Fragile X syndrome (FXS) is a common cause of inherited mental retardation in boys. (More information about FXS can be found on the next page.) It is caused by a defect in a gene located on the X chromosome that is inherited from the mother. The gene in the mother carries a “premutation” which, when passed on to her son, expands to a “full” mutation that produces the signs of fragile X syndrome. The mother who carries the “premutation” does not have mental retardation because she also carries a normal X chromosome. She may have inherited the premutation from her father. This grandfather does not have mental retardation either because the gene only carries a “premutation.” However, some of these grandfathers develop a progressive tremor (shaking) and gait ataxia (unsteadiness) later in life, known as fragile X tremor-ataxia syndrome (FXTAS). Even more rarely, the mother with the premutation may develop FXTAS.

This issue of Neurology has two papers that further describe FXTAS, as well as an editorial on the subject. One of the papers, by Hall et al., is from the same group of researchers who originally reported this syndrome in 2001. In the clinics where the boys with FXS were treated, the mothers indicated that their fathers (the boys’ maternal grandfathers) were having neurologic problems. Sixty-two family members were found to have the fragile X premutation by genetic testing. “Definite” FXTAS was diagnosed if the patients had a tremor with movement (intention tremor) or ataxia when walking with either 1) a very typical abnormality on brain MRI scan or 2) the disease was confirmed on autopsy. Twenty of the 62 met this criterion; all 20 were men. “Probable” FXTAS was diagnosed when patients had tremor and ataxia but no typical MRI change, or the patient had the MRI change with a disorder that looked like Parkinson disease (PD) or memory loss. Forty-two of the 62 fit in this category; 35 were men and seven were women. It was noted that these 62 patients had been diagnosed by other doctors (mostly neurologists and family doctors) as having some other disease such as PD (24%), essential or alcohol-related tremor (20%), ataxia of various causes (17%), dementia (13%) and stroke (10%). Thus, in families with fragile X syndrome, family members over age 50 who have been diagnosed with these other neurologic conditions may need a second look by a clinician who is more familiar with FXTAS to exclude the diagnosis.

A second paper, by O’Dwyer et al., describes a woman with the fragile X premutation who developed severe ataxia when given a usually nontoxic dose of chemotherapy (carboplatin) for a cancer. The authors thought the gene abnormality made her unusually vulnerable to damage to the nervous system. Of interest, her symptoms returned to her baseline level of mild ataxia, intention tremor and some problems with thinking when chemotherapy was stopped. Kamm and Gasser, who wrote an editorial on FXTAS, suggested that environmental factors might contribute to the severity of FXTAS.

Most of the information on FXTAS has come from studying family members of children with known fragile X syndrome. Other studies have tried to see if the fragile X premutation is present in a subset of people with some of the other diagnoses that have been confused with FXTAS. It was not found in any of 81 patients diagnosed with essential tremor or 414 patients diagnosed with PD. However, in two reports of patients with “ataxia” of uncertain type, a small number turned out to have the premutation.

So, where do we go from here? Since it is estimated that as many as one in 3,000 men over age 50 may have FXTAS, larger studies are needed to find out how many patients with “ataxia” or tremor, previously undefined, have the fragile X premutation. The basic scientists need to examine if such premutations can indeed cause similar nervous system problems in laboratory animals. In the mean time, the guidelines suggested by Hall and colleagues seem reasonable (table 1). Although fragile X premutations may explain only a very small fraction of the cases of ataxia, finding the premutation will make a major difference to the families with fragile X syndrome. Genetic counseling will be needed regarding the chances of fragile X mental retardation in their grandsons.

Table Guidelines for genetic testing for fragile X in older persons with neurologic disease

| 1. Men older than 50 with cerebellar ataxia that cannot be explained by other causes |
| 2. Men older than 50 with tremor, parkinsonism or dementia and one of the following: |
| a. A family history in the younger generation of retardation, developmental delay, autism or early menopause |
| b. MRI of the brain shows an abnormal white intensity in the structure known as the middle cerebellar peduncle |

