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Hypermobile Ehlers-Danlos Syndrome (hEDS) Phenotype in Fragile X Premutation Carriers: Case series

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Contributors RJH, ELC, and NT made substantial contributions to the conception of the work. RJH, ELC, NT, EM, KN, and ICP drafted the manuscript. RJH, ELC, CBB, and CR wrote case histories. FJM, FT, and PJH wrote the method section. FT, MJJ, and PJH did the molecular analysis and provided the results. NT and KN wrote the discussion. FJM, YAM, EM, FT, RJH, and ELC made critical revisions. RJH, ELC, and CBB made substantial contributions to funding, patient recruitment and ascertainment, and data collection. All authors approved the submitted version of the manuscript.

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Abstract

Background—While an association between full mutation CGG-repeat expansions of the fragile X mental retardation 1 (*FMR1*) gene and connective tissue problems are clearly described, problems in fragile X premutation carriers (fXPCs) CGG-repeat range (55–200 repeats) of the *FMR1 gene,* may be overlooked.

Objective—To report five *FMR1* fXPCs cases with the hypermobile Ehlers-Danlos syndrome (hEDS) phenotype.

Methods—We collected medical histories and *FMR1* molecular measures from five cases who presented with joint hypermobility and loose connective tissue and met inclusion criteria for hEDS.

Results—Five cases were female and ranged between 16 and 49 years. The range of CGG repeat allele sizes ranged from 66 to 150 repeats. All had symptoms of hEDS since early childhood. Commonalities in molecular pathogenesis and coexisting conditions between the fXPCs and hEDS are also presented. The premutation can lead to a reduction of fragile X mental retardation protein (FMRP), which is crucial in maintaining functions of extracellular matrix (ECM)-related proteins, particularly matrix metallopeptidase 9 (MMP9) and elastin. Moreover, elevated *FMR1* messenger (mRNA) causes sequestration of proteins, which results in RNA toxicity.

Conclusion—Both hEDS phenotype and premutation involvement may co-occur because of related commonalities in pathogenesis.

Keywords

FMR1 ; fragile X mental retardation 1; fragile X premutation; hypermobile Ehlers-Danlos syndrome; hypermobility spectrum disorders

INTRODUCTION

The Ehlers-Danlos syndromes (EDS) are a group of clinically-related heritable connective tissue disorders (HCTD) that present with varying degrees of joint hypermobility, skin hyperextensibility, tissue fragility, and musculoskeletal pain and instability. Currently, 13 types of EDS are recognized, the most common of which is hypermobile EDS (hEDS) (EDSHMB [MIM: %130020]).[1] Its unclear genetic etiology is likely complex, encompassing a range of rare and common genetic variants with variable penetrance.[1 2]

Fragile X syndrome (FXS; [MIM: #300624] >200 CGG repeats) is the most common inherited cause of intellectual disability and autism spectrum disorder. Some physical features including hyperextensible finger joints, large ears, connective tissue dysplasia, including flat feet, long face, high-arched palate, aortic root dilation, and mitral valve prolapse, have been reported.[3]

The fragile X premutation (55–200 CGG expansion) is more prevalent than FXS (>200 CGG expansion), with the premutation occurring approximately in 1 in 209 females and 1 in 430 males in the general population.[4] The higher the CGG-repeat number in the premutation the lower the level of FMRP, which regulates the translation of other proteins associated with connective tissues. Those with repeats over 120 are likely to have more connective tissue problems.[3 5] A mild deficit of FMRP sometimes associates with features of connective tissue disorders.[5] In one study, over 20,000 individuals were blindly tested for the premutation and the 100 fragile X premutation carriers (fXPCs) identified presented with more clinic visits related to musculoskeletal problems than those without the premutation.[6] Further, recent case reports have also identified the rare occurrence of spontaneous coronary artery dissection (SCAD), which may be related to connective tissue problems, in three women with the premutation.[7 8]

However, connective tissue problems are usually overlooked among the other difficulties that fXPCs may have, including fragile X-associated primary ovarian insufficiency (FXPOI [MIM: #311360]), fragile X-associated neuropsychiatric disorders (FXAND), and fragile X-associated tremor/ataxia syndrome (FXTAS [MIM: #300623]). The term fragile X -associated Premutation Conditions (FXPAC) is a general term that covers all premutation conditions perhaps including the connective tissue problems reported here. Research studies regarding the mechanisms of connective tissue problems in the premutation are still lacking. Here, we present five cases of fXPCs diagnosed with the hEDS phenotype.

