MedPress
Neurology and Neurosurgery

Fragile X-associated Tremor/Ataxia Syndrome: A Rare Case with Unusually Extensive Neuropathy

Mbachu CNP[1,2], Schneider A[2,3], Santos E[2,3], Tassone F[2,4] and Hagerman R[2,3]*

[1] Department of Paediatrics, Faculty of Medicine, College of Health Sciences, Nnamdi Azikiwe University, Anambra State, Nigeria
[2] Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, University of California Davis, USA
[3] Department of Pediatrics, University of California Davis School of Medicine, Sacramento, USA
[4] Department of Biochemistry and Molecular Medicine, University of California Davis School of Medicine, USA

Case Report

***Corresponding author**
Randi Hagerman,
Endowed Chair in Fragile X Research
MIND Institute, UC Davis Health System, 2825 50th Street,
Sacramento, CA 95817, USA,
Email: rjhagerman@ucdavis.edu

Article Information
Received: 10 March 2024;
Accepted: 15 March 2024;
Published: 18 March 2024.

Abstract

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) is a late-onset neurodegenerative disorder associated with abnormalities in balance, movement, tremor, and neuropathy. We report a 64 year old male who presented with atypical progressive neuropathy. His neurological examination revealed loss of sensation in both lower limbs up to the mid thighs, and upper limbs up to the upper arms. He had absent vibration and proprioception sensation, and deep tendon reflexes bilaterally in all extremities. Electrodiagnostic studies revealed polyneuropathy. A genetic test revealed the presence of unstable pattern of alleles in the upper premutation range in the (186-200 CGG repeats) fragile X messenger ribonucleoprotein 1 (*FMR1*) gene. He was diagnosed with FXTAS, but the severity of this neuropathy is atypical for those with FXTAS.

Introduction

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) is one of the disorders associated with the a trinucleotide expansion in the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene, which also includes fragile X syndrome (FXS) caused by the full mutation (> 200 CGG repeats) leading to a deficiency of lack of the *FMR1* protein, FMRP; additional premutation (55 to 200 CGG repeats) disorders are Fragile X-Associated Primary Ovarian Insufficiency (FXPOI) and Fragile X-Associated Neuropsychiatric Disorders (FXAND) [1]. Carriers of a premutation have a higher incidence of immune mediated disorders, sleep apnea, insomnia, hypertension and migraine which together with FXTAS, FXPOI and FXAND, fall all under the umbrella of the fragile X premutation associated conditions (FXPAC) [2]. FXTAS, is a neurodegenerative disorder, which starts in older carriers and is caused by the excess mRNA produced by the premutation in the *FMR1* gene [3,4]. Normal CGG repeats at the 5'end of *FMR1* are less than 45 repeats, while gray zone carriers have between 46 -54 repeats [1,3]. FXTAS is more common and more severe in males than females, with a male-to-female ratio (M:F) ratio of about 2-3:1 and typically noted in carriers over 50 years old [5,6]. The penetrance of FXTAS increases with age, with more than 3 out of every 4 male carriers being affected by the 8th decade of life [3,7].

The clinical features of this syndrome vary, and typically include features of cerebellar ataxia, cognitive impairment initially involving deficits in executive function and memory, but eventually leading to dementia, tremor, parkinsonism, anxiety, irritability, neuropsychiatric problems, autonomic dysfunction including hypertension and erectile dysfunction, and neuropathy [8-12,13]. Definite diagnostic criteria are the finding of one major clinical (gait ataxia or intention tremor) and one major radiological (white matter lesions in the middle cerebellar peduncles on Magnetic Resonance Imaging (MRI)) in an affected person. Additional minor criteria include neuropathy, executive function deficits, Parkinsonism, global brain atrophy and involvement of the splenium of the Corpus Callosum, can be used to arrive at a possible or probable diagnosis of FXTAS when combined with an intention tremor or ataxia [1,14].