From the Departments of Neurology (Dr. Subramony) and Preventive Medicine (Dr. Freidrich), University of Mississippi Medical Center, Jackson, MS.
What is fragile X syndrome (FXS)?
Fragile X syndrome is the most common inherited cause of mental retardation in boys. Normally, women have two X chromosomes, one that is passed on from their mother and the other from their father. On the other hand, men have one X chromosome and one Y chromosome, the X from their mother and the Y from their father. In fragile X syndrome, there is a defect in a gene (FMR 1) located on one of the mother’s X chromosomes (figure 1). The defective gene contains an abnormal expansion of a chain of DNA “nucleotides” known as the “CGG repeat.” Normal X chromosomes have fewer than 54 CGG repeats. The mother who passes on a “fragile X” has a gene that carries a “premutation” with 55 to 200 CGG repeats. She does not have mental retardation because she also has a second X chromosome that is normal. However, in her son, the gene may expand to a “full” mutation with more than 200 CGG repeats. This results in FXS. Because this disease is inherited through the mother it is called an “X-linked” disease.

What is fragile X tremor/ataxia syndrome (FXTAS)?
Some of the maternal grandfathers of the boys with FXS carry the “premutation” on their X chromosome and may develop a progressive shaking and unsteadiness as they get older. “Ataxia” refers to a problem with coordination and balance. The “tremor” (shaking) and ataxia in FXTAS are due to damage to a part of the brain called the cerebellum and its connections. In even more rare cases, mothers of boys with FXS who carry the premutation can also develop FXTAS.

What are the symptoms and signs of FXTAS?
FXTAS generally comes on slowly in men (and rarely women) over 50 years old. Problems may include:

- Tremor (shaking) that can occur with activity or at rest.
- Poor balance and falls.
- Poor hand coordination and unclear speech.
- Slow movements, stiff muscles, lack of facial expression and poor balance that may look like Parkinson disease (PD).
- Fainting that occurs with standing due to a drop in blood pressure and problems with erection that suggest problems with the autonomic nervous system (part of the nervous system that controls more “automatic” functions such as heart rate, blood pressure, and sweating).

Is FXTAS easy for doctors to recognize?
FXTAS has only been recognized in the last 5 years or so and many doctors are not yet familiar with it. Also, there seems to be a wide variety of symptoms and signs in different patients and the disease progresses at different rates. Many patients may be given other diagnoses, such as PD, essential tremor, stroke, dementia, or other more unusual neurologic diseases. However, special studies such as an MRI of the brain is helpful because it shows some typical changes in an area close to the cerebellum called the middle cerebellar peduncles. The diagnosis is made by finding the premutation in such a patient by DNA analysis.

Why is it important to recognize FXTAS?
At this time, FXTAS cannot be treated with any medication that will stop it. However, discovering it brings “diagnostic” closure to patients who may have been told that the cause of their neurologic disease is “unknown.” Also, it is very important for families with FXTAS to get genetic counseling because all the daughters of men with FXTAS will carry the gene defect. This means that these daughters can have sons with mental retardation and the daughter herself may go through early menopause and rarely even develop FXTAS.

For more information
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www.thebrainmatters.org
American Academy of Neurology
www.aan.com
National Fragile X Foundation
www.fragilex.org

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Bilateral substantia nigra involvement in vaccine-associated poliomyelitis

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Parkinsonism is a complication of some viral encephalitis,1 and poliovirus infection is a possible risk factor for late development of Parkinson disease (PD).2 There are several reports of PD arising in adults who had poliomyelitis (PM) as children,3 and pathologic specimens from fatal PM cases disclosed substantia nigra (SN) damage.3

In this setting, we report a child with vaccine-associated paralytic poliomyelitis (VAP-PM) presenting bilateral SN involvement on MRI.

Case report. A 3-month-old boy came for evaluation 20 days after his first oral poliovirus vaccine (OPV) because of persistent fever, chills, and irritability. Over 5 days, he developed asymmetric lower limb weakness without discernible sensory loss. In the next week, his arms became weak, and poor suckling was noticed. Soon thereafter, frequent apneic episodes and somnolence appeared, and the child required ventilatory support. He was born healthy from cesarean section, and his mother denied any complication during pregnancy. His familial and past medical histories were otherwise unremarkable. On examination, he had asymmetric flaccid quadriplegia with diffuse areflexia and fasciculations. There was obvious bulbar involvement but no objective sensory dysfunction. Pupillary size and reactivity remained normal throughout. Typical ocular bobbing was identified in the first 2 weeks.

