

adjunctive investigation in patients with borderline EDB decrement.

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## Symptomatic Treatment in the Fragile X–Associated Tremor/Ataxia Syndrome

Deborah A. Hall, MD,<sup>1\*</sup>  
Elizabeth Berry-Kravis, MD, PhD,<sup>2</sup>  
Randi J. Hagerman, MD,<sup>3</sup>  
Paul J. Hagerman, MD, PhD,<sup>4</sup> Cathlin D. Rice, MS,<sup>5</sup>  
and Maureen A. Leehey, MD<sup>1</sup>

<sup>1</sup>Department of Neurology, University of Colorado Health Sciences Center at Denver, Denver, Colorado, USA

<sup>2</sup>Departments of Neurological Sciences, Pediatrics, and Biochemistry, RUSH University Medical Center, Chicago, Illinois, USA <sup>3</sup>M.I.N.D. Institute, University of California at Davis Medical Center, Sacramento, California, USA

<sup>4</sup>Department of Biochemistry and Molecular Medicine, University of California at Davis School of Medicine, Davis, California, USA <sup>5</sup>Department of Clinical Genetics and Metabolism, The Children's Hospital, Denver, Colorado, USA

**Abstract:** There is no established treatment for the neurological features of the recently discovered fragile X–associated tremor/ataxia syndrome (FXTAS). Fifty-six patients with FXTAS completed a questionnaire to determine whether any medications had been effective for neurological symptoms. Of 11 subjects with definite FXTAS, 8 (70%) were on medications for their neurological symptoms, whereas most subjects with possible or probable FXTAS, 31 (70%) of 45 subjects, were not on medications. Although no therapy was uniformly effective for intention tremor, ataxia, Parkinsonism, memory loss, or anxiety, some subjects with intention tremor or Parkinsonism reported improvement with medications frequently used in other movement disorders. Overall, all 22 subjects on medications reported improvement in one or more symptoms. Lack of insight, recall bias, and cognitive impairment may have resulted in an underestimation of the beneficial effect of medical therapy. This study suggests that patients with FXTAS can derive improvement from medication treatment for some of their symptoms. © 2006 Movement Disorder Society

**Key words:** tremor; ataxia; fragile X; FXTAS; medications

Fragile X–associated tremor/ataxia syndrome (FXTAS) manifests as cerebellar ataxia, intention tremor, Parkinsonism, peripheral neuropathy, and cognitive decline in individuals with premutation expansions (55–200 CGG repeats) in the fragile X mental retardation

\*Correspondence to: Dr. Deborah A. Hall, Department of Neurology, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, B183, Denver, CO 80262. E-mail: deborah.hall@uchsc.edu  
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gene.<sup>1-3</sup> Prominent disabling symptoms in FXTAS (intention tremor, Parkinsonism, and memory impairment) are present in other disorders, such as essential tremor and idiopathic Parkinson's disease. Our initial (working) hypothesis was that medications used to treat symptoms that occur in other neurological disorders would also be effective in FXTAS. This hypothesis is supported by anecdotal reports from persons with FXTAS regarding symptomatic treatment.<sup>4</sup> However, although the pathophysiology of the neurological features in FXTAS is not yet well understood, at least some of the signs in FXTAS are expected to have different underlying mechanisms compared to other disorders in which they are present. For example, a study investigating dopamine transporter imaging in FXTAS subjects showed normal striatal iodine-123 fluoropropyl beta-carbomethoxy-3 beta-(4-iodophenyltropane) (<sup>123</sup>IJFP-CIT) uptake compared to reduced uptake in mild Parkinson's disease, suggesting that dopamine replacement may be less effective in these patients.<sup>5</sup>

As FXTAS is a recently described disorder, there have been no controlled studies to evaluate medications for the symptoms of the disorder. The goal of this study was to gather preliminary data on medications used for the neurological signs in FXTAS to facilitate the subsequent development of therapeutic trials.

#### PATIENTS AND METHODS

A questionnaire study was conducted in *fMRI* pre-mutation carriers with possible, probable, or definite FXTAS. All known FXTAS patients at three academic institutions (University of Colorado, Rush University, and University of California at Davis) were recruited. There were no exclusion criteria. The study was designed to explore potential agents for pilot studies. Diagnostic categories were modified from criteria previously proposed from our research group, excluding radiographic requirements as many of the subjects lacked magnetic resonance imaging scans. Most subjects participated in a FXTAS neurological phenotype study, and all subjects had been examined by a movement disorders specialist or physician with fragile X expertise to confirm the diagnosis. Subjects were located across the United States and Canada; they responded to the questionnaire either in person or by telephone. Spouses and caregivers were also interviewed if the subject had a Folstein Mini-Mental Status Examination score less than 26. The study was approved by the Colorado Multiple Institutional Review Board, and informed consent was obtained from all subjects.

