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Improving Fragile X–Associated Tremor/Ataxia Syndrome Symptoms With Memantine and Venlafaxine

Melina C. Ortigas, BA,
MIND Institute and Department of Pediatrics, University of California Davis Medical Center, Sacramento, CA

James A. Bourgeois, OD, MD,
Department of Psychiatry and Behavioural Neurosciences, Faculty of Medicine, McMaster University, Hamilton, Ontario

Andrea Schneider, PhD,
MIND Institute and Department of Psychiatry and Behavioral Sciences, University of California Davis Medical Center, Sacramento, CA

John Olichney, MD,
Department of Neurology, University of California Davis Medical Center, Sacramento, CA

Danh V. Nguyen, PhD,
Department of Public Health Sciences, University of California Davis, Davis, CA

Jennifer B. Cogswell, BA,
MIND Institute and Department of Pediatrics, University of California Davis Medical Center, Sacramento, CA

Deborah A. Hall, MD, PhD, and
Department of Neurological Sciences, Rush University, Chicago, IL

Randi J. Hagerman, MD
MIND Institute and Department of Pediatrics, University of California Davis Medical Center, Sacramento, CA

James A. Bourgeois: bourgej@mcmaster.ca

To the Editors

Fragile X–associated tremor/ataxia syndrome (FXTAS) is a recently discovered (2001) neurodegenerative disorder affecting a subgroup of older premutation carriers (predominantly men) of the fragile X mental retardation 1 gene, *FMR1*. The premutation range is defined as a tri-nucleotide expansion of 55 to 200 CGG repeats in the 5′ untranslated region of the *FMR1* gene.[1] This same gene causes fragile X syndrome when the repeat size expands to a number greater than 200. The premutation range exhibits increased

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levels of messenger RNA (mRNA) of *FMR1*, leading to an RNA toxic gain of function and thus causes dysregulation in proteins such as lamin A/C and αB-crystallin.[2,3] The primary symptoms of FXTAS are kinetic tremor, gait ataxia, and neuroimaging findings such as cortical atrophy, white matter lesions in the peri-ventricular region, and enhanced lucency of middle cerebellar peduncles on T2-weighted magnetic resonance images, known as the middle cerebral peduncle sign.[4] Other symptoms include peripheral neuropathy, autonomic dysfunction, and cognitive impairment, particularly in executive function and short-term memory.[5] One in 130 to 250 women and 1 in 250 to 800 men are premutation carriers.[6] Eight to 16% of female premutation carriers older than 50 years develop FXTAS.[7] Treatment of FXTAS has been limited to symptomatic relief via medications used effectively for other diseases sharing significant symptoms with FXTAS.[8,9] Memantine is a noncompetitive *N*-methyl-D-aspartate receptor antagonist currently approved for moderate to severe Alzheimer disease. It is believed to attenuate glutamate toxicity and serves as a neuroprotective drug that may slow neurodegeneration.[10]

CASE REPORT

SC was a 65-year old white woman with an *FMR1* expansion in the low pre-mutation range (57 CGG repeats) on genetic testing, an mRNA level twice normal (mRNA level, 2.47; SE, 0.06), and an activation ratio (the proportion of cells with the normal X as the active X) of 0.46. Her family first noticed a subtle head tremor when she was 60 years old, with subsequent development of tremor and postural instability. In the previous year, she developed cognitive symptoms such as difficulties with planning and organizing. Her daughter reported an increased “irritability and moodiness” in the year before evaluation. She also presented some lower extremity neuropathy sensory symptoms. Physical examination in March 2008 revealed a subtle intention tremor, a continuous horizontal “no-no” head tremor, and a positional tremor. She was mildly unsteady during tandem walking. She showed some degree of dysphoria and tearfulness.

SC’s self-evaluation of anxiety symptoms (Beck Anxiety Inventory) fell in the mildly impaired range. The Neuro-psychiatric Inventory (NPI), a caregiver-report tool, reinforced SC’s elevated anxiety levels.[11] The NPI also revealed irritability, agitation and aggression, sleep difficulties, disinhibition, and depression. Cognitive test results are summarized in Table 1.

