the cases involve a CGG expansion (>200 triplet repeats) in the 5' untranslated region (UTR) of the gene and abnormal DNA methylation, which silence the expression of *FMR1* gene. FMR1 protein is believed to be instrumental for normal neurological and behavioral development.

FXS is inherited in an X-linked pattern.Males tend to consistently have frank intellectual disability, while females will have a wide range of phenotypesdue to random X-inactivation [3]. The phenotype of FXS can manifest in a variety of ways. In addition to intellectual disability and autism, FXS may have an array of characteristic physical features that become more apparent with age including a prominent jaw and forehead, long and narrow face, and in males, enlarged testicles (macroorchidism) after puberty. Individuals with FXS can also have a number of comorbidities include mitral valve prolapse, otitis media, seizures, joint laxity, sleep disturbances, and gastrointestinal problems [4,5].

The most commonly reported ocular finding with FXS is strabismus [3]. Strabismus is defined as any misalignment of the eyes. Strabismus can progress to permanent visual deficits if not identified and treated. Here we describe three siblings with FXS with various clinical presentations. Two of our patients had ophthalmologic findings including strabismus, lagophthalmos and ptosis. Since ophthalmologic disorders are reversible if corrected early in life it is important for every child with FXS to receive a thorough ophthalmologic examination before the age of 4 [4,5].

Patient Information

Patient 1

AO is a 6-year-old boy who presented initially with speech delays when he was two years old. An Ages & Stages Questionnaire (ASQ) done at 4 years of age demonstrated he had communication, fine motor, and problem-solving delays. The patient's family history is significant for a cousin with autism and a sister with galactosemia trait. This prompted the family to get a referral to pediatric clinics when he was 5 years old. He was noted to have a history of multiple ear infections but was cleared by audiology. His mother also noted that he had "lazy eye bilaterally". On examination, the patient was noted to be macrocephalic with frontal bossing. He had large ears measuring 7 cm on the right and 6.5 cm on the left and a class 3 malocclusion. Given the patient's developmental delays fragile X testing, chromosomal microarray, and metabolic screening was ordered. His fragile X testing was positive fora full mutation with over 200 CGG repeats (Figure 1). Methylation study was consistent with the presence of a completely methylated *FMR1* full mutation allele (data not shown). Chromosomal microarray could not be performed due to insurance issue. Metabolic screening was negative.

Given that the patient's mother noticed "lazy eye", the patient was referred to pediatric ophthalmology for evaluation of strabismus. Caregivers endorse that the patient has had a problem of the left eye "drifting out". This has been present since birth and occurs at least 10 times per day and lasts up to one minute before resolving. Patient had central, steady, and maintained (CSM) fixation bilaterally. Intraocular pressure was soft bilaterally. Pupils were round and equally reactive to light with no relative afferent pupillary defects. Visual fields and extraocular movements were full bilaterally. External, anterior segment, and fundus examinations were unremarkable bilaterally. Stereopsis could not be assessed. Cycloplegic refraction demonstrated hypermetropia and regular astigmatism of both eyes, which was within normal limits for age. Strabismus exam revealed 20-30 prism diopters of exotropia of the left eye. This patient is currently being monitored, he has not required any active treatment to this point.

Patient 2

BO is a 17-month-old male who is the younger sibling of patient AO described above. He was born to a triplet pregnancy with fetal demise of one of the triplets in their 5th week. The other twin does not have symptoms of fragile X syndrome. He underwent fragile X testing after his older sibling was diagnosed. His fragile X testing was positive fora full mutation with over 200 CGG repeats (Figure 1). Methylation study was consistent with the presence of a completely methylated *FMR1* full mutation allele (data not shown). He also was evaluated in the pediatric clinic, where it was noted he was delayed in speech and gross motor. Physical examination did not show any dysmorphic features.

He was referred to Ophthalmology for ptosis and strabismus noticed by a caregiver. The grandmother endorses that the patient's left upper eyelid droops slightly more than the right. Additionally, the patient has episodes of his left eye "drifting out". This occurs less than once per day and only lasts for a few seconds before resolving. On examination, patient had central, steady, and maintained (CSM) fixation bilaterally. Intraocular pressure was soft bilaterally. Pupils were round and equally reactive to light with no relative afferent pupillary defects. Visual fields and extraocular movements were full bilaterally. External, anterior segment, and fundus examinations were unremarkable bilaterally. Stereopsis could not be assessed. Cycloplegic refraction demonstrated myopia and regular astigmatism of both eyes, which was within normal limits for age. The patient's margin reflex distance 1, the distance in millimeters between the patient's light reflex on the patient's cornea and the level of the center of the upper-eyelid margin, was 4 mm OD and 3 mm OS. Additionally, this patient had 1 mm lagophthalmos, inability to completely close the eye on attempted closure. Sensorimotor exam revealed mild flick exophoria OS. This patient is currently being closely monitored.

