



# Initial diagnoses given to persons with the fragile X associated tremor/ataxia syndrome (FXTAS)

**Abstract**—Fragile X-associated tremor/ataxia syndrome (FXTAS) is a newly described disorder that occurs in premutation carriers of the fragile X mental retardation 1 (*FMR1*) gene. Fifty-six patients with FXTAS were given 98 prior diagnoses: most were in the categories of parkinsonism, tremor, ataxia, dementia, or stroke. Data from this study and others were used to develop guidelines for *FMR1* diagnostic testing for FXTAS.

NEUROLOGY 2005;65:299–301

D.A. Hall, MD; E. Berry-Kravis, MD, PhD; S. Jacquemont, MD; C.D. Rice, MS; J. Cogswell, BA; L. Zhang, MD, PhD; R.J. Hagerman, MD; P.J. Hagerman, MD, PhD; and M.A. Leehey, MD

We recently described a late-onset neurodegenerative disorder, the fragile X-associated tremor/ataxia syndrome (FXTAS),<sup>1</sup> in individuals with premutation expansions of the fragile X mental retardation 1 (*FMR1*) gene. FXTAS is characterized by cerebellar gait ataxia and intention tremor. Other features include parkinsonism, peripheral neuropathy, autonomic dysfunction, and dementia. Onset is typically in the sixth to seventh decade and penetrance is age-dependent, affecting on average 30% of males over age 50.<sup>2</sup> MRI shows generalized atrophy, white matter changes, and distinctive T2 hyperintensities in the middle cerebellar peduncles (the MCP sign). Neuropathology shows neuronal and glial intranuclear inclusions, loss of Purkinje cells, and cerebellar axonal dystrophic changes. FXTAS affects females less frequently than males.

Based on a carrier frequency of the *FMR1* premutation of approximately 1 in 813 men and a 30% penetrance rate for males over the age of 50, FXTAS may affect as many as 1 in 3,000 men over age 50. As FXTAS is only recently described, many patients have been diagnosed with other disorders. We sought to determine what previous diagnoses were given to patients with FXTAS and what specialists evaluated them. Using this information and data from other-

studies, we propose guidelines for diagnostic testing for FXTAS.

**Methods.** Patients were ascertained through families with known fragile X syndrome; most were participating in FXTAS studies at the University of California at Davis, Rush University, or the University of Colorado. All patients who met formal diagnostic criteria for probable or definite FXTAS and on whom reliable medical information could be obtained were included. A patient with probable FXTAS is defined as a premutation carrier who has both intention tremor and gait ataxia, or who has the MCP sign accompanied by parkinsonism, moderate to severe short-term memory deficiency, or executive function deficits. A patient with definite FXTAS is defined as a premutation carrier who has either intention tremor or gait ataxia and either the MCP sign or neuropathologic confirmation.

**Results.** Seventy-nine patients with FXTAS were screened and 62 with adequate data were included. Forty-two patients (35 men, 7 women) had probable FXTAS and 20 (all men) had definite FXTAS. Eleven patients were deceased. Age at onset was  $60.2 \pm 7.1$  years (average  $\pm$  SD), age at examination was  $69.4 \pm 7.8$ , and average disease duration was  $10.0 \pm 7.0$ . All patients were ascertained through a family history of fragile X syndrome. Although records generally lacked information about a family history of premature ovarian failure, three men had a first-degree relative and one woman had the disorder. Data were collected from records and phone survey ( $n = 18$ ), records only ( $n = 40$ ), and phone survey only ( $n = 4$ ). Of the 62 patients in the study, six did not seek medical care for their symptoms. The remaining 56 patients were given 98 diagnoses (table 1). Most patients received multiple diagnoses as their disease evolved and as they were seen by different physicians. Diagnoses were usually given by general neurologists (70%), and less often by primary care physicians (26%) and movement disorders specialists (4%).

One of our patients with multiple prior diagnoses is a 69-year-old man with definite FXTAS. He had onset of tremor and gait ataxia at age 58 and falling at age 63. Currently he cannot walk independently, has freezing of gait, bladder and occasionally bowel incontinence, and is moderately demented. Brain MRI shows generalized atro-

From the University of Colorado Health Sciences Center (Drs. Hall and Leehey, C.D. Rice), Denver; Departments of Neurological Sciences, Pediatrics, and Biochemistry (Dr. Berry-Kravis), Rush University Medical Center, Chicago, IL; M.I.N.D. Institute and Department of Pediatrics (Drs. Jacquemont and R.J. Hagerman, J. Cogswell), University of California at Davis Medical Center, Sacramento; and Departments of Biochemistry and Molecular Medicine (Dr. P.J. Hagerman) and Neurology (Dr. Zhang), University of California at Davis School of Medicine.

