

## Clinical/Scientific Notes

### Do Serotonin Reuptake Inhibitor Antidepressants Worsen Parkinson's Disease? A Retrospective Case Series

There have been concerns that when used to treat depression in patients with Parkinson's disease (PD), selective serotonin reuptake inhibitors (SSRIs) might worsen parkinsonian motor function. Several cases have been reported of SSRI-induced worsening of parkinsonism<sup>1,2</sup> and of SSRI-induced extrapyramidal symptoms in non-parkinsonian patients.<sup>3</sup> Forty-three percent of 49 PD specialists who we surveyed were concerned that SSRIs might worsen motor function, and 37% had observed at least one case in which they thought this had occurred.<sup>4</sup> Proposed mechanisms for SSRI-related extrapyramidal side effects have included serotonergic inhibition of nigrostriatal dopamine release<sup>2,3</sup> and direct effects on sigma 2 receptors.<sup>5</sup> The mechanisms remain unclear, however, as does the relative frequency with which this phenomenon occurs. To better assess the frequency and character of SSRI-induced worsening of parkinsonian motor function, we performed a detailed chart review of our PD clinic patients.

#### Methods

We reviewed 476 patient records that were selected consecutively (in alphabetical order) from our "active" patient files. All patients had been seen within the past 5 years. One-hundred one patients, at some point, were treated with an antidepressant medication. The charts of these patients were reviewed in detail for information surrounding exposure to antidepressant medications including the indication for their use, agent used, dosage, therapeutic response, motor function, and adverse effects. Because of the variable indications for use, variable durations of treatment, and variable degree to which dosage adjustments were made, we were unable to uniformly record the dosage used, antidepressant efficacy, and side effect profiles. It should also be noted that we only looked for worsening, not improvement, in motor function potentially associated with antidepressant use.

#### Results

Seventy patients received a tricyclic antidepressant (TCA), 58 patients received an SSRI, and 12 patients received other antidepressant agents (trazadone, nefazodone, bupropion, and venlafaxine). Some patients received trials of different agents from different classes. Sertraline accounted for 51% of the SSRIs prescribed, followed by paroxetine (27%), fluoxetine

(16%), and fluvoxamine (6%). We identified five cases of possible antidepressant-induced worsening of motor function based on comments by the treating clinician and/or evidence of a distinct temporal relationship between antidepressant initiation and reported or observed worsening of motor function. All five cases involved SSRIs. No cases of motor worsening associated with tricyclic antidepressants or other agents were identified. The details of these cases are presented in Table 1.

The indication for prescription of an antidepressant agent varied. Depression was the indication for antidepressant use in 55% of the cases, anxiety in 21%, insomnia in 18%, and other (for example, pain) in 3%. The indication was unknown in 4% of the cases.

Although we could not systematically evaluate the efficacy or adverse experiences associated with the antidepressant agents, we did note whether or not patients were, at the time of our chart review, still on the first antidepressant that they were prescribed. If they were not, the reason for discontinuation was recorded. It is important to keep in mind, however, that patients were on their first prescribed antidepressant for variable indications and periods of time and at variable dosages. For those individuals who were first prescribed a TCA, 41% were still on the agent. Nineteen percent discontinued the agent as a result of perceived lack of efficacy, 17% as a result of side effects, 11% as a result of a combination of the above, 8% as a result of no further need for the medication, and 4% for unknown reasons. For the SSRIs, 53% were still on the agent. Nine percent discontinued as a result of perceived lack of efficacy, 20% as a result of side effects, 7% as a result of a combination of the above, 5% as a result of no further need for the medication, and 5% for unknown reasons.

#### Discussion

In all cases, we found potential alternative explanations or contributing factors other than a direct SSRI-induced worsening of parkinsonism. In Case 1, the slight worsening of tremor may have occurred as a result of an additive tremor-inducing effect of fluoxetine, because tremor is a common side effect of this medication.<sup>6</sup> In Cases 2 and 3, it is not clear if the motor worsening was the result of discontinuing the previously prescribed tricyclic antidepressant (which can have antiparkinsonian effects based on anticholinergic properties) or starting the SSRI, or some combination of the two events. Discontinuation of nortriptyline in Case 3, however, may be unlikely to cause a significant worsening of parkinsonism given the drug's low anticholinergic profile. The only controlled study of nortriptyline in PD suggested that it did not affect motor function.<sup>7</sup> Case 4 worsened with the SSRI but improved despite its continuation when the dosage of the concomitantly prescribed neuroleptic (used to treat levodopa-induced psychosis) was reduced. It may be that the combination of a neuroleptic and an SSRI was responsible for this patient's motor deterioration, because acute onset of parkinsonism has been reported in adults with Tourette's syndrome who were treated with this combination of

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**TABLE 1.** Results of patients with Parkinson's disease assessed for frequency and character of SSRI-induced worsening of parkinsonian motor function

Patient no.	Age/ Sex	SSRI/dosage	Clinical scenario	Behavioral features	*HY stage	Concomitant medications
1	61/M	Fluoxetine 20 mg/day	"Tremor more noticeable over last 2 weeks since starting fluoxetine but not interfering."	Depression; anxiety; dementia	3	†CD/LD 800 mg/day Aspirin
2	52/F	Sertraline 50 mg/day	Amitriptyline discontinued Sertraline started at 50 mg/day; increased tremor and decrease mobility noted within 10 days but dosage increased to 100 mg/day as a result of persistent depression Trihexyphenidyl increased without benefit Sertraline discontinued and amitriptyline reinstated with improvement in mobility within 1 week	Depression	2	CD/LD 200 mg/day Trihexyphenidyl 3 mg/day Selegiline 5 mg/day Diphenhydramine 50 mg/day
3	74/F	Sertraline 50 mg/day	Nortriptyline discontinued Sertraline started Increased "off periods" noted several weeks later CD/LD and selegiline increased without benefit Motor function improved after discontinuation of sertraline and reinitiating nortriptyline	Depression; anxiety	4	CD/LD 900 mg/day Selegiline 5 mg/day Diazepam 2 mg twice a day by mouth
4	63/F	Fluoxetine 20 mg/day Sertraline 150 mg/day	Imipramine discontinued Fluoxetine started 2 weeks later Reported worsened mobility Fluoxetine discontinued Sertraline started 2 days later Reported worsened mobility Molindone dosage decreased with improvement in mobility	Depression; anxiety; dementia; hallucinations	5	CD/LD 1200 mg/day Selegiline 7.5 mg/day Pergolide 4 mg/day
5	52/M	Sertraline 600 mg/day	On 100 mg/day sertraline without problems Instructed to increase to 150 mg/day but increased to 150 four times a day Developed confusion, worsened PD motor function (worsened balance/gait, increased dyskinesias)	Depression; anxiety; dementia; hallucinations	4	CD/LD 700 mg/day Selegiline 5 mg/day Amantadine 100 mg/day

\* Current Hoehn and Yahr stage.<sup>11</sup>

† Carbidopa/levodopa.

medications.<sup>8</sup> Case 5 worsened only after the SSRI dosage was increased far above the recommended dosage, suggesting a possible dose-dependent or toxic effect. Furthermore, whereas this patient's worsening gait and balance may represent worsening PD, he was described as having increased peak dose dyskinesias (generally thought to be reflective of an increased dopaminergic effect).

Given the fact that we identified only five patients, it is difficult to determine if there are particular patient characteristics that might render individuals susceptible to SSRI-induced worsening of motor function. Both genders, a range of ages, and a range of parkinsonian disease severity are represented in our cases. All five patients were prescribed the SSRI for the treatment of depression and the cases include patients both with and without anxiety, dementia, and drug-induced hallucinations. Their concomitant medications (except for Case 4 who was taking a neuroleptic) do not appear to differ from the other patients exposed to SSRIs who did not experience a worsening of motor function. We did find that four of the five patients (80%) who experienced motor changes while on SSRIs were on deprenyl whereas only 14 of the 53 patients (26%) without

SSRI-induced worsening of motor function were taking deprenyl. There appears to be little theoretical basis to support the notion that deprenyl, an MAO-B inhibitor, and an SSRI would interact to worsen PD motor function. However, the manufacturer of deprenyl cautions against combining this drug with antidepressant medications (both SSRIs and TCAs) because of reports of central nervous system toxicity which they felt might be consistent with the serotonin syndrome. The serotonin syndrome can have motor findings that include rigidity, tremor, and balance difficulties but usually also manifests with mental status and autonomic changes.<sup>9</sup> None of the cases of possible SSRI-induced motor worsening in our series met criteria for the serotonin syndrome as proposed by Sternbach.<sup>9</sup> We previously reported on this topic and think the frequency of this syndrome is rare in PD patients treated with the combination of antidepressants and deprenyl.<sup>10</sup> The apparent increased frequency of this medication combination in our patient series may lead to speculation as to whether or not more subtle forms of the serotonin syndrome exist and contribute to what is interpreted as a worsening of parkinsonism.

No patient who developed worsened motor function was

receiving paroxetine despite the fact that it was the second most commonly prescribed SSRI. Worsened parkinsonism attributable to paroxetine has, however, been reported.<sup>2</sup> It is difficult with so few cases to try to determine the relative tendencies of individual SSRIs to worsen motor function.

The results of our study must be interpreted with caution because of its retrospective nature and its small sample size. Limitations inherent in this approach include selection or ascertainment, interpretation, and reporting biases. Approximately 10% of PD patients in our study who were exposed to SSRIs appear to have experienced motor worsening. Whether or not this worsening was attributable solely to the SSRI is, however, unclear because we frequently found other potential contributing factors. There have, to date, been no published placebo-controlled clinical trials of SSRIs in PD. The few open-label trials that have been published suggest that motor function is not worsened by SSRIs.<sup>12-14</sup> A potential interaction between deprenyl and an SSRI leading to worsened motor function is a possibility that deserves further study. A placebo-controlled clinical trial would be useful to better determine the frequency, nature, and clinical significance of SSRI-induced worsening of motor function in patients with PD.

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## Safety of Transcranial Magnetic Stimulation in Patients With Implanted Deep Brain Stimulators

Deep brain stimulation has been shown to be useful in the control of tremor<sup>1</sup> and parkinsonism.<sup>2,3</sup> The mechanism of action is still uncertain but effects may be transmitted through the cortex. The excitability of the human motor cortex can be examined with transcranial magnetic stimulation (TMS).<sup>4</sup> This tool would be particularly useful for elucidating the mechanisms of deep brain stimulation. Before attempting to use TMS in patients with deep brain stimulators, we investigated the safety of the procedure, addressing two questions: (1) Does TMS induce currents in the leads coiled in the scalp that could deliver damaging stimuli to the patient's brain or to the implanted stimulator? (2) Would inadvertent stimulation close to the implanted stimulator harm it? We carried out experiments to answer these questions.

Two time-expired, fully implantable stimulators (Medtronic Itrel Model 3625; Medtronic, Minneapolis, MN, U.S.A.) with the connecting leads and the quadripolar electrode (Model 3382) were used. Single or paired magnetic stimuli were delivered with a magstim 200 through either a butterfly coil (which has a figure-8 coil configuration with an outer diameter of 9 cm) or a circular coil (with an outer diameter of 13 cm).

### Does Stimulation Over the Scalp Leads Induce Currents in the Quadripolar Electrodes That Could Damage the Patient's Brain?

For these experiments the quadripolar electrode was embedded in a conducting gel which gave an impedance of 1200 Ω on repeated measures (similar to the impedances found when this electrode is in the brain). The leads from the electrode were coiled into a 5-cm diameter loop that had three turns. The proximal end of the lead was attached to a high-impedance oscilloscope. The magnetic stimulator coil was placed 1 cm above the looped leads and stimuli at 100% of the machine's output were delivered. With the butterfly coil, the voltage transient recorded on the oscilloscope was 0.08 V indicating a transient current flow of approximately 70 μA. With the circular coil the transient current was approximately 125 μA.

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These currents are 20 times smaller than those normally produced by the stimulator when it is used in patients. For example, with the Itrel stimulator set at 3 V and an electrode impedance of  $1200\ \Omega$ , the current flow between a pair of electrodes would be approximately 2.5 mA. With the stimulator set at 5 V, this would be 4.2 mA.

*We conclude that magnetic stimulation over the coiled scalp leads does not deliver damaging stimuli to the patient's brain.*

### Does Stimulation Over the Scalp Leads Induce Currents That Could Damage the Implanted Stimulator?

The Itrel stimulator was now connected to the coiled leads with the quadripolar electrode remaining in the conductive material (the impedance was still  $1200\ \Omega$ ). Magnetic stimuli were delivered directly over the coiled leads at 100% of the stimulator output. After each stimulus the function of the Itrel was reviewed. We used single pulses of the circular coil (both sides A and B), the butterfly coil in four different orientations at right angles to each other. In addition, we used paired stimuli 2 msec apart generated by two magstim 200 units both set at 100% output connected by a Bistim module. We did this with the Itrel both off and on at typical stimulator settings. None of these maneuvers altered the function of the Itrel.

*We conclude that magnetic stimulation over the scalp leads does not deliver damaging currents to the implanted stimulator.*

### Does Stimulation Directly Over the Implanted Stimulator Damage It?

Magnetic stimuli were now applied directly over the Itrel stimulator. After each stimulus, the device was tested. When stimulation (60% full scale) was applied with the butterfly coil held between 30 and 10 cm above the Itrel, there were no effects. Between 10 and 3 cm the device was switched off if it had been on and on if it had been off. Following a stimulus given at a distance of 2 cm the first Itrel no longer responded to programming. When stimulation was applied with the circular coil 2.5 cm above the Itrel, a second device was unaffected by a stimulus of 100% of the output. However, when the magnetic coil was placed directly over the Itrel, and the stimulus increased in 5% increments, it failed to respond to further programming after a stimulus of 60% full scale. A metal thyroid shield offered no protection.

*We conclude that inadvertent stimulation directly over the implanted stimulator can cause it to malfunction. The magnetic coil has to be very close. The patient could be protected by taping a paper plate or similar device over the skin to prevent the magnetic coil inadvertently approaching within 2.5 cm of the implanted device.*

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### Levodopa Therapy Can Ameliorate Tetrabenazine-Induced Parkinsonism

Tetrabenazine is a useful treatment for hyperkinetic movement disorders such as tardive dyskinesia but parkinsonism is a common side effect. Parkinsonism was reported in 28.5% of 400 patients treated with this drug,<sup>1</sup> frequently causing marked disability that requires its discontinuation. We now report two patients with tardive dyskinesia who developed tetrabenazine-induced parkinsonism in whom add-on treatment with levodopa resulted in marked improvement of the parkinsonian symptoms with no consequent deterioration of the involuntary movements.

