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Case report: Dystonia in a Fragile X Carrier

Lin Zhang, MD, PhD[1], **Dina Sukharev, MD**[2], **Andrea Schneider, PhD**[2], **John M. Olichney, MD**[1], **Andreea Seritan, MD**[3], and **Randi J. Hagerman, MD**[2,4]

[1] Department of Neurology, University of California, Davis, School of Medicine, Sacramento, CA, USA

[2] M.I.N.D. Institute, University of California Davis, School of Medicine, Sacramento, CA, USA

[3] Department of Psychiatry and Behavioral Sciences, University of California Davis, Sacramento, CA, USA

[4] Department of Pediatrics, University of California, Davis, School of Medicine, Sacramento, CA, USA

Introduction

The Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that can affect both male and female carriers of a premutation expansion (55-200 CGG repeats) of the fragile X mental retardation 1 (*FMR1*) gene. It is presumed to be caused by elevated *FMR1*-mRNA leading to toxicity. Clinical features of FXTAS include progressive cerebellar ataxia and intention tremor [1]. Associated symptoms are peripheral neuropathy, cognitive impairment and dementia [2]. MRI findings of brain atrophy and white matter disease are present in almost all cases but involvement of the middle cerebellar peduncles occurs in 59% of males and 13% of females affected by FXTAS [3].

Correspondence: Lin Zhang MD, PhD, Department of Neurology, UC Davis School of Medicine, Tel. (916) 734-6523, Fax. (916) 734-6525, lin.zhang@ucdmc.ucdavis.edu.

Authors' roles:

1. Lin Zhang. Patient evaluation. Manuscript: Writing of the final draft; Review and Critique.
2. Dina Sukharev. Organization. Manuscript: Writing of the first draft. Literature review.
3. Andrea Schneider. Patient evaluation. Manuscript: Table design; Review and Critique.
4. Andreea Seritan. Manuscript: Review and critique.
5. John Olichney. Patient evaluation. Manuscript: Review and critique.
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Oromandibular dystonia (OMD), on the other hand, is a variant of focal dystonia that affects women more often then men with the age of onset between 31-58 years [4]. In this report, we present a patient with the premutation, symptoms of early FXTAS and severe OMD.

Case Report

About four years after beginning a new job that included conducting phone surveys a 48-year-old female with 150 CGG repeats in her FMR1 gene noticed slurred speech and uncontrollable tongue and jaw movements (Video). In the past year she developed a mild tremor in her arms but it was not persistent. She has a history of poor balance throughout her life that became worse over the two years prior to her initial study visit. She was subsequently diagnosed with FXTAS. She also has a history of headaches, restless leg syndrome, osteoarthritis, type II diabetes, sensory neuropathy, and borderline hypertension. Over the last year she has a history of weakness and chronic fatigue in addition to irritability.

On clinical examination the patient exhibited hyperkinetic dystonic spontaneous movements of tongue and jaw (Video). Her tongue was large, protruding, and weak. Her exam, based on FXTAS rating scale [5], revealed a slight terminal tremor during finger-to-nose touching with no postural or resting tremor. She was mildly ataxic on heel to shin movements (Video). However her gait was normal. Deep tendon reflexes were decreased in the upper extremities and in ankles bilaterally, but were normal at the knees. Muscle strength was normal in all 4 extremities. Vibration sensation was decreased in the big toes bilaterally. Plantar reflexes were flexor bilaterally. Snout reflex positive for 1-3 taps, jaw jerk reflex was present. Her neuropsychological examination results are represented in table 1.

On her previous MRI there is some mild cerebellar atrophy noted. Our MRI demonstrated prominent perivascular spaces and mild dilation of the ventricles but no significant white matter disease.

The patient was treated with carbidopa/levodopa 25/100 with a gradual increasing dose up to 2 ½ pills three time a day. Her symptoms improved but the occasional vocal slurring and mild problems with chewing were still present.

Discussion

This case represents the first diagnosis of OMD in a patient with the premutation who has possible mild symptoms of FXTAS, however she does not have radiological features of FXTAS; nor does she have the pattern of cognitive/executive impairments typically associated with FXTAS as her MMSE, WMS-III, COWAT and CVLT were normal (Table 1).

Her clinical course were thought to be classic of OMD with typical tongue movements and suppression of her hyperkinesis by a self-discovered sensory trick (suppression of the involuntary movements with chewing on a pencil). We were somewhat surprised to see her dramatic improvement on Levodopa since Levodopa has not been consistently shown effective in treating focal dystonia and, in contrast, has been implicated in causing certain

forms of facial dystonia [6]. An alternative treatment for OMD would be botulinum injections [4].

This is the first case of OMD in a carrier female. It is not certain whether her OMD is a clinical expression of her premutation or represents an independent disorder. It is speculated however that the findings of inclusions in the hypoglossal nuclei in some autopsy FXTAS cases [7] may suggest a common pathology contributing to the tongue hyperkinesis as observed in this case.

It is possible that the OMD is part of a neurological spectrum seen in premutation carriers that is related to RNA toxicity, particularly in the thalamus. More cases of OMD would have to be seen to know if there is a relationship with FXTAS or the premutation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Berry-Kravis E, et al. Fragile X-associated tremor/ataxia syndrome: clinical features, genetics, and testing guidelines. Mov Disord. 2007; 22(14):2018–30. quiz 2140. [PubMed: 17618523]
2. Bourgeois JA, et al. A review of fragile X premutation disorders: expanding the psychiatric perspective. J Clin Psychiatry. 2009; 70(6):852–62. [PubMed: 19422761]
3. Adams JS, et al. Volumetric brain changes in females with fragile X-associated tremor/ataxia syndrome (FXTAS). Neurology. 2007; 69(9):851–9. [PubMed: 17724287]
4. Tan EK, Jankovic J. Botulinum toxin A in patients with oromandibular dystonia: long-term follow-up. Neurology. 1999; 53(9):2102–7. [PubMed: 10599789]
5. Berry-Kravis E, et al. Tremor and ataxia in fragile X premutation carriers: blinded videotape study. Ann Neurol. 2003; 53(5):616–23. [PubMed: 12730995]
6. Tan EK, Chan LL, Wong MC. Levodopa-induced oromandibular dystonia in progressive supranuclear palsy. Clin Neurol Neurosurg. 2003; 105(2):132–4. [PubMed: 12691807]
7. Greco CM, et al. Neuropathology of fragile X-associated tremor/ataxia syndrome (FXTAS). Brain. 2006; 129(Pt 1):243–55. [PubMed: 16332642]

Table 1

Neuropsychological Assessment

Assessment	Scale	Score
MMSE		30 of 30
WAIS-III	IQ $_{\text{verbal}}$	94
	IQ $_{\text{performance}}$	84
	IQ $_{\text{full scale}}$	89
WMS-III	General Memory Score	89
Purdue Pegboard		25th percentile
COWAT / CVLT		No impairment
SCL-90-R	Somatization	T 60
	Interpersonal Sensitivity	T 66
	Depression	T 64
	Psychoticism	T 60
	Global Severity Index	T 61
SCID	Social Phobia (300.23)	
	Adjustment disorder with depressed mood (309.0)	

T = normative score with an average range of 40-59

MMSE = Mini-Mental State Examination (Folstein [10]1975), WAIS = Wechsler Adult Intelligence Scale [11], COWAT = Controlled Oral Word Association Test [12], CVLT = California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober 1987, 2000), WMS-III = Wechsler Memory Scale-Third Edition [13], SCL-90-R = Symptom Checklist 90-Revised [14], SCID = Structured Clinical Interview for DSM-IV Axis I [15 2002]