METHODS

Participants

Three of the patients were participants in a research study for carriers and selected because of their connective problems. The fourth and fifth cases were found in clinic and all signed consent to report these findings.

CGG sizing and *FMR1* mRNA expression level

A combination of PCR and Southern Blot analysis, as described previously was used to determine the CGG sizing and methylation pattern on isolated genomic DNA.[9 10] Activation ratio (the percentage of cells with the normal X as the active X) was measured as reported in Tassone *et al.*[11] cDNA synthesis reaction and qRT-PCR for measuring gene expression levels were performed as described by Tassone *et al.*[12]

FMRP determination

FMRP quantification closely followed the homogeneous time-resolved fluorescence protocol described in Kim et al.[13] The protocol utilizes the Cisbio Human FMRP assay kit. Total protein concentrations were determined using the Thermo Fisher Micro BCA Assay (Thermo Fisher; Waltham, MA; cat. no. 23235) and were used to determine the ratio of interplated FMRP to total protein.

Plasma matrix metallopeptidase 9 (MMP9) expression measurement

Plasma collection was performed by centrifugation of 3 mL of peripheral blood in EDTA-containing tubes for 10 min at 1000 x g within 2 h of blood collection. Plasma measurements of two analytes, MMP9 and MMP2, were carried out in human plasma using Human MMP Magnetic Bead Panel 2 (Millipore Sigma), per the manufacturer's instructions. MMP9 concentration was normalized to MMP2 concentration to correct for plate-to-plate variability. Quality controls, negative and positive controls, and target samples were run in duplicates.

Editorial Policies and Ethical Considerations

All patients or guardians signed IRB approved informed consents for the inclusion of their or their child's relevant medical information in this report.

RESULTS

Case history

Case 1 is a 49-year-old woman with a history of loose connective tissue problems with notable flexibility. She has hyperextensibility in her fingers and elbows, cervical disc problems, mild idiopathic scoliosis at L1-L5, patella-femoral syndrome, chronic pain in muscles and joints, and Raynaud's phenomenon. She had rectocele and enterocele, which were repaired at 48. A geneticist diagnosed her with hEDS, but she was not diagnosed with the premutation until she had a son with FXS.

She has a long-term generalized anxiety disorder and chronic pain syndrome. She also experiences occasional vertigo and tinnitus and is oversensitive to sensory stimuli, which her doctor diagnosed as fibromyalgia.

Case 2 is a 36-year-old woman with a long history of muscle pain, neuropathic pain, chronic fatigue, and hyperextensibility of her elbows and thumbs. Her pain symptoms affect her quality of life. She was diagnosed with fibromyalgia when she was in her 20s, followed by hEDS diagnosis. She reports her hips dislocate easily while bending over, and her pregnancy and delivery were complicated because of connective tissue problems. Her mother also had joint hypermobility, although her CGG repeats were in the normal range.

She had frequent infections and a fracture when she was young. She had anxiety and panic attacks throughout her life and some obsessive-compulsive symptoms, which have been treated with sertraline 50 mg/day. Other health problems include orthostatic hypotension, mitral valve prolapse, visual migraines, vertigo, gastroesophageal reflux, irritable bowel syndrome, subclinical hypothyroidism, and factor V Leiden.

Her father had the premutation and FXTAS combined with myotonic dystrophy type 2. Subsequent to her father's diagnosis, she was diagnosed with the premutation.

Case 3 is a 16-year-old girl with a normal early development. She has loose joints including her elbows, shoulders, hips, and ankles. Her comfortable sleeping position includes contorted extremities. She has fear avoidance with some movements, afraid her

joints will dislocate. At age 13, while running, she dislocated a facet in her neck while turning to look back; her neck was relocated by a physician. She does not have chronic pain. She is being treated for anxiety with 75 mg/day of sertraline.

On examination, her finger joints showed metacarpophalangeal extension to 80 degrees, her thumbs were double-jointed, her elbows were hyperextensible, and her feet had moderate pronation and were completely flat. She was able to contort her hands with a 360-degree supination, and her thumb can touch her forearm. The Adam's forward bending test demonstrated a scoliosis. Her mother also has a history of hyperextensible joints, but she does not have the premutation. Genetic evaluation for connective tissue disorders was done in the past, and she was diagnosed with hEDS.