A 1.5-T magnetic resonance image with T1- and T2-weighted sequences for ventricle size, cerebral and cerebellar sulci, and brain stem showed no pathological signal intensity changes, including no MCP sign. Cognitive event-related potential (ERP) studies found that her auditory N1, N2, and P3 components, related to early sensory processing and attention, were normal. The language processing-related N400 component (elicited by visual words) showed reduced effects of semantic congruity and word repetition (with amplitudes ≤1.0 μV in right posterior temporal channel T6 for both effects). The amplitude of the P600 repetition effect, an event-related late positive component that normally shows a decrement in amplitude when semantically congruous words are repeated, was also small (1.1 μV at channel Cz). The Coordination-Tremor-Balance Test System was used to assess SC’s tremor and balance (Table 1).[12,13] SC showed impairment in the tremor and maximum frequency

assessments.[14] She also showed significant balance problems, falling within the higher range of the FXTAS group for the sway task. Her FXTAS motor rating scale (a locally developed scale for motor symptoms in FXTAS) score was 18.

For the next several months, she kept a detailed diary of her symptoms. In June 2008, she began taking 37.5 mg of venlafaxine extended release every day. In August 2008, she wrote, “Feeling better in myself. Prickles and pains still around.” In August 2008, she started memantine, which was titrated up to 10 mg twice a day. In November 2008, she logged, “Feeling really good. Beginning to notice my memory is improving.” By January 2009, her head tremor was the only persisting symptom, and she reported, “… My mood is good. My energy levels are back to what they were 5 years ago. My self-esteem and confidence have returned. I am more tolerant of others and am much more able to cope with the daily issues of a busy life…”

Follow-up studies in March 2009 (Table 1) showed significant improvements, particularly on the auditory immediate recall in the Wechsler Memory Scale and the Behavior Dyscontrol Scale, an assessment of executive function.[15] The BAI symptom ratings for fear, nervousness, shakiness/unsteadiness, and trembling hands decreased to 0. The NPI showed a reduction in agitation and aggression and anxiety, whereas depression disappeared completely. Repeated ERP testing showed larger N400 effect amplitudes (eg, the congruity effect at T6 increased from 1.0 to 2.46 μV) and an improvement in the N400 word repetition effect (from −0.72 μV indicating a baseline effect of reversed polarity to 0.60 μV at T6). The P600 word repetition effect amplitude also increased (eg, from 1.11 to 3.46 μV at central electrode Cz). This effect has shown highly significant correlations with verbal learning and recall abilities in both normal and memory disorder cohorts.[16] The Coordination-Tremor-Balance Test System revealed an overall improvement in tremor intensity, balance, and reaction time. Most remarkable was her improvement in balance (sway task). Follow-up FXTAS motor rating scale score was 10.

DISCUSSION

This patient demonstrated almost 50% improvement of her FXTAS symptoms on the FXTAS motor rating scale, with improved head and hand tremor, ataxia, neuropathy, depression, and anxiety. Recent studies have also demonstrated that the level of anxiety in women with the premutation is associated with decreasing size of the hippocampus.[17] Improvement in her ERP findings suggests a beneficial effect of memantine in cortical connectivity and cognitive processing. The *N*-methyl-D-aspartate antagonist ketamine has been shown to reduce the N400 potential and eliminate the N400 word repetition effect.[18] A recent report showed clinical improvement in 4 of 6 patients with fragile X syndrome treated with memantine, supporting an association between glutamatergic dysfunction and fragile X–associated conditions.[19] This case is the first woman with FXTAS who has had documented improvement in neuropsychiatric symptoms with memantine in addition to venlafaxine.

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TABLE 1

Physical and Cognitive Testing Results, Baseline and 1-Year Follow-Up

		Baseline	Visit 2	FXTAS Mean (SD)	Non-FXTAS Mean (SD)	Controls Mean (SD)
Physical (Coordination-Tremor-Balance Test System)	Intention tremor RH, m/s^2	1.83	0.7	2.93 (2.93)	2.23 (0.97)	2.65 (1.30)
	Intention tremor LH, m/s^2	2.59	1.51	2.97 (2.59)	2.31 (0.81)	2.39 (1.02)
	Postural sway eyes open 30 s, mm^2	71	21	28 (17.50)	4.00 (2.00)	4.00 (1.00)
	Postural sway eyes closed 30 s, mm^2	83	21	56 (22.00)	6.00 (3.00)	5.50 (2.50)
Cognitive (percentile scores)	California verbal learning test list A, trials 1–5	73rd	86th			
	Wechsler Memory Scale III					
	Auditory immediate	47th	95th			
	Working memory	91st	96th			
	Controlled oral word associations test	72nd–81st	90th–94th			
	Stroop test	18th	24th			
	Behavioral Dyscontrol Scale-2	24th	55th			