Patient 3

CO is a 10-year-old girl who is the older sibling of both AO and BO described above. She had a normal birth history. Growing up, CO had concerns about development, specifically in speech. The patient also reported significant anxiety which precluded her from enjoying certain events growing up. CO has also had significant difficulties with fine motor tasks including handwriting. She is currently enrolled in the second grade where she is mainstreamed for part of the day and receives special education in a separate classroom for certain classes. Her mother also reports that she struggles with changes in routine or environment. She was tested for fragile X when her younger sibling (patient 1, AO)was diagnosed and the result was 21 CGG repeats on one X chromosome and a full mutation *FMR1* allele on the other X chromosome (Figure 1). Methylation studies were consistent with the presence of a completely methylated *FMR1* full mutation allele and partially methylated normal allele (data not shown).

Physical exam was unremarkable except for increased joint laxity. CO had no apparent ophthalmic manifestations of FXS and did not refer to Ophthalmology due primarily to her age and lack of subjective symptoms.

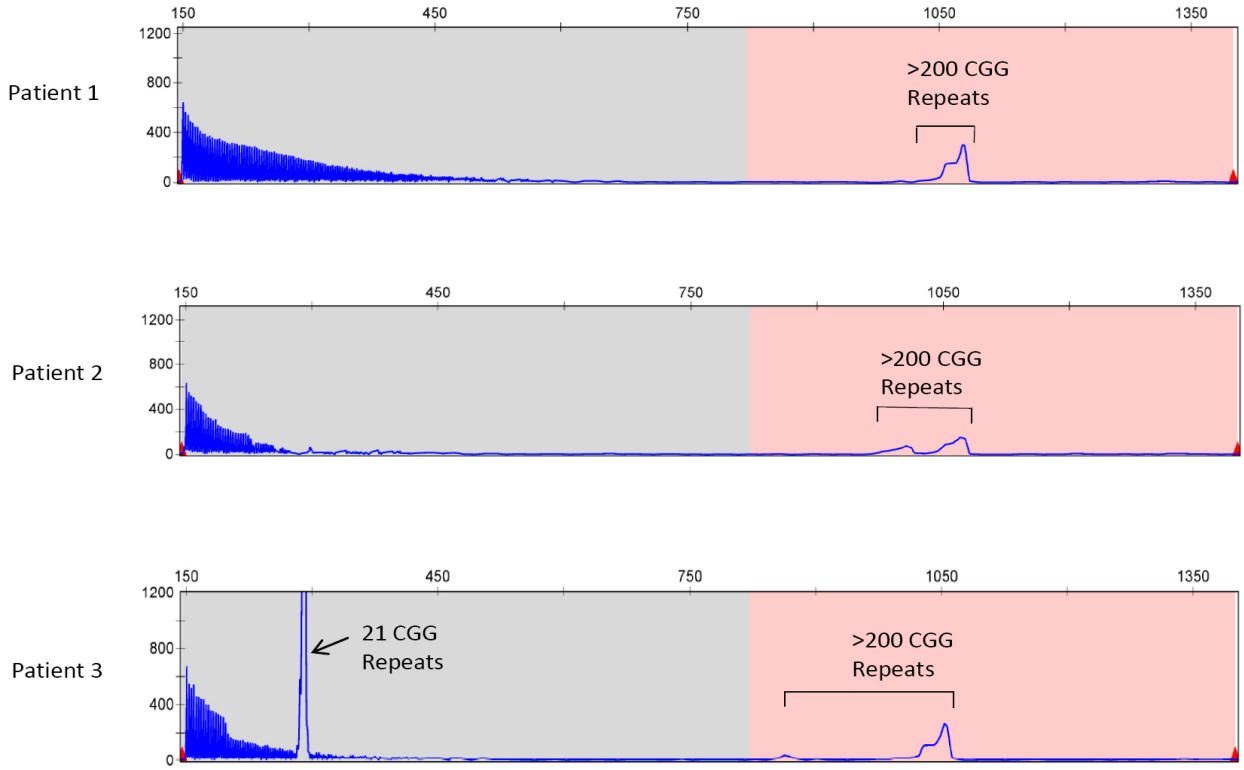

Figure1. *Capillary electrophoresis profiles of the three patients.*
X-axis represents fragment length in base pairs (bp)and corresponding sizes of CGG repeats, and Y-axis represents Relative Fluorescence Units (RFUs). The numbers of CGG repeats were marked for each of the three patients.

