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Concise report

Fibromyalgia in *fragile X mental retardation 1* gene premutation carriers

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Abstract

Objective. FM is a disorder of altered pain regulation and is characterized by pain, fatigue, poor sleep and psychological impairments; thus, it is classified as a central sensitivity syndrome. Female carriers of a premutation in the *fragile X mental retardation 1* (*FMR1*) gene frequently have widespread musculoskeletal pain and sometimes have been diagnosed with FM, especially if they have the motor signs of fragile X-associated tremor ataxia syndrome (FXTAS). Studies suggest that FM occurs in persons with a genetic predisposition. We describe the clinical features of female *FMR1* premutation carriers with symptoms of FM.

Methods. A sample of patients was selected that participated in studies at two tertiary referral academic centres on the phenotype and therapy of FXTAS.

Results. This selected sample of patients, five female premutation carriers, has FM symptoms or diagnoses and other central sensitivity syndromes.

Conclusion. Since FM affects 2–4% of the world's population and about 1 in 250 females are *FMR1* carriers, a study screening females with FM for the presence of the *FMR1* premutation is worthwhile. A finding of increased prevalence of *FMR1* carriers among females with FM would impact the standard evaluation of FM. Presently, guidelines for *FMR1* genetic testing includes early menopause, congenital intellectual disability, autism spectrum disorder, tremor or ataxia, and a family history of FXTAS or fragile X syndrome. The latter is a common cause of autism and developmental delay. Such testing is important because female carriers are at risk of having a child with fragile X syndrome.

Key words: Fibromyalgia, Fragile X-associated tremor ataxia syndrome, *Fragile X mental retardation 1* gene, Genetic counselling.

CLINICAL SCIENCE

Introduction

FM is characterized by chronic widespread musculoskeletal pain and diffuse tenderness, along with symptoms of fatigue, poor sleep and psychiatric illness. Female carriers of a premutation in *fragile X mental retardation 1* (*FMR1*) gene frequently have similar symptoms and sometimes have been diagnosed with FM [1, 2], especially if they have the motor signs of fragile X-associated tremor ataxia syndrome (FXTAS) [1]. FXTAS is a disorder that occurs in ageing *FMR1* premutation carriers, especially males, and is characterized by kinetic tremor, cerebellar gait ataxia, mild parkinsonism, neuropathy and cognitive, psychiatric and autonomic dysfunction [3, 4]. The *FMR1* gene has a CGG trinucleotide in the 5′-untranslated region, which is normally repeated about 30 times, but when repeated 55–200 times it is termed as premutation. Approximately 8–16% of female premutation carriers identified from families with known *FMR1*-related pathology over the age of 50 years develop FXTAS [1, 2]. In addition, ~20% develop primary ovarian insufficiency [5] manifested as fertility problems and early menopause. Furthermore, female carriers are at risk of having a child with fragile X syndrome, the most common known heritable cause of cognitive disability and autism, which is caused by a CGG repeat of >200 in *FMR1.* Here, we present case histories of some of the female *FMR1*

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premutation carriers that we have identified with diagnoses or symptoms of FM.

Patients and methods

The five patients that are presented either participated in a National Institutes of Health-funded study that investigated the phenotype and therapy of FXTAS (RL1AG032115, UL1 DE019583) or a study of genotype–phenotype features of carriers (HD036071), who were identified by cascade testing after a proband was identified with fragile X syndrome. Subjects were mainly from the Rocky Mountain region and California, since they were recruited through fragile X clinics associated with the University of Colorado Denver and the University of California, Davis, Medical Investigation of Neurodevelopmental Disorders (M.I.N.D) Institute, and also through local and national fragile X patient support groups. The studies were approved by institutional review boards at each institution. The five cases presented were selected because they had a recent study visit and were felt to be representative of the chronic pain phenotype of many of our female subjects. Two of the patients were included in a prior publication [1], which did not include detailed clinical histories. Data were acquired from medical histories obtained during study visits.

Females with *FMR1*-related disorders are generally expected to have less severe signs than males because of the presence of the normal allele on the other X chromosome. Non-random X activation with predominant expression of the expanded allele on the active X chromosome would be expected to produce more severe disease. Thus, activation ratio (which expresses the percentage of cells that carry the normal allele on the active X chromosome) as well as CGG repeat size was measured in blood as previously described in Tassone *et al*. [6]. The *FMR1* mRNA levels were measured in blood as previously described in Tassone *et al*. [7]; mean (S.E.) in normal controls is 1.26 (0.26).

