

Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X

Article abstract—The authors report five elderly men with the fragile X premutation who had a progressive action tremor associated with executive function deficits and generalized brain atrophy. These individuals had elevated fragile X mental retardation 1 gene (*FMR1*) messenger RNA and normal or borderline levels of *FMR1* protein. The authors propose that elevations of *FMR1* messenger RNA may be causative for a neurodegenerative syndrome in a subgroup of elderly men with the *FMR1* premutation.

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Fragile X syndrome (FXS) is caused by a trinucleotide repeat expansion (the full mutation is >200 CGG repeats) in the fragile X mental retardation 1 gene (*FMR1*). The full mutation leads to methylation and subsequent transcriptional silencing with a consequent deficit of *FMR1* protein (FMRP).¹ The premutation, an expansion of 50 to 200 CGG repeats, has a prevalence in the general population of approximately 1 per 700 men and 1 per 250 women.² Carriers of the premutation typically do not show the full FXS phenotype, but comprise a subgroup that may have some physical features of FXS^{1,3} or mild cognitive and emotional problems.^{4–6} Premature menopause, present in approximately 16% of women carrying the premutation but in none with the full mutation, is considered a phenotypic characteristic unique to the premutation.⁷ Men with 55 to 100 CGG repeats have *FMR1* messenger RNA (mRNA) levels that are two to four times higher than normal, and men with 100 to 200 CGG repeats have *FMR1* mRNA levels four to ten times normal, despite mildly reduced FMRP levels.⁸ Thus, elevated *FMR1* mRNA represents a molecular phenotype for men with the premutation, and may reflect a defect in translation of the mRNA into FMRP.⁸ We report five men with the premutation and elevated *FMR1* mRNA levels who had action tremors associated with executive function deficits and slowly progressive neurodegenerative disorders.

Case reports. *Patient 1.* A 63-year-old right-handed grandfather of a boy with FXS had onset of an action

tremor in his right hand at age 54. The tremor progressed over 2 years to involve his left hand, interfering with fine motor abilities and causing him to retire from his career as an electrician at age 58 years. His handwriting became illegible at age 58, and by age 61 he required help from his wife for many activities of daily living. His tremor occurred at rest, but was most prominent with action. His gait was wide-based, and he frequently fell.

On examination he had masked facies, monotonous, slurred speech, mild saccadic pursuit, and bilateral hearing loss. He had a relatively symmetric, 4- to 6-Hz, large-amplitude intention tremor of the upper extremities, a static bilateral upper extremity postural tremor, and an intermittent resting tremor of his right thumb. On finger-to-nose testing he had bradyteleokinesia without hypo- or hypermetria. Handwriting was large and completely illegible. He had upper extremity dysdiadochokinesia, ataxia on heel-to-shin movements, and a wide-based, slow, and lurching gait. Muscle stretch reflexes were reduced in all extremities and absent at the ankles, and plantar responses were flexor. Vibration sense was absent but position sense was preserved in the great toes. The table contains the results of molecular studies, cognitive testing, and MRI.

Patient 2. A 63-year-old right-handed grandfather of two children with FXS, with a PhD in education, had gradual onset of shaking in his right hand at age 55, which interfered with writing. The tremor worsened and became bilateral. Over the past 2 years his wife noticed a resting tremor in his right hand and a general slowing of movement. His activities of daily living took longer to perform. He had difficulty with balance, and fell occasionally. Memory problems were present for 2 years. He took sertraline for depression, anxiety, and obsessive-compulsive symptoms. Neurologic examination revealed a mild postural tremor of the right upper extremity, and a 4- to 6-Hz intention tremor with finger-to-nose testing. The tremor was most pronounced with handwriting, which was large and poorly legible. He had masked facies, diminished amplitude of finger tapping, mild rigidity, and an intermittent slow resting tremor in the right upper extremity. Vibration sense was reduced in his great toes.