Discussion

Fragile X is an inherited disease caused by a loss of function mutation in the *FMR1* gene that causes a wide range of medical problems. Herein describe three siblings with FXS each with differing phenotypes. The prevalence of strabismus in fragile X is considerably higher when compared to the general population. Early studies found a prevalence to be somewhere between 30-50%. Later studies have found that the prevalence may have been overstated due to a selection bias in the earlier studies. The most recent study reports that the prevalence

is closer to 4-8%. In any case, the prevalence in patients with FXS is significantly higher than in the general population (roughly 0.01%)[2,6].

Depending on the severity, strabismus in patients with FXS can be missed by caregivers and healthcare providers. Although strabismus may appear obvious at times, the frequently intermittent nature of strabismus can make for a challenging diagnosis. Indeed, patients with learning disabilities and mental illness frequently have oculo-visual, behavioral, and vision information processing defects that require careful examinations to ensure an accurate diagnosis [7]. It is essential that strabismus be identified at a young age. Untreated strabismus can lead to several poor outcomes for patients which include poor visual acuity, deviated eyes, and reduced depth perception. For stereopsis (depth perception) to work, visual inputs from two eyes must converge on binocular neurons in the visual cortex. Proper eye alignment is crucial to the maturation of these neurons. Untreated strabismus can therefore result in a permanent loss of stereopsis. Additionally, strabismus can lead to amblyopia (decrease in best corrected visual acuity in otherwise healthy eye) by a suppression of the visual input from the deviated eye. This suppression results in shrinking of the neurons in the visual cortex and lateral geniculate nucleus driven by the affected eye. Last, strabismus can lead to a permanent 'lazy eye' if untreated which can have lasting cosmetic consequences for these patients. It is known that aberrations in the visual system after the age of 5 do not lead to amblyopia, therefore it is imperative that children at risk are identified and treated early on. In general, patients that are treated early tend to have minimal, if any, long term consequences [8].

Strabismus is not the only visually significant ophthalmic abnormality that is associated with FXS. Other findingsinclude: nystagmus, high myopia, blepharospasm, hyperopia, cataracts, congenital optic atrophy, adult onset glaucoma, ptosis, and astigmatism [3,6,9]. Of all of the findings, strabismus and refractive error areby far and away the most common [3,6,9]. There are several options for treating strabismus early on. Non-surgical treatment approaches include watchful waiting, occlusion therapy, minus lens therapy, miotic eye drops and orthoptic exercises and vision therapy. Frequently, a trial of one or more of these conservative treatments is done prior to considering surgical management. The goals of therapy are typically to improve ocular alignment and binocularity [10].

To summarize, we describe three siblings with full fragile X mutations. Two of these patients have ocular findings which warranted evaluation by a pediatric ophthalmologist. Patients with FXS are an at-risk population for several ocular abnormalities and would benefit from ophthalmic evaluation early in order to prevent potentially permanent ocular deficits.

Laboratory Role in Diagnosis

Triplet-repeat primed polymerase chain reaction (RP-PCR) method was used for sizing *FMR1* CGG repeat expansions[11,12]. Briefly, genomic DNA was extracted from 200 uL of peripheral blood with the GentraPuregene Blood Kit (Qiagen, Germantown, MD). The number of CGG trinucleotide repeat within the *FMR1* 5'-UTR was examined using Amplide X PCR/CE *FMR1* kit according to manufacturer's instructions (Asuragen, Austin, TX). Briefly, gene-specific and CGG RP-PCR reactions were performed. Capillary electrophoresis (CE) was employed to analyze amplicon products using Applied Biosystems 3030xl DNA analyzer (Thermo Fisher Scientific, Waltham, MA). CE generated electropherograms were analyzed using Gene Mapper 5.0 software (Thermo Fisher Scientific, Waltham, MA). Methylation-specific PCR analysis was performed for CGG repeat of 55 or greater to distinguish between premutation and full mutation alleles using Amplide X*FMR1*mPCR kit according to manufacturer's instructions (Asuragen, Austin, TX). Figure 1 shows the electropherograms of the three patients.

Research Involving Human Subjects

The study was approved by the University of Texas Medical Branch (UTMB) institutional review board (IRB)

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