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Spontaneous distal middle cerebral artery aneurysm in a young male with full mutation of the fragile X syndrome with a high-functioning phenotype: illustrative case

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BACKGROUND Fragile X syndrome (FXS) is a genetic disorder that typically presents with neurodevelopmental abnormalities. Patients with FXS can present with signs and symptoms of connective tissue disorder (CTD) and occasionally with vascular disease. However, cerebrovascular disease is not well documented in these patients, and it is unknown whether there is a direct link between abnormal levels of fragile X protein (FMRP) and its mRNA.

OBSERVATIONS Here, the authors present a rare case of an adult male with full mutation FXS of a high-functioning phenotype who presented with syncope, and on further evaluation, a fusiform dissecting aneurysm of the distal middle cerebral artery was identified. The patient was treated for the aneurysm and recovered successfully.

LESSONS Previous clinical evidence suggests that there might be an association between FMRP and increased mRNA levels on CTD and vascular pathologies in patients with FXS. This leads the authors to believe that their patient's previous FXS diagnosis might have played a role in the spontaneous aneurysm and presents a novel area of inquiry in the clinical and pathological manifestations of this disease. Therefore, screening for underlying FXS genetic abnormalities in patients with CNS aneurysms and screening for aneurysms in those with these mutations might need to be considered.

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KEYWORDS fragile X syndrome; cerebrovascular; aneurysm; connective tissue disorder

Fragile X syndrome (FXS) is an X-linked genetic disorder causing a range of neurodevelopmental abnormalities. FXS is typically diagnosed during early childhood, but with milder cases, the diagnosis is often delayed, especially in girls, who are less affected generally compared with boys due to males only having 1 X chromosome.[1] The disorder is caused by an expansion and hypermethylation of the cytosine-guanine-guanine (CGG) repeat sequence in the 5' untranslated region of the Fragile X Messenger Ribonucleoprotein 1 (*FMR1*) gene. This mutation ultimately leads to the decreased expression of the *FMR1* protein (FMRP).[2] The severity of FXS directly correlates with the number of CGG repeats, with > 200 repeats associated with the full mutation. However, in rare reported cases, patients with > 200 repeats present with a high-functioning phenotype; low methylation status in these cases produces higher FMRP levels, leading to higher IQs.[3] The premutation (55–200 CGG repeats), also called the carrier state, is not associated with intellectual disability but is assoicated with an increase in *FMR1* mRNA levels up to 2 to 8 times the normal value. This leads to aging problems due to RNA toxicity and neurodegeneration in the CNS called "fragile X–associated tremor/ataxia syndrome" (FXTAS).[3]

Presenting signs and symptoms of FXS include developmental delays, intellectual disability, macro-orchidism, seizures, and the typical appearance of a long face with a prominent forehead and ears.[4] Connective tissue problems are associated with FXS, including symptoms of soft skin, loose joints, extremity hyperextensibility, flat feet, and occasional vascular manifestations such as dilation of the base of the aorta. Yet, the relationship between FMRP and connective tissue disease in these patients is still not well understood. Additionally, cerebrovascular abnormalities have not been historically reported in individuals with this disease.

In this report, we demonstrate, to our knowledge, the first reported case of a patient with > 200 CGG repeats and a high-functioning phenotype, presenting with a spontaneous distal dissecting intracerebral aneurysm of the middle cerebral artery (MCA) requiring treatment.

ABBREVIATIONS CGG = cytosine-guanine-guanine; CTD = connective tissue disorder; ECM = extracellular matrix; FXS = fragile X syndrome; FXTAS = fragile X–associated tremor/ataxia syndrome; MCA = middle cerebral artery; MMP9 = metalloproteinase 9; MRA = MR angiography.

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Illustrative Case

A male in his early 30s presented to the hospital with syncope. Initial workup included MR angiography (MRA), which revealed an unruptured distal left MCA aneurysm (Fig. 1A). The patient was neurologically intact without headache. Further workup suggested that the syncopal episode was related to a panic attack secondary to an underlying anxiety disorder, which is common in FXS.[5]

Regarding his FXS history, the patient had a molecular diagnosis of FXS at the age of 1 year. His mother and aunt were known carriers of the premutation, and his mother died of FXTAS, leading to testing being performed. Genetically, the patient had 280–300 CGG repeats in the 5' region of *FMR1*, but is only 10% methylated, producing 80% of normal levels of FMRP. His mRNA level was 2.84 ± 0.43. This level of *FMR1* mRNA is almost 3 times the normal value, which is because of the lack of methylation of his full mutation.