Supported by grants from the American Academy of Neurology (D.A.H.), National Institute of Neurological Disorders and Stroke (NS43532 to P.J.H.), and the National Institute of Child Health and Human Development (HD36071 to R.J.H.).

Received October 14, 2004. Accepted in final form March 3, 2005.

Address correspondence and reprint requests to Dr. Maureen A. Leehey, University of Colorado Health Sciences Center, Department of Neurology, B183, 4200 East Ninth Ave., Denver, CO 80262; e-mail: maureen.leehey@uchsc.edu

Editorial, see page 190  
See also page 331

**Table 1** Prior diagnoses given to patients with fragile X-associated tremor/ataxia syndrome (FXTAS)

Diagnoses (% of total diagnoses given)	No. of patients*
Parkinsonism (24%)	11
Idiopathic Parkinson disease	6
Atypical Parkinson disease	3
Multiple system atrophy	2
Parkinsonism plus	1
Extrapyramidal dysfunction	
Tremor (20%)	15
Essential tremor	1
Cerebellar tremor	1
Alcoholic tremor	1
Dystonic tremor	1
Tremor, unspecified	
Ataxia (17%)	3
Ataxia from strokes	2
Ataxia from cervical spine disease	2
Ataxia from pituitary tumor	1
Ataxia from lumbosacral radiculopathy	1
Ataxia from a car accident	2
Cerebellar ataxia	2
Olivopontocerebellar atrophy	2
Spinocerebellar degeneration	1
Cerebellar syndrome	1
Cerebellar degeneration	
Dementia (13%)	6
Dementia	3
Alzheimer disease	2
Vascular dementia	1
Binswanger disease	1
Multi-infarct dementia	
Cerebrovascular disease (10%)	4
Stroke	3
Multiple strokes	2
Transient ischemic attacks	1
Cognitive disorder secondary to cerebrovascular disease	
Miscellaneous (16%)	4
Depression	3
Peripheral neuropathy	2
Benign positional vertigo	1
Multiple sclerosis	1
Possible multiple sclerosis	1
Possible NARP	1
Psychogenic	1
Myasthenia gravis	1
Normopressure hydrocephalus	1
Total number of diagnoses	98

\* Fifty-six persons with FXTAS were given a total of 98 prior diagnoses.

NARP = neurogenic weakness, ataxia, and retinitis pigmentosa.

phy, confluent periventricular leukomalacia, and bilateral MCP signs. His original diagnosis was Parkinson disease (PD); then he was told that his symptoms were secondary to strokes. Subsequent (consecutive) diagnoses were atypical PD, multiple system atrophy, and finally, FXTAS. All these diagnoses were given by general neurologists.

**Discussion.** This study shows that a wide variety of prior diagnoses, mainly within categories of parkinsonism, tremor, ataxia, and dementia, have been given to patients with FXTAS (see table 1). These conclusions apply to persons with a family history of fragile X syndrome, since those without were not investigated. Although intention tremor and gait ataxia are the principal features of the disease, patients may initially present with parkinsonism or cognitive decline. A detailed analysis of the natural history of FXTAS is needed, which may lead to modification of the existing diagnostic criteria for FXTAS.

Prior diagnoses were usually related to FXTAS but some were not. Examples of related diagnoses are peripheral neuropathy and atypical parkinsonism. In some cases, a disorder unrelated to FXTAS was assumed to cause a feature that was probably a manifestation of FXTAS, e.g., pituitary tumor causing ataxia. Patients sometimes had coexisting, unrelated disorders, e.g., autopsy confirmed primary PD and FXTAS. In this latter example a synergistic interaction between the two disorders is possible.

Currently, the diagnosis may be missed because many physicians are unfamiliar with FXTAS or do not ask the right questions regarding family history. An understanding of the inheritance pattern of the *FMR1* premutation and full mutation and of the phenotypic variation of fragile X syndrome would help physicians know when *FMR1* testing is appropriate. Male carriers transmit the premutation to all daughters and to none of their sons. Thus, physicians should ask men with suspected FXTAS if their daughters' children have disorders suggestive of fragile X syndrome: mental retardation, developmental delay, or autism. Female carriers have a 50% chance of transmitting the *FMR1* expansion to each child, and may transmit a premutation or full mutation. Accordingly, women with suspected FXTAS should be asked if their children have these disorders. Furthermore, siblings or the siblings' children of men or women with suspected FXTAS may have these disorders. Additionally, patients with FXTAS also may have a family history of premature ovarian failure or disorders that are clinically consistent with FXTAS.

We found that individuals with FXTAS have frequently been given prior diagnoses that are common neurologic illnesses (e.g., PD, essential tremor [ET]). Studies screening for the *FMR1* premutation in older men report that 0/74 with ET,<sup>3,4</sup> 0/389 with PD,<sup>5</sup> 0/40 with atypical parkinsonism,<sup>3,5</sup> 0/63 with multiple system atrophy,<sup>3,6</sup> and 16/539 (3.0%) with cerebellar ataxia syndromes<sup>3,6-10</sup> were carriers.