Characteristic pathological findings are intranuclear, ubiquitin-positive inclusions, in neurons, astrocytes, and Purkinje cells of the brain, spinal cord, and autonomic ganglia [15-17]. FXTAS may share similarities with some other neurodegenerative disorders such as late-onset cerebellar ataxia, essential tremor, multiple sclerosis, vascular dementia, Parkinson's Disease (PD), Multiple System Atrophy (MSA), Alzheimer Disorders (AD), spinocerebellar ataxia, normal pressure hydrocephalus, and peripheral

Citation: Mbachu CNP, Schneider A, Santos E, Tassone F and Hagerman R. Fragile X-associated Tremor/Ataxia Syndrome: A Rare Case with Unusually Extensive Neuropathy. Medp Neurol Neurosurg. 2024; 4(1): mpnns-202403001.

neuropathy [18,19] but it is the only neurodegenerative disorder caused by the *FMR1* premutation. FXTAS is a hereditary cause of neuropathy. Other hereditary causes of peripheral neuropathy include Amyloidosis, Charcot-Marie-Tooth disease, Fabry disease, Refsum disease and Adrenoleukodystrophy, while acquired causes are usually from metabolic disorders such as diabetes, metabolic syndrome, electrolyte imbalance (hyperkalemia), drugs, toxins, immune disorders, cancers, infections (leprosy), compressive and cryptogenic disorders [20-25]. Neuropathies are a common feature of FXTAS, seen in over 50% of affected persons [14,26,27]. However, slowly progressive neuropathy involving most of the four limbs is a feature yet to be reported. Here, we report this atypical case of slowly progressive extensive neuropathy in a middle-aged man with FXTAS.

Case Report

This is a case of a 64-year-old man, first seen in our clinic at 59 years of age. He presented with intention tremor, balance problems, and some numbness in his upper and lower limbs for over 3 years duration, which affected his daily activities and quality of life. Over the subsequent 5 years, his neuropathy extended from 5 inches below his knees bilaterally, and below both elbows in his arms, to his mid-thigh and further up his upper arms bilaterally. Two years prior to his presentation at 57 years, he had hypothyroidism, absent-mindedness, difficulty focusing, reduced agility, balance problems, tingling in hands, and sensory deficits resulting in burns to the hands.

On examination at age 59 he showed bilateral intention tremor, mild bilateral rigidity in arms, dysmetria which was more on the left, mild dysdiadochokinesia, a positive Romberg sign, mildly impaired tandem walk, and reduced pinprick sensation on the left, more than the right upper limb. His nerve conduction studies revealed attenuated peroneal response with normal peroneal motor response and focal right ulnar neuropathy at the elbow. Nerve stimulation studies also noted normal responses with upper limb median stimulation, while the tibial Somatosensory Evoked Potential (SSEPs) showed some delay bilaterally. At this time, he was thought to have myelopathy following either vitamin B12 or folate deficiency. These were ruled out after normal findings of folate and vitamin B12 were obtained. He continued his regular medications (omeprazole, and sildenafil), but increased the dose of levothyroxine. A few months later, he was referred to a neurologist and movement disorder specialist with complaints of progressive imbalance, anxiety, obsessive-compulsive disorder, reduced pain sensation, leading to frequent injuries to his hands and some shooting pain in his extremities. Examination findings at this time (age 60) showed sensory and autonomic neuropathy in a syringomyelic-like fashion. Subsequently, six months later, his molecular studies revealed the presence of *FMR1* expanded alleles. Then he was referred to our clinic for further evaluation and management.

On presentation, he had anxiety, memory loss, difficulty with word retrieval, inability to tandem walk because of ataxia, tinnitus, hearing loss, a severely enlarged right and left atrium with preserved heart function, occasional joint pain, low back pain, and hypothyroidism. When he was initially seen we recommended a reduction in alcohol from his regular intake of one glass every day to one glass every 2 weeks and daily exercise and oral antioxidants. He subsequently retired from his regular work at 60 years of age. He is college educated and has worked in human resources.