Complete blood counts, creatine kinase, electrolytes, hepatic, renal, and thyroid function tests were normal. Serologies for HIV, viral hepatitis, cytomegalovirus, and toxoplasmosis were negative. CSF disclosed 213 leukocytes/mm3 (90% lymphocytes), 165 mg/dL of protein, and 61.5 mg/dL of glucose. CSF cultures and immunologic tests for syphilis were all negative, as well as a CSF PCR assay for poliovirus. Subsequently, stool culture grew out vaccine-related poliovirus type III. An extensive investigation ruled out any immune deficiency.

Sural and radial sensory action potential amplitudes and conduction velocities were within normal limits. Motor conduction studies revealed small-amplitude compound muscle action potentials with preserved latencies and velocities for age. Although no voluntary muscle activity could be recorded on needle electromyography, prominent spontaneous activity (fasciculations and positive sharp waves) was found in gastrocnemius, quadriceps, deltoid, and biceps brachii 1 month after the onset of paralysis.

Brain MRI showed bilateral brainstem abnormalities (figure, A through C). MRI of the cervical, thoracic, and lumbar spine identified lesions in the region of anterior horn cells (figure, D).

Four weeks later, spontaneous breathing and motor recovery began. He was discharged after 2 months and has been followed for 2 years. His cognitive performance is adequate for age, but motor development has been poor. He is not able to stand unassisted. There is residual hypotonia with clear wasting of left leg and right hand muscles. However, no parkinsonian features are currently identified.

Follow-up MRI was performed after 1 and 2 years. There is progressive spinal cord atrophy. Small T2 hyperintense and T1 hypointense lesions are still identified on SN (figure, E).

Discussion. A febrile illness with meningeal signs, flaccid weakness, and residual paralysis lasting more than 60 days after OPV exposure defines VAP-PM.4 Besides meeting these criteria, our child disclosed ocular bobbing, somnolence, and central apneic episodes, findings consistent with associated brainstem involvement. As proposed previously,5 this presentation would indeed have features of encephalitis lethargica, which prompted a more extensive neuroimaging investigation.

SN damage documented on MRI has been rarely reported in viral encephalitis. In a few cases of St. Louis, Japanese B, and West Nile encephalitis, parkinsonism was the presenting feature, and SN was found to be involved, particularly the pars compacta.1 As VAP-PM is a rare condition, neuroimaging findings are scarcely available, particularly with long-term follow-up and with associated brainstem involvement. Despite extensive SN involvement, it is interesting to note that extrapyramidal manifestations were not identified in this patient. They were possibly overshadowed by peripheral findings, namely, hypotonia and weakness.

In a recent Danish study, history of PM was associated with a twofold increased risk for PD.6 As SN was shown to be affected in fatal PM cases,7 direct poliovirus damage would be responsible for this increased risk. In fact, viral-mediated neuronal death would not cause PD per se. It would instead make patients especially prone to the consequences of age-related neuronal loss, in a mechanism resembling the postpolio syndrome.7 By showing SN involvement in vivo, our report gives further support to this hypothesis. Long-term follow-up of this child may help to clarify this issue.

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Figure. Brain MRI on admission. (A) Axial T2-weighted image showing bilateral hyperintense lesions in substantia nigra. (B) Axial T1-weighted image showing bilateral hypointense lesions in substantia nigra. (C) Axial T2-weighted image showing small hyperintense foci in dorsal medulla oblongata. Cervical spinal cord MRI on admission. (D) Axial T2-weighted image showing symmetric hyperintensities of ventral horns. Brain MRI 1 year later. (E) Residual hyperintense substantia nigra lesions seen on T2-weighted image.
Ocular neuromyotonia secondary to a cavernous sinus meningioma
Maud Jacob, MD; Alain Vighetto, MD; Martine Bernard, MD; and Caroline Tilikete, MD

Transient diplopia is a common presenting complaint in ophthalmology and neurology clinics. Ocular neuromyotonia (ONM) is a rare cause of transient diplopia and is diagnosed through clinical examination, using specific maneuvers to trigger intermittent spasms. We describe a case of left ONM, secondary to ipsilateral cavernous sinus meningioma.