Following admission, the patient underwent cerebral angiography, which confirmed the presence of a fusiform dissecting aneurysm of the distal MCA (Fig. 1B). Additional workup for possible mycotic sources, including blood cultures and inflammatory markers, was unrevealing. Given the aneurysm's high-risk characteristics, including its size, location, and morphology, as well as the patient's young age, the decision was made to proceed with aneurysm embolization with placement of a flow-diverting stent.

The patient was given a loading dose of aspirin and ticagrelor, with a therapeutic response on postloading P2Y12 levels. He was subsequently taken to the operating room for aneurysm embolization. Right-sided femoral artery access was obtained with a 6-Fr sheath using the Seldinger technique. The left internal carotid artery was selected, and a 6-Fr Benchmark (Penumbra) catheter was advanced into the distal cervical internal carotid artery. A headway 21 microcatheter (MicroVention) was advanced into the distal MCA under roadmap guidance, and a 2.5 × 26–mm FRED X flow-diverting stent (MicroVention) was placed in the distal MCA, centering on the aneurysm. Repeat injections demonstrated contrast stasis in the aneurysm (Fig. 1C). The immediate postoperative course was without complications, and the patient was discharged home. Following treatment, the patient had intermittent returns to the emergency department for similar panic attacks. Repeat noninvasive imaging demonstrated no evidence of stent thrombosis, hemorrhage, or ischemia. A 6-month follow-up angiogram demonstrated complete obliteration of the aneurysm (Fig. 1D).

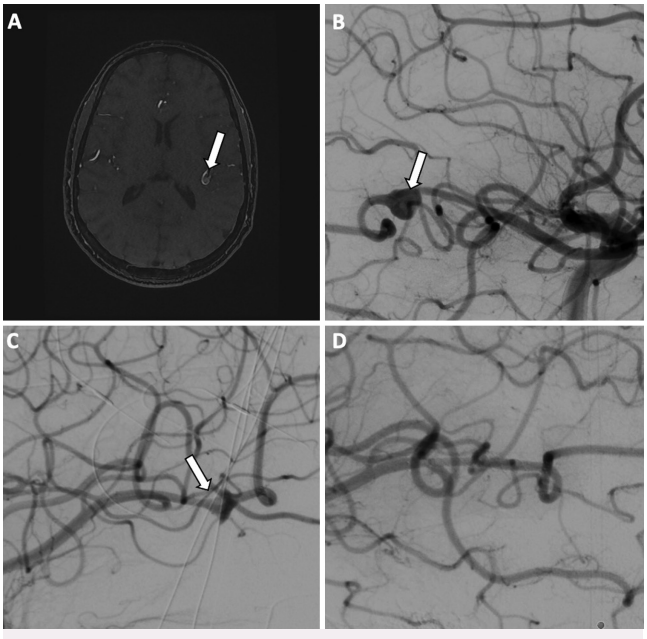

FIG. 1. A: Axial MR angiogram demonstrating a distal left MCA flow signal suspicious for an aneurysm (*arrow*). **B:** Digital subtraction angiogram demonstrating a fusiform-appearing distal left MCA aneurysm (*arrow*). **C:** Intraoperative digital subtraction angiogram obtained after placement of a flow-diverting stent with intra-aneurysmal contrast stasis (*arrow*), suggesting adequate aneurysm coverage and treatment effect. **D:** Long-term follow-up digital subtraction angiogram demonstrating successful aneurysm obliteration with vascular remodeling.

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

Our case represents the first report, to our knowledge, of a patient with > 200 CGG repeats in the *FMR1* gene and a high-functioning phenotype presenting with a dissecting intracerebral aneurysm. The severity of FXS is typically determined by the number of CGG repeats on the 5' end of the *FMR1* gene.[2] This unique circumstance with co-occurrence of FXS and elevated mRNA due to a lack of methylation is noteworthy. However, it is unclear to what extent other clinical features associated with FXS might be present in these patients, which raises the question of whether there is a potential link between connective tissue dysregulation, cerebral vasculature abnormalities, and FMRP expression.

