Pearls & Oy-sters:

Fragile X tremor/ataxia syndrome

A diagnostic dilemma

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PEARLS

1. Fragile X tremor/ataxia syndrome (FXTAS) can include kinetic or resting tremor, ataxia, cognitive decline, and autonomic symptoms.
2. FXTAS should be suspected when a patient demonstrates the above findings and has a family history of a male relative with mental retardation.
3. The hyperintense middle cerebellar peduncle (MCP) sign is bilateral T2 hyperintensities in the MCPs. This is commonly seen in FXTAS.
4. Diagnosis can only be confirmed with genetic testing by identifying the CGG premutation on the X chromosome.

OY-STERS

1. The clinical symptoms of FXTAS are variable and can be indistinguishable from essential tremor or multiple system atrophy.
2. Patients may not report a family history of mental retardation.
3. The hyperintense MCP sign is not specific for FXTAS and can also be seen in multiple system atrophy.

Fragile X tremor/ataxia syndrome (FXTAS) is a progressive, adult-onset, X-linked genetic disorder caused by the CGG premutation *FMR1* gene. The clinical features of the syndrome are diverse, as patients can present with parkinsonism, bilateral hand tremor, ataxia, and cognitive decline. The syndrome can mimic more common neurodegenerative disorders such as Parkinson disease or the atypical parkinsonian syndromes, Alzheimer disorders, essential tremor, or pure ataxia. Ultimately the diagnosis is supported by recognition of the clinical features, family history, neuroimaging clues, and finally confirmation with genetic testing.

CASE REPORT A 56-year-old man with hypertension and prediabetes developed a slowly progressive bilateral upper extremity kinetic tremor. The tremor was marked with writing, and lacked a clear postural or rest component. His brother, who was 1 year older, had a similar tremor. He had no children. The patient

was diagnosed with essential tremor but declined medical therapy. Two years later, he was amenable to medical therapy. He was treated with gabapentin 100 mg every morning and 200 mg every evening for 3 years with mild improvement. Seven years after developing the tremor, he had severe difficulty writing (figure, A, Archimedes spiral), and was unable to sign his name. Neurologic examination was remarkable for marked kinetic tremor, mild postural tremor, absent rest tremor, and a mild large-fiber symmetric sensory polyneuropathy. He had mild difficulty with tandem gait. His cognitive evaluation was normal, and he showed no signs of parkinsonism. The patient was started on propranolol 40 mg twice daily with modest subjective improvement and further increase in dose was limited by bradycardia. Amiodarone was then added to the patient's medication regimen and, with gradual titration, reached 125 mg twice daily. Although the tremor persisted, the patient noticed some improvement (figure, B, Archimedes spiral). Sinemet 25/100 mg was tried without success. Due to medication-refractory symptoms and development of mild dysmetria on right heel-to-shin test, the patient underwent a brain MRI (figure, C), which showed increased T2 signal in the bilateral middle cerebellar peduncles (MCPs). He was tested for a premutation for the *FMR1* gene, which was positive with 155 CGG repeats. He had no relatives with fragile X syndrome.

DISCUSSION FXTAS is caused by the fragile X premutation with CGG repeat expansion on the X chromosome. Although the fragile X syndrome of cognitive impairment, learning disability, autism, hyperactivity, elongated facies, large ears, macroorchidism, and low muscle tone occurs when the CGG repeat length exceeds 200 repeats, FXTAS is seen with repeat lengths between 55 and 200. The mean repeat length is 88.5 and typical age at onset is usually over 50 years, with an average age in the 60s–70s.^{1,2} Although FXTAS is a disease of male carriers, 20% of female carriers undergo premature menopause.³ The genetic abnormality can be accompanied by *FMR1* mRNA

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Dr. Eye and Dr. Hawley are active duty medical officers in the United States Army. The opinions expressed in this paper are the views of the authors alone, and do not necessarily reflect the views of the United States Department of Defense or any other Federal Government Agency.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Archimedes spiral before (A) and after (B) initiation of treatment for essential tremor. T2-weighted MRI demonstrates the hyperintense middle cerebellar peduncle sign and is indicated by the 2 arrows (C).

elevations and normal to borderline levels of FMR1 protein.^{2,4} The prevalence of the premutation is 1 in 259 women and 1 in 813 men.^{5,6} Prevalence of FXTAS in a male carrier population increases with age and ranges from 17% in a population aged 50–59 years to 75% in men older than 80 years.⁷ Classically these patients will have a family history of mental retardation; however, it is possible that they will report only a family history of tremor or no pertinent family history.

This case demonstrates the diagnostic and treatment challenge with FXTAS. Part of the challenge lies in the diverse symptomatology of FXTAS and the overlap with essential tremor. Patients may complain of gait impairment, fine motor incoordination, writing impairment, weakness, lower extremity sensory impairment, impotence, and urinary or bowel incontinence. Cognitive findings include executive impairment and decreased verbal fluency. The 4 most common examination findings in patients with this syndrome are gait ataxia, kinetic tremor, parkinsonism, and a lower extremity sensory or motor neuropathy.² It is important to note that, in addition to essential tremor or primary writing tremor, which were the most likely clinical entities on this patient's differential, another common confounder for FXTAS is multiple system atrophy, which is characterized by parkinsonism, rest tremor, gait impairment, autonomic dysfunction, and T2 hyperintensity of the MCPs.⁷

The tremor in FXTAS is typically 3–5 Hz and typically present with purposeful movement; however, 30% of tremors can be present at rest. The tremor typically begins in the dominant hand and progresses to involve the contralateral hand. Only 20% of patients with this condition deny tremor.²

In this case, the patient demonstrated the most common findings associated with FXTAS: kinetic tremor and mild cerebellar ataxia. Additionally, this

patient's tremor was typical although nonspecific for FXTAS. The kinetic tremor and writing impairment may mimic that of essential tremor and writing tremor, respectively. On further review, this patient also had a lower extremity sensory neuropathy, but lacked other symptoms associated with FXTAS. Of note, because this patient presented in his 50s, it is possible that his condition will progress to involve cognitive and gait impairment.²

The finding that informed the diagnosis in this case was the T2 hyperintensity of the MCPs that was found on MRI. Along with generalized brain atrophy, the T2 hyperintensity in the MCPs is the most common imaging finding associated with FXTAS.³ In this case, the imaging finding directly informed the diagnosis and prompted genetic testing. Associated findings on pathology include white matter disease, enlarged inclusion-bearing astrocytes in white matter, and intranuclear inclusions in the CNS.⁸

FXTAS is a relatively rare movement disorder with diverse clinical symptomatology including motor, sensory, and cognitive findings. The disorder may mimic essential tremor for years and is not necessarily characterized by a family history of fragile X syndrome. Based on the above case, we would recommend a low threshold for MRI in a patient with refractory essential tremor or primary writing tremor.

AUTHOR CONTRIBUTIONS

Philip Eye: introduction, case summary, discussion, and citations. Jason Hawley: project supervision, patient information, and manuscript revisions.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Neurology®

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Neurology 2015;84:e43-e45

DOI 10.1212/WNL.0000000000001267

This information is current as of February 16, 2015

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