Case report. A 41-year-old previously well woman had episodes of recurrent binocular diplopia for 1 year. These episodes lasted 10 to 20 seconds, occurred 5 to 10 times a day, and were triggered by specific eye movements. She had paroxysmal electrical discharges in the ophthalmic division of the left trigeminal nerve. Examination showed mild proptosis, slight ptosis, and a mild supraduction deficit of the left eye. Diplopia was elicited only after 15 seconds of sustained extreme gaze (see the video, on the Neurology Web site at www.neurology.org). Sustained up gaze triggered retraction of the left upper eyelid, most marked in down gaze. Following sustained right gaze, on attempted return to the primary position, the left eye stayed in an esotropic position and could not abduct for a few seconds. After sustained down gaze, the left hypotropia increased and supraduction was limited. There was no abnormal eye movement after sustained left gaze. Pupil reactions were normal between and during these episodes. A diagnosis was made of a left oculomotor neuromyotonia with a pupil-sparing partial oculomotor nerve palsy and symptomatic left trigeminal neuralgia. Single-fiber electromyography in the frontalis muscle and distal extremity muscles and tension test were unremarkable. MRI showed a tumor suggestive of meningioma of the left cavernous sinus (figure). She received oxcarbazepine 450 mg od, followed by acetazolamide 250 mg od, which were both ineffective. Clonazepam 0.5 mg bd relieved both intermittent ONM and trigeminal neuralgia dramatically. Ocular posture and movements became normal, and ptosis was reduced. Left eyelid retraction after sustained extreme gaze after sustained up gaze decreased both in magnitude and in duration. Sustained right gaze induced only mild transient esotropia, and sustained down gaze induced no abnormal movements.

Discussion. This patient presented with a left ONM involving nerve fibers to the levator palpebrae superioris, the medial rectus, and the inferior rectus muscles. ONM is an intermittent ocular deviation due to spasm of one or more eye muscles innervated by the same nerve. Typically spasm is triggered by sustained extremes of gaze.

ONM has been described in 42 patients and involved the oculomotor nerve in 24 of these. Interestingly, sustained eccentric gaze triggered spasm in only 14 cases. The nerve was paretic in 19 cases. ONM was secondary to radiotherapy in 21 cases. Other rarer reported causes include internal carotid artery aneurysm, basilar artery dolichoectasia, midbrain stroke, Grave disease, Paget disease, alcohol, clivus chordoma operated 3 years earlier, cavernous sinus thrombosis secondary to mucormycosis, and diffuse chronic arachnoiditis secondary to thorium dioxide toxicity. The etiology was unknown in 10 cases. We report a case of oculomotor nerve neuromyotonia due to meningioma.

Current treatment is based on cell membrane–stabilizing drugs. Carbamazepine was reported to be effective in 22 of 25 patients. Phenytoin, gabapentine, and acetazolamide were ineffective. In our case, clonazepam was effective for intermittent symptoms, such as diplopia and pain, but oxcarbazepine and acetazolamide were not. The chronic ocular motor defects also improved after treatment, which has been reported in three previous cases. The mechanism of chronic eye movement defects in ONM is not fully understood. In our case, ptosis and hypotropia could possibly be due to ocular motor nerve compression by the meningioma, but these would be unlikely to improve with drug treatment. Spontaneous improvement of chronic oculomotor defects has been previously reported with benign basal skull or cavernous sinus lesions. We postulate that a functional paresis of supraductor eye muscles or a chronic spasm of the infraductor eye muscles could give rise to these signs. But only functional paresis could also explain the successful treatment of our patient’s ptosis, which also occurred in another reported patient.

ONM is rare, but probably underdiagnosed. Radiotherapy remains the most frequent cause, but MRI is essential to rule out other pathology, particularly compressive lesions. Medical treatment can be effective and may dramatically improve the symptoms.

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Additional material related to this article can be found on the Neurology Web site. Go to www.neurology.org and scroll down the Table of Contents for the May 23 issue to find the title link for this article.

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Transient downbeat nystagmus from West Nile virus encephalomyelitis

Sashank Prasad, MD; Mark J. Brown, MD; and Steven L. Galetta, MD

Most human West Nile virus (WNV) infections are asymptomatic, but a minority of patients develops neuroinvasive disease, including a poliomyelitis-like syndrome. Reported ophthalmologic manifestations include optic neuritis, uveitis, multifocal choroiditis, ocular motor palsies, and opsoclonus. We cared for a patient with WNV who developed downbeat nystagmus and ocular flutter with acute areflexic quadripareisis.

