New observations in the fragile X-associated tremor/ataxia syndrome (FXTAS) phenotype

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INTRODUCTION

Fragile X-associated tremor/ataxia syndrome (FXTAS) is caused by expansion in the trinucleotide CGG repeat in the promoter region of the fragile X mental retardation 1 (FMR1) gene. Classical clinical manifestations include kinetic tremor, cerebellar ataxia, cognitive decline, psychiatric problems, and parkinsonism (Jacquemont et al., 2003, 2004; Berry-Kravis et al., 2007a). Other features include peripheral neuropathy (Berry-Kravis et al., 2007b), impotence and autonomic dysfunction (including bowel and/or bladder dysfunction and erectile dysfunction) (Louis et al., 2006; Leehey, 2009). Cognitive decline manifests as a frontal subcortical dementia, with memory loss and executive function deficits and often lack of insight into these deficits (Grigsby et al., 2007). Psychiatric effects of FXTAS include anxiety, mood lability, apathy, and social phobias (Bourgeois et al., 2006). It is most frequently seen in individuals over the age of fifty who carry between 55 and 200 CGG repeats, also known as the “premutation.” Fragile X syndrome (FXS), the most common inherited form of intellectual disability, results from the presence of more than 200 CGG repeats and is characterized by intellectual disability, autism, attention deficit disorder, and often seizures.

FXTAS has distinct features on magnetic resonance imaging (MRI), including severe generalized atrophy, cerebellar atrophy, and sub-cortical and/or ponto-cerebellar white matter lesions (Greco et al., 2006). About 60% of males with FXTAS have what is known as the “MCP sign,” or T2 hyperintensity in the middle cerebellar peduncle (Adams et al., 2007). Hyperintensities in the splenium of the corpus callosum on MRI may also be seen (Aparits et al., 2012).

Purpose: Fragile X-associated tremor/ataxia syndrome (FXTAS) was originally defined as tremor, ataxia, cognitive decline, and parkinsonism in individuals who carry between 55 and 200 CGG repeats in the promoter region of the fragile X mental retardation 1 (FMR1) gene. This paper describes a series of patients who meet the definition of FXTAS who presented for care between 2009 and 2014.

Methods/Results: Retrospective chart review of patients seen in the FXTAS clinic at Rush University in Chicago.

Conclusions: Patients with FXTAS may present with a progressive supranuclear palsy-like phenotype and other eye movement abnormalities are common in these patients as well. Rapid worsening of gait abnormalities in FXTAS may be due to a secondary spinal issue and should be aggressively treated to regain function. Finally, the FXTAS Rating Scale score does not reliably inform the certainty of diagnosis or CGG repeat size in these patients.

Keywords: FXTAS, FMR1, FXS, CGG, premutation

The estimated prevalence of the FMR1 premutation is between 1/151 and 1/209 in women and 1/430—1/468 in men (Seltzer et al., 2012; Tassone et al., 2012b). Since its initial description, more women with FXTAS are being identified. Some medical comorbidities may be more common in premutation carrier women, including thyroid disease, hypertension, seizures, and fibromyalgia (Coffey et al., 2008; Leehey et al., 2011). The purpose of this project is to demonstrate the heterogeneity in patients presenting for clinical care of FXTAS.

BACKGROUND

Thirty patients with FXTAS were seen between 2009 and 2014 for clinical care in the FXTAS Clinic. Nineteen cases with complete clinical information were summarized for this study. Their clinical characteristics are described in Table 1. FXTAS Motor Rating Scale scores are listed in the table and encompass the major movement disorder signs seen in FXTAS: tremor, ataxia, and parkinsonism. This rating scale was developed in 2008. It is a combination of the Clinical Rating Scale for Tremor (CRST), the International Cooperative Ataxia Rating Scale (ICARS) and the Unified Parkinson’s Disease Rating Scale (UPDRS). It also includes a tandem test for cerebellar gait ataxia (Leehey et al., 2008). Four cases illustrative of the series have been included.