Patient 3. A 62-year-old right-handed grandfather of a boy with the full mutation, this patient had consumed alcohol heavily, stopping at age 57 years, when he noticed a tremor in his right arm. The tremor became much more apparent and disabling when he stopped drinking, and progressed to bilateral involvement by age 58. For the past

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Table Clinical and molecular findings in elderly men with the fragile X premutation

Findings	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Cerebellar features	Intention tremor, mild dyssynergia, mild gait ataxia, unable to tandem	Intention tremor, unable to tandem	Intention tremor, mild dyssynergia, dysmetria, loss of check, wide based gait, unable to tandem	Intention tremor, unable to tandem, eventually unable to walk	Intention tremor, mild dyssynergia, dysmetria, loss of check, wide based gait, unable to tandem
Parkinsonian features	Resting tremor, masked face, minimal bradykinesia, response to L-dopa	Resting tremor, masked face, mild bradykinesia, slight rigidity	Resting tremor, masked face, minimal bradykinesia, mild rigidity	Resting tremor, rigidity, response to L-dopa	Resting tremor, masked face, mild bradykinesia, slight rigidity
Tremor severity*					
CRST PGI	2	1	4	Not done	1
CRST ADL, % disabled	67	14	67		30
CGG repeat	98	94	93	Obligate carrier	78
FMRP level, %†	69	74	75	Not done	89
mRNA level (±SE)‡	3.38 × normal (0.48)	2.35 × normal (0.13)	2.4 × normal (0.36)	Not done	4.4 × normal (0.11)
IQ testing on WAIS III	VIQ 93, PIQ 73, FSIQ 83	VIQ 115, PIQ 78, FSIQ 98	VIQ 82, PIQ 57, FSIQ 68	VIQ 121, PIQ 118, FSIQ 116	VIQ 117, PIQ 107, FSIQ 113
Wisconsin Card Sort Test					
Total errors, percentile (T score)	6th (35)	3rd (31)	Unable to complete	Significant deficits	6th to 10th (30)
MRI	Mild to moderate generalized atrophy, enlarged ventricles	Moderate generalized atrophy, enlarged ventricles, mild white matter changes in periventricular area	Moderate generalized atrophy, enlarged ventricles (figure 1)	CT scan with mild atrophy	Moderate generalized atrophy with enlarged ventricles, minimal white matter changes
Other medical problems	Impotence, hypertension	Impotence	Impotence, hypertension	Impotence	Impotence

* Tremor severity is measured using the Clinical Rating Scale for Tremor (CRST). The PGI (patient global impression) is a subjective rating based on how disabled the patient feels, with 0 being no disability and 4 severe disability, 75 to 100% impaired. The CRST activities of daily living (ADL) scores the functional disabilities.

† Percentage of lymphocytes positive for fragile X mental retardation 1 protein (FMRP) on immunocytochemical studies described in Tassone et al.⁸

‡ Methodology for messenger RNA (mRNA) studies described in Tassone et al.⁸

2 years he drank liquids through a straw because of difficulty holding a cup; his wife cut his foods, his writing was illegible, and he required assistance with buttons and dressing. He switched from using his right hand primarily to his left at age 58, and stopped driving at age 61. He was unsteady, sometimes listing to the right, with frequent stumbling in the forward direction and occasional falls. He had used a cane for the past 2 years and a walker for the past year.

Examination of the cranial nerves showed facial masking, mild saccadic pursuit, monotone speech, and bilateral hearing loss. With finger-to-nose testing he had a bilateral, upper extremity, 4- to 6-Hz, large-amplitude intention tremor and dysmetria. A resting and a static, postural tremor were present in both arms. He was unable to write. There was loss of check in the upper extremities and dysdiadochokinesis. Heel-to-shin movements were ataxic. He had slight cogwheel rigidity in the right arm and mild rigidity in both legs. His gait was wide-based and slow, his steps were short, his arm swing was reduced, and he turned en bloc. Muscle stretch reflexes were reduced in all

extremities and absent at the ankles. Vibration sense was markedly reduced in the right great toe and absent in the left. MR images from Patient 3 are shown in the figure.

Patient 4. This case was identified retrospectively. The patient, who died in 1988, was the grandfather of a boy with FXS. As his daughter had 75 CGG repeats and his wife was negative for the *FMR1* mutation, Patient 4 was therefore an obligate premutation carrier. He had first experienced an intermittent intention tremor in his left hand at age 57 years while working as a professor in Nigeria. His handwriting became tremulous, and he found it difficult to button clothing and tie shoelaces. His wife noted the gradual development of memory and concentration problems.