Case report. A 64-year-old previously healthy retired steel mill worker presented after 7 days of leg and arm pain and 4 days of progressive weakness. He reported horizontal binocular diplopia, decreased strength, mild dyspnea, and arm tremor. On admission, temperature was 39.2 °C. He was oriented and followed requests. Visual fields were full. Pupils were equal and reactive. He had a mild esotropia in the primary position, with a partial right abduction deficit with right lateral gaze. Downbeat nystagmus was present in primary gaze, and the amplitude increased in up gaze and lateral gaze (video, on the Neurology Web site at www.neurology.org). Pursuit was saccadic in all directions, but particularly in vertical gaze. He had intermittent horizontal ocular flutter (video). The optic discs appeared normal. He had asymmetric bilateral facial weakness. There were decreased spontaneous facial movements and normal reaction to pinprick. Facial electromyography showed decreased motor unit amplitudes and increased insertional activity with rare fibrillation potentials. These findings indicated an acute, mixed, predominantly motor neuronopathy or neuropathy.

On admission, the 7th day of illness, the serum sodium was 131 mg/dL, and the white blood cell count was 9.8 mg/dL. The CSF white blood cell count was 813 cells/µL (83% lymphocytes, 5% neutrophils, 12% monocytes), red blood cell count 17,200 cells/µL, protein 226 mg/dL, and glucose 53 mg/dL. An MRI of the brain was normal. MRI of the spine demonstrated T2 hyperintensity to the conus (figure).

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Figure. Sagittal and axial T2-weighted MRI of upper cervical (A and B) and thoracic spine (C and D), demonstrating central cord hyperintensity (arrows).

The patient's vital capacity declined, and he was electively intubated on the 10th day of illness. He received acyclovir and ceftriaxone. He developed meningismus and complete areflexic paralysis. A second lumbar puncture on the 13th day of illness showed a white blood cell count of 38/µL (90% lymphocytes, 5% neutrophils, 5% monocytes), red blood cell count of 60,000/µL, protein 226 mg/dL, and glucose 53 mg/dL. An MRI of the brain was normal. MRI of the spine demonstrated T2 hyperintensity throughout the cord extending from the cervico-medullary junction to the conus (figure).

Spinal fluid WNV PCR was positive. Serum ELISAs showed an increased IgM titer of 2.28 and IgG titer of 3.0. Antimicrobials were discontinued. The patient was successfully extubated after 3 weeks. The downbeat nystagmus, ocular flutter, and right abduction deficit resolved 3 weeks after the onset of symptoms, and strength had improved to 4 in the upper extremities and 1 in the lower extremities.

Discussion. Our patient with WNV encephalomyelitis had two unusual neuro-ophthalmologic findings: downbeat nystagmus and ocular flutter. Downbeat nystagmus usually results from lesions involving the cervicomedullary region or the cerebellar flocculus. Relative excitation of the anterior semicircular canal pathways is thought to be the primary generator of the nystagmus. In our patient, high
Orthostatic tremor in monozygotic twins

Maria Fiorella Contarino, MD; Marie Laure Welter, MD; Yves Agid, MD, PhD; and Andreas Hartmann, MD

Orthostatic tremor (OT) is characterized by a feeling of unsteadiness during stance that disappears when sitting or lying, associated with a fine-amplitude leg rippling while standing. Surface electromyography (EMG) recordings show a characteristic 13- to 18-Hz tremor.1 Tremor intensity is slowly progressive, sometimes spreading to other body regions, whereas the interval between standing and tremor triggering decreases over time. OT etiology remains unknown. Although most described cases of OT are sporadic, this disorder could be genetic, as suggested by few familial cases2-6 (see table E-1 on the Neurology Web site; go to www.neurology.org). We report two monozygotic twins with OT.

Case report. The patients were two male monozygotic twins. Parents were not consanguineous, came from different villages, and remained healthy until their deaths (ages 76 and 87). Family history was negative for tremor or other neurologic disorders. The patients grew up together, lived in the same village, and worked as farmers until age 55, using agriculture chemical products. At age 68, in our outpatient clinic, they had tremor of both legs, occurring when standing and relieved when sitting or lying. Daily living activities were impaired; queuing, talking, and writing while standing were almost impossible. Clonazepam was soon interrupted by both patients because of fatigue and somnolence.