CASE 7

A 70 year-old man with history of myeloproliferative disorder presented with 3 years of balance problems and falls. He felt he was veering to one side when he was walking. He denied...
| Case | Age | Sex | FMR1 premutation size | Diagnosis of FXTAS | Tremor | Ataxia | Nystagmus or other eye movement abnormality | Neuropathy symptoms or signs | Cognition | Neuropsychiatric rating scale score | MRI | Family history of fragile X disorders | Other features |
|------|-----|-----|----------------------|-------------------|--------|--------|-------------------------------------------|-----------------------------|-----------|-----------------------------------|------|---------------------------------|---------------|
| 1    | 56  | M   | 150                  | Definite          | Mild   | Severe | Saccadic pursuits                         | Diminished vibration and proprioception in feet | MMSE 11/30, moderate severe dementia | Aggressive behavior | 87   | White matter hyperintensities, moderate diffuse volume loss, left frontal mass | Grandson and grandnephew with FXS | Metastatic brain cancer |
| 2    | 75  | M   | 124                  | Definite          | Severe | Mild   | No vertical OKN, lateral endgaze nystagmus, decreased lateral OKN | Decreased vibration in feet | 18/30 MMSE, Depression | Apathy, withdrawn socially | 73   | Two nieces with FXS | Monoclonal Gammopathy of Unknown Significance |
| 3    | 62  | F   | 23, 120              | Possible          | No     | Mild   | Horizontal endgaze nystagmus               | No                          | 23/30 MMSE, deficit in encoding new information | Depression | 7    | Mild cerebral volume loss, scattered white matter changes | Daughter FXS | Severe fibromyalgia |
| 4    | 69  | F   | 26, 91               | Definite          | Mild   | Moderate | Saccadic pursuits                          | No                          | MMSE 30/30, Irritability, auditory hallucinations, anxiety, depression | Poor insight | 75   | Mild cerebellar vermal volume loss, MCP sign | Grandson with FXS | Alcoholism, transient global amnesia |
| 5    | 72  | M   | 105                  | Probable          | Mild   | Mild   | No                                        | 23/30 MOCA, deficits in executive function and recent memory | 47  | Depression, anger, apathy | Cerebral and cerebellar volume loss | Non-epileptic spells |
| 6    | 46  | F   | 20, 102              | Possible          | Mild   | Mild   | Lateral endgaze nystagmus, saccadic saccades | Decreased vibration in feet | MMSE 30/30 | Mild depression | Cerebral volume loss, hyperintensity in cerebral peduncles, MCP sign | Sister, grandson, granddaughter with FXS, Mother with FXPOI | Myelodysplastic disorder, spinal cord mass |
| 7    | 71  | M   | 99                   | Definite          | Moderate| Moderate | Dysmetric saccades                         | Vibratory loss in feet and temperature loss in limbs | 24/30 MMSE, deficits in attention, executive function, recent memory | Agitation | 51   | Brother with intellectual disability, autism | Impotence, urinary issues |
| 8    | 70  | M   | 99                   | Definite          | Moderate| Moderate | Saccadic pursuits                          | Decreased vibration in feet | MMSE 24/30, mild, generalized dementia | Depression, anger, apathy | 64   | Vitiligo, diabetes, IgA deficiency, end stage renal disease | |
| 9    | 79  | F   | 29, 90               | Definite          | Mild   | Mild   | Saccadic pursuit, transient endgaze nystagmus | Decreased temperature, no reflexes | 27/30 MMSE, deficit in recent memory, executive function, and language | Psychosis, delusions and visual hallucinations, agitation | 47   | Cerebral and cerebellar volume loss | | | | |