His current medications include levothyroxine 150mg/175mg on alternate days, sertraline 25 mg daily, sildenafil 100mg prn, metformin 500mg bid with meals, testosterone injection 100mg every 16 weeks, omeprazole 20mg as needed, omega 3 fatty acids and multivitamin supplements. Significant family and social history include a daughter who is a premutation carrier with 156 CGG repeats and a history of thyroid cancer at 18 years old and now depression at 31 years old, a deceased sister (from a pulmonary embolism at 52 years), a nephew and a niece who have FXS with a full mutation. His mother died at 87 with a significant tremor that was consistent with FXTAS.

On examination at age 64 in follow-up, the patient was alert and oriented with fluent speech. His vital signs were mostly within normal limits (PR – 51 bpm, RR- 14, Temperature-36.5 C, BP – 130/77), while BMI was 26.6 kg/m^2. Cranial nerves examination was normal except for hearing loss and hearing aids were in place. Positional tremor in hands was seen on the left side with eyes closed but not on the right. Positive intention tremor bilaterally on finger-to-nose testing and a positive Romberg sign were also noted. There was a sluggish movement of pupils in response to light but normal eye movement in all directions. He had normal muscle strength in all 4 extremities, but unsteady gait and inability to tandem walk. Vibration, temperature, and touch sensations were normal on his face, shoulders, and sternum but sensations were absent in both lower extremities up to the mid thighs, and upper extremities up to the upper arms. He had a positive snout reflex, but absent jaw jerk, palmomental, and glabellar reflexes. His deep tendon reflexes were absent in all extremities. Our genetic testing revealed a very unstable pattern ranging from ~90 to 160 CGG repeats in size with the presence of a very small tail into the full mutation up to 220 repeats. The detected alleles were 90 to 180 CGG repeat in size and appear to be all unmethylated. *FMR1* mRNA level was 2.25 ($\pm$ 0.14) times normal.

An MRI of the brain revealed mild cortical atrophy, mild white matter changes, with a faint middle cerebellar peduncle (MCP) sign, significant white matter hyperintensity at the insula, mild peri-ventricular white matter changes, thin corpus callosum, and a prominent splenium sign. An MRI of the cervical spine appeared normal. Neurocognitive testing over multiple visits were all normal without deterioration (Table 1).

Table 1: WAIS-IV scores from 2018 to 2024.

	2018 IQ Index score	2020 IQ Index score	2022 IQ Index score	2024 IQ Index score	Interpretation
Verbal comprehension (VCI)	112	112	NA	110	Measures ability to utilize and comprehend verbal information to solve problems
Perceptual reasoning (PRI)	104	113	NA	98	Measures ability to analyse and manipulate visual information in non-verbal problem-solving
Working memory (WMI)	95	108	108	114	Measures of mental utilization of information, attention, concentration, and immediate memory recall
Processing speed (PSI)	97	94	94	108	Measures the ability to rapidly and correctly process basic or regular visual information
Full scale IQ (FSIQ)	104	110	NA	108	Composite score
NA = Not Available, Index scores average = 100, average range 80-119.					

Discussion

FXTAS is more common in males, occurring in about 40% of males greater than 50 years with the *FMR1* premutation [8]. Neuropathy in FXTAS including absent reflexes, and loss of touch, pain, and vibration sensation are typically limited to the distal lower limbs and seen in about six of every ten patients and it may be the initial finding [8]. Our patient's history and exam revealed

atypical clinical features of neuropathy with FXTAS: sensations were absent in both lower extremities up to the mid thighs, and upper extremities up to the upper arms. As the neuropathy worsened his cognitive testing was relatively stable and did not deteriorate (Figures 1A,B,C) and this is unusual also for FXTAS.