Disease history and presentation were nearly identical in the two brothers when excluding onset age (age 65 for the first born, age 67 for the second born) and milder tremor intensity in the second born. Since youth, bilateral arm tremor had been noticed by both patients while holding objects, which, however, was not bothersome; thus, onset could not be specified. Bilateral leg tremor was observed when standing and abolished when sitting, lying, or leaning against a wall. Latency from standing to tremor onset was about 30 seconds. Mild bilateral arms tremor was noticed when maintaining posture and holding objects, but not at rest. Neurologic examination was otherwise normal in both subjects, revealing no parkinsonian or cerebellar signs.

Surface EMG recordings of bilateral anterior tibial, soleus, deltoid, extensor, and flexor carpi, masseter, and sternocleidomastoid muscles were performed in both patients while sitting at rest, standing, walking in place, pressing palms against a table with arms outstretched from standing position, and maintaining posture with arms flexed at elbows. An accelerometer was placed on one index. A rhythmic 13-Hz EMG activity, alternating between agonists and antagonists and synchronous between the two sides, was recorded in leg muscles (standing, stance phase of walking) and in arms (pressing against a table) (figure). No tremor was recorded in sternocleidomastoids or masseters during posture or contractions.

Discussion. We describe two monozygotic twins affected by OT in which onset age, clinical characteristics, and neurophysiologic findings were similar and correspond to published criteria for OT diagnosis.1 As both patients presented a mild postural arms tremor, a diagnosis of essential tremor (ET) could be evoked. Indeed, the description of coexistent 6- to 8-Hz postural or action tremor in arms in selected OT patients may suggest that OT is pathogenically related to ET or a task-specific variant of ET.2 However,
the prevalence of family history of essential tremor in OT patients is similar to that of the general population (11.5 to 25% vs 17.9%). Moreover, in our patients, there was no family history for tremor, nor did the clinical or the neurophysiologic findings support the diagnosis of ET. Finally, when appropriately recorded (while pushing against a table from standing), arm tremor had the 13-Hz frequency characteristic of OT.

As both brothers used potential toxic agents (pesticides), this could suggest an environmental etiology, all the more since most reported OT cases are sporadic. Even if no acquired factors have ever been reported in association with OT to date, it is not possible to definitely rule out a role for toxic agents.

A genetic cause might be proposed in both brothers, given that they are monozygotic twins and that symptom onset was almost simultaneous. Few previously described OT patients reported other OT cases among first-degree relatives (see table E-1). Neither the family we describe nor other published pedigrees allow definite conclusions about the possible transmission modality. As our patients’ parents were unaffected, a recessive or dominant transmission (with incomplete penetrance) could be hypothesized. However, a “second hit” or multifactorial etiology (gene–gene or gene–environment interaction) can also be envisaged, especially with regard to pesticide exposure.

In conclusion, OT is a potentially debilitating disorder with limited treatment options. Elucidating a potential genetic cause may provide hope for identifying causal therapeutic targets. Therefore, we encourage physicians confronted with OT patients to elicit a careful family history and not dismiss the disease as sporadic.

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Disclosure: The authors report no conflicts of interest.

In conclusion, OT is a potentially debilitating disorder with limited treatment options. Elucidating a potential genetic cause may provide hope for identifying causal therapeutic targets. Therefore, we encourage physicians confronted with OT patients to elicit a careful family history and not dismiss the disease as sporadic.

Co-occurrence of a cavernous malformation and contralateral moyamoya

G.A. Kercher, MD, PhD; W. Smith, MD, PhD; M.T. Lawton, MD; and V. Singh, MD

We report a young woman who had an intracerebral hemorrhage in her left caudate head from a ruptured cavernous malformation (CM). During her workup, we found an asymptomatic, moyamoya-like occlusion of her right middle cerebral artery.

Case presentation. A 37-year-old Brazilian woman with a history of recurrent frontal headache presented to our emergency room complaining of new, worsening biocapital pain for 1 week with nausea, stiff neck, and intermittent right hand weakness. Detailed history revealed no risk for neurovascular disease. She was normotensive with no neurologic deficits. Non-contrast head CT revealed an area of hyperattenuation at the left caudate head consistent with a 20 mL intracerebral hemorrhage (figure, A, page 1602). CT angiogram of the neck and head revealed neither a vascular lesion nor evidence of active contrast extravasation in the area of the hemorrhage; however, it did reveal, contralateral to the hemorrhage, a complete interruption of the proximal portion of the right middle cerebral artery along with well-developed collateral vessels (figure, B), fulfilling criteria for probable moyamoya disease.