### Case Histories

#### Case 1

A 64-year-old woman was treated with sulpiride for idiopathic blepharospasm. When she was on 800 mg/day sulpiride, the blepharospasm was still present but she developed severe parkinsonism with bradykinesia, rigidity, and rest tremor affecting the jaw and all four limbs. Sulpiride was gradually stopped with disappearance of parkinsonian signs but severe tardive orobuccolingual dyskinesia emerged and persisted. Tetrabenazine was initiated at a dose of 12.5 mg/day and gradually increased up to 125 mg/day with complete disappearance of the involuntary movements. However, several months later, when still on tetrabenazine, she developed severe drug-induced parkinsonism manifested mainly with generalized bradykinesia and rigidity. Treatment with 125/12.5 mg levodopa/carbidopa three times a day was initiated, and 2 weeks later there was marked improvement in her parkinsonian symptoms without any worsening of the orobuccolingual movements.

For the subsequent 2 years she was treated with the combination of 75 mg/day tetrabenazine and levodopa/carbidopa, remained almost free of any orobuccolingual dyskinetic symptoms, and had no signs or symptoms of parkinsonism. Several attempts to stop tetrabenazine or decrease its dosage caused rapid worsening of the involuntary movements.

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## Case 2

A 65-year-old woman with severe tardive cranial dystonia resulting from treatment with sulpiride was treated with a combination of 75 mg/day tetrabenazine, trihexiphenidyl, and botulinum toxin injections with good improvement. However, parkinsonism developed and worsened gradually. Levodopa/carbidopa was added and slowly increased up to three doses of 250/25 mg daily with marked improvement in her parkinsonian symptoms and no worsening of the dystonia. The patient is currently being treated with a combination of 75 mg/day tetrabenazine and 250/25 mg levodopa/carbidopa three times a day with almost no symptoms or signs of parkinsonism except for some decreased arm swing while walking. The effect of tetrabenazine on her cranial dystonia remains remarkable. Any attempt to decrease the dosage of tetrabenazine over the subsequent 2.5 years caused an immediate deterioration in her cranial dystonic movements.

## Discussion

These two patients represent the difficulties of using tetrabenazine in the elderly population resulting from the common appearance of parkinsonism as a limiting side effect. We found that the strategy of keeping the lowest effective dosage of tetrabenazine with the addition of levodopa/carbidopa may maintain the antidykinetic benefit of tetrabenazine and at the same time improve the drug-induced parkinsonism.

It is surprising and rather unexpected that levodopa can relieve tetrabenazine-induced parkinsonism without simultaneously enhancing the involuntary movements. This observation raises several theoretical points of interest. Pharmacologically, tetrabenazine is a specific, high-affinity inhibitor of monoamine uptake into granular vesicles of presynaptic neurons in the central nervous system.<sup>2</sup> It depletes dopamine presynaptically by exposing it to monoamine oxidase (MAO) in the cytoplasm. It also mildly blocks the postsynaptic dopamine receptors.<sup>3</sup>

Exogenous levodopa is beneficial in Parkinson's disease because it is decarboxylated to dopamine in the striatum, but the precise compartment where this process takes place after loss of the majority of dopaminergic nerve terminals is inexplicable. It was suggested that levodopa is converted to dopamine mainly or exclusively in the surviving nigrostriatal nerve endings and that the formed dopamine is stored in their vesicles. Tetrabenazine depletes dopamine from nigrostriatal nerve endings by blocking the vesicular apparatus.<sup>2</sup> The fact that treatment with levodopa was effective against tetrabenazine-induced parkinsonism suggests that either the dopamine formed from exogenous levodopa does not require storage in vesicles to induce benefit or that levodopa is decarboxylated to dopamine in nondopaminergic striatal cells where tetrabenazine is not active.<sup>4,5</sup> Another possible explanation is that the dosage of tetrabenazine used in our cases was too low to exert an effective depletion presynaptically or receptor blockade postsynaptically. However, this possibility is unlikely because an adequate dosage of up to 125 mg tetrabenazine was administered.

We conclude that there is a clinical benefit of administering levodopa to patients with tetrabenazine-induced parkinsonism. Levodopa in combination with tetrabenazine was effective in decreasing the parkinsonian side effect of tetrabenazine and did not exacerbate the involuntary movements. This beneficial effect supports a long-standing theory that a fraction of exogenous

levodopa is decarboxylated in a nondopaminergic striatal site where presynaptic storage of dopamine is not crucial.

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## Parkinsonism as a Result of a Giant Aneurysm



Among vascular causes of parkinsonism, those resulting from unruptured giant aneurysms are exceptional.<sup>1</sup> Giant aneurysms (diameter greater than 25 mm) are rare, representing less than 5% of the total number of intracranial aneurysms.<sup>1,2</sup> We briefly report the case of a patient who developed a predominantly right-sided parkinsonism probably as a result of a giant aneurysm of the terminal portion of the left internal carotid artery.

## Case Report

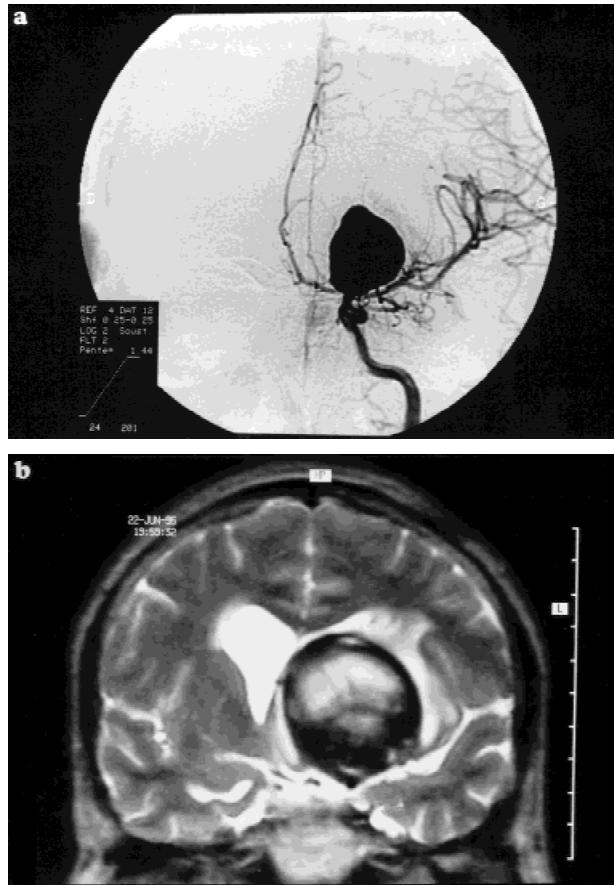
This 51-year-old man progressively developed a right arm tremor at rest. Six months later he presented a clinical picture of subacute intracranial hypertension with headaches, vomit-

A videotape accompanies this article.

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ing, and then altered consciousness. Clinical examination also revealed bilateral but asymmetric parkinsonism, predominantly on the right, with a right-sided non-paretic pyramidal syndrome and hypoesthesia. Head computed tomography and angiography (Fig. 1A) disclosed a giant aneurysm (70 mm × 35 mm) of the terminal portion of the left internal carotid artery. Magnetic resonance image showed that the giant aneurysm exerts a marked lateral displacement and compression of the left basal ganglia. There was also a mass effect on the left lateral and third ventricles and right basal ganglia, and a dilatation of the right lateral ventricle (Fig. 1B). There were no signs of major parenchymal ischemia or edema. The patient underwent a ligation of the left internal carotid artery. The procedure resolved the intracranial hypertension but did not modify the parkinsonism. When seen by us 6 months after surgery, the patient still presented a bilateral but asymmetric parkinsonism predominantly on the right with a masked face. Gait was impaired with reduced right arm swing, right leg dragging, and some start and turn hesitation (see the videotape). He had a right hand atypical and irregular tremor at rest (videotape). Cogwheel rigidity was marked on the right and slight on the left. Rapid alternative movements were slowed and reduced in amplitude with move-



**FIG. 1.** Giant aneurysm of the terminal portion of the left carotid artery demonstrated by (A) angiography and (B) MRI on T2-weighted coronal images. The aneurysm exerts a marked lateral displacement and compression of the left basal ganglia and a mass effect on the midline and right basal ganglia with dilatation of the right lateral ventricle.

ment arrests and early fatiguing especially on the right (videotape). Unified Parkinson's Disease Rating Scale (UPDRS), part III—motor score was 35. There was no short- or long-term response of the parkinsonism to dopaminergic stimulation; no change occurred in the UPDRS—part III score and CAPIT scores after an acute challenge test using oral levodopa (200 mg plus 50 mg benserazide) or apomorphine (up to 5 mg subcutaneously) and after a 6-month treatment with oral levodopa (up to 1 g plus 250 mg benserazide daily).

## Discussion

Secondary parkinsonism resulting from unruptured giant aneurysms is extremely rare.<sup>2,3</sup> This case illustrates such a condition. The parkinsonism was accompanied by pyramidal and sensory signs and did not respond to acute and chronic dopaminergic stimulation, and thus could not be confused with idiopathic Parkinson's disease. The right parkinsonism presented by our patient is probably as a result of an impairment of the left basal ganglia (caudate-putamen) functions by a mechanical pressure effect. Such a deleterious effect is well known in extra-axial tumors, such as meningiomas and subdural hematomas.<sup>4,5</sup> As recently discussed by Turjanski et al.,<sup>5</sup> several mechanisms can be invoked to explain the occurrence of parkinsonism: altered perfusion of the basal ganglia,<sup>4</sup> locally induced anatomic distortion, and induced mesencephalic compression.<sup>5</sup> Milder left parkinsonism of our patient may be the result of the mass effect on the contralateral basal ganglia to the right lateral ventricle dilatation as observed in hydrocephalic parkinsonism,<sup>6</sup> or to the contralateral nigrostriatal dopaminergic fiber dysfunction resulting from the mechanical and/or chronic ischemic effect of the lesion.<sup>5</sup> Levodopa and apomorphine unresponsiveness in this case is well explained by striatal postsynaptic involvement. No improvement of parkinsonism occurred following left internal carotid ligation. This may be explained by the fact that the aneurysm volume remained unchanged. Although unmasked latent Parkinson's disease could not be ruled out, we think our case is a rare example of secondary parkinsonism resulting from a giant aneurysm.

## Legend to the Videotape

The patient has reduced right arm swing and right leg dragging, irregular tremor at rest on the right hand, and bradykinesia predominantly on the right.

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## Catatonia Responsive to Lorazepam: A Case Report



Catatonia is a neurobehavioral disorder that exists in two discrete forms.<sup>1</sup> One is an akinetic rigid form with mutism or negativism and the other an agitated form with manic behavior. Although bizarre postures and waxy flexibility are often thought to be intrinsic to the disorder, they are frequently not present.<sup>2</sup> Until recently catatonia was considered to be a form of schizophrenia<sup>3</sup> although it had been noted in other psychiatric conditions as well as in some medical disorders.<sup>4</sup> Increasing evidence forced a re-evaluation<sup>5</sup> and reclassification<sup>1</sup> because catatonia frequently complicated non-schizophrenic affective disorders.<sup>6,7</sup>

Catatonia may mimic parkinsonism but its treatment is different than that of parkinsonism.<sup>8</sup> The following case illustrates how dramatic the response to lorazepam may be.

### Case Report

J.W. is a 70-year-old woman with a 50-year history of major mental illness diagnosed variably as bipolar or schizoaffective disorder. Her most recent psychiatric diagnosis was bipolar disorder. She was admitted for treatment of a hip fracture. She described falling while walking her dog. There was no known history of substance abuse or catatonia. On admission she was taking 4 mg trifluoperazine, 600 mg lithium carbonate, 20 mg fluoxetine, 75 mg trazodone, 150 µg synthroid, and 200 mg carbamazepine. The patient was treated with a total of five doses of 50 mg meperidine administered intravenously for pain control, and 1 day after admission she had a total right hip replacement without complications. In the recovery room she was conversant and coherent. The patient seemed fine until 48 hours after admission when she was noted to be awake but unresponsive. Vital signs were normal. Physical examination was unremarkable except for her mental status. Eyes were open and she blinked to threat. She was akinetic, mute, and unresponsive to verbal commands. She withdrew to deep painful stimuli in all extremities and had markedly increased tone. When arms were passively elevated, she slowly lowered them. Otherwise she was neurologically intact. She did not have waxy flexibility. The creatine phosphokinase was initially elevated after surgery but corrected within 2 days. Her carbamazepine level was 4.4 µg/mL and her lithium level equaled 0.3 mmol/L. Her thyroid function tests and other metabolic work-up did not

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reveal a cause for her mental status change. Head computed tomography scan revealed mild atrophy. She had received minimal meperidine during the first 48 hours.

After initial evaluation, J.W. was restarted on her psychiatric medications but remained in this unresponsive state for a total of 3 days. One dose of 2 mg lorazepam was administered intravenously for the presumptive treatment of catatonia and the patient awoke within 2 minutes. She became alert but mildly disoriented, displaying pressured speech and racing thoughts with loose associations. She answered questions appropriately and was able to participate in the neurologic examination, which revealed mild parkinsonism.

The patient remained awake and responsive to her environment for 48 hours but slowly returned to her prior unresponsive state during which an electroencephalogram (EEG) was performed. This revealed mild bilateral slowing without epileptiform or seizure activity. The patient was challenged with a placebo of intravenous normal saline but had no response after several minutes. She was then given the 2 mg of lorazepam intravenously and again awakened and responded in a dramatic fashion after a few minutes. She was maintained on oral lorazepam and transferred to a subacute nursing home for rehabilitation and optimization of her psychiatric medicines, still psychotic.

### Discussion

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) describes three forms of catatonia: medical catatonia, in which a systemic disease is implicated; catatonic schizophrenia; and catatonia as a modifier for a major affective disorder. Two of the following five criteria are required: motor immobility, excessive motor activity, extreme negativism or mutism, peculiarities of voluntary movement, and echolalia or echopraxia.

We think our patient met criteria for a diagnosis of catatonia with an affective disorder. She had a known history of psychotic behavior from bipolar affective disease requiring frequent psychiatric hospitalizations, and she clearly met the two motor criteria of muteness and immobility. Furthermore, we can think of no other explanation. The patient had no history of seizures, displayed no automatisms, repeatedly blinked appropriately to visual threats, ignored painful stimuli, had no epileptiform activity on EEG, and had a response to intravenous lorazepam that we think could not occur in a patient who had been in complex partial status epilepticus for 3 days. In addition, the patient was manic within 2 minutes of receiving lorazepam. There was no fever to support a diagnosis of neuroleptic malignant syndrome and the recovery was fast. We cannot determine if her catatonia was "reactive" to her sudden change in circumstances, from being independent at home to being postoperative in the hospital, or to her altered medications. Although catatonia has been reported after withdrawal of benzodiazepines,<sup>9</sup> this patient had not been taking them before the catatonia developed.