Case 4 is a 37-year-old female premutation carrier with a history of notable flexibility, chronic pain, and other connective tissue features. She scored 6/9 on the Beighton criteria. She had unusually soft and hyperextensible skin, unexplained striae on her back present prior to puberty, bilateral piezogenic papules, bladder prolapse post childbirth, dental crowding, a heart murmur, mild right ventricular dilatation, and a Marfanoid habitus, specifically arachnodactyly (positive Walker and Steinberg signs) and arm span-to-height ratio > 1.05. She also had an earlier diagnosis of scoliosis, and experienced chronic migraines, endometriosis, and chronic musculoskeletal pain across most joints. This patient met full inclusion criteria for hEDS.

She also reported numerous chronic immune-mediated symptoms potentially indicative of a mast cell-like disorder. She was suspected of some form of autonomic disorder as well, evidenced by episodes of syncope/presyncope, brain fog, heart palpitations, chest pains, shortness of breath, decreased sense of smell, insomnia, abnormal patterns of sweating, and gastrointestinal distress. However, her tilt table test result was considered normal.

Case 5 is a 36-year-old female premutation carrier. Her premutation was inherited maternally and she is also diagnosed with FXPOI and severe osteoporosis. The patient has a history of hypermobility (current Beighton: 6/9), chronic pain, joint dislocations, mild scoliosis, and a diagnosis of fibromyalgia. She displayed unusually soft, velvety skin as well as mild skin hyperextensibility, bilateral piezogenic papules, hiatal hernia, dental crowding and high narrow palate, easy bruising, difficulty wound healing, significant tooth decay, a chronic noticeable loss in muscle mass, and arachnodactyly. The patient also appears to have a right supernumerary rib, accessory navicular bones, cavus foot, nerve entrapment issues, and prominent ears—the latter typical of her carrier status. The patient met full inclusion criteria for hEDS.

Similar to the previous case, the patient also reported symptoms potentially characteristic of a mast cell disorder, including chronic respiratory allergies and rhinosinusitis, sinus headaches, urinary tract infections, stomach ulcers and acid reflux, chronic ear infections in childhood, and sensitivity to certain chemicals like cleaning fluids/perfumes and to medications, especially sulfa drugs.

She also reported many symptoms indicative of autonomic dysregulation, including chronic fatigue, syncope/presyncope, "coat hanger" pain along the shoulders and neck, brain

fog, muscle weakness and tremors, increased urination, unusual weight loss, temperature dysregulation, numbness/burning/tingling in the extremities, abnormal patterns of sweating, restless legs, memory problems, and gastrointestinal symptoms such as abdominal pain/bloating/gas, nausea, and vacillating diarrhea and constipation. Many of these symptoms were present before her diagnosis of FXPOI.

Molecular Results

Molecular studies, including CGG repeat sizing, methylation status, *FMR1* mRNA expression levels, FMRP expression levels, and MMP9 plasma levels, were carried out in three of the four cases. Results are as shown in Table 1. Elevated *FMR1* mRNA levels were observed in case 1, 2, and 3. FMRP levels were found deficient in cases 1 and 3. Increased MMP9 levels were detected in cases 1 and 2. Molecular results beyond CGG repeats were not collected for case 4 and 5.

DISCUSSION

Connective tissue problems in fXPCs presented here led to the diagnosis of hEDS prior to the *FMR1* premutation diagnosis in three of the four patients.

Since the *FMR1* gene contributes to the regulation of normal structure and function of connective tissue, a mutation could lead to connective tissue problems, evident in various physical features, and in molecular and pathological findings.[3 5 6 14] Three possible mechanisms may lead to connective tissue problems for fXPCs: 1) FMRP deficiency, 2) mRNA toxicity, and 3) secondary gene effects, or perhaps all three suggested mechanisms are compounded.

1) FMRP deficiency

FMRP is the key protein regulating translation of extracellular matrix (ECM)-related proteins, particularly in MMP9, elastin, and actin.[3] Therefore, FMRP deficiency, which happens in both FXS and sometimes with the premutation, could lead to altered expression of these proteins. For example, MMP9 overexpression in FXS is associated with ECM connective tissue defects and was explained in a study on dermal fibroblasts of hEDS/HDS.[3 15]

Levels of FMRP depletion correlate with degrees of connective tissue involvement in those with FXS and in premutation carriers.[5] Autopsy findings of an 18-year-old male with FXS showed irregular, fractured, and fragmented elastin fibers of the aorta, mitral valve, and tricuspid valve, with an increase in thick collagen.[14] Elastin fibers in the forearm skin and dermis lacked the normal arborization structure and were fragmented and decreased in number.[14]