The patient was admitted to our neurointensive care unit for observation. Digital subtraction angiography (DSA) (figure, D) and MRI (figure, E) failed to reveal the etiology of the patient’s hemorrhage. The presence of heterogeneous signal within the hemorrhage on CT (see the figure, A), along with the fact that the caudate head is an uncommon location of spontaneous intracerebral hemorrhage, led us to suspect an underlying lesion predisposed to bleeding. The absence of an arterial malformation demonstrated on CT angiography or DSA raised our suspicion of a CM. Because the patient remained stable with a non-focal neurologic examination, we discharged her, planning further outpatient workup.

Three days later, she returned to the emergency room complaining of drowsiness and vomiting. CT revealed an enlarged left caudate head with mass effect, reactive hydrocephalus, and subfalcine herniation (figure, C). Two days into her neurointensive care unit stay, she experienced rapid neurologic decompensation, with dilated pupils and extensor posturing. After receiving emergent mannitol therapy and placement of an external ventricular drain 3 days later, she awoke and followed commands.

The following day, she underwent surgical evacuation of the hematoma. Although we faced an unstable lesion in the patient’s dominant hemisphere, as well as the potential risks posed by the presence of fragile moyamoya vessels contralaterally, the patient’s declining neurologic status compelled us to intervene. We performed a bifrontal craniotomy, using an anterior interhemispheric approach as the most direct path to the lesion. Pathologic examination of the resected specimen confirmed a CM (figure, F).

She tolerated extubation the day after surgery, and removal of the external ventricular drain 3 days later. Slowly resolving cognitive impairment complicated her hospital discharge, but after about 1 month at a supervised residential facility, she returned home at her previously normal baseline. Six months after her initial presentation, she returned for a successful superior temporal artery to middle cerebral artery bypass procedure, to reduce the risk of rupture from the moyamoya vessels.

Discussion. We cannot explain whether the CM and contralateral moyamoya disease occurred together in our patient by an associated pathogenic mechanism, or simply by chance. It is not surprising that occlusive vasculopathy in one hemisphere may engender hemodynamic changes in the opposite one; however, CMs do not experience arterial pressures, and a direct physical link is not immediately evident. Perhaps, then, a more complex mechanism is at work. Fibroblast growth factor 2 (FGF2, also termed basic fibroblast growth factor or b-FGF), an autocrine/paracrine chemical that stimulates endothelial cell growth and promotes angiogenesis, is found in histochemical association with CMs, with particularly strong expression in the case of a CM that arose de novo in an adult patient. FGF2 is also elevated in the CSF of patients with moyamoya, although this association does not seem to hold in patients with strictly unilateral disease. Although such a mechanism may explain the association of moyamoya disease and ipsilateral CM formation (see the figure, E), it would not account for occurrence of the lesions in opposite hemispheres.

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Reduced penetrance of intermediate size alleles in spinocerebellar ataxia type 10

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Triplet repeat expansions are the disease-causing mutations in nine dominantly inherited spinocerebellar ataxias (SCAs). In 2000, a new type of dynamic mutation was reported in Mexican patients with SCA and seizures, consisting of a (ATTCT)n expansion found in intron 9 of the SCA10 gene; normal alleles have 10 to 29 and pathologic 800 to 4,500 repeats.

Methods. We studied 329 unrelated SCA patients. Ataxia was sometimes associated with other features, such as epilepsy, mental retardation, seizures, paraplegia, or tremor; 290 were Portuguese, 39 were from Brazil. Peripheral blood was collected from patients and their relatives, after written informed consent. The
(ATTCT)ₙ was amplified by PCR with flanking primers and Southern blot was performed as described elsewhere.²,³

Results. The modified PCR analysis for (ATTCT)ₙ expansion showed that three patients (figure, A and B), from two unrelated Brazilian families, with an admixture of Portuguese and Amerindian ancestry, had a continuous ladder exceeding the product range observed for normal alleles at the SCA10 locus. These patients had first shown a single band after PCR for normal allele sizing (figure, C). Expansion size assessment (figure, D) identified one allele with 400 repeats in Patient II-2 from Family 1, and alleles with 760 and 750 repeat units in Patients I-1 and II-1 from Family 2.