A movement disorders specialist reviewed all medications each subject was taking. Medications with known

central nervous system activity were rated by the patient for relative efficacy in alleviating neurological motor symptoms (tremor, Parkinsonism, gait abnormalities), memory difficulties, or anxiety using a five-point scale, -1 to +3. Worsening was denoted with a -1 and no improvement with a zero. Improvement was scored if they had improved at any point in time, with a range of responses, including mild, moderate, or marked improvement of symptoms. Response to medication over time was not assessed. Side effect profiles of each medication were obtained. Medical records, when available, were used to determine whether the results of the questionnaire survey were consistent with documentation of the treating physician.

Descriptive statistics were performed using the mean for age and frequency statistics for category of diagnosis, gender, and number of subjects with improvement on each medication. Correlation between category of FXTAS and medication status was performed with the Spearman correlation coefficient. Medication effectiveness scores were not normally distributed, so the Kruskal-Wallis statistic for nonparametric data was used to analyze medications used within each symptom category. Statistical significance was considered if the *P* value was less than 0.05.

#### RESULTS

The mean age of the 56 subjects was  $69.1 \pm 8.8$  years, and 73% were male. There were 16 patients who had possible FXTAS, 29 had probable FXTAS, and 11 had definite FXTAS. Thirty-four subjects (60%) were not receiving medications for their neurological symptoms. For the 22 subjects receiving medication, there was a significant ( $P = 0.046$ ) correlation between category of FXTAS (possible, probable, or definite) and whether the subject was on medications for symptomatic therapy. Of those subjects who met criteria for definite FXTAS, 8 (70%) of 11 subjects were taking medications for various neurological symptoms and 14 (30%) of 45 subjects meeting criteria for possible/probable FXTAS were on medications. Table 1 shows the medications being taken and that the most commonly prescribed medications were for memory or anxiety symptoms.

Of the subjects receiving therapy for intention tremor, 3 of 6 reported mild to moderate improvement on primidone, 3 of 8 had moderate improvement in tremor on beta-blockers, 2 of 8 had moderate improvement on benzodiazepines. One subject had improved tremor on memantine. Parkinsonism (rest tremor, slowness, or stiffness) improved on carbidopa/levodopa in 2 of 8 subjects and on pramipexole in 1 of 2 subjects. Slowing of cognitive decline was reported in 2 of 6 on venlafaxine and

**TABLE 1.** Medications prescribed for the neurological signs of FXTAS

Medication	No. of subjects on medication
Beta-blockers	15 <sup>a</sup>
Selective serotonin reuptake inhibitors	11
Acetylcholinesterase inhibitors	10
Carbidopa/levodopa	8
Benzodiazepines	8
Primidone	6
Venlafaxine	6
Dopamine agonists	3
Gabapentin	3
Quetiapine	1
Memantine	1
Bupropion	1
Benztropine	1
Selegiline	1
Amantadine	1

<sup>a</sup>Seven of fifteen prescribed for hypertension.

3 of 9 subjects on acetylcholinesterase inhibitors. Anxiety improved in 2 of 6 subjects on venlafaxine and 5 of 8 subjects on benzodiazepines. There was no improvement in these neurological symptoms for the single subject on bromocriptine, or for two subjects on gabapentin. Reported benefit from the medications did not reach statistical significance.

Medical records were available for 10 of the 22 subjects on medications. The treating physician's notes did not conform to the questionnaire results 50% of the time. In addition, 5 of the 22 subjects had been on medications for their neurological signs but did not disclose such medication use to the investigator. In all instances of disagreement, the subject underestimated the response to medication.

## CONCLUSIONS

The goal of this study was to gather preliminary data on medications used in FXTAS to aid in the design of therapeutic clinical trials. The results showed that neurological motor signs are not usually treated in patients with possible or probable FXTAS. Those subjects with definite FXTAS were much more likely to be on medications, suggesting that patients with milder disease may not find their symptoms intrusive enough to warrant therapy. A population-based case control study in essential tremor recently reported similar results, with only 6% of patients with essential tremor on medications.<sup>6</sup>

Subjects were treated with a variety of medications, especially medications typically prescribed for essential tremor or Parkinsonism. The heterogeneity of medications prescribed is likely due to differing phenotypes between the subjects, with some subjects having a more

parkinsonian phenotype and others more affected with intention tremor, ataxia, or cognitive decline. The finding that medications for anxiety were more frequently prescribed than medications for neurological signs may be because anxiety is a prominent symptom in *FMRI* pre-mutation carriers.

This study has some limitations, particularly with respect to the subjective nature of the patient evaluations and small sample size. In this study, subjects underestimated the response they had to medications for neurological signs, suggesting the presence of recall bias. One reason for the lack of reports of effectiveness by the subjects might be related to lack of insight of the neurological signs of the disease, which itself is a manifestation of the executive dysfunction seen in FXTAS. Despite their having met criteria for FXTAS on examination by a movement disorders specialist or fragile X expert, many subjects denied having tremor or ataxia when they were interviewed regarding their medications. Memory impairment may have impacted the ability of subjects to recall medications or response to medication. Questions regarding depression were not asked and may have affected responses as well.