Lessons

The connection between connective tissue disorder (CTD) and FXS has not been completely elucidated. Clinically, presenting signs and symptoms associated with CTD in patients with FXS include hypermobile joints, scoliosis, flat feet, and abnormal cardiovascular anatomy, such as aortic root dilation and mitral valve prolapse. Two putative mechanisms for CTD in FXS are the role FMRP plays in extracellular matrix (ECM)–related protein regulation and the potential for mRNA toxicity on connective tissue proteins. *FMR1* CGG repeats are inversely correlated with FMRP levels. FMRP plays a crucial role in the translation and regulation of ECM proteins such as elastin, actin, and matrix metalloproteinase 9 (MMP9), which are important for maintaining endothelial integrity.[6] In particular, MMP9, which breaks down protein in the ECM, is increased when FMRP expression is low.[6] Decreased expression of MMP9 can lead to abnormal vascular remodeling and the onset of various pathological disorders such as hypertension, atherosclerosis, aneurysm formation, and lower extremity venous disease.[7] Increases in *FMR1* mRNA toxicity, which occurs in unmethylated full mutation carriers and in those with the premutation (who are typically unmethylated), can sequester proteins important for neuronal function, leading to FXTAS in older carriers. Increases in mRNA levels can result in increased binding to RNA-binding proteins, resulting in decreased production of microRNAs that maintain normal cellular functioning.[8] It seems plausible that, given our patient's abnormal mRNA levels, this might have played a role in the spontaneous dissecting intracerebral aneurysm that occurred.

FMRP under expression has been proposed as a potential pathological mechanism for less common vasculature CTD presentations

of FXS. Vasculature irregularities reported from autopsy findings of a young male with FXS showed fragmented and fractured elastin fibers in the aorta, mitral valves, and tricuspid valves.[9] Furthermore, a report of 2 female *FMR1* premutation carriers with spontaneous coronary artery dissection cites FMRP underexpression as a possible cause of dissection onset. Specifically, the increase in ECM breakdown due to decreased FMRP expression and increased MMP9 might have led to the weakening of the arterial wall, resulting in arterial dissection.[10] Although our patient was producing 80% of normal levels of FMRP, it is likely that, along with high levels of mRNA, both types of molecular disorganization contributed to the connective tissue problems in this patient, warranting further investigation.

Additionally, intranuclear inclusions are a pathological hallmark of FXTAS postmortem studies have shown mild vascular changes in the cerebral white matter, widened perivascular spaces, and parenchymal rarefaction around abnormal small arteries and arterioles.[11] This suggests a role of intranuclear inclusions in impacting the structural integrity of the vasculature potentiating clinical comorbid pathologies of FXTAS.[12] Further investigation is needed to determine whether there is an association with nuclear inclusions in patients with unmethylated full mutation FXS without the FXTAS subtype, which could explain the cerebrovascular phenomenon observed in our patient.

We describe the first reported case of a spontaneous dissecting intracranial aneurysm in a young male patient with unmethylated full mutation FXS, high *FMR1* mRNA levels, and a normal IQ. Our case suggests that *FMR1* mutations alone might predispose patients to pathologies associated with CTD; however, there is no current explanation for CTD signs with this full mutation genotype of FXS.[13] Furthermore, a limitation of our observations is the unknown complex biochemical interactions of FMRP and mRNA toxicity that might have contributed to this patient's rather unique presentation of a dissecting distal intracerebral artery aneurysm. These types of distal aneurysms are extremely rare, especially in young patients without any evidence of inflammatory or infectious conditions.[14,15] We can only assume, based on previously documented associations between *FMR1* mutations, FMRP expression, and both CTD and intracerebral vascular pathology, that FXS likely played a role in this presentation. Further investigation is warranted to assess how our case might translate into clinical practice, but it may seem reasonable to consider screening patients with significant CGG repeats in the premutation or full mutation range. However, elucidating the clinical manifestations of patients with this rare normal-functioning phenotype is necessary to make definitive claims or recommendations.

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Disclosures

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Author Contributions

Conception and design: Schmidt, Papadopoulos, Zarzour. Acquisition of data: Schmidt, Hagerman. Analysis and interpretation of data: Schmidt, Zarzour, Hagerman. Drafting the article: Schmidt, Papadopoulos, Abrimian, Zarzour. Critically revising the article: all authors. Reviewed submitted version of manuscript: Schmidt, Papadopoulos, Hagerman. Approved the final version of the manuscript on behalf of all authors: Schmidt. Statistical analysis: Schmidt. Administrative/technical/material support: Schmidt. Study supervision: Schmidt. Performed literature review: Abrimian.

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