These families, unrelated to Brazilian families previously reported, presented a phenotype of SCA without seizures. In Family 1 (see the figure, A), the proband (II-2) was a 59-year-old woman, who reported gait ataxia since age 50 years. Several cases of alcoholism were reported in her ancestry, though the proband was not alcohol-addicted. On neurologic examination, she had gait ataxia, though she was still able to walk independently, together with mild limb ataxia and dysarthria, Babinski sign, and moderate sensory loss in distal portions of the lower extremities. Nerve conduction studies confirmed the presence of axonal polyneuropathy. Cranial MRI showed cerebellar atrophy. The proband (II-1) of Family 2 (see the figure, A) was a 56-year-old man, with slowly progressive gait ataxia since age 20 years. His mother had symptoms since her second decade of life, though clinical assessment was difficult due to the coexistence of a history of alcoholism, absent in him. On neurologic examination, the proband had gait ataxia, mild dysarthria, limb ataxia and pursuit eye movement impairment, limb fasciculations, and bradykinesia. No sensory deficits were found, but nerve conduction studies detected an axonal polyneuropathy. MRI showed atrophy of the vermis.

The (ATTCT)ₙ showed instability upon transmission (see the figure). In Family 1, the proband had 400 repeats, whereas her father and two of her sibs, all unaffected on neurologic examination, aged 90, 65, and 56, had alleles of 370 and 360 units; her other asymptomatic sib, aged 49 years, also had an abnormal allele, but its size was not assessed due to lack of DNA. In Family 2, the proband inherited an allele of 750 ATTCTs from his affected mother, who had 760 repeats.

Discussion. We describe two Brazilian families of mixed Portuguese and Amerindian ancestry, with an (ATTCT)ₙ, at the SCA10 locus smaller than 800 units. Patients had repeat sizes of 400 to 760 units, thus lowering the threshold for pathogenesis. Alleles with 360 and 370 repeats showed so far no penetrance in asymptomatic subjects aged of 56, 65, and 90. Together with the finding of a 280 repeats allele in an individual with ataxia whose asymptomatic mother had the same size expansion,⁴ this suggests a range of reduced penetrance for alleles of 280 to 370 repeats. Information on additional chromosomes with 400 repeats is needed to fully understand its pathogenic role. The risk for the offspring of unaffected parents with intermediate alleles, which show reduced penetrance and meiotic instability, is not negligible and, thus, has to be considered according to their instability rate.

Figure. ATTCT repeat expansions detected in two Brazilian families. (A) Pedigrees from families. Current age and age at onset of ataxia are given at the top and bottom right-hand corners, or age at death†. (B) Modified PCR analysis for the SCA10 ATTCT repeat expansion. A normal individual homozygous for an ATTCT repeat with 14 units is shown (N). SCA10 patients and carriers show a continuous ladder exceeding the product range shown for normal alleles. (C) Normal alleles in patients detected by PCR analysis. (D) Southern blot analysis to assess the size of the EcoRI restriction fragment containing the expanded ATTCT repeat; normal alleles generate an EcoRI fragment of 2.5 Kb. At the bottom, repeat sizes of normal and expanded alleles are indicated.
and parental origin. Reduced penetrance alleles have been reported for several repeat disorders, including Huntington’s disease\(^5\) and SCA17.\(^6\)

This expansion was initially described in Mexican families\(^2\) and more recently in Brazilians with admixture Portuguese and Amerindian ancestry.\(^4\) Though we cannot exclude the possibility of a Spanish or Portuguese mutation origin, its complete absence so far in several European populations, including Spanish\(^7\) and Portuguese families, makes it more likely to have arisen in Indian populations from the American continent.

Brazilian SCA10 families are characterized by a cerebellar phenotype without seizures irrespective of the repeat size.\(^4\) Considering the intermediate allele sizes in our families, the clinical phenotype seen in Brazilian patients does not seem to be due solely to repeat length, suggesting the involvement of genetic modifiers.

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References


Correction

Fragile X and company: Finding the right diagnosis

In the Patient Page “Fragile X and company: Finding the right diagnosis” by S.H. Subramony, C.A. Friedrich, and J. Jankowiak (Neurology 2005;65:E3–E4), the second author’s name was misspelled. The author’s name is C.A. Friedrich.

The publisher regrets the error.