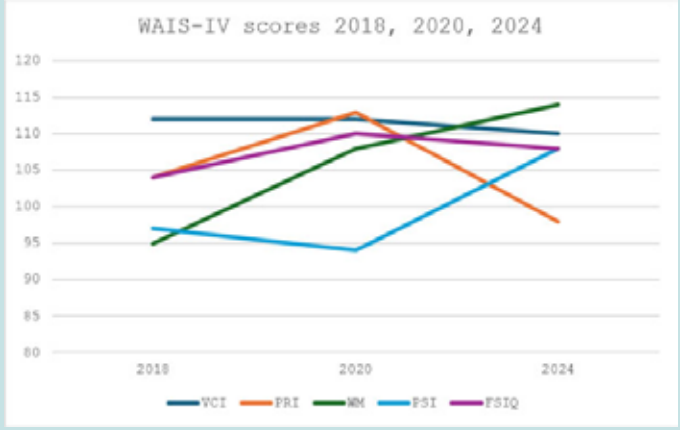

Figure 1A: Cognitive Testing Index Scores WAIS-IV 2018, 2020, 2024, VCI = Verbal Comprehension Index, PRI = Perceptual Reasoning Index, WM = Working Memory Index, PSI = Processing Speed Index, FSIQ = Full Scale IQ score.

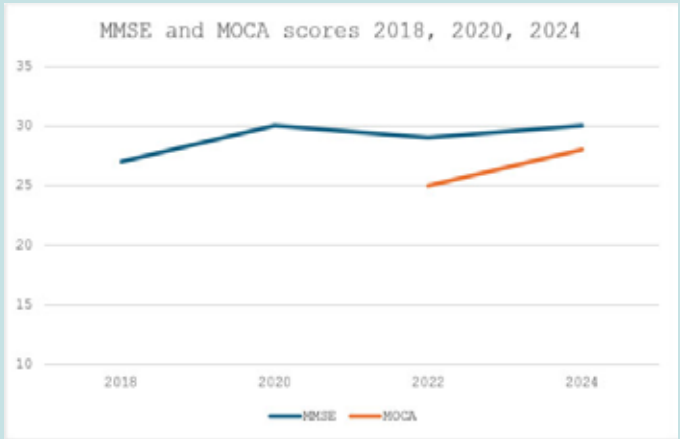

Figure 1B: Mini Mental State Exam (MMSE) and Montreal Cognitive Assessment (MOCA) Total Score (maximum possible = 30), 2018, 2020, 2024.

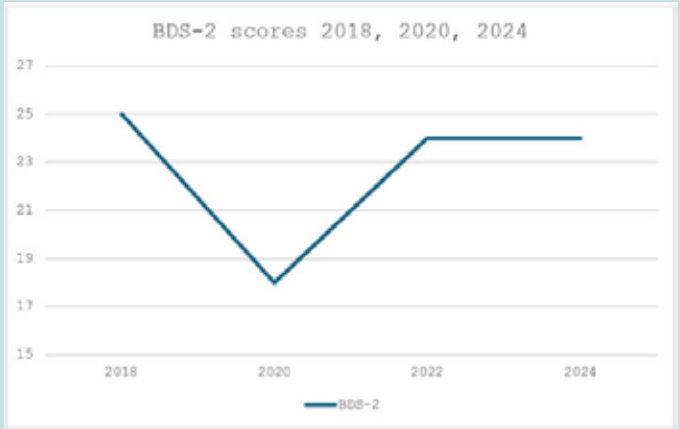

Figure 1C: Behavioral Dyscontrol Scale, 2nd Edition, Total Score (Maximum possible = 27).

MRI brain findings showed mild cerebral atrophy and white matter disease which are typical for FXTAS, although this degree of neuropathy has never been seen in those with FXTAS alone. Other possible causes of neuropathy were also excluded including vitamin deficiency, and other genetic problems with whole genome sequencing. However, we equally note that his high CGG repeat of mainly in the 130 to 180 range can have a severe neuropathy but not this extensive [28]. It is pertinent that he appeared stable on his other presenting symptoms of FXTAS since he started treatment recommendations including increasing his daily exercise, little to no alcohol and antioxidants including sulforaphane containing vegetables, and he continues levothyroxine, sertraline, and testosterone. Thus, highlighting the atypical nature of the neuropathy, we were not able to find an additional cause beyond FXTAS.