(Continued)
| Case | Age | Sex | FMR1 premutation size | Diagnosis of FXTAS | Tremor | Ataxia | Nystagmus or other eye movement abnormality | Neuropathy symptoms or signs | Cognition | Neuropsychiatric FXTAS rating scale score | MRI | Family history of fragile X disorders | Other features |
|------|-----|-----|-----------------------|-------------------|--------|--------|---------------------------------------------|-----------------------------|-----------|---------------------------------------|------|-----------------------------------------|----------------|
| 10   | 68  | M   | 95                    | Possible          | Mild   | Mild   | Normal                                      | Length dependent sensory neuropathy | Cognition reported to be normal | No         | 38                                   | Cerebral and cerebellar volume loss, lesion in cerebral peduncle (CT) | Sister with premature menopause |
| 11   | 70  | M   | 91                    | Definite          | Moderate| Mild   | Dysmetric saccades                          | Decreased in stocking distribution | 25/30 MMSE, deficits in executive function and recent memory | Disinhibition | 72                                   | MCP sign, scattered white matter ds | Niece and nephew with FXS |
| 12** | 75  | F   | 88                    | Definite          | Moderate| Moderate| No vertical OKN, slowed vertical saccades, + square wave jerks | Dec all modalities in feet | MMSE 25/30, deficits in executive function, recent memory, verbal fluency | Depression, apathy | 69                                   | Extensive white matter lesions in the pons and periventricular area | Sister with FXPOI, father and cousin with FXTAS |
| 13   | 72  | M   | 85                    | Possible          | Mild   | Mild   | Saccadic smooth pursuit vertically, hypometric vertical saccades, decreased convergence | Distal sensory loss feet, normal EMG/NCV | 30/30 MMSE | Anxiety, irritability, subjective memory loss | 41 | Greater than age appropriate atrophy | Daughter and nephew with FXS, Father with possible FXTAS |
| 14   | 76  | M   | 80                    | Probable          | Moderate| Severe | Apraxia of eye movements, saccadic pursuits | Diminished reflexes at patella and ankle | 27/30 MMSE, deficit in short-term memory | No | 81 | Not available | Grandson with FXS |
| 15   | 64  | F   | 79                    | Probable          | Mild   | Mild   | Normal                                      | No | 29/30 MMSE, deficit in executive function | Anxiety | 27 | Moderate volume loss, white matter hyperintensities | Two sons with FXS | Autonomic symptoms, brady-cardiac/tachycardia |
| 16   | 80  | M   | 75                    | Definite          | Mild   | Moderate| Saccadic pursuits                           | Decreased vibration in feet, absent reflexes at ankle | 24/28 MMSE, deficits in attention and recent memory | Irritability | 31 | MCP sign | Grandnephew has FXS |
| 17   | 75  | F   | 74                    | Definite          | Mild   | Mild   | Overshoot, dysmetria of saccades, slowed vertical saccades with OKN, saccadic pursuits | Decreased reflexes in legs | 29/30 MMSE | Irritability, impulsiveness | 20 | Scattered white matter hyperintensities | Two sons with FXS |
|      |     |     |                       |                   |        |        |                                             |                             |            |                                        |                      | Stage IV squamous cell lung cancer |

(Continued)
tremors and memory problems. On examination, he scored a 24/30 on the Folstein Mini Mental Status Exam (MMSE) (Folstein et al., 1975) with deficits in attention, recent memory, and executive function. He had dysmetric saccades. Sensory exam was notable for inconsistent vibratory loss in the feet and temperature loss in all extremities. He had mildly increased tone in both arms and mild kinetic tremor when drawing spirals. He had mild bradykinesia bilaterally. He had no evidence of dysmetria. His gait was wide based and ataxic. He was profoundly unstable when standing or walking, with almost immediate falling. He refused to use a walking aid. Brain MRI showed cerebral volume loss, hyperintensity in the cerebral peduncles, and the MCP sign. He was admitted due to a lack of safety with his balance and had a three-week rehabilitation stay. There he developed a sudden onset bilateral leg weakness. Workup revealed a large soft tissue mass in his spinal cord extending from T1 to T9 causing significant cord compression. It was resected and pathology was consistent with extramedullary hematopoiesis. He then underwent successful radiation therapy. After continued rehabilitation, he was able to regain prior function and is currently walking with a walker. His family history was remarkable for a sister and multiple grandchildren with FXS. His mother had fragile X-associated primary ovarian insufficiency (FXPOI). His FMR1 CGG repeat size was 99. He met criteria for definite FXTAS, with tremor, ataxia, and the MCP sign on MRI.