Thought to have PD with left-sided rigidity, the patient was given carbidopa and L-dopa, which improved his tremor and rigidity. His condition continued to deteriorate, and by age 64 he had developed a marked resting and intention tremor bilaterally, cogwheeling in his lower extremities, and dementia. His diagnosis was modified to atypical PD. His symptoms gradually worsened and he

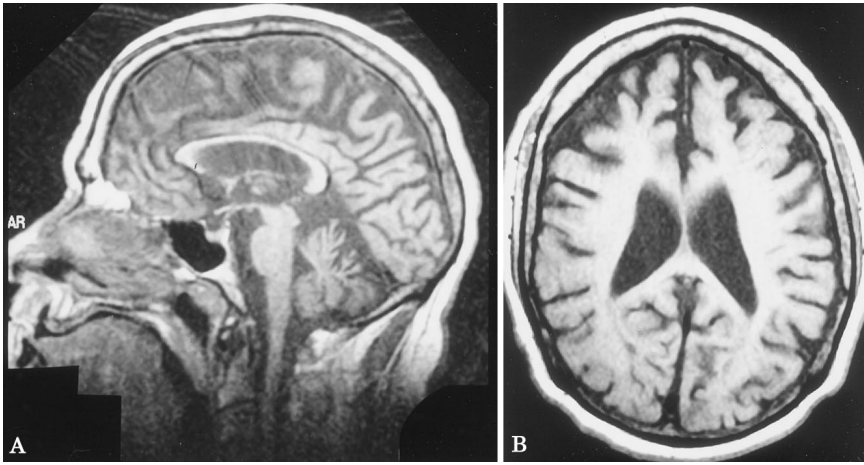


Figure. (A and B) Patient 3. T1 axial and sagittal images demonstrate prominent ventricles with cerebral, brain-stem, and cerebellar atrophy. Note the particularly severe frontal and parietal atrophy, which has led to excess fluid graying the sulci seen frontally on sagittal view.

eventually became bedridden before dying from complications of a kidney infection at age 69.

Patient 5. Patient 5 was a 70-year-old, right-handed former college professor and grandfather of two children with FXS. At age 61 years he first noticed a tremor in his right hand, which subsequently developed in the left hand and began interfering with his handwriting. Over the past 3 years his tremor was present daily with movement, and intermittently at rest. At age 66, he found it difficult to get a key into the car door lock because of his tremor. Within the past year, he had problems with spilling liquids. Over the past 4 years he had fallen occasionally, and his gait sometimes drifted to one side. His wife noticed that he had mild short-term memory problems and compulsive hand washing. Results of his neurologic examination were similar to those of the first three cases, including impaired vibration and position sense in the distal lower extremities. The cerebellar and parkinsonian findings are described in the table.

Discussion. All five men appear to have similar findings of differing severity: a progressive action tremor, cerebellar dysfunction, cognitive decline, and parkinsonism associated with generalized brain atrophy (see the table). The slow intention tremor is the most obvious clinical feature, suggesting particular involvement of the dentate nuclei or cerebellar outflow tracts. Additionally, all five men were impotent and had signs of peripheral neuropathy. The cognitive component appears to begin with executive function deficits (see the table) but such problems may be common in premutation male carriers without an intention tremor.⁹ The cognitive decline appears to be progressive, with memory loss, decline in executive functioning, and eventual dementia in two of the patients described here.

The prevalence of this progressive neurologic problem among men with the premutation is not known, and warrants a survey of this population. The syndrome described here is different from the previous problems, such as attention deficit hyperactivity disorder, anxiety, and premature menopause, that have been reported in individuals with the premutation,^{1,4-7} suggesting that heterogeneity in the clinical phenotype depends on age and perhaps sex.