In conclusion, FXTAS is an evolving entity with a variable clinical presentation. Although FXTAS has been known to co-occur with Alzheimer's disease, Parkinson's disease, and Lewy body dementia [29], such severe neuropathy that is atypical of FXTAS suggests an additional factor may cause it, although toxic exposures have been ruled out and even whole exome sequencing studies are negative for additional genetic changes associated with these problems. This is the first case we have seen with such severe and progressive neuropathy. More reports on atypical presentations are needed to clarify the extent of variability in this phenotype.

Reference

1. Martinez-Cerdeno V, Wang Jun Yi, Grigsby Jim, Hall Deborah, Hagerman RJ. (2020). FXTAS: New Advances and Treatments In: Fragile X syndrome and Premutation Disorders New developments and treatments. In: Hagerman RJ, Hagerman PJ, editors. London: Mac Keith Press. 83-93.
2. Tassone F, Protic D, Allen EG, Archibald AD, Baud A, et al. (2023). Insight and Recommendations for Fragile X-Premutation-Associated Conditions from the Fifth International Conference on FMR1 Premutation. Cells. Multidisciplinary Digital Publishing Institute. 12: 2330.
3. Hagerman RJ, Hagerman P. (2016). Fragile X-associated tremor/ataxia syndrome-features, mechanisms and management. Nature Reviews Neurology. Nature Publishing Group. 12: 403-412.
4. Todd PK, Oh SY, Krans A, He F, Sellier C, et al. (2013). CGG repeat-associated translation mediates neurodegeneration in fragile X tremor ataxia syndrome. Neuron. 78: 440-455.
5. Leehey MA. (2009). Fragile X- Associated Tremor/Ataxia Syndrome: Clinical Phenotype, Diagnosis, and Treatment. Journal of Investigative Medicine. 57: 830-836.
6. Jacquemont S, Hagerman RJ, Leehey M, Grigsby J, Zhang L, et al. (2003). Fragile X Premutation Tremor/Ataxia Syndrome: Molecular, Clinical, and Neuroimaging Correlates. Am J Hum Genet. 72: 869-878.
7. Jacquemont S, Hagerman RJ, Leehey MA, Hall DA, Levine RA, et al. (2004). Penetrance of the Fragile X-Associated Tremor/Ataxia Syndrome in a Premutation Carrier Population. 291: 460-491.
8. Zhao C, Liu Y, Wang Y, Li H, Zhang B, et al. (2020). A Chinese case of fragile X-associated tremor/ataxia syndrome (FXTAS) with orthostatic tremor:case report and literature review on tremor in FXTAS. BMC Neurology. 20: 145.