Catatonia, "the tension insanity,"<sup>10</sup> was first described in 1874<sup>11</sup> and was considered an organic disorder. It was incorporated into the symptom complex of dementia praecox and considered a common form of schizophrenia earlier this century.<sup>12</sup> Catatonic schizophrenia became less common<sup>13</sup> for unknown reasons. When looked for prospectively however, "catatonic features" were noted in 37.7% of 30 consecutive

drug-free psychiatric admissions to one university hospital<sup>6</sup> and frank catatonia was diagnosed in 9% of 140 consecutive psychiatric admissions<sup>8</sup> in another.

Treatment of catatonia has never been subjected to clinical trials. Extremely good results are reported with lorazepam with most patients responding within 2 hours to intravenous lorazepam<sup>8</sup> or longer with the oral form.<sup>14</sup> Lorazepam works better than other benzodiazepines for unknown reasons.<sup>8</sup> One report describes reversal of a lorazepam response with a benzodiazepine antagonist.<sup>15</sup>

We think catatonia is an underdiagnosed syndrome, especially on the general medical and surgical services. Although complex partial status epilepticus needs to be considered and ruled out early on, differentiating catatonia from parkinsonism is equally important and in some cases more difficult. It should be considered in every mute or uncooperative patient with parkinsonism and a major psychiatric problem even in the presence of neuroleptics. It is on the differential diagnosis lists of neuroleptic malignant syndrome and neuroleptic-induced parkinsonism. Catatonia is treated differently than other forms of parkinsonism and the response may be far more gratifying. Unlike other akinetic rigid patients, catatonics may improve with long-term neuroleptics. Diagnosis may be supported by a dramatic improvement after intravenous lorazepam.

### Legends to the Videotape

**Segment 1:** Patient before receiving lorazepam. She had been in this clinical condition for 3 days.

**Segment 2:** Two minutes after receiving 2 mg lorazepam intravenously. Note that in addition to being alert, the patient is manic.

**Segment 3:** Second episode of catatonia during EEG, which showed diffuse slowing.

**Segment 4:** Lack of response to intravenous saline given single blind.

**Segment 5:** Beneficial response to 2 mg intravenous lorazepam given single blind.

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### Ideomotor Apraxia in Progressive Supranuclear Palsy: A Case Study



Steele, Richardson, and Olszewski described progressive supranuclear palsy (PSP) in 1964 as a clinicopathologic entity characterized clinically by supranuclear vertical ophthalmoplegia, pseudobulbar palsy, dystonic rigidity of the neck and upper trunk, and dementia, and neuropathologically by the presence of abundant neurofibrillary tangles, cell loss and gliosis in the basal ganglia, brain stem, and cerebellum.<sup>1</sup> Ten years later, Albert et al.<sup>2</sup> suggested that the cognitive changes in PSP corresponded to those of a “subcortical dementia.” Since then, many clinical and neuropathologic studies have attempted to understand better the cognitive and pathologic changes in PSP.<sup>3,4</sup> Recent clinical and pathologic studies suggest that there is more cortical involvement than heretofore considered.<sup>4–7</sup>

There is controversy not only about whether apraxia exists in PSP<sup>8–10</sup> but also about its nature. Gimenez-Roldan et al. compared the records of patients with PSP with those with corticobasal degeneration (CBD) and found that PSP patients did not exhibit apraxia on initial evaluation or follow-up visits but 75% of the CBD patients exhibited ideomotor apraxia at initial presentation and 100% at follow up.<sup>8</sup> However, this study was retrospective and did not assess the apraxia systematically. Pillon et al.,<sup>10</sup> in a prospective study, suggested that patients with PSP, in contrast to those with CBD, did not exhibit ideomotor apraxia. Although in the Pillon et al.<sup>10</sup> study PSP patients made some errors on tests of symbolic gesture evocation (not differing significantly from CBD patients) and object use pantomime (significantly better than CBD patients), the authors did not interpret the errors as indicative of ideomotor apraxia. However, Pillon and colleagues<sup>10</sup> used a scoring system for gestures that may not allow for enough gradations of perfor-

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mance or an understanding of the nature of the errors. Using the criteria for ideomotor apraxia applied by Leiguarda et al.,<sup>9</sup> the errors Pillon's PSP patients exhibited on symbolic gesture evocation are enough to qualify them as having ideomotor apraxia. Leiguarda et al.<sup>9</sup> investigated both the severity and nature of the ideomotor apraxia in patients with PSP and reported that 75% had ideomotor apraxia for transitive movements and slightly over 30% for intransitive movements. Most of the errors committed were spatial and temporal but not content errors.

We report an autopsy-confirmed patient with PSP who showed limb apraxia in the middle stages of the disease and discuss this issue in view of the autopsy findings.

### Case Report

A 64-year-old, left-handed man presented with a 4-year history of imbalance and frequent falls and a 2-year history of bradykinesia and neck stiffness. He also reported difficulty focusing and diplopia. He had progressive dysarthria and dysphagia for liquids for over 1 year. He reported apathy and difficulty with planning. Carbidopa/levodopa at a dosage of 112.5/1125 mg/day and 200 mg levodopa retard every night had no beneficial effects. Medical history was relevant for myocardial infarction, cardiac bypass surgery, atrial fibrillation, hypercholesterolemia, and 13-year history of dystonia of the vocal cords (episodic changes in the speech volume). He smoked two to three packs of cigarettes per day until 13 years before his visit. Family history was relevant for possible Alzheimer's disease (AD) in his mother and a cousin with juvenile parkinsonism.

On examination, he was alert, oriented, with a normal Mini-Mental State Examination score (27/30). Aphasia was not present. Moderate impairments of voice were noted: hoarse quality, soft intensity, and monotone stress. Patient would "lose voice for periods of time." His maximum phonation time was 3 seconds (average is about 15 seconds). He exhibited ideomotor apraxia (see below) not noted on neurologic examination 1 year previously. There was a severe vertical supranuclear palsy (absence of optokinetic nystagmus; gaze limited to only 5–10° downward and absence of upward gaze; and significant improvement with the doll's head maneuver); square wave jerks; and minimal horizontal gaze palsy (slow horizontal saccades but preserved horizontal optokinetic nystagmus without horizontal gaze limitation). Motor examination showed normal strength throughout, symmetric hyperactive reflexes, and downgoing plantar reflexes. There was no myoclonus or alien limb syndrome. Tone was increased axially and anterocollis was evident. Sensory examination and coordination were normal. His gait was wide-based and unstable. The evaluation took place 18 months before the patient's death.

### Neuropsychologic Tests

This patient showed mild dementia (scored 115 on the Mattis Dementia Rating Scale),<sup>11</sup> failing the Initiation/Perseveration and Construction subtests. He showed frontal lobe dysfunction, completing only two categories of the Wisconsin Card Sorting Test (WCST),<sup>12</sup> making 29 perseverative responses and 28 perseverative errors. His naming ability was normal (Boston Naming Test),<sup>13,14</sup> but his word production was reduced on a verbal fluency task (FAS Test: the patient was asked to produce words beginning with each of these letters for 90 seconds).<sup>15</sup> On the Visual Object and Space Perception battery, he failed

subtests suggestive of problems discriminating spatial information.<sup>16</sup> His memory was impaired on the Wechsler Memory Scale-Revised<sup>17</sup> (Verbal Memory, 90; Visual Memory, 80; General Memory, 85; Attention/Concentration, 89; Delayed Recall, 88). On the Warrington's Recognition Memory Test,<sup>18</sup> his score for word recognition was less impaired (38/50; 2 standard deviations below the mean score for the normal sample, approximately 10th percentile) than his score for face recognition (35/50, almost 5th percentile).

To evaluate the apraxia, the patient was asked to perform 20 gestures from the Test of Oral and Limb Apraxia (TOLA).<sup>19</sup> The TOLA separates gestures into four major categories: proximal intransitive (for example, wave "good-bye"), proximal transitive (for example, iron a tablecloth), distal intransitive (that is, make a "v" for victory), and distal transitive (for example, dial a phone). [Note that the examples provided are the gestures presented on videotape. All of the gestures were videotaped and scored later by three independent raters. For all gestures, the right hand was used because the norms of the TOLA suggest using the nondominant limb for apraxia testing. We did not score movements of the left hand according to apraxia scales. However, on neurologic evaluation, apraxia was noted in both upper extremities.]

We used several different scoring systems to analyze the apraxia test performance. When scoring gestures, two of three raters had to agree on: (1) whether the gesture was correct or incorrect, and (2) if incorrect, the error type(s) committed. Using the 0- to 3-point TOLA system designed for scoring the 20 gestures, the average total apraxia score by the three raters was 80.67/120, or 67% correct, which is 2 standard deviations below the mean score for normal subjects tested on the TOLA (mean score of normative group: 118.5/120, SD ± 3.4). His performance falls near the 25th percentile according to normative data gathered on a sample consisting of both patients and normal control subjects.<sup>19</sup> We additionally applied the Leiguarda et al.<sup>9</sup> scoring system (0–2 points for intransitive movements and 0–3 points for transitive movements) to evaluate if the patient would be considered apraxic using a different scoring system. He was also apraxic using Leiguarda et al.'s system<sup>9</sup>: the apraxia score for an average of gestures to command and imitation was 36.5/50. He also fell below Leiguarda's cut-offs of >1 error on intransitive movements and >4 errors on transitive movements,<sup>9</sup> showing apraxia for both transitive and intransitive movements. At the time the patient was tested, his errors were considered to be apraxic rather than related to his motor dysfunction alone because he did not exhibit any involuntary motor movement, was able to understand the commands, and did not correct himself when performing a gesture incorrectly. He had fewer problems with distal intransitive movements on which he only committed one error to command and no errors to imitation. The other three categories were equally problematic.

To explain the nature of apraxia, we also implemented the Florida Apraxia Battery's error pattern analysis (FAB).<sup>20,21</sup> Four categories of error types were considered using this system: content, temporal, spatial, and other (no response, unrecognizable response, concretization). This patient's errors were mainly spatial or temporal in nature,<sup>21</sup> committing all five of the different spatial errors (that is, amplitude [19% of all errors]; gestures were amplified or reduced from what would normally be characteristic), internal configuration (14.3%; the fingers and hand were not in the correct configuration for an

imagined tool or gesture), body part as tool (4.8%; the hand was used as the imagined tool), external configuration (28.6%; the spatial relationship between the fingers, hand, arm, and the imagined tool or audience was not characteristic), and movement (14.3%; a disturbance of the characteristic action).<sup>21</sup> His temporal errors were mainly occurrence errors (14.3% of all errors; repeating gestures that typically involve a single movement cycle). He only committed one timing (4.8%) error for which the rate of a gesture was irregular and changed across the trial.

### Neuropathologic Findings

Gross examination of the brain revealed mild-to-moderate diffuse cortical atrophy of the temporal and parietal lobes. The brain weighed 1270 g. No focal abnormalities were noted over the cerebral, cerebellar, or brain stem surfaces. On cut section, the substantia nigra and locus ceruleus were significantly depigmented, and a small colloid cyst (0.9 cm) was identified in the third ventricle. Microscopic examination of hematoxylin & eosin, silver-stained (Hirano method), and tau-immunostained sections of the brain showed changes that were diagnostic of PSP, including neurofibrillary tangles (NFTs) and neuronal degeneration in the brain stem, globus pallidus, cerebellar dentate nucleus, and tau inclusions in glial cells.<sup>1,22</sup> In the substantia nigra, severe loss of pigmented neurons was accompanied by prominent pigment incontinence and reactive gliosis. Within the few remaining nigral neurons, globular NFTs were identified. Loss of neurons and numerous NFTs were also seen in the dentate nucleus of the cerebellum. Although lesser in number, NFTs could be readily identified throughout the nuclei of the pons and medulla. In all cases, tangles showed strong staining for tau. Examination of the basal ganglia showed degenerative changes and globular NFTs in the internal and external globus pallidus, with most severe changes noted in the internal pallidum.

The frontal, temporal, parietal, and occipital cortices showed focal neuronal loss as well as occasional diffuse and neuritic plaques. Among neocortical regions sectioned, the maximal senile plaque count was 10 per mm<sup>2</sup> with 20% of these representing neuritic plaques. Using the CERAD criteria, the maximal density of neuritic plaques was sparse.<sup>23</sup> By both silver staining and immunohistochemistry for tau, NFTs were identified most readily in the superior parietal cortex but were also seen in the mid-frontal gyrus and inferior parietal cortex. Rare NFTs were noted in striate and non-striate occipital cortex. Throughout the cerebral cortex, tau staining could be seen in glial cells. Tau-positive inclusions were noted within cell bodies of glial cells as well as in perivascular foot processes of astrocytes. Tau-positive neuropil threads were also present, occurring in highest frequency in the entorhinal cortex and inferior temporal cortex. In the hippocampus, silver staining revealed occasional diffuse amyloid plaques and moderate NFTs. The entorhinal cortex showed moderate numbers of plaques and tangles. Mild degenerative changes were seen in the basal forebrain. In sections from the brain stem, cerebral cortex, and cerebellum, immunostaining with ubiquitin antibodies showed immunoreactivity in neuritic processes and highlighted NFTs of affected neurons. No Lewy bodies were identified in the brain stem or cerebral cortex.

The above histopathologic and immunohistochemical findings are consistent with the diagnosis of PSP.<sup>22</sup> In addition, according to guidelines established by the CERAD, the patient

fulfills criteria for possible AD. Strict application of the Braak grading system<sup>24</sup> to this case would be consistent with a score of 6 based on the finding of NFTs in the cerebral cortex, including the visual striate cortex. However, because NFTs are common in PSP as well as AD, application of the Braak grading system is questionable in this particular case. Furthermore, neocortical NFT have been described before in the absence of senile plaques in cases of PSP.<sup>7</sup>

### Discussion

Our patient fits the typical clinical and pathologic criteria for the diagnosis of PSP except that he showed ideomotor apraxia, and neuropathologic examination revealed frontoparietal neurodegenerative changes suggesting early AD. Although the sparse neurofibrillary tangles in the frontoparietal area may be secondary to PSP, the senile plaques cannot be attributed to this condition.