Case reports

Case 1, a 71-year-old retired Caucasian female rancher developed pain between her shoulders in her early 40s, which progressed to widespread body pain that she describes as feeling like a painful force field over her body, and is associated with fatigue. She was diagnosed with FM by her primary-care physician based on her symptoms, as well as chronic fatigue syndrome and irritable bowel syndrome. Medical history is notable for rheumatic fever in childhood, anxiety, hypercholesterolaemia, bilateral hand action tremor since the age of 65 years, peripheral neuropathy diagnosed at the age of 67 years, chronic cough, RP, osteoporosis and episodic vertigo. She takes three prescriptions and seven over-the-counter medications. Brain MRI shows mild non-specific white matter abnormality and mild volume loss. Her two *FMR1* alleles have 30 and 106 CGG repeats with an activation ratio of 0.7. Her mRNA level is elevated at 3.12 (0.35). She meets diagnostic criteria for possible FXTAS [4] and has two grandsons and a nephew with fragile X syndrome.

Case 2, a 60-year-old Caucasian woman was well until pain developed in her hands at the age of 50 years, which progressed to severe OA, requiring reconstruction of the base of her thumbs. Also, in her early 50s, she developed muscle aches and tenderness associated with poor sleep and severe fatigue; this was diagnosed as FM based on her symptoms, tender point examination and negative laboratory testing by her rheumatologist. The symptoms particularly flair up in the autumn and winter. In addition, she has been depressed and noticed impaired balance for 2 years. Medical history is remarkable for menopause at the age of 42 years, hypertension, hyperlipidaemia, osteopenia, temporal-mandibular disorder, rheumatic fever in childhood, gastric reflux, mitral valve regurgitation and supraventricular tachycardia. Brain MRI shows mild non-specific white matter abnormality. She has 35 and 73 CGG repeats with an activation ratio of 0.48 and mRNA is 1.93 (0.04). She does not have FXTAS, but has a family history of both fragile X syndrome and FXTAS.

Case 3 is a 49-year-old Caucasian female bookkeeper with gradual onset of muscle pain everywhere 3 years ago, which is now associated with severe fatigue. These worsened over the past 1.5 years, with symptoms being worst during autumn and winter. She was diagnosed with FM after an extensive negative laboratory evaluation. After an unsuccessful trial of duloxetine, she found relief with amitriptyline 20 mg at night and marked benefit from a yoga programme. Medical history is notable for menopause at the age of 39 years, depression, history of alcoholism with abstinence for 4 years, RP, vertigo, Bell's palsy, OA and scoliosis. She takes amitriptyline, vitamins and acetaminophen. Brain MRI shows mild non-specific white matter abnormality. She has 31 and 74 CGG repeats with an activation ratio of 0.64 and mRNA level of 1.35 (0.04). While she does not have FXTAS, her son has fragile X syndrome and her father had symptoms consistent with FXTAS.

Case 4, a 48-year-old retired Native American female human resource manager, had onset of muscle pain 5 years ago in her back, shoulders and arms. The pain worsened over the past 2 years and progressed to include her thighs and to be associated with severe fatigue. Medical history is significant for bilateral action hand tremor, neuropathy, SS/sicca syndrome (Ro negative), inflammatory polyarthropathy particularly involving her hands and feet, RP, irritable bowel syndrome, migraine, depression, panic attacks, cardiac arrhythmia, scoliosis and that she has had eight orthopaedic surgeries on her feet and knees. She takes 15 prescriptions, nine over the counter, and five as needed medications. Detailed immunological workup was negative. Brain MRI demonstrates mild left lateral ventricular enlargement, but no white matter disease. She has 20 and 108 CGG repeats with an activation ratio of 0.56 and mRNA level of 3.09 (0.41). She meets diagnostic criteria for possible FXTAS, and has two sons with fragile X syndrome.

Case 5, a 49-year-old Caucasian woman, has a 15-year history of FM, diagnosed by her rheumatologist, which began with pain in her back, arms and thighs and progressed to include her feet, chest and face. In recent years she developed chronic fatigue. She has a history of severe migraines, hypothyroidism, carpel tunnel surgery twice, intention tremor since the age of 47 years, ataxia with more than 10 falls over the past few years, vertigo episodes, bulimia and chronic depression. Her brain MRI shows mild atrophy and white matter disease in the frontal regions. She has 30 and 93 CGG repeats, an activation ratio of 0.15 and mRNA level of 3.71 (0.48). She meets diagnostic criteria for probable FXTAS, and has a son with fragile X syndrome. Also, her father died of FXTAS and sister with the premutation has FM and migraines.