**CASE 9**

A 75 year-old woman presented with a one-year history of balance problems, which she described as wobbling when she walked. She had fallen once. She denied tremors, but had decreased hearing in both ears, urinary frequency, and fatigue. Her past history was remarkable for diabetes, end stage renal disease, and vitiligo. On examination, she had normal cognition, saccadic pursuits, and transient endgaze nystagmus. She had increased tone in the right arm without cogwheel rigidity, anterocollis, and mild kinetic tremor with handwriting. Reflexes were absent in the extremities and sensation was decreased to temperature. Dysdiadochokinesia was present in the left hand and bradykinesia in the left leg. She was unable to stand or walk in tandem and got off balance when she turned quickly. There was no retropulsion on the pull test. Brain MRI showed cerebral and cerebellar volume loss with white matter hyperintensities in the periventricular region.

The following year, she had a fall and had surgery for a “pinched nerve” in the neck. She began to have visual hallucinations in the hospital and was started on haloperidol. Her examination had dramatically worsened: she was wheelchair bound and was no longer able to walk unless she had assistance. Her MMSE was 18/30. She then developed delusions and depression. Quetiapine and venlafaxine were added and haloperidol discontinued. She received aggressive inpatient and outpatient rehabilitation over the next 3 months and regained the ability to walk using a walker. Her FMR1 CGG repeat sizes were 90 and 29. She had a daughter, two nephews, and one niece with FXS. She met criteria for definite FXTAS, with tremor, ataxia, and white matter disease on MRI.
CASE 12
A 72 year-old woman presented with progressive difficulty walking since 1998. She initially attributed this difficulty to pain in her feet, and was subsequently diagnosed with plantar fasciitis. By 2000–2001, she developed postural dizziness and soon developed a slow, festinating gait with decreased arm swing as well as fatigue, cognitive slowing, and trouble sleeping. By 2009 she was wheelchair bound. MRI of her brain revealed white matter lesions in the pons and periventricular regions. Testing for autoimmune disorders and spinocerebellar ataxias (SCA) was negative. She failed treatment with amantadine and was started on carbidopa/levodopa 25–100 mg twice daily and her walking improved.

On examination at age 75, her MMSE was 25/30, with deficits in executive function, recent memory and verbal fluency. She had apraxia in her left hand and foot, a positive glabellary reflex, and trouble mimicking on the left side. She had absent vertical optokinetic nystagmus, slowed vertical saccades, and square wave jerks. She was bradykinetic and had resting tremor in both arms. Her gait was remarkable for short stride length, frequent freezing, difficulty with tandem gait and impaired postural reflexes. Her carbidopa-levodopa was weaned due to persistent nausea. Donepezil 10 mg daily was started given her cognitive decline. She continued frequent physical therapy at home, but her symptoms continued to progress. She is a FMR1 premutation carrier with 88 FMR1 CGG repeats. Her son has intellectual disability but has not been tested for FXS. Her father had severe tremor and ataxia. Her sister has fragile X-associated premature ovarian insufficiency (FXPOI). She has a male cousin with FXTAS and three female cousins who are also premutation carriers. Based on her MRI as well as ataxia and tremor, she met criteria for definite FXTAS.