2) mRNA toxicity

The premutation causes enhanced production of *FMR1* mRNA, and the higher the CGG-repeat number, the higher the level of mRNA. Excess mRNA leads to sequestration of important proteins such as DROSHA and DGCR8, which are essential for

maturing miRNAs and normal neuronal function.[16] RNA toxicity also leads to Ca^{2+} dysregulation, mitochondrial dysfunction, enhanced production of reactive oxygen species, and inflammation, which contribute to intranuclear inclusion formations.[17] The inclusions are also found in non-neuronal cells where cellular dysfunction can occur.[17 18] mRNA toxicity may contribute to the connective tissue problems in fXPCs with < 100 CGG repeats, as they usually have an average level of FMRP.

3) Secondary gene effects

The mothers of our second and third cases have connective tissue problems without the premutation. Many genes are identified in HCTD with manifestation of joint hyperlaxity.[2] In the case of the Ehlers-Danlos syndromes, genes involved in collagen-related pathways are most often implicated, although hEDS, the most common form of EDS, has no associated rare gene variants and is likely heterogeneous and perhaps polygenic in nature.

4) Potential sex effects

All of the cases presented here are female. One likely reason for this is the sex-skewed nature of the premutation itself. Approximately twice as many women inherit Fragile X premutation as men.[4] As such, women are also more likely to pass down the premutation to their children. Many parents are diagnosed as carriers when their children are assessed for FXS, suggesting more mothers than fathers are ultimately diagnosed.

Another potential factor is the extreme sex-skewed nature of hEDS itself, which may also be reflected in the hEDS-like phenotype we are currently reporting in some females with fragile X premutation. The vast majority of hEDS cases diagnosed are female, suggesting sex plays a significant role in expression of the syndrome.[19] Although the mechanisms are not well understood, the variable effects of sex steroids on muscle tone and tendon/ligament strength are considerable (men > women).[19] Similarly, pain perception and modulation differ between the sexes and women in general report greater musculoskeletal pain than men.[20] Because chronic musculoskeletal pain is an integral component to the hEDS criteria, this may lead to higher diagnostic rates in females despite the presence of hypermobility in males.

With regards to the hEDS-like phenotype described here, it remains to be seen whether a similar sex skewing is observable in premutation carriers and therefore requires further experimental investigation.

CONCLUSION

These cases suggest a possible connection between the *FMR1* premutation and hEDS, particularly in those with higher CGG repeats and lower FMRP, due to an increased probability of ECM-related protein dysregulation. RNA toxicity may also compound problems with connective tissue through mitochondrial dysfunction and inflammation. The finding of SCAD in two females with the premutation has not been reported in those with a full mutation who have an absence of FMRP.[10] Therefore, additional factors in fXPCs may add to the risk of connective tissue problems that are beyond what is seen in FXS.

The commonality of symptoms beyond the connective tissue problems in those with the premutation and those with hEDS is also remarkable; psychiatric and neurodevelopmental problems, chronic pain, gastrointestinal disorders, autonomic dysfunction, should all be considered. Because of the occurrence of the hEDS phenotype in fXPC cases, clinicians may want to consider testing for the premutation when evaluating those diagnosed with hEDS, and vice versa. This possible association will further our understanding of the genetic causes of hEDS.

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Table 1

Molecular findings for the fXPC cases

Participants	CGG repeat	Activation ratio	*FMR1* mRNA (SD)	FMRP (SEM)*	MMP9**
Case 1	22, **119**	0.68	**2.58 (0.11)**	**0.62 (0.06) [0.51 (0.08)]**	**2-fold**
Case 2	30, **105**	0.71	**2.35 (0.21)**	1.38 (0.14) [1.14 (0.18)]	**3-fold**
Case 3	30, **66**	0.48	**1.97 (0.13)**	**0.29 (0.04) [0.24 (0.05)]**	no difference
Case 4	32, **100–150**	NA	NA	NA	NA
Case 5	31, **78**	NA	NA	NA	NA

Bold numbers indicate premutation CGG-repeat sizes, elevated *FMR1* mRNA levels, depleted FMRP levels, and increased MMP9 levels.

*The average FMRP level among a control population with normal CGG repeats is 1.21 (SEM, 0.15). FMRP levels normalized to a normal FMRP = 1.0 are given in square brackets, with SEMs reflecting the standard errors of both cases and population control.

**Plasma MMP9 levels, relative to MMP2, compared with a normal age- and gender-control