The association between AD and PSP may be more common than appreciated<sup>25</sup> and may partially explain the apraxia in this case. A recent clinicopathologic study, comparing PSP patients with classic presentation ( $n = 5$ ) to those with unusual signs (limb apraxia, focal dystonia, and arm levitation) ( $n = 3$ ) and to those with CBD ( $n = 4$ ).<sup>26</sup> showed that PSP patients with atypical signs (mostly parietal cognitive features) had more severe cortical degeneration than classic PSP patients but less cortical pathology than patients with CBD. The cortical changes for all three patient groups were most severe in the frontal lobe and milder in the inferior parietal and middle temporal lobe. Unfortunately, in this retrospective study, there is no detailed information regarding the nature of the apraxia.

Independent of the scoring system used, our patient was considered to have ideomotor apraxia. The TOLA scoring system allowed us to compare our patient's results with an age-matched sample. However, a numeric value (as given by the TOLA) does not reveal much about the types of errors committed. Thus, classifying the gestures using the FAB's error types further enhanced the understanding of apraxia in our patient.

Our patient presented apraxia for both transitive and intransitive movements. However, the gestures produced were always identifiable despite the errors committed. He did not have marked hesitation except on one gesture and he was not particularly clumsy in his movements. Most of the errors our patient committed were spatial in nature and could not be explained as movement problems alone. The spatial errors committed by our PSP patient may reflect an overall deficit in visuospatial function also shown by his impaired performance on the Visual Object and Space Perception Battery. That is, our patient may not have been able to construct an accurate three-dimensional representation of space around his own body to perform the skilled movements. Leiguarda et al.<sup>9</sup> suggested that the apraxia exhibited by PSP patients could be explained by a combination of basal ganglia and cortical dysfunction. Although none of their patients had an autopsy-confirmed diagnosis, they found that their PSP patients primarily committed spatial errors (with few temporal errors committed), a similar pattern of apraxia as that exhibited by CBD patients.<sup>27</sup>

Our patient also showed dysfunction in some temporal aspects of the gestures such as repeating movements that should typically be performed only once. Perseveration is typically observed in patients with frontal dysfunction and was shown in

our patient's performance on the WCST and on the Initiation/Perseveration section of the Mattis Dementia Rating Scale. Our findings also fit the proposition that the errors observed in the apraxia testing of PSP patients could be secondary to frontal dysfunction.<sup>9</sup> In fact, in our case, neurodegenerative changes were found in both the frontal and parietal cortices.

In view of our findings and the literature review, it is still unclear if ideomotor apraxia really occurs in PSP patients *without* associated cortical lesions. Whether some of the patients described by Leiguarda et al.<sup>9</sup> had associated cortical pathology is unclear. However, this is likely because not all their PSP patients exhibited apraxia. There are inaccuracies in the clinical diagnosis of PSP,<sup>28</sup> and PSP may be associated with AD<sup>25</sup> or with cortical lesions<sup>4,22</sup> more frequently than previously thought. Moreover, lesions of the basal ganglia alone are usually not responsible for ideomotor apraxia.<sup>29</sup>

This case report and the reviewed literature suggest that when a patient with a clinical picture suggestive of PSP exhibits moderate-to-severe ideomotor apraxia, the diagnosis should be questioned because the ideomotor apraxia seen in PSP patients is usually mild. When there is moderate to severe apraxia, it may be assumed that the patient has associated cortical pathology (neuronal loss and neurofibrillary tangles<sup>26</sup> or associated AD changes<sup>25</sup>) or an alternate diagnosis. It could be argued that the mild cortical AD-type changes (which might cause little or no cognitive abnormalities in a normal brain) may have contributed to the development of the observed apraxia in a patient affected by PSP. On the other hand, given the presence of cortical pathology in PSP, one cannot exclude the possibility that PSP pathology was sufficient in its own right to cause the apraxia. In fact, the mild nature of the additional cortical changes favors this possibility. Only after more patients are studied in equally careful detail before and after death will we know the right answer.

### Legends to the Videotape

**Segment 1:** "Wave 'good-bye'" on command. On waving, the patient commits a movement error (he squeezes or grips his fingers in a fist and releases the fist several times).

**Segment 2:** "Wave 'good-bye'" to imitation. The patient did not exhibit the abnormal movement he showed when he waved good-bye on command.

**Segment 3:** "Iron a tablecloth" on command. The patient commits a body part-as-tool error.

**Segment 4:** "Iron a tablecloth" to imitation. The patient commits an external configuration error, as his movements begin high and move downward, showing that he does not respect the correct plane of action for this gesture.

**Segment 5:** "Make a 'v' for victory" on command. The patient commits an external configuration error by holding the v toward the ground. It could be argued that the patient's anterocollis is responsible for the errors committed in this segment. However, despite his abnormal neck posture when performing other gestures, he did not always ignore the correct plane for the action.

**Segment 6:** "Make a 'v' for victory" to imitation. On imitation, he performs the gesture correctly.

**Segment 7:** "Dial a phone" on command. The patient commits both an external configuration error and movement error (His movement errors include moving fingers from side to side instead of in a circular motion as well as turning the index

finger in small circles at the end of the gesture. As the location of the imagined phone changes throughout the course of the gesture, an external configuration error is also observed.).

**Segment 8:** "Dial a phone" to imitation. To imitation, he commits a movement error only (that is, moves fingers/hand straight across, or side to side, rather than in a circular motion that is characteristic of dialing a rotary phone).

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## Progressive, Asymmetric Cortical Visual Disturbances and Movement Disorders in Two Patients

Neuropathologic and clinical overlap and heterogeneity among the neurodegenerative diseases is increasingly recognized. This overlap is not only confined to Alzheimer's disease (AD) and Parkinson's disease (PD). In fact, one of the most controversial topics in current neurology is the existence of such an overlap between degenerative diseases clinically characterized by the presence of asymmetric cortical signs, movement disorders, and dementia. Among these, corticobasal ganglionic degeneration (CBGD) and the asymmetric cortical degeneration syndromes, including Pick disease, frontotemporal dementia, and posterior cortical atrophy (PCA), are the most frequently discussed.<sup>1</sup> CBGD is a distinctive and relatively uncommon movement disorder. It is clinically characterized by markedly asymmetric extrapyramidal symptoms and signs, such as rigidity, akinesia, dystonia, irregular tremor, and myoclonus, associated with abnormalities of cortical function that include apraxia, cortical-sensory loss, and alien limb phenomenon.<sup>2–5</sup> The pathologic hallmark is a corticodentatotrigonal degeneration with neuronal achromasia. Cortical atrophy is usually asymmetric and predominates in the frontoparietal cortex. In the few pathologic studies performed until now, hippocampal damage is not significant and the occipital cortex is generally preserved.<sup>5</sup>

Posterior cortical atrophy (PCA) is a rare form of the asymmetric cortical degeneration syndromes. The earliest clinical finding is a lateralized disturbance of higher visual functions accompanied or followed by a progressive mental deterioration.<sup>6–8</sup> At present, considerable controversy exists about the cause and pathologic basis of PCA. The majority of pathologically verified cases show the typical changes of AD. However, the presence of many atypical clinical and radiologic features for AD could imply that some cases of clinically probable PCA may be unrelated to AD. Except for the presence of myoclonic arm jerking and pyramidal signs in some patients, no other movement disorder (that is, dystonia or parkinsonism) has been described in PCA.

We report two patients with a progressive clinical syndrome characterized by a combination of asymmetric cortical visual disturbances and movement disorders suggesting the involvement of both the occipital cortex and the basal ganglia.

### Case Reports

#### Case 1

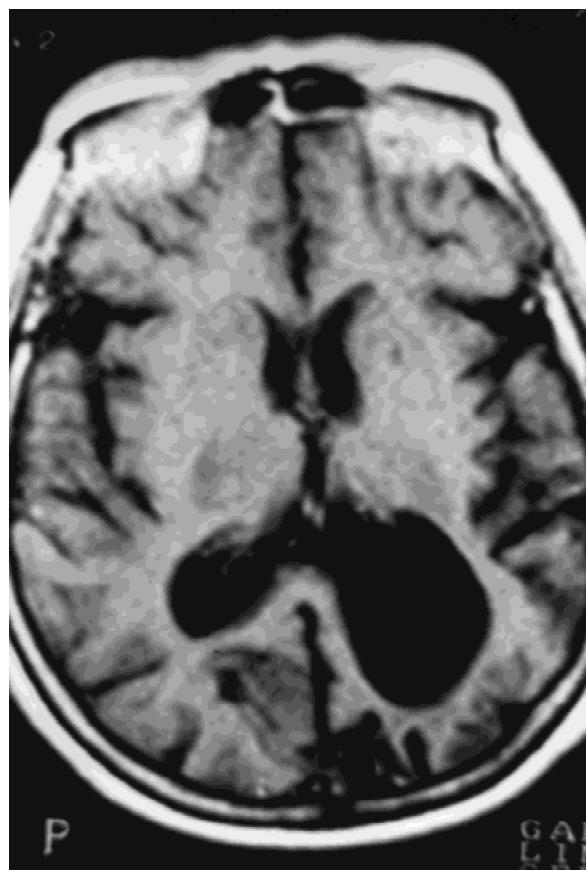
A 66-year-old, right-handed woman with no significant previous medical record and no family history presented with in-

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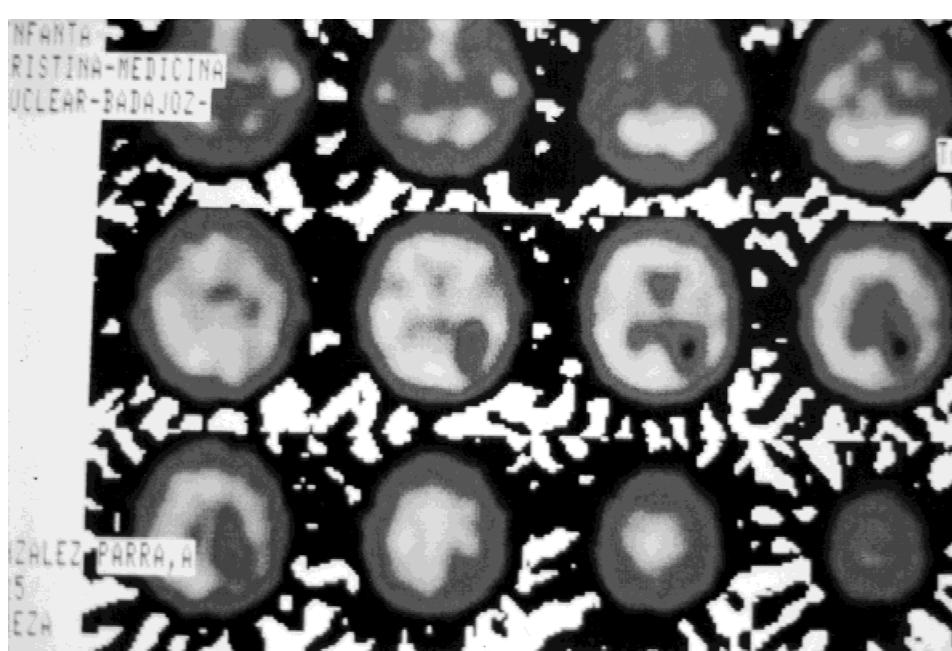
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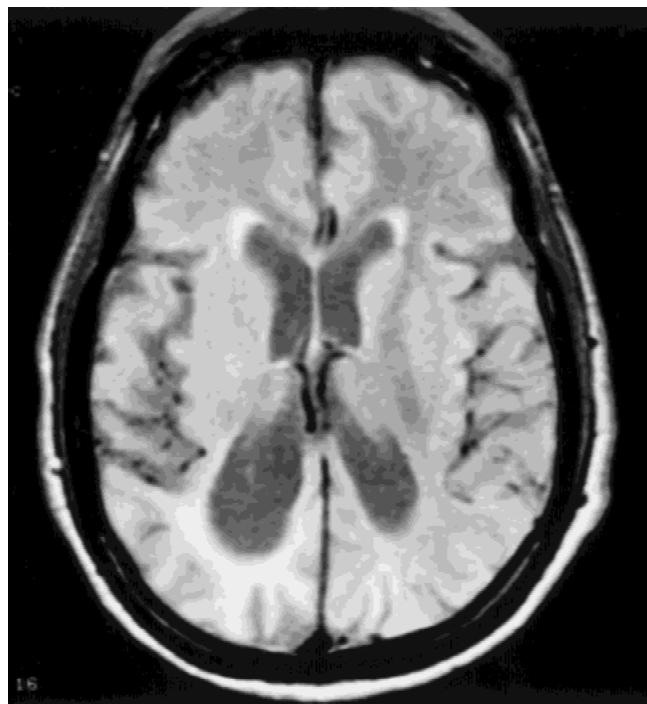
sidious and progressive visual disturbances. She had difficulty manipulating objects in her visual field and she abandoned some housework. Two years after the onset of the symptoms she was first seen at the outpatient clinic. At that time, she had some memory and calculation disturbances as well as clumsiness of the right hand and slowness of gait. Neurologic examination showed rigidity (3 of 4 on the Unified Parkinson's Disease Rating Scale [UPDRS]) and bradykinesia (2 of 4) in the right hemibody, more severe in the upper extremity. The parkinsonian syndrome was associated with reflex myoclonus and a dystonic posture in the same arm. She exhibited a festinating gait and an alteration of the postural reflexes. Apraxia, the alien hand phenomenon and hyposthesia, tactile extinction and stereognosia were present in the right hand. Neuropsychologic assessment (Barcelona test<sup>9</sup>) revealed a memory disturbance, mainly of the visual memory, spatiotemporal disorientation, ideomotor and constructional apraxia, buccofacial apraxia, a severe impairment of the abstraction capacity and associative thinking, and a moderate language disturbance. Higher visual functions were severely impaired and the assessment showed a loss of the visuoverbal functions, visual agnosia, spatial neglect, alexia, and agraphia. Blood count, erythrocyte sedimentation rate (ESR), glucose, creatinine, sodium, potassium, hepatic enzymes, proteinogram, T3, T4, thyroid-stimulating hormone (TSH), VDRL, folic acid, vitamin B12, and urinalysis were normal. Electroencephalogram (EEG) was normal. Visual evoked potential (VEP) failed to show any abnormality. Magnetic resonance image (MRI) (Fig. 1) demonstrated the existence of a diffuse cerebral atrophy, much more marked at the level of the left occipitoparietal region with a dilation of the left occipital horn of the lateral ventricle. Cerebral SPECT (Fig. 2) with  $^{99m}$ Tc-HMPAO revealed the existence of a marked hypoperfusion in the left parieto-occipital region. The parkinsonian syndrome failed to improve with levodopa. In the last few months she has experienced a gradual worsening of all the symptoms and is at present demented and wheelchair-bound.