Discussion

In this report, we present five female *FMR1* carriers that are representative of the many carriers we have evaluated with chronic muscle pain. We frequently see chronic muscle pain in this population and have reported a controlled study showing a significant correlation [1]. Twenty-five per cent of female carriers without FXTAS ($n = 125$) with a mean (S.D.) age of 42.3 (11.5) years reported chronic muscle pain, defined as persistent myalgia for >2 months unrelated to injury, compared with 8.9% of age-matched controls ($n = 56$; $P = 0.01$), and 43.8% of carriers with FXTAS ($n = 16$) with a mean (S.D.) age of 59.2 (10.3) years reported being diagnosed with FM, compared with 9.4% age-matched controls ($n = 32$; $P = 0.01$). However, the association still requires confirmation. Two additional groups have investigated medical diagnoses that occur in female carriers [2, 8]. One administered a questionnaire to carriers from families with fragile X syndrome, and found that chronic muscle pain was reported in ~25% of female carriers [mean (S.D.) age 70.3 (13) years], and did not have a control group [2]. The other did not ask specifically about muscle pain or FM and did not find any difference between controls and carriers [8], perhaps because the mean age was only 35 years, and the prevalence of FM increases with age. Of note, the cases presented here are from families with fragile X syndrome, and it is possible that undiagnosed *FMR1* carriers that are not from a family with fragile X syndrome could have a different clinical presentation, e.g. without pain.

While further research is indicated, we and others continue to evaluate *FMR1* carriers for FM, and to consider what mechanism could underlie a possible association. FM results from disordered pain regulation in the CNS. Recent studies suggest that environmental factors, e.g. infection, physical or emotional stress, may trigger the symptoms of FM in genetically predisposed individuals [9]. The genetic basis of FM is supported by studies finding increased rates of the disorder and of muscle tenderness within families [10] and a possible association of genetic polymorphisms in monoamine systems with FM [9]. Further, Fabry disease, an X-linked lysosomal storage disease, is an example of a known genetic mimic of FM. Widespread pain results from deposition of glycosphingolipids throughout the body. Affected persons have often been misdiagnosed as simply having FM [11].

FM is a member of a set of disorders, the functional somatic syndromes, which recently have been suggested to be renamed central sensitivity syndromes [12]. Besides FM, these disorders include chronic fatigue syndrome, irritable bowel syndrome, migraine, temporomandibular disorder and others. Similar features among the disorders include pain, fatigue, poor sleep and psychological distress. The unifying feature of these syndromes, in addition to the fact that they all manifest medically unexplainable symptoms, is that their pathophysiology involves hyperexcitability of central neurons through various synaptic and neurotransmitter/neurochemical mechanisms [12]. Thus, the mechanism through which female *FMR1* premutation carriers develop FM symptoms is likely to be via alteration of pain neurotransmission. Pain dysregulation in these carriers may result from damaging effects of increased rates of transcription of expanded *FMR1* mRNA, since the latter is the cause of the symptoms of FXTAS and primary ovarian insufficiency [13], and four of the five cases presented here have increased levels. The *FMR1* expression levels observed in our cases are consistent with previous studies which indicate that expression levels are associated with the methylation status in females (activation ratio) and with CGG repeat number [14–16].

Studies in human cell culture and brain tissue indicate that the damaging effect of elevated mRNA transcription leads to mitochondrial dysfunction in premutation carriers with and without FXTAS [17]. It is possible that the chronic fatigue that many of these women experience may also be related to the mitochondrial dysfunction that appears to become more severe as FXTAS progresses [17]. Research into the mechanisms that cause chronic muscle pain in *FMR1* carriers may yield information on the pathogenesis of FM.

Since FM affects ~2–4% of the world's population [18] and ~1 : 130–250 females are premutation carriers [19], a research study screening females with FM for the presence of the *FMR1* premutation is worthwhile. A finding of an increased prevalence of *FMR1* carriers among females with FM would impact recommendations for genetic testing for *FMR1* and the evaluation of FM. Presently, medical care providers can remain vigilant about the current guidelines for *FMR1* genetic testing, which includes early menopause, the presence of tremor or ataxia and a family history of FXTAS or fragile X syndrome, congenital intellectual disability and an autism spectrum disorder. Such testing is important because a positive result would predict the risk of having a child with fragile X syndrome or the premutation and other medical problems associated with the premutation. Even if the person considered for testing is past child-bearing age, a positive result impacts the whole family. *FMR1* gene testing should be accompanied by counselling that being a carrier may also be associated with other medical

problems with ageing and risk for involvement of other family members.

Rheumatology key message

- FM-like symptoms frequently affect female premutation carriers of the *FMR1* gene.

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