CASE 18
An 80 year-old man presented with a three-year history of worsening falls. He had developed shuffling gait, a soft voice, was choking on food, and had a masked facial expression. He denied tremor. He had been diagnosed by a prior neurologist with Parkinson disease and started on 3.5 tablets of 25–100 mg carbidopa/levodopa. By report, his symptoms did not improve. On examination at the age of 80, his MMSE was 28/30. He had a positive glabellar reflex and negative applause sign. He had impaired vertical gaze, impaired vertical optokinetic nystagmus, and slowed saccades. He had symmetrically increased tone in both upper extremities and bradykinesia in all four extremities. He had left sided shoulder elevation with a mild rightward head turn. He had mild rest tremor in the left hand and mild kinetic tremor when drawing spirals. There was no evidence of dysmetria. He had a positive pull test, was unable to perform tandem gait, and took multiple steps to turn. His steps were slow and short. He was unable to have a MRI, but brain CT showed ventriculomegaly. He was started on 5 mg twice daily of memantine given complaints of poor memory, however this was subsequently discontinued as it proved ineffective. His falls initially decreased in frequency after physical therapy. Within 8 months of presentation, he was unable to walk on his own, even with a walker. He had a retrait of carbidopa/levodopa 25–100 mg three pills daily. His bradykinesia improved mildly, but he began experiencing delusions and hallucinations. The psychosis improved and entacapone 200 mg three times daily was added. The patients’ family felt the entacapone helped the speech problems, but not the other motor features. He was a FMR1 premutation carrier with 68 FMR1 CGG repeats. His grandson had FXS. He met criteria for probable FXTAS given his tremor and ataxia, but lack of a MRI.

DISCUSSION
These cases have some similarities and differences to previously reported FXTAS phenotypes. The majority of the patients have a mixed movement disorder, with signs of tremor, ataxia, and parkinsonism. In addition, neuropathic findings and neuropsychiatric issues are common, with many having cognitive deficits on presentation. Our cases were found primarily in families with known fragile X-associated disorders. All of these features have been previously described.

Case 12 describes a woman with a strong family history of FMR1 mutation associated diseases. Her course began with gait difficulty and evolved to include eye movement abnormalities consistent with progressive supranuclear palsy (PSP). In Case 18, the patient’s history of falls at symptom onset, absence of response to carbidopa/levodopa, and upgaze palsy is most consistent diagnostically with PSP. This is a neurodegenerative movement disorder characterized by early falls, supranuclear ophthalmoplegia (particularly of vertical eye movements), parkinsonism, and later cognitive decline. In addition, several of the other cases in Table 1 had eye findings often seen in PSP, including decreased optokinetic nystagmus, especially in the vertical direction, slowed vertical saccades, and the presence of square wave jerks (Litvan et al., 1996). Case 2 demonstrated lack of vertical optokinetic nystagmus. Cases 13 and 17 demonstrated saccades which were hypometric and slow, respectively. A PSP phenotype has not been reported in FXTAS in the past. Schrag et al. (2006) estimated the prevalence of PSP in the general population at about 6 per 100,000. The prevalence of FXTAS has been reported at 1/4000 in men over 55 (Hall and Jacquemont, 2010). Given the rarity of these two disorders, it may be more than coincidence that five individuals in our series had a PSP-like phenotype.

It is unclear in our patients whether the PSP-like phenotype is a variation of FXTAS, whether this represents the presence of PSP in FMR1 premutation carriers, or whether these patients have two neurodegenerative disorders. Most likely, the pathways involved with the classic eye findings and falls in PSP located in the brainstem are also involved in FXTAS, resulting in similar phenotypic presentations. However, previous case series have shown that FMR1 premutation carriers may have dual pathology on autopsy, specifically in cases of FXTAS and Alzheimer disease, and suggest that they may be synergistic in creating a worse neurological phenotype (Tassone et al., 2012a). Autopsy on our cases will help to clarify this issue. The typical neuropathology associated with FXTAS is enlarged, inclusion-bearing astrocytes in the cerebral white matter and intra-nuclear inclusions in both the brain and spinal cord (Greco et al., 2006). This differs from the neuropathological findings seen in PSP, in particular neurofibrillary tangles and/or neurophil threads in the striatum, substantia nigra, occulomotor complex, peri-aqueductal gray, superior colliculi, basis pontis, dentate nucleus, and prefrontal cortex (Litvan,
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