**FIG. 1.** MRI of case 1 showing atrophic changes with ventricular dilatation in the left occipital lobe.



**FIG. 2.** Case 1. SPECT study of  $^{99m}$ Tc-HMPAO uptake showing marked hypoperfusion in the left parieto-occipital region.



**FIG. 3.** MRI of case 2 showing diffuse atrophic changes more marked in the right occipital lobe with ventricular dilatation.

### Case 2

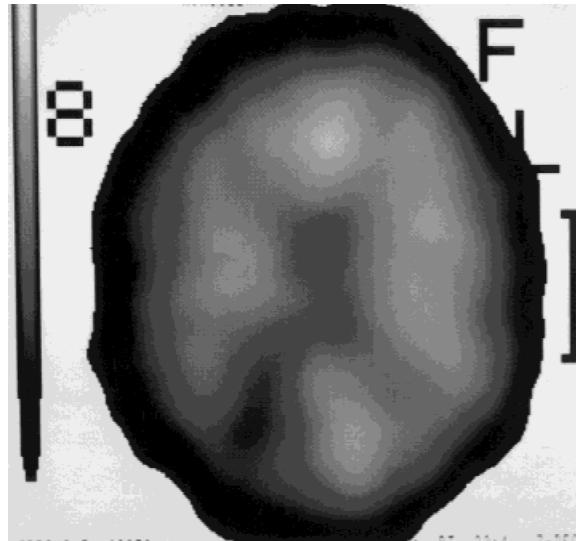
A 50-year-old man presented with difficulty finding his way in familiar areas (environmental agnosia) and in performing visually mediated tasks. He attributed these problems to a loss of visual acuity and a difficulty in concentration and orientation. His family referred to a gradual loss of recent memory. The problems slowly progressed. Two months before his ad-

**TABLE 1.** Summary of clinical features and complementary tests

	Case 1	Case 2
Asymmetric distribution	+++	+++
Visual disturbances	+++	+++
Apraxia	+++	?
Alien hand phenomenon	+++	?
Parkinsonism	+++	++
Dystonia	+++	++
Myoclonus	++	++
Pyramidal signs	-	+
Dementia	+++	+++
MRI: Occipital atrophy	+++	+++
HMPAO SPECT: Asymmetric occipital hypoperfusion	+++	+++

+++ Severe; ++ Moderate; + Mild; - Absent; ? Not properly assessed.

mission to the hospital he began to exhibit an irregular tremor and clumsiness in the left arm. On examination he was alert and oriented. Moderate parkinsonian signs were found in the left arm. An irregular jerky "tremor" and reflex myoclonus were present in the left arm. It was impossible to carry on a formal neuropsychologic assessment because of the lack of collaboration by the patient. Language was apparently normal. A diagnosis of cortical blindness of unknown origin was made. Six months later he was seen at the outpatient clinic. At that time, the most remarkable data of the neurologic examination were a left tonic deviation of the head, impairment of eye movement, loss of postural reflexes, marked rigidity in the left arm and leg, left bradykinesia, myoclonus and dystonic posture of the left hand, and left Babinski sign. It was impossible to properly assess any cortical function and he gave the impression of being profoundly demented. A trial with levodopa was ineffective against the parkinsonian symptoms. Blood count, ESR, glucose, creatinine, sodium, potassium, hepatic enzymes, proteinogram, T3, T4, TSH, VDRL, folic acid, vitamin B12, and urinalysis were normal. Several EEGs were normal. VEP were not done because of the lack of collaboration. MRI (Fig. 3) showed a generalized atrophy, more marked in the right occipital region.



**FIG. 4.** Case 2. SPECT study of 99m-Tc-HMPAO uptake showing marked hypoperfusion in the right occipital region.

**TABLE 2.** Characteristics of CBGD, PCA, and present cases

	CBGD	PCA	Present cases
Clinical asymmetry	+++	+++	+++
Cortical visual disturbances	-	+++	+++
Parietal cortical disturbances	+++	+	++
Dementia	+	+++	+++
Parkinsonism	+++	-	+++
Dystonia	+++	-	+++
Myoclonus	+++	+	+++
MRI: Asymmetric parietal atrophy	+++	-	-
MRI: Asymmetric occipital atrophy	-	+++	+++
SPECT: Asymmetric parietal hypoperfusion	+++	-	-
SPECT: Asymmetric occipital hypoperfusion	-	+++	+++

CBGD, corticobasal ganglionic degeneration; PCA, posterior cortical atrophy.

+++ Severe; ++ Moderate; + Mild; -Absent.

cipital lobe, and a dilation of the right occipital horn of the lateral ventricle. A cranial SPECT study with  $99m$  Tc-HMPAO (Fig. 4) showed marked hypoperfusion in the right temporo-occipital area. Eventually he died in an advanced state of mental and motor deterioration 5 years after the onset of the symptoms. It was not possible to perform a pathologic study of the brain.

### Discussion

These cases developed a clinical syndrome exhibiting a combination of symptoms and signs of cortical and basal ganglia origin (Table 1). The earliest symptom was a cortical visual disturbance. Later an asymmetric non-levodopa responsive parkinsonian syndrome, dystonic postures and reflex and spontaneous myoclonic jerks (in both cases), alien limb phenomenon and apraxia (in one of them) were associated. In the final stages, generalized parkinsonism and severe dementia were present. Anatomic and functional image studies (MRI and SPECT) demonstrated the existence of striking asymmetric abnormalities, mainly at the level of the occipital cortex, although in advanced stages a more diffuse pattern of abnormalities was observed, especially on MRI. These observations correlated with the laterality of the clinical features.

This combination of signs and symptoms can be seen in many diseases, such as Pick disease, progressive supranuclear palsy (PSP), Jakob-Creutzfeldt and other prion diseases, typical Alzheimer's disease, diffuse Lewy body disease, CBGD, PCA, and other more unusual disorders. Although brain biopsy or autopsy could not be performed, most of these diseases could be reasonably excluded based exclusively on clinical and imaging grounds. Therefore, the progressive and asymmetric clinical picture exhibited by these patients most likely corresponds to either clinically probable CBGD or PCA. However, there are some atypical features for each of these disorders (Table 2). To our knowledge, occipital cortex involvement in CBGD has only been described by Rey et al.<sup>10</sup> These authors reported the case of a patient who developed a left visual field inattention, atypical dementia, and psychiatric features. A mild neuronal loss and gliosis in the right occipital cortex was observed at necropsy. This finding is uncommon and, indeed, Watts et al. in their recent review<sup>5</sup> state that "occipital cortex is generally unremarkable" in this disease. Consequently, the presence of higher visual dysfunction has never been described in extensive clinical series.<sup>3,4</sup> Moreover, dementia is infrequent in CBGD and usually appears in the final stages of the disease. Indeed, some authors consider the presence of early cognitive impairment as an exclusion diagnostic criteria,<sup>3</sup> although this idea is changing because early cognitive loss may occur in more than one third of patients.<sup>4,5</sup> Regarding the neuroimaging studies findings, they are more compatible with a presumptive diagnosis of PCA.<sup>6-8</sup> However, none of the cases with pathologically confirmed or clinically probable PCA displayed a highly lateralized motor disturbance (mainly parkinsonism and dystonia) during the course of the disease.

In summary, our cases share the clinical features typically found in both CBGD and PCA. Although pathologic diagnostic confirmation is not available, we think these two cases may represent atypical variants of either CBGD or PCA rather than a new clinicopathologic entity. This report supports the idea that a high degree of clinicopathologic heterogeneity exists in these syndromes. More necropsy studies can serve to better delineate the clinical picture of this type of asymmetric corti-

cobasal ganglionic degenerative syndromes, although even their neuropathologic characteristics are under discussion.<sup>11</sup> In the meantime, the clinical study of atypical cases may contribute to expand our current understanding of these syndromes.

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### The Eye of the Tiger Sign in Cortical-Basal Ganglionic Degeneration

Corticobasal ganglionic degeneration (CBG) is a progressive degenerative disorder of the central nervous system character-

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**FIG. 1.** Axial T2-weighted magnetic resonance image presenting diffuse low-signal intensity with an anteromedial area of high signal intensity confined to the globus pallidus, the "eye of the tiger" sign.

ized by cortical sensory loss, focal reflex myoclonus, limb dystonia, "alien limb" phenomenon, apraxia, rigidity, postural instability, and akinesia which develops with striking asymmetry.<sup>1</sup> Differentiation from other parkinsonian disorders may be misleading with an early diagnosis sensitivity of 35% in the first visit.<sup>2</sup>

Neuroradiologic studies may help in the differential diagnosis of CBD from other parkinsonian syndromes. Magnetic resonance imaging (MRI) in CBD usually shows asymmetric cortical atrophy. Hypodensity in the putamen and the globus pallidus on T2-weighted images recently has been reported.<sup>3</sup> To our knowledge, the "eye of the tiger" sign has not been previously described in patients with CBD.

In this case report we present a patient with the clinical diagnosis of corticobasal ganglionic degeneration (CBD) and the "eye of the tiger" sign on magnetic resonance imaging (MRI).

### Case Report

A 76-year-old right-handed man with chronic hypertension and ischemic heart disease experienced progressive left-hand "clumsiness" with parkinsonism over a 4-year period. His hand clumsiness first presented associated with left shoulder pain. After a course of antiinflammatory treatment the pain

disappeared but his left-hand weakness progressed. At age 74 he had severe difficulties dressing himself with the left hand, and he became unable to perform skilled movements such as doing up buttons and cutting food. His walking got slower with shorter steps. Three years after the onset of symptoms his arm started to adopt "strange" postures, drawing up on its own while walking, and he was no longer able to leave an object after having held it. He completely stopped using his left arm 6 months later. Neurologic examination at this time disclosed a normal mental status with preserved memory and language skills. Ocular motility was normal. Motor examination showed normal strength. Deep tendon reflexes were slightly brisk on his left side but plantar cutaneous responses were flexor. His left arm was modestly rigid and substantial bradykinesia involving the left-sided extremities was detected. He exhibited severe apraxia when using his left arm. Asterognosia was prominent in the left arm with preservation of proprioception, tactile, pain, and temperature sensations. Finger-to-nose and heel-to-shin tests were normal. His gait was slow with short, shuffling steps without associated arm movements. He turned in block, and freezing or start hesitation was occasionally seen. When walking, his left arm unintentionally tended to move up behind his back adopting a flexed, dystonic posture of the forearm and fingers. No tremor or myoclonus was present. Routine laboratory tests were normal. Cranial computerized tomography was normal. T2-weighted magnetic resonance images revealed diffuse low signal intensity with an anteromedial area of high signal intensity confined to the globus pallidus, the so-called "eye of the tiger" sign (Fig. 1). A small hyperintense lesion on T2-weighted images and hypointense on T1-weighted images, compatible with a lacunar infarction, was located over the right pons.

He was started on 1000 mg/day levodopa without any benefit after 9 months of therapy. On his last follow-up visit he could not walk because of severe freezing, and moderate bradykinesia also affected his right-sided extremities. His left arm exhibited the alien hand phenomenon presenting involuntary, purposeless movements while eating with the right hand. Neurologic signs suggestive of other degenerative disease such as oculomotor abnormalities were not present.

### Discussion

The "eye of the tiger" sign has been considered specific for Halleervorden Spatz syndrome (HSS).<sup>4</sup> However, recent articles have disclosed other parkinsonian syndromes with this radiologic sign. Barbosa et al.<sup>5</sup> described the case of an early-onset levodopa-responsive parkinsonism with the "eye of the tiger" sign, and Davie et al. have recently reported three patients with the diagnosis of PSP, one of them pathologic-proven, presenting the same neuroradiologic abnormality.<sup>6</sup>

We do not think our patient had HSS because it commonly presents as a young-onset extrapyramidal disorder characterized by dystonic postures, rigidity, and choreoathetoid movements accompanied by mental deterioration with a chronic progressive course.<sup>7</sup> Although it occasionally may begin during the adult years, the oldest case reported was in the fifth decade and it presented as a familial symmetric parkinsonism with marked cognitive impairment,<sup>8</sup> features that were not observed in our patient. In contrast, our case exhibited four major clinical signs for the diagnosis of CBD<sup>9</sup>: ideomotor apraxia, limb dystonia, an asymmetric akinetic rigid syndrome, and the "alien

hand" phenomenon. He initially also exhibited unilateral arm clumsiness, a symptom reported as the most common initial symptom in these patients.<sup>10</sup>

The "gold standard" for the diagnosis of CBD is the neuropathologic examination, but a recent clinicopathologic study on the accuracy of its clinical diagnosis has disclosed a low sensitivity (48.3%) but a near-perfect specificity (99.6%) in the clinical diagnosis of this disorder.<sup>2</sup> False-positive diagnoses were also a rare finding.<sup>2</sup> This study has also shown that the best predictors for a correct diagnosis were limb dystonia, ideo-motor apraxia, myoclonus, and an asymmetric-akinetic rigid syndrome and late onset of gait and balance disturbances, symptoms which were almost all present in our patient.

In patients with HSS, the diffuse low signal hypointensity detected on MRI has been attributed to iron accumulation, and although there is no clear explanation for the central hyperintense signal, it has been hypothesized that it could be related to gliosis, increased water content, or neuronal loss with vacuolization.<sup>4,11</sup> Postmortem examination in one patient with HSS and the "eye of the tiger" sign on MRI revealed widespread iron deposition and axonal spheroids in both pallidi, and an area of total disintegration of the neuropil with complete cavitation in the medial part of both nuclei, which was responsible for the central high signal aspect of the "eye of the tiger" sign.<sup>12</sup> In CBD, postmortem neuropathologic studies have disclosed cell loss and gliosis affecting the lateral thalamic nuclei, globus pallidus, subthalamic nucleus, locus ceruleus, and red nucleus.<sup>1</sup> Because iron accumulation has not been described in the globus pallidus, the radiologic findings in our patient might be related to cell loss and gliosis.

Our case corroborates that the "eye of the tiger" sign is not a specific neuroradiologic finding for HSS because it can be found in other parkinsonian syndromes. Further postmortem studies are necessary to clarify the different pathologic lesions responsible for its appearance.

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## French Horn Embouchure Dystonia



Musicians are subject to a high rate of occupational injuries, including overuse syndromes, nerve entrapments, and focal task-specific dystonias. Relatively few examples of musicians with task-specific dystonia of the oral-facial region have been reported. We present two French horn players with task-specific dystonia and demonstrate an interesting technique for retraining oral musculature.