Although the molecular basis of this neurologic phenotype is unknown, its apparent restriction to the premutation range argues against a causative role of lowered FMRP levels, which are more pronounced in the full mutation range. As a tentative alternative hypothesis, progressive nervous system degeneration may result from either direct or indirect effects of the elevated *FMR1* mRNA levels, which were seen in four of the five case studies (see the table). Analogous gain-of-function effects of abnormal mRNA production or localization have been proposed for the CTG expansion in myotonic dystrophy.¹⁰ In any case, it is imperative that additional individuals with both premutation and full mutation alleles be screened for tremor, and that individuals with action tremor associated with cognitive decline and mild parkinsonism be screened for fragile X. Further studies of the biological consequences of elevated *FMR1* mRNA, including neuropathologic studies of autopsy material, are warranted.

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Headache characteristics in patients after migrainous stroke

Article abstract—Six patients who fulfilled strictly defined criteria for migrainous cerebral infarction and in whom other causes of stroke were ruled out were observed. All had a long-standing history of migraine with aura. In most, stroke was mild with good recovery and no recurrence. Headache frequency and severity decreased after the stroke. It is hypothesized that the improvement in migraine may be due to reduced nociceptive transmission as result of loss in vasoreactivity of the affected cerebral blood vessel.

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A coincidence of migraine and stroke has been recognized in several epidemiologic studies^{1–3} but stroke occurring during a migraine attack—migrainous stroke (MIGS)—is uncommon. The prognosis and headache characteristics before and after the complicating MIGS are not well documented. The few studies that have tried to characterize patients with MIGS did not adhere to the International Headache Society criteria for migrainous infarction⁴ and followed-up heterogeneous groups of patients, including patients with antiphospholipid syndrome.⁵ In order to better characterize headache patterns and clinical outcome of patients with MIGS, we prospectively followed-up patients who fulfilled the strictly defined International Headache Society criteria for MIGS and in whom other causes of stroke were ruled out.

Patients and methods. We prospectively evaluated six consecutive patients with MIGS, admitted to our department from 1995 to 1998. The patients developed a cerebral infarction during the course of a typical migraine attack, with a neurologic deficit that was not completely reversible after 7 days and manifested in the same vascular distribution as the aura. All patients underwent a thorough evaluation for the presence of hematologic disorders, hypercoagulability syndromes (including tests for protein C and S and antithrombin-3 deficiencies, activated protein C resistance, and antiphospholipid antibodies), collagen disorders, and syphilis. Possible sources of cardiac and systemic emboli (including patent foramen ovale) were excluded by routine physical examination, EKG, chest radi-

ography, transesophageal echocardiography, carotid duplex, and transcranial Doppler. On the ultrasonographic studies there was no narrowing of lumen or resistance to flow that would suggest dissection, but this was not entirely ruled out by plain or MR angiography. Neurologic dysfunction was evaluated with the NIH Stroke Scale on admission and discharge. Outcome was evaluated at discharge, after 3 months, and on follow-up appointments over an additional 1 to 3 years with the Glasgow Outcome Scale and the Barthel Index. We specifically questioned the patients regarding the type and history of migraine before and during the stroke and about occurrence and recurrence of headache after the stroke. Headache severity was graded using a visual analog scale from 0 (no pain) to 10 (maximal pain). Headache frequency after the index stroke was determined by using migraine diaries. Two patients gave informed consent for a breath-holding test, performed 3 years after the stroke. The middle cerebral arteries were imaged after a 20-minute rest in a quiet room and at least 14 days from the most recent migraine attack. Baseline velocities were recorded continuously for 3 to 5 minutes and then during breath holding. Breath-holding index (BHI) was calculated by dividing the percentage change in velocity by the actual apnea time, as previously described.⁶ BHI of the affected side was compared with the nonaffected side and to 10 healthy, age-matched volunteers with no history of migraine.

Results. Of 750 patients with stroke admitted during the study period, five women and one man, aged 39 to 65 years (mean \pm SD, 52.7 \pm 11.5), fulfilled the entry criteria. All patients had a long-standing history of migraine with aura—15 to 46 years (mean, 31 \pm 10)—before the MIGS (table). They were treated with analgesics, nonsteroidal anti-inflammatory drugs, and 50 to 100 mg sumatriptan during attacks. All recognized their headache and aura during the index stroke as being similar and on the same side as previous attacks. Most had a visual aura and they continued to complain of visual defects during the stroke. However, their stroke manifested mainly as motor and sensory deficits, and only one patient had evident hemianopsia on bedside examination. Two patients had mild,

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