9. Cabal-Herrera AM, Tassanakijpanich N, Salcedo-Arellano MJ, Hagerman RJ. (2020). Fragile X-associated tremor/ataxia syndrome (FXTAS): Pathophysiology and clinical implications. International Journal of Molecular Sciences. MDPI AG. 21: 1-23.
10. Hall DA, O'keefe JA. (2012). Fragile X-Associated Tremor Ataxia Syndrome: The Expanding Clinical Picture, Pathophysiology, Epidemiology, and Update on Treatment [Internet]. 2: tre-02-56-352-1.
11. Peters N, Kamm C, Asmus F, Holinski-Feder E, Kraft E, et al. (2006). Intrafamilial variability in fragile x-associated tremor/ ataxia syndrome. Movement Disorders. 21: 98-102.
12. Fraint A, Vittal P, Szewka A, Bernard B, Berry-Kravis E, et al. (2014). New observations in the fragile X-associated tremor/ ataxia syndrome (FXTAS) phenotype. Front Genet. 5: 365.
13. Islam F, Lee W. (2020). A Case of Generalized Chorea Presenting as an Early Feature of Fragile-X Associated Tremor/Ataxia Syndrome. Mov Disord Clin Pract. 7: 464-466.
14. Hall DA, Birch RC, Anheim M, Jønch AE, Pintado E, et al. (2014). Emerging topics in FXTAS. J Neurodev Disord. 6.
15. Wenzel HJ, Hunsaker MR, Greco CM, Willemsen R, Berman RF. (2010). Ubiquitin-positive intranuclear inclusions in neuronal and glial cells in a mouse model of the fragile X premutation. Brain Res. 1318: 155-166.
16. Greco CM, Berman RF, Martin RM, Tassone F, Schwartz PH, et al. (2006). Neuropathology of fragile X-associated tremor/ ataxia syndrome (FXTAS). Brain. 129: 243-255.
17. Hagerman P. (2013). Fragile X-associated tremor/ataxia syndrome (FXTAS): Pathology and mechanisms. Vol. 126, Acta Neuropathologica. 1-19.
18. Willemsen R, Mientjes E, Oostra BA. (2005). FXTAS: A Progressive Neurologic Syndrome Associated with Fragile X Premutation. Curr Neurol Neurosci Rep. 5: 405-410.
19. Robertson EE, Hall DA, McAsey AR, O'Keefe JA. (2016). Fragile X-associated tremor/ataxia syndrome: phenotypic comparisons with other movement disorders. Clinical Neuropsychologist. Routledge. 30: 849-900.
20. Siao P, Kaku M. (2019). A Clinician's Approach to Peripheral Neuropathy. Semin Neurol. 39: 519-530.
21. Kazamel M, Stino AM, Smith AG. (2021). Metabolic syndrome and peripheral neuropathy. Muscle Nerve. 63: 285-293.
22. Rosenberger DC, Blechschmidt V, Timmerman H, Wolff A, Treede RD. (2020). Challenges of neuropathic pain: focus on diabetic neuropathy. J Neural Transm (Vienna). 127: 589-624.
23. Kaur D, Tiwana H, Stino A, Sandroni P. (2021). Autonomic neuropathies. Muscle Nerve. 63: 10-21.
24. Hunter RW, Bailey MA. (2019). Hyperkalemia: pathophysiology, risk factors and consequences. Nephrology Dialysis Transplantation. 34: iii2.
25. Ebenezer GJ, Scollard DM. (2021). Treatment and Evaluation Advances in Leprosy Neuropathy. Neurotherapeutics. 18: 2337-2350.
26. Apartis E, Blancher A, Meissner WG, Guyant-Maréchal L, Maltête D, et al. (2012). New insights and the need for revised diagnostic criteria. Neurol. 79: 1898-1907.
27. Chanson JB, Boehm N, Samama B, Echaniz-Laguna A, Anheim M. (2015). Small fiber neuropathy in a woman with fragile X-associated tremor/ataxia syndrome (FXTAS). Journal of Neurology. 262: 226-227.
28. Berry-Kravis E, Goetz CG, Leehey MA, Hagerman RJ, et al. (2007). Neuropathic features in fragile X premutation carriers. Am J Med Genet A. 143: 19-26.
29. Salcedo-Arellano MJ, Wolf-Ochoa MW, Hong T, Amina S, Tassone F, et al. (2020). Parkinsonism Versus Concomitant Parkinson's Disease in Fragile X-Associated Tremor/Ataxia Syndrome. Mov Disord Clin Pract. 7: 413-418.

Citation: Mbachu CNP, Schneider A, Santos E, Tassone F and Hagerman R. Fragile X-associated Tremor/Ataxia Syndrome: A Rare Case with Unusually Extensive Neuropathy. Medp Neurol Neurosurg. 2024; 4(1): mpnns-202403001.