The sample included several subjects who had possible FXTAS, rather than probable or definite FXTAS. Of note, most of these possible FXTAS subjects were recruited as part of large fragile X syndrome family screening study, in which the investigator traveled locally to the subject's homes. These subjects with possible FXTAS are less likely to have been prescribed medications, because their symptoms were milder and they were less likely to have sought care from a physician.

Overall, the results showed that mainly patients with more definitive disease seek symptomatic therapy and that a variety of medications have been prescribed (consistent with the variable phenotype of FXTAS). In addition, FXTAS patients frequently have at least mild benefit from therapy, and patient reports regarding therapy are frequently unreliable. Design of therapeutic trials will need to take into account recall bias, lack of insight, and underlying memory disturbances. Medications that slow or improve the most disabling features of the disorder, that is, cognitive decline, ataxia, or tremor, may be the most appropriate for pilot and controlled therapeutic studies in FXTAS subjects, especially those who require symptomatic treatment.

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## Hyperhidrosis in Parkinson's Disease

Pedro Schestatsky, MD,<sup>1</sup> Josep Valls-Solé, MD,<sup>2\*</sup>  
 João Arthur Ehlers, MD,<sup>1</sup> Carlos R. M. Rieder, PhD,<sup>1</sup>  
 and Irênio Gomes, PhD<sup>1</sup>

<sup>1</sup>Unidade de EMG, Serviço de Neurologia, Hospital de Clínicas de Porto Alegre, Porto Alegre; <sup>2</sup>Unitat d'EMG. Servei de Neurologia, Hospital Clínic, Barcelona, Spain, Facultat de Medicina, IDIBAPS (Institut D'Investigació Biomèdica August Pi i Sunyer)

**Abstract:** We studied the sudomotor skin response (SSR) in patients with Parkinson's disease with and without symptomatic hyperhidrosis. The study was carried out in 13 patients who complained of excessive sweating and in 37 patients who did not have excessive sweating. Patients were matched for age, sex, degree of impairment, duration of the disease, and number and severity of autonomic disturbances. Excessive sweating involved mainly the face, head, and trunk. The SSR was recorded from the palm of the hands to electrical stimulation of the median nerve at the wrist. We analyzed onset latency, peak to peak amplitude, and waveform. Patients with hyperhidrosis had more often absent responses ( $\chi^2 = 5.292$ ;  $P = 0.021$ ), their responses were of lower mean amplitude (analysis of variance [ANOVA];  $F[2,101] = 11.678$ ;  $P < 0.001$ ), and they had a reduced number of responses with a predominantly negative component ( $\chi^2 = 8.493$ ;  $P = 0.004$ ) than patients who

did not complain of sweating disturbances. Our results indicate that excessive sweating in Parkinson's disease concurs with decreased activation of sweat glands in the palms of the hands and suggests that axial hyperhidrosis could be a compensatory phenomenon for reduced sympathetic function in the extremities. © 2006 Movement Disorder Society

**Key words:** hyperhidrosis; sweating; Parkinson's disease; sympathetic skin response; autonomic nervous system

Hyperhidrosis is a frequent nonmotor complaint of patients with Parkinson's disease<sup>1,2</sup> (PD) that may reveal autonomic dysfunction.<sup>3,4</sup> One of the simplest tests used in the evaluation of sweating disturbances is the sympathetic sudomotor skin reflex response (SSR), a noninvasive recording of the galvanic potential of the skin.<sup>5–7</sup> The SSR has been studied in patients with idiopathic PD (IPD), and the abnormalities found have been interpreted as a sign of autonomic dysfunction.<sup>8–10</sup> However, these studies have not specifically addressed the possible relationship between SSR abnormalities and sweating disturbances. Knowing that patients with hyperhidrosis are likely to exhibit SSR abnormalities,<sup>11,12</sup> we decided to study the characteristics of the SSR in patients with IPD and sweating complaints.

### SUBJECTS AND METHODS

The study was performed in patients with probable IPD, diagnosed according to standard criteria.<sup>13</sup> As part of a more complete questionnaire for autonomic disturbances, patients were requested to answer "yes" or "no" to the following question: "Have you experienced problems with sweating?" In the case of an affirmative response, we specifically asked, "Are these problems due to excessive sweating or lack of sweating," and "In what region of your body do you experience the problems with sweating?" We did not specifically ask for the possible relationship between signs of autonomic dysfunction and medication-related fluctuations.

#### Selection Criteria

We excluded from the study patients with clinical signs suggesting non-IPD Parkinsonism, coincidental diseases potentially involving the autonomic nervous system, or use of drugs known to influence autonomic function. Selected patients were scheduled for a conventional electrophysiological testing of nerve conduction, and those who had electrophysiological signs suggesting polyneuropathy<sup>14</sup> were also excluded. For comparison, we studied a group of 54 healthy control subjects of the same age range. All patients and controls gave their informed consent for the study, which was approved by

\*Correspondence to: Dr. Josep Valls-Solé, Servei de Neurologia, Hospital Clínic, Villarroel 170, Barcelona, Spain 08036. E-mail: jvalls@clinic.ub.es

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