## Case Reports

### Patient 1

A 26-year-old woman, who was a professional French hornist, presented to our movement disorders center with a 16-month history of progressive difficulty performing. Several months before the onset of symptoms, her playing time and the demands of her repertoire increased significantly. Two months before her symptoms, she changed the angle of the lead pipe of her horn, altering the relative position of the mouthpiece of the instrument to her lips. This change was not made in response to difficulty performing. Soon thereafter, she felt that her embouchure (the set position of facial muscles involved in producing and controlling the air stream necessary for playing) was uncomfortable. Her ability to play high and low notes and the clarity of her sound deteriorated. When playing the horn, or simply blowing into the mouthpiece, she found that both lips pulled upward, involuntarily separating at their edges and producing an air leak around the mouthpiece. She was unable to suppress the tendency of her lips to separate and had not discovered a sensory trick to attenuate the involuntary movements.

A videotape accompanies this article.

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Although she was able to produce sharp, brief attacks without difficulty, sustaining a tone was impossible secondary to leakage of air from the corners of her mouth and an upper lip tremor which was readily audible. She was unable to play 6 months after symptoms began. She began a program of retraining, adopting a trombone style of playing to the French horn. She altered her embouchure by lowering the corners of her mouth (imitating a trombonist's approach to their instrument) and also began practicing with a trombone mouthpiece (which has a larger diameter and covers a larger fraction of the lips). This technique was moderately successful, although she continued to have involuntary pulling at the corners of her mouth which interfered with performance. The patient had no significant medical history or history of trauma, no family history of dystonia, and no history of neuroleptic exposure. There was no history of difficulty swallowing or eating, except that when she drank from a cup or from a soda bottle, liquid would leak from the corners of her mouth.

On examination, there was no dystonia of the lips, face, or tongue with routine action. Her speech was normal and she could whistle and sing without difficulty. There were no perioral or facial sensory deficits, and no facial weakness was present. When sustaining tones using the French horn mouthpiece or playing the instrument, involuntary upward pulling at the lateral corners of the mouth separated the lips, causing an air leak around the mouthpiece (videotape segment 1). A fine tremor of the upper lip was also visible and audible. She compensated for the dystonia by fixing both lips in a down-turned position (a trombone embouchure) enabling her to play (albeit with difficulty). She practiced this new embouchure using the larger-diameter trombone mouthpiece with considerable success. At the time of this report, she has continued to perform in her symphony orchestra using this approach. She declined trials of medication or injection with botulinum toxin A.

## Patient 2

A 20-year-old French hornist, who was enrolled at a major conservatory, was referred to our center with a 7-month history of difficulty playing. Two months before the onset of her problem, she altered her embouchure in an attempt to change her sound. She and her teacher then noted an insidious decline in her previously natural and proficient playing with loss of precision and inability to begin and connect tones. Within 2 months she was unable to play. She altered her embouchure again and began retraining her muscles using a trombone mouthpiece in a program similar to our first patient's regime (both were referred by the same teacher). Her playing gradually improved with a return of ability to play high pitches. However, her playing of low notes remained poor. There was no family history of dystonia, no history of neuroleptic exposure, and no history of trauma. Other than playing the horn, her only other symptom (which occurred concurrently with the dystonia) was a tendency to spill liquids from her mouth when drinking from a soda bottle.

Examination 7 months after symptoms began was normal except for task-specific dystonia. When using the French horn mouthpiece (alone or when playing), both upper and lower lips puckered out and separated, destroying her air seal. These movements did not occur when playing high pitches. As she descended into the lower register of the instrument, her lips puckered and she lost air pressure. Continuing to descend, her

disability became progressively more severe. When practicing with the trombone mouthpiece, the tendency of her lips to separate was significantly attenuated (videotape segment 2). She declined trials of medication or botulinum toxin A injection.

## Discussion

Examples of task-specific dystonias include hand dystonia afflicting tailors, shoemakers, and cobblers, writer's cramp, telegraphist's cramp, auctioneer's jaw,<sup>1</sup> golfer's cramp ("the yips"), and various focal dystonias affecting musicians.<sup>2</sup> Among musicians, the hand required to perform the greater volume and difficulty of finger movements is typically affected. Among keyboard players, the right hand is more commonly afflicted, whereas left hand dystonia is more common among string instrumentalists.<sup>3,4</sup>

Playing a brass instrument puts extraordinary demands on the muscles of the face and tongue. The embouchure not only directs the considerable force needed to produce the sound, but also exquisitely modulates airflow, changing timbre, pitch, and articulation. In an ideal embouchure, air pressure is directed into the orifice of the mouthpiece with an airtight seal. Involuntary activation of the risorius and zygomaticus muscles may be responsible for our first patient's lip movements. Descending into the lower register triggered our second patient's dystonia. It was not only task-specific, but also register-specific, triggered by a precise combination of tension and separation of the lips.

Our patients illustrate many common features of task-specific dystonia. As in most cases, the disorder was painless and there was no identifiable sensory trick. Both patients significantly changed their technique shortly before the onset of their difficulty. It is uncertain whether these changes were usual adjustments or whether they occurred in response to the onset of dystonia. In one series of musicians with task-specific dystonia, eight of 58 patients changed technique before the onset of dystonia.<sup>4</sup> Both of our patients reported involuntary separation of the lips with dribbling when they drank from a standard soda bottle. This problem occurred concurrently with dystonia of the embouchure. It is plausible that the ring of the French horn mouthpiece and the opening of a soda bottle are sufficiently similar to trigger an embouchure dystonia during drinking. Training with a trombone mouthpiece may provide a mechanical stimulus that inhibits the dystonic movements.

Therapy of task-specific musician's dystonia has been disappointing. In a series of musicians with arm dystonia treated with botulinum toxin, mild benefits in function were seen, but difficulty with coordination and fine motor control were not improved.<sup>5</sup> Given the extreme force requirements of the brass embouchure, even a small amount of oral weakness associated with botulinum toxin would be poorly tolerated by a performing artist. At this time both patients have declined trials of botulinum toxin injections. Retraining or altering technique may offer their best hope for improvement. We are encouraged that this approach has already proven to be of some benefit.

## Legends to the Videotape

**Segment 1:** Patient 1 demonstrates (without the mouthpiece) the French horn embouchure (or "set") and the trombone set she used in retraining. The trombone set is identified by the fixed downward position of the lower lips. Next, using a French

horn mouthpiece to sustain a tone, involuntary elevation and separation of the upper lips are seen when she uses the French horn set and are far less evident with the trombone set. When blowing into a trombone mouthpiece (larger diameter), far less elevation and separation of the lips occurs. The final sequence shows the patient playing the French horn. Fast repeated notes pose no problem for her. However, attempting to sustain a tone with her old (French horn) set, involuntary lip movements are evident with loss of air seal and a fine tremor of the upper lip, visible and audible. This is less evident when she uses the trombone set.

**Segment 2A:** Patient 2 plays the French horn and then trombone mouthpiece, "free buzzing." When using the French horn mouthpiece, puckering of the upper and lower lips occurs as she descends into the lower register. Far less dystonic movements are evident with the trombone mouthpiece.

**Segment 2B:** The patient uses the French horn mouthpiece, playing a descending scale. Dystonic lip puckering and tremor occur and progressively worsen as she plays lower.

**Segment 2C:** As the patient plays a descending scale on the French horn, dystonic lip puckering and tremor occur (as in Segment 2B) and worsen with descent. The loss of air seal is audible.

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### Mexiletine in the Treatment of Blepharospasm: Experience With the First Three Patients



Blepharospasm is the second most common form of adult-onset focal dystonia<sup>1</sup>; its medical treatment is difficult. Re-

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cently we found that mexiletine, a derivative form of lidocaine, was useful in a small number of patients with spastic torticollis.<sup>2-4</sup> During that study, we found that the drug is also useful for coexistent focal or segmental dystonias. We then extended our experience to three patients with blepharospasm. Patients 1 and 3 were reported previously in abstract form.<sup>3</sup>

### Methods

Pertinent clinical features are summarized in Table 1. All patients were previously tried on several conventional medications without substantial benefit. All had blepharospasm and patient 1 also had oromandibular dystonia (Meige syndrome). Neurologic examinations were otherwise unremarkable. Magnetic resonance imaging (MRI) in patient 1 showed T2 high densities of unknown significance in the cerebral white matter. The other two were normal.

Before starting patients on mexiletine, we followed the same exclusion criteria and dose increment schedule as in our previous study.<sup>4</sup> It is important to note that we excluded patients with a medical history of symptomatic cardiac diseases or those with evidence of cardiac conduction block on electrocardiogram at the time of initial evaluation. Written informed consent was obtained from each patient. For patients 1 and 2, after placebo intravenous injection of normal saline, 100 mg lidocaine over 5 minutes was infused to see whether a favorable response might predict beneficial effects of mexiletine.

During the test injections, the patient sat comfortably without speaking and looked straight ahead into the video camera lens placed 3 m away. In patient 1, surface electromyograms (EMGs) from facial muscles were also recorded. Mexiletine was started at 100 mg three times a day except patient 2 who was started at 50 mg three times a day. The dose was increased by 150 mg/day every 2 weeks to the point where desirable effects were obtained or side effects developed. Patients were followed once a month in our outpatient clinic. Monthly structured video recordings and the Fahn blepharospasm rating scale score<sup>5</sup> were used for evaluation. This is a movement scale comprised of several parts concerning the locations of the abnormal contractions in individual muscles (each involved muscle component receives one point), influencing factors (such as sunlight or watching TV), frequency and severity of eyelid closure with a maximum score possible of 39. Videotapes were rated in an open-label fashion by an evaluator aware of the treatment status of the patient.

### Patient 1

Patient 1, a 55-year-old man, was well until 1 year 2 months earlier when he observed increased frequency of eyelid blinking while driving. Six months later, the blink had become forceful closure of the eyelids and was followed by involuntary opening of his mouth. He would bump into passersby while walking on the street and twice had traffic accidents.

On examination, he showed persistent blinking more than 70 times per minute. This was interrupted frequently by forceful spasms of orbicularis oculi muscles and opening of the jaw.

Intravenous injection of lidocaine transiently aborted the forceful eyelid closures (Fig. 1). With increasing doses both frequency of blinking and forceful spasms decreased. He resumed driving. A month later he began to have epigastric discomfort and nausea, which required the reduction of dose to

**TABLE 1.** Patient profiles

Patient No.	Age	Sex	Duration	Previous medications	Response to IV lidocaine	Mexiletine dose/day	Rating scale score		Side effects (dosage developed)
							initial	final (mos)	
1	55	M	1 yr 2 mos	clonazepam, trihexiphenidyl	+	750 mg	27	16 (6)	heartburn, nausea (900 mg/day)
2	79	F	3 yrs	trihexiphenidyl, tiapride	±	450 mg	22	8 (3)	gait ataxia (600 mg/day)
3	35	F	3 yrs	trihexiphenidyl, clonazepam, carbamazepine	not done	700 mg	14	4 (11)	finger tremor (800 mg/day)

Patient 1 had an oromandibular dystonia and blepharospasm (Meige syndrome).

750 mg/day with the addition of antacids. Over the next 6 months, he continued to have variable but frequent forceful eye closures without facial grimacing or opening of the jaw. He is now scheduled to have botulinum toxin injections which was recently approved in Japan for treatment of blepharospasm.

### Patient 2

This 79-year-old woman experienced intermittent dull pain around the right eye at age 76 which persisted on and off for a year. She then noticed gradually increased involuntary grimacing of the right side of the face together with difficulty in keeping the right eye open. During the next year, her right eye was kept closed almost all of the time and her left eye became increasingly difficult to keep open because of frequent spasms (see video segment 1). At age 78, when she had a test injection of lidocaine, she reported a subjective sense of "eyelids become lighter," although the right eye was still kept closed and the left eye showed only less frequent blinks. Following the introduction of 450 mg/day oral mexiletine, she was able to see with both eyes (see video segment 2). With the dose increased to 600 mg/day at her request, she started feeling drugged and slightly ataxic in gait. The dose was reduced to 450 mg/day for the next 3 months without significant change in the symptoms.

### Patient 3

A 35-year-old woman first experienced difficulty keeping her eyes open when she "got nervous" followed by difficulty driving because of frequent eye closure. Eventually she had to retire from her job. Various medications were without benefit.

On examination, she blinked incessantly and was able to open only her right eye 2–3 mm and keep it open for only 1–2 seconds. Her left eye was kept closed. When asked to open both eyes, she was able to do so briefly but this was immediately

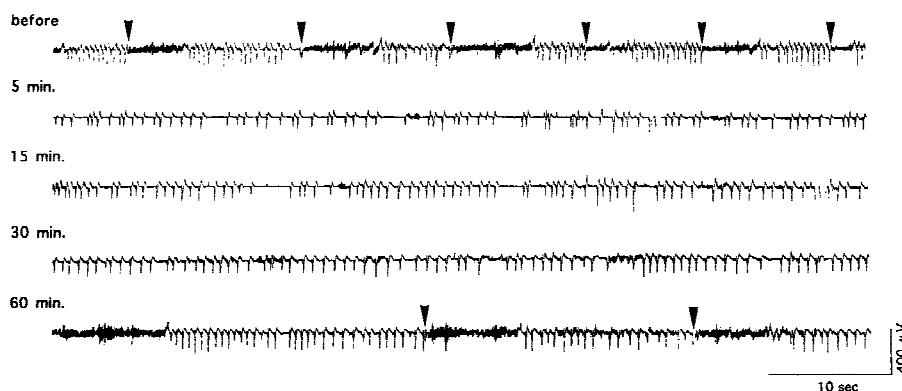
followed by forceful spasms of orbicularis oculi which lasted 3–4 seconds. The patient declined the intravenous lidocaine infusion test. Oral mexiletine at a dose of 300 mg/day produced no appreciable improvement (see video segment 3). With the dose of 600 mg/day she did not have forceful eye closures and resumed driving (see video segment 4). She had mild dyspepsia which resolved with antacids. When the dose was increased to 800 mg/day, a fine action tremor of the fingers appeared. This resolved at a dose of 700 mg/day. She remained on 700 mg mexiletine for the next 11 months without significant change of the symptoms (see video segment 5).

### Discussion

Medical treatment for disabling blepharospasm is known to be difficult and injection of botulinum toxin is now regarded as the best therapy.<sup>1,6</sup> In Japan, botulinum toxin has only recently (1997) been approved for the treatment of blepharospasm. The patients presented here could have had the toxin injection if it had been available.

In our previous open case trial with mexiletine in spastic torticollis, we learned that the drug could be beneficial for other focal or segmental dystonias. Our three patients showed moderate to marked improvement which had not been attainable with conventional medications such as anticholinergics and benzodiazepines. It appears that increased frequency of blinks is not as disabling for the patients as sustained blepharospasm which can produce functional blindness. All of our patients on mexiletine continued to have increased blink rates more than double those of control subjects (mean blink rate at least 17/min<sup>7</sup>), yet their activities of daily living were markedly improved.

