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Parkinsonism and Cognitive Decline in a Fragile X Mosaic Male

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Fragile X syndrome (FXS) is the most common cause of inherited form of mental retardation and results from a fragile X mental retardation 1 gene (*FMRI*) repeat expansion of greater than 200 CGG repeats. Individuals who carry an expanded allele in the premutation range of the *FMRI* gene (55–200 CGG repeats) may be affected by the fragile X-associated tremor/ ataxia syndrome (FXTAS), a progressive neurodegenerative disorder characterized by kinetic tremor, ataxia, parkinsonism, and cognitive decline.¹ The parkinsonism may or may not be associated with kinetic tremor or ataxia and can be dopamine responsive.² In this case report, we describe a high functioning man with fragile X syndrome (FXS) and *FMRI* premutation mosaicism who has parkinsonism and cognitive decline.

The patient was diagnosed with FXS at age 60 years after a history of behavioral problems including outbursts in his adult life, shyness and social anxiety in childhood. On examination, he had macroorchidism, long ear pinna, a single palmar crease, flat feet, poor eye contact, perseveration in his language, paranoid ideation, verbal outbursts, and excessive worries that interfered with sleep. The first documented cognitive testing was at age 60, with the WAIS-R showing a VIQ of 69, PIQ of 67, and FSIQ of 67. He was then placed on buspirone and aripiprazole for behavioral issues. At the age of 71, the patient was seen for a

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two year history of gait problems with falls and slowness of movement. The patient described mild short term memory problems. His mental state examination was 25/30, with items missing on multiple domains. Speech was hypophonic, facial expression was masked, and tone was increased in the upper extremities, without cogwheel rigidity or tremor. He had decrement and decreased amplitude with finger tapping and hand grasping. He had stooped posture, shuffling, took six steps to turn, and had retropulsion on the pull test. MRI of the brain showed moderate subcortical white matter disease. Three years later, on a stable dose of aripiprazole, his mental state exam was 22/30, with worsening of his bradykinesia, rigidity, and balance difficulties. New findings on exam included anterocollis and gait initiation difficulties. IQ and mental state testing were repeated at the age of 77 with a WASI, with VIQ of 70 (66–77, CI 95%), PIQ of 67 (63–74, CI 95%), FSIQ of 65 (62–70, CI 95%), and MMSE of 13/30. Orientation was intact, but all other domains were impaired.

FMRI DNA testing revealed two methylated alleles of 540 and 447 CGG repeat sizes and an unmethylated allele of 73 CGG repeats. The percentage of cells carrying the premutation expansion was 23%, and his fragile X mental retardation protein (FMRP) level was 20% of normal levels. *FMRI* mRNA level was 0.37 (± 0.01).

We report a case of a man with FXS and mosaicism who has a progressive neurodegenerative syndrome. Individuals with the full mutation have never been reported with FXTAS. In the full mutation, the *FMRI* gene is methylated leading to a lack of transcription and therefore an absence of FMRP. In contrast, the premutation is associated with elevated *FMRI* mRNA. Mosaicism occurs in 20%–40% of cases of FXS.^{3–5} In mosaic individuals, a mixture of cells carrying either the premutation or the full mutation may produce a normal or higher than normal level of mRNA, leading to the production of sufficient FMRP.⁴ The level of FMRP correlates with the overall IQ level in FXS.^{3,6} Our patient had a FMRP expression level of 20%, which may be why he had only mild intellectual disability. However, it is important to note that the cells in the brain are theoretically a mix of cells that have no *FMRI* mRNA (those with the full mutation) and a percent of cells that likely have elevated *FMRI* mRNA (those with the premutation). Thus, one cannot rule out the possibility of premutation neurotoxicity affecting just a fraction of the cells in the brain resulting in a “patchy” presentation of FXTAS-like symptoms.

Our patient developed parkinsonism and cognitive decline, which may be due to the development of a FXTAS-like syndrome, Parkinson disease (PD), or another dementing illness with parkinsonism, such as Alzheimer disease. The prominence of the movement disorder, with milder cognitive changes, supports a parkinsonian disorder. Decompensation of motor deficits in FXS may occur over time, but the development of parkinsonism, with rigidity, bradykinesia, and postural instability, has not been reported with aging in FXS. Although it is possible that the development of a movement disorder is coincidental in our patient, parkinsonism syndromes without FXTAS have been reported in *FMRI* premutation carriers.² Our patient was on aripiprazole,⁷ which can cause parkinsonism in some patients, but his symptoms continued to progress despite a stable dose of medication.

The change in mental state exam score may be a function of variation in performance from the patient’s baseline level, but a declining score on three separate mental state exams in this

patient suggests cognitive decline. Although the mental state exam test is not the ideal test for dementia in individuals with intellectual disability,^{8,9} persons with IQ greater than 55 should function adequately on this test.¹⁰ The patient's IQ score remained constant despite worsening on the mental state exam, but this patient's IQ score should be interpreted with caution. His original IQ scores was low, falling at or below the 1st percentile and outside the normative sample.¹¹ For individuals with scores in this range, change in performance, or in this case cognitive decline, may not be reflected in changes in IQ score because the original score is so low. Data that support cognitive decline in our patient (despite a stable IQ on testing), include reports from both the patient and his family that he had worsening memory and cognitive problems. In addition, he had prominent deficits on perceptual tasks on the second IQ testing, which tend to be first part of the IQ scale affected in dementia related to Down syndrome.

FMRP was recently found to regulate neurogenesis making a lack of FMRP in FXS a potential enhancer of neurodegenerative disease. FMRP also regulates the translation of amyloid precursor protein (APP), such that APP levels are elevated in those with FXS.¹² This may predispose individuals with FXS to develop Alzheimer disease as they age. However, there has never been a systematic study of aging in individuals with FXS.

The importance of this case report is that clinicians who see adults with movement disorders and intellectual disability should consider the presence of multiple neurological disease processes. Challenges in assessment and diagnosis in this area have been documented within the Down syndrome literature, with the resulting proposal of multidisciplinary assessment batteries.^{13,14} Based on the neurobiology of FXS and FXTAS, it is unlikely that our patient's cognitive decline is related to the mechanisms causing FXTAS due to the lack of elevated mRNA levels, but additional study of aging in FXS is needed to clarify progressive cognitive changes in these patients.

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