Our central finding—that tremor, parkinsonism, and ataxia are common previous diagnoses given to patients with FXTAS—is apparently in conflict with the screening studies cited above.<sup>3-10</sup> However, the screenings of patients with ET and PD are unlikely to identify *FMR1* alleles because the prevalence of ET and PD is substantially higher than FXTAS, and because many patients with FXTAS would be excluded because they do not fit the diagnostic criteria for ET and PD utilized in the studies. Although persons with FXTAS may be included in screens for atypical PD, the number of patients studied is too small to be meaningful. One might have expected to find premutation alleles in persons with MSA, since the two disorders have some clinical features in common and may have a similar prevalence. The negative result may indicate that strict diagnostic criteria for MSA reliably exclude persons with FXTAS. The reason that only a small fraction of screened ataxia patients were premutation carriers is likely because most persons with FXTAS are not given a diagnosis of ataxia and rarely undergo genetic analysis for ataxia.

The finding that on average 3% of persons undergoing genetic analysis for ataxia have FXTAS is important. At present, the etiology of ataxia in older men can only occasionally be identified, with 11% due to a (CAG)<sub>n</sub> expansion of one of the spinocerebellar ataxia (SCA) genes. In one study,<sup>9</sup> the individual SCA genes accounted for 0.7 to 5.8% of cases. Thus the frequency of the *FMR1* premutation is found as commonly as the individual SCA genes.

Since FXTAS may affect as many as 1 in 3,000 men over age 50, guidelines are needed regarding who should undergo *FMR1* testing. Based on this study, our experience with FXTAS to date, and the literature, we propose guidelines for testing (table 2).

**Table 2** Phenotypic groups recommended for *FMR1* DNA testing\*

1. Unexplained cerebellar ataxia in men  $\geq 50$  y
2. Action tremor, parkinsonism, or dementia in men  $\geq 50$  y with one of the following:
  - a) A family history of developmental delay, autism, mental retardation, or premature ovarian failure
  - b) The middle cerebellar peduncle sign on MR imaging

\* These are not absolute guidelines. Physicians should consider that the family history may be negative and that women also have been reported with fragile X-associated tremor/ataxia syndrome (FXTAS).

Genetic counseling should be offered for patients who are *FMR1* carriers.

## References

1. Hagerman RJ, Leehey M, Heinrichs W, et al. Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X. *Neurology* 2001;57:127-130.
2. Jacquemont S, Hagerman RJ, Leehey MA, et al. Penetrance of the fragile X associated tremor/ataxia syndrome in a premutation carrier population. *JAMA* 2004;291:460-469.
3. Tan EK, Zhao Y, Puong MS, et al. Fragile X premutation alleles in SCA, ET, and parkinsonism in an Asian cohort. *Neurology* 2004;63:362-363.
4. Arocena DG, Louis ED, Tassone Flora, et al. Screen for expanded *FMR1* alleles in patients with essential tremor. *Mov Disord* 2004;19:930-933.
5. Toft M, Aasly J, Bisceglia G, et al. Parkinsonism, FXTAS and *FMR1* premutations. *Mov Disord* 2005;20:230-233.
6. Biancalana V, Toft M, Le Ber I, et al. *FMR1* premutations, associated with fragile X associated tremor/ataxia syndrome, are rare in multiple system atrophy. *Arch Neurol* 2005 (in press).
7. Macpherson J, Waghorn A, Hammans S, Jacobs P. Observation of an excess of fragile-X premutations in a populations of males referred with spinocerebellar ataxia. *Hum Genet* 2003;112:619-620.
8. Milunsky JM. Fragile X carrier screening and spinocerebellar ataxia in older males. *Am J Med Genet* 2004;125A:320.
9. Van Esch H, Dom R, Bex D, et al. Screening for *FMR1* premutations in 122 older Flemish males presenting with ataxia. *Eur J Hum Genet* 2005;13:121-123.
10. Brussino A, Gellera C, Saluto A, et al. *FMR1* gene premutation is a frequent genetic cause of late-onset sporadic cerebellar ataxia. *Neurology* 2005;64:145-147.

## RESIDENT AND FELLOW PAGE

### Call for teaching videos

The *Neurology* Resident page is featured online at [www.neurology.org](http://www.neurology.org). The Editorial Team of this section is seeking teaching videos that will illustrate classic or uncommon findings on movement disorders. Such videos will aid in the recognition of such disorders. Instructions for formatting videos can be found in the Information for Authors at [www.neurology.org](http://www.neurology.org). Please contact the Editor, Karen Johnston (kj4v@virginia.edu), for more information or submit teaching videos online at <http://submit.neurology.org>.