Mexiletine, an oral form of a lidocaine derivative, is a well-known cardiac antiarrhythmic agent with an elimination half-



**FIG. 1.** The effect of intravenous injection of lidocaine on blepharospasm of patient 1. The activity of the right orbicularis oculi was recorded using surface electrodes. Before lidocaine injection, the patient blinked 10–12 times per second, often interrupted by forceful eye closures (arrows). After the injection, the frequency of blinks started to decrease at 5 minutes with disappearance of forceful eye closures. The effect was most evident at 15 minutes with gradual return to baseline at 60 minutes.

life of 9–15 hours.<sup>8</sup> It may therefore be expected that the response to intravenous injection of lidocaine might predict the therapeutic outcome with oral mexiletine. The result of a test injection of lidocaine in patient 1 (Fig. 1) was promising in this respect. We are now planning to develop a properly controlled therapeutic study on the clinical efficacy of lidocaine/mexiletine for the treatment of blepharospasm. Mexiletine may become a drug of value for this condition.

### Legends to the Videotape

**Segment 1:** Patient 2 before treatment. Her right eye was kept closed despite her repeated attempts to open it. The left eye showed intermittent blepharospasm. Reading aloud was often interrupted by blepharospasm.

**Segment 2:** Patient 2 at 6 weeks on 450 mg/day mexiletine. She was able to look forward for awhile with both eyes open, although blepharospasm was still seen intermittently. She could read aloud using both eyes and reading was less interrupted by blepharospasm than it was before treatment.

**Segment 3:** Patient 3. Blepharospasm was not affected on 300 mg/day oral mexiletine.

**Segment 4:** Patient 3 on 600 mg/day mexiletine. She was able to see with both eyes without forceful eye closure.

**Segment 5:** Patient 3 11 months later on 700 mg/day mexiletine.

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### Meige's Syndrome in a Patient Treated With Ranitidine



Drug intake can be responsible for a wide variety of movement disorders: parkinsonism, tremor, chorea, limb or facial dyskinesias, blepharospasm, and myoclonic movements.<sup>1</sup> The mechanisms putatively responsible for the occurrence of such disorders are numerous, but a disorder of the dopaminergic transmission of the extrapyramidal system is the most common one.<sup>1</sup> In this respect, neuroleptics and dopamine agonists are the most frequent providers of drug-induced movement disorders. We report a case of reversible Meige's syndrome (blepharospasm and orofacial dyskinesia) related to the intake of amitriptyline and ranitidine which are not known to alter predominantly the central dopaminergic transmission.

### Case Report

A 72-year-old woman was admitted to the hospital for painful neuropathy related to hepatitis C. During hospitalization she developed gastric pain which led to the discovery of a pyloric ulcer. This was related to auto-administration of a nonsteroidal anti-inflammatory agent used as an antalgic. The patient was treated with 300 mg ranitidine per day. Three days later amitriptyline was started to abate the paresthesia related to the neuropathy. The doses were increased to 75 mg to obtain improvement. At this time, only distal hypoesthesia and decreased tendon reflexes in the lower limbs related to the neuropathy were observed. She was then discharged from the hospital. Six weeks later she developed orofacial dyskinesia associated with mild blepharospasm and also slight modifications of behavior. Neurologic examination showed no akineto-hypertonic syndrome or tremor, abnormal ocular motility, or abnormal movements in the limbs (video sequence 1). The abnormal movements disappeared 1 week after ranitidine withdrawal and a decrease in the dose of amitriptyline to 50 mg per day. Similar neurologic symptoms occurred again after 2 days of rechallenge with 150 mg ranitidine per day. Definitive discontinuation of ranitidine while amitriptyline was still being administered led to complete recovery (4 months' follow up). At this time, there were no neurologic symptoms except the symptoms related to the neuropathy.

### Discussion

In our patient the chronology of events demonstrates a temporal relationship between the occurrence and the disappear-

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ance of facial abnormal movements and ranitidine intake and discontinuation. No radiologic or biologic investigations were performed but the regression of the symptoms after ranitidine discontinuation allowed us to rule out all of the usual causes of facial dyskinesia.

The coincidence between ranitidine intake and the occurrence of abnormal movements could be interpreted in two not mutually exclusive ways: (1) the direct effect of ranitidine, and (2) the direct effect of amitriptyline favored by ranitidine related to a pharmacokinetic or a pharmacodynamic interaction.

Tricyclic antidepressants in general are known to induce abnormal movements.<sup>2</sup> Fann et al.<sup>3</sup> described two patients with orofacial dyskinesia associated with amitriptyline intake. The potential inhibition<sup>4,5</sup> of the hepatic metabolism of amitriptyline by ranitidine may have been the cause of the symptoms, but the absence of modification of the bioavailability of amitriptyline in normal volunteers co-medicated with ranitidine<sup>6,7</sup> makes this hypothesis unlikely.

Ranitidine is therefore the most likely candidate responsible for the occurrence of the involuntary movements.

Movement disorders associated with ranitidine are seldom reported in the literature. Ranitidine is presumed to be responsible for parkinsonian symptoms in one patient<sup>8</sup> and for chorea in another.<sup>9</sup> In this latter case the disorder recurred after the administration of cimetidine. Observations of movement disorders associated with cimetidine must also be mentioned indicating a class effect: acute dystonia of the foot,<sup>10</sup> restless legs syndrome with oral dyskinesia,<sup>11</sup> parkinsonism, and cerebellar syndrome.<sup>12</sup>

The theoretical question raised by this observation is the mechanism by which the intake of a drug known to interact with histamine is the cause behind abnormal movements.

Drug-induced movement disorders are mainly described with neuroleptics<sup>13</sup> but also with L-dopa,<sup>14</sup> benzodiazepines,<sup>15</sup> and ketamine,<sup>16</sup> as well as with tricyclic antidepressants<sup>2</sup> as shown above. Considering the pathophysiology of neuroleptic-induced movement disorders, the two main neurotransmitters implicated appear to be dopamine and acetylcholine.<sup>13</sup>

Histaminergic neurons possibly involved in our case appear not to be directly implicated in the pathophysiology of extrapyramidal abnormal movements. They are not involved in what we know from normal functioning of the extrapyramidal system.<sup>17</sup> The role played by histamine mediated by two kinds of receptors ( $H_1$  and  $H_2$ ) is not completely understood but does not directly concern motricity.<sup>18</sup> Thus, the blocking of the  $H_2$  receptors in the central nervous system is probably not the mechanism responsible for the extrapyramidal manifestations in our case. Interaction between ranitidine and dopamine receptors is a possible candidate but with no experimental data. Another possible mechanism is an increase of the cholinergic neurotransmission because ranitidine is known to have anticholinesterase activity.<sup>19</sup>

### Legends to the Videotape

**Segment 1:** The patient exhibits predominant blepharospasm associated with orofacial dyskinesia affecting the lips and the superficial muscles of the neck. These symptoms are present at rest and are not modified by intellectual exercise. The limbs are free of abnormal movements.

**Segment 2:** After ranitidine discontinuation, the patient exhibits no abnormal movements.

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## Paroxysmal Dystonia in Behcet's Disease



Behcet's disease (BD) is a chronic relapsing-remitting, multisystem inflammatory disorder first described by the Turkish dermatologist Hulusi Behcet in 1937. The disease is characterized by the triad of relapsing iridocyclitis, oral and genital ulcerations.<sup>1</sup> Vasculitis is responsible for the disseminated systemic involvement.<sup>2</sup> BD has an estimated prevalence of 100 in 100,000 in parts of Japan and it is also fairly common in the Middle East and many Mediterranean countries.<sup>3</sup> It mainly affects males between 11 and 30 years of age.<sup>4,5</sup> The neurologic involvement of the disease was first described in 1941 and its incidence has been variously estimated to range from 3.2-26.6%.<sup>2,6</sup> In 5% of patients neurologic manifestations occur at presentation.<sup>7</sup> Three patterns of neurologic disorders are generally observed: organic confusion, brain stem and meningoencephalitic syndromes.<sup>3</sup> The fluctuation of clinical signs, the relapsing-remitting course, the demyelinating and inflammatory lesions, and the age of onset may lead to the mistaken diagnosis of multiple sclerosis.<sup>8</sup> We describe, with a related videotape, the case of a patient with BD who developed paroxysmal dystonia. These attacks, frequently reported in the course of multiple sclerosis,<sup>9</sup> have never been reported in neuro-Behcet. Some similarities between multiple sclerosis and BD are discussed.

### Case Report

A 39-year-old woman was diagnosed as affected by BD in 1988 according to the diagnostic criteria of the International Study Group for Behcet's disease.<sup>10</sup> She presented recurrent oral and genital aphthosis, uveitis, and arthralgias. In December 1992, during re-exacerbation of BD, she had for the first time recurrent nocturnal tonic spasms lasting a few seconds. These episodes were characterized by abdominal muscle contraction, followed by dystonic jerks of the right arm, platysma and trapezius muscles, and spasmodic dysphonia. These attacks were of sudden onset, spontaneous, lasting 10-20 seconds and occurring three to five times a night. Her general medical examination showed oral aphthosis, genital ulcerations, and nodosus erythema. Neurologic examination revealed horizontal nystagmus, left arm hyperreflexia, and weakness. Blood chemistry, complete blood cell count, erythrocyte sedimentation rate, an-

ticardiolipin and antinuclear antibodies, complement level, and serum immunoglobulins were normal. Her tissue group typing did not include B51. Repeated electroencephalograms (EEGs) and cranial computed tomography (CT) scans both during and between attacks were all normal. A magnetic resonance imaging (MRI) study, which was performed a few days after the attacks stopped, was normal. The patient was treated with 25 mg deflazacort and 6 mg clonazepam. The attacks became less frequent and in a few days ceased completely. Clonazepam was suspended whereas deflazacort was continued as a maintenance therapy. The patient was well until December 1995 when, after steroid reduction, she experienced a re-exacerbation of both BD symptoms and paroxysmal dystonic jerks. The latter resembled the jerks previously experienced but were more frequent (five to 10 times a day) and also diurnal. Neurologic examination showed weakness, hyperreflexia, rigidity, and wrist cogwheel phenomenon of the right arm. Blood chemistry, blood cell count, and video-EEG recordings during attacks were normal. During the exacerbation of BD, MRI study, performed at 0.5 Tesla, without contrast and analyzing 7.0-mm thick slices, was normal. After 5 days of 50 mg deflazacort we observed the complete remission of neurologic symptoms and partial remission of oral, genital, and skin lesions.

### Discussion

Behcet's disease can present with a variety of neurologic symptoms including headache, weakness, signs of brain stem or cerebellar involvement, mental disturbances, and disorders of consciousness.<sup>11</sup> We report the first case of paroxysmal dystonia in a patient affected by BD. As previously reported for other neurologic symptoms, paroxysmal dystonia was concomitant with re-exacerbation of BD and was responsive to corticosteroids.<sup>12-14</sup> It is reported that basal ganglia, after the brain stem, are second in frequency among brain structures involved in BD as investigated by a neuroimaging technique.<sup>3,15</sup> For example, Herskovitz et al.<sup>16</sup> found neuroimaging lesions in basal ganglia in seven of 15 patients. Despite the common involvement of basal ganglia, few extrapyramidal disorders have been reported. In a review by Kozin et al.,<sup>7</sup> only 3% of patients presented extrapyramidal signs; these characteristics were not reported. Williams et al.<sup>17</sup> described a case with dystonic posturing, right hemiparesis, mild dysphasia, left third nerve paresis, and a mass in the left basal ganglia at CT scan. More recently, Terao et al.<sup>18</sup> reported a case with dyskinesia of the right limbs and a lesion in the internal segment of the left globus pallidus through MRI studies. Our patient presented paroxysmal dystonia as the unique neurologic manifestation. Paroxysmal features of dystonia can resemble motor focal seizures; video-EEG, however, excluded cortical firing during the attack. Neuro-Behcet and multiple sclerosis share several clinical, pathologic, and instrumental features. Both diseases are disseminated, demyelinating, inflammatory, and may have remitting-relapsing course.<sup>8,12</sup> Therefore, differential diagnosis between these two diseases may be difficult, especially when systemic involvement of BD is not evident. Neurologic features in both diseases are related to a perivascular infiltration by lymphocytes and mononuclear cells with inflammatory and demyelinating lesions.<sup>8,19</sup> The neuroradiologic findings in multiple sclerosis and neuro-Behcet may also resemble each other; however, in neuro-Behcet the main lesions are in the brain stem, thalamus, or basal ganglia and more rarely periventricular.

A videotape accompanies this article.

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lar.<sup>12,20</sup> The clinical features of our case resembled the dystonic jerks observed in multiple sclerosis.<sup>21,22</sup> We were not able to find any focal lesion through MRI, possibly as a result of technical reasons, that is, MRI without contrast or thickness of the slices. However, MRI imaging, which shows abnormalities in neuro-Behcet especially during the re-exacerbations,<sup>7,23-25</sup> has been reported as normal in several cases.<sup>26-28</sup> On the other hand, paroxysmal dystonia in multiple sclerosis has been constantly associated with a focal lesion at MRI, usually in the cerebral peduncle<sup>22,28,29</sup> or internal capsule.<sup>31-33</sup> This report further expands the spectrum of the neurologic manifestations of BD and indicates that the diagnosis of BD should be considered alternatively to that of multiple sclerosis in patients presenting with paroxysmal dystonia.

### Legends to the Videotape

**Segment 1:** A patient with paroxysmal dystonia. The onset is sudden and the jerks last a few seconds. The patient had reduced corticosteroid therapy a few days before the occurrence of the attacks. She had five to 10 attacks a day. Note dystonia of the right arm, neck dystonia, and horizontal nystagmus.

**Segment 2:** Video-EEG recording during paroxysmal dystonic attacks. Note fast symmetric electrical activity with no cortical correlate with paroxysmal dystonia.

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## Essential Palatal Tremor: Evidence of Heterogeneity Based on Clinical Features and Response to Sumatriptan

Essential palatal tremor (EPT) has been reported to be abolished following the administration of Sumatriptan,<sup>1</sup> implicating a pathogenetic role of trigeminal system 5-HT1b and 5-HT1d receptors.<sup>2</sup> We have treated two patients with Sumatriptan who had presumed essential palatal myoclonus/tremor. The failure to benefit in these cases, particularly when combined with other clinical features, supports the concept that EPT may be a heterogeneous disorder.

### Case Reports

A 40-year-old woman had a several-year history of tightness and pressure in the deep midfacial region accompanied by intermittent clicking sounds. Her symptoms were improved when lying down, especially on her right side. Examination was remarkable only for palatal myoclonus/tremor which included the anterior aspect of the soft palate; it was of variable rhythmicity and would at times suppress with distraction. Brain magnetic resonance imaging (MRI) showed normal brain parenchyma and a tortuous left vertebral artery with an associated mild indentation of the pyramid at the level of the lower medulla. No abnormalities were evident in the region of the inferior olive. She was treated with 20 mg Sumatriptan intranasally and was observed over the next hour to have no change in her tremor.

A 42-year-old man had audible clicking for the past 2 years. He had somewhat irregular palatal myoclonus/tremor, which included the anterior aspect of the soft palate, that would occasionally abate and could, in addition, be intermittently entrained to the frequency of volitional finger-tapping movements. An accompanying clicking sound was audible to the patient and observers. He reported being able to control the symptoms for short periods but that they were otherwise present 95% of the time. Brain MRI was normal. Sumatriptan at a dosage of 20 mg intranasally did not alter the movements in any way.

### Discussion

Palatal tremor (palatal myoclonus) characteristically consists of rhythmic involuntary palatal movements resulting from contraction of the tensor veli palatini (TVP) accompanied by ear clicking in the case of EPT and of the levator veli palatini (LVP) without ear clicks in symptomatic palatal tremor (SPT).<sup>3,4</sup> Whereas EPT appears without a known precipitant, SPT usually occurs in the context of a definable disorder affecting the dentato-rubro-olivary pathway. In SPT, there is typically an imaging correlate consisting of olfactory hypertrophy and increased signal intensity on T2- or proton-weighted MRI.<sup>3</sup> No such abnormality is present in EPT.

Although the presence of a tortuous vertebral artery in our first patient raises the question of symptomatic palatal myoclonus, other features are more in keeping with EPT. These include the presence of prominent ear clicking, the characteristic appearance of the palatal movements with tensor veli palatini contractions, and the absence of inferior olivary hypertrophy or signal abnormality on MRI.

Positional improvement, as was present in our first patient, has been reported in other cases of EPT including induction by anterior and lateral neck flexion<sup>5,6</sup> and abatement during anterior neck flexion.<sup>7</sup> Volitional control as seen in our second patient has also been previously described and in some instances palatal myoclonus has been found to be under full volitional control,<sup>8,9</sup> including cases with a familial presentation.<sup>10</sup> Other heterogeneous features among reported cases of EPT include a patient with audible ear clicks in whom the palatal myoclonus/tremor arose from the LVP rather than the typical TVP<sup>11</sup> and others with the origin of tremor and resultant ear clicks from the tongue base.<sup>12</sup>

Whether the presence or absence of these factors indicates the occurrence of different subcategories or types of "essential palatal myoclonus/tremor" is uncertain because most patients reported in the literature have not been evaluated carefully for these factors (for example, irregularities in frequency, volitional control, suppression with concentration, entrainment, or other effects of volitional movement of other body parts). The failure of our patients to respond to Sumatriptan, despite a convincing response in another case,<sup>1</sup> further supports the possibility of heterogeneity in the underlying pathophysiology of EPT. In the future, careful clinical and electrophysiological evaluation of cases of presumed EPT should include assessments for variability in the frequency and presence of the movement (sometimes variations in amplitude of tremor bursts can lead to the clinical appearance of variability in frequency), influence (for example, suppression, entrainment) of other volitional movements, postures and non-motor tasks, voluntary suppressibility or driving, presence of clicks and the localization of the source of the sound (for example, eustachian tube, base of tongue) and the specific muscles involved in the movements (tensor versus levator veli palatini or other oropharyngeal muscles), and finally the pharmacologic response profile (for example, benefit from drugs affecting specific serotonin receptor subtypes). This approach may allow the development of a classification scheme which will provide a better understanding of the pathogenesis of this potentially heterogeneous disorder.

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## Hereditary Chin Tremor/Myoclonus: A Report From Latin America



Hereditary chin tremor (HCT) or familial geniospasm has been regarded as an unusual autosomal-dominant condition characterized by recurrent episodes of involuntary oscillatory rhythmic movements of the chin muscles. Originally described by Domenico Massaro in 1894 in Italy,<sup>1</sup> in the English literature, it was first reported by Stocks<sup>2</sup> in 1922 as an inherited facial spasm. To date, 23 families with this condition have been documented.<sup>2-20</sup> We present the first family with HCT reported in Latin America comprising 28 members spanning four generations.

### Patients

The pedigree is shown in Figure 1.

### Index Case

This 63-year-old woman first presented with chin quivering in early childhood. Symptoms developed gradually without affecting chewing, swallowing, or speech articulation. Tremor disappeared during sleep and worsened with stress. During wakefulness there were tremor-free periods but tremor was often triggered by gazing at flying objects, as in several other affected family members. The movement disorder improved spontaneously although not entirely from ages 15-30 only to recur later and plateau in the mid-50s to date. Even at peak severity, tremor represented little more than a cosmetic impairment. Relevant family history is depicted in the family tree (Fig. 1).

A videotape accompanies this article.

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Neurologic examination was otherwise normal. Laboratory studies, including blood count, serum, and urinary copper and ceruloplasmin were unremarkable. Surface electromyogram (EMG) recording over each mentalis muscle showed overall synchrony of motor unit firing without evidence of denervation. Needle EMG of the mentalis muscle showed bursts of motor units of normal morphology firing pseudorhythmically throughout the muscle at 7-8 Hz. Treatment with botulinum toxin injections into the mentalis muscles was offered but refused by the patient.

Affected members comprised a total of 28 of 63 in four generations. We had the opportunity to examine 13 (Fig. 1) in all of whom abnormal movements developed at birth or in early childhood, remitting spontaneously in only two after 3 years' follow up. As in the index case, tremor worsened with stress and in some it could be induced by asking them to pay attention to an object (for example, flying balloon) but disappeared during sleep. Severity of chin movements peaked in the third decade of life and decreased thereafter. Symptoms represented a mere cosmetic discomfort in all except one whose tremor was severe enough to cause occasional speech disturbance.

### Discussion

Affected families described in the literature have been found in Europe and the United States although predominating in Europe. Except for a single black father and son<sup>21</sup> all were white. Ours is the first family to be reported in Latin America and would probably be loosely regarded as Hispanic rather than white given their birthplace in a Spanish-speaking country. However, our family members mainly descended from Italian natives with traces of other European ethnics, such as Spanish and Croatian. In a genome-wide genetic linkage study performed in two British families, Jarman et al.<sup>22</sup> were able to assign a locus for HCT to the proximal long arm of chromosome 9q13-q21 in only one of the families, indicating genetic heterogeneity.

As in other cases previously described, the characteristic feature in our family is the presence of intermittent bilateral chin movements associated with more prolonged spastic contractions. Although these episodes were usually spontaneous, they could also be triggered by stress or specific activities but not by cutaneous facial stimuli. Also, they could not be precipitated or suppressed at will. They usually disappeared during sleep but in severe cases have been found to persist.

It has been reported that chin tremor begins at birth or in early childhood with variations in frequency and severity throughout life. Soland et al.<sup>11</sup> found that the frequency and severity of tremor episodes in females peaked in early adulthood to decrease gradually and even disappear in some by the fourth or fifth decade of life. In men the condition appears to continue throughout life with only a marginal decrease in severity with increasing age.

Other neurologic features, including tongue biting, myoclonus, nystagmus, rapid eye movements, sleep behavioral disorder, EEG abnormalities, otosclerosis, and hereditary sensory motor neuropathy type I (HSMN I), which have occasionally been described associated with HCT, were not encountered in our family members.<sup>3-6,14,23</sup>

The phenomenology of this movement disorder has recently been challenged by Destee et al.,<sup>24</sup> as the neurophysiological recording in their family was consistent with myoclonus rather

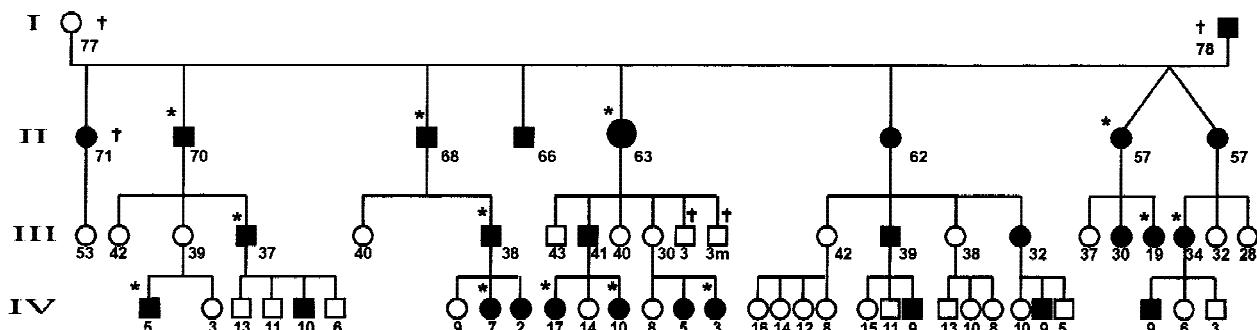


FIG. 1. Family tree. Black circles and squares indicate affected members; †deceased; \*examined; large black circle indicates the index case.

than tremor. Patterns disclosed brief bursts of activity especially associated with stressful or playing activities. As bursts at times discharged in a rhythmic fashion, they clinically resembled tremor, although the frequency tended to be irregular. As our findings closely agree with the above, we speculate that perhaps chin tremor should better be defined as a subtype of essential myoclonus and not tremor.

As illustrated in our family, treatment of chin tremor is often unnecessary because it causes few disabilities. However, because of cosmetic disturbances leading to social embarrassment, some patients may require therapy. Drug treatment has usually been disappointing<sup>6–8</sup> but botulinum toxin infiltrations of the chin muscles can provide relief.<sup>11,25</sup>

### Legend to the Videotape

Illustrative cases depicting chin jerking in eight related patients belonging to II, III, and IV generations.

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## Stimulus-Sensitive Spinal Segmental Myoclonus Improved With Injections of Botulinum Toxin Type A



We report a stimulus-sensitive case of spinal segmental myoclonus (SSM). SSM is the result of abnormal spontaneous discharges of motor neurons in a limited area of the spinal cord inducing involuntary rhythmic or semirhythmic jerks in a muscle or group of muscles. SSM is usually unresponsive to stimuli, but rare cases of stimulus-sensitive myoclonus have been reported.<sup>1-4</sup>

### Case Report

For 2 years a 40-year-old woman had involuntary repetitive jerks of her left shoulder. They were most often precipitated by voluntary movements of the left arm, and they became increasingly violent and painful. At the age of 5 years, she had sustained a traction injury of the left brachial plexus. The after-effects consisted of atrophy, weakness, and altered sensation of the left arm. Her condition remained unchanged for 33 years until she experienced a minor traction injury of the left arm. Three days later the jerks appeared. She found, however, that she could sometimes use this arm, without jerks appearing, to perform some of her domestic activities. The jerks could occur after a loud noise or for no apparent reason, and they sometimes awakened her during the night. Clonazepam and sodium valproate were given without effect. Baclofen slightly reduced the intensity of the jerks.

At the neurologic examination, the entire left arm was atrophic and dangled when she walked. Violent rhythmic jerks of retropulsion and adduction of the scapula, and lesser jerks elevating the left shoulder appeared when she attempted to lift her left arm. Sometimes small simultaneous rhythmic contractions of the right trapezius could be seen but without obvious scapula or shoulder movements. She could stop the jerks herself by pressing on the head of the left humerus with her right fist or more often by putting her left arm in adduction, as well as in hyperadduction behind her back with the help of her right hand (video segment 1). All the muscles of the left arm were weak with sensory loss and areflexia. On the other hand, the strength of the left trapezius and rhomboid was normal. The sensation over the left shoulder and neck was also normal. Tendon reflexes were absent in the left arm. The rest of the

neurologic examination was normal with no signs of long tract involvement in the spinal cord. The examiner could trigger the left shoulder jerks by tapping the tendons of the legs, or on testing pin-prick or light-touch sensation of the right arm. He could also stop the jerks by pressing and stretching the left middle trapezius along the inner border of the scapula (video segment 1). The jerks could be triggered by a clap but not by voluntary movements of her other limbs or by mental calculation. Routine biochemistry showed no abnormalities. Magnetic resonance imaging (MRI) of the spinal cord showed a large cyst with low intensity in T1-weighted images and an intensity as high as the cerebrospinal fluid in T2-weighted images. The cyst extended on the left border of the spinal cord from C4 to C7 and through the intervertebral foramen consistent with a posttraumatic pseudomeningocele. The spinal cord was compressed to the right in the spinal canal by the cyst (Fig. 1).

Coxial needle electromyogram (EMG) of the left arm showed a neurogenic pattern during full effort with no fibrillation potentials at rest. On the other hand, a full interference pattern was recorded from the left trapezius and rhomboid, and the latencies of the CMAPs, recorded from the left upper and middle trapezius by stimulating the spinal accessory nerve at the neck, were normal. On her attempts to lift her left arm, the jerks appeared, and the coaxial needle recorded semirhythmic EMG bursts between 1 Hz and 4 Hz in the trapezius and rhomboids bilaterally, but not in the denervated muscles of the left arm, except the biceps where rare EMG discharges were recorded. The largest bursts were recorded in the left middle trapezius. The duration of the bursts ranged from 50 to over 500 msec. The bursts of the initial jerks were usually of a longer duration and greater amplitude than for the following jerks. The rate was usually higher at the beginning of the series which generally lasted approximately 30 seconds but often stopped before that by the patient putting her left arm in adduction. Following electrical stimulation of the median nerve at the wrist, of the tibial nerve at the ankle, and of the supraorbital nerve at the supraorbital notch, the latency of the first EMG activity coinciding with the onset of the jerk attack was between 150 and 180 msec, whichever nerve or side was stimulated. No response was recorded in the orbicularis oculi following the limb stimulations which triggered the myoclonus. The interwave latencies of the somatosensory-evoked potentials (SSEPs) between the cervical (N13) and the cortical (N19) waves for the arms following median nerve stimulation at the wrist, and between the lumbar (N20) and the cortical (P39) waves for the legs following tibial nerve stimulation at the ankle were normal on stimulation of the right side but delayed on stimulation of the left. The routine electroencephalogram (EEG) was normal. Polymyography showed semirhythmic EMG bursts triggered by voluntary movement of the left arm, by a tap on a tendon, or by a loud noise but not by mental activity. The bursts in the two trapezi and, although sparse, in the left biceps were all synchronous. However, they alternated with those from the left pectoralis (Fig. 2). Injection of 10 mL lidocaine (1% xylocaine) in the middle trapezius at the motor point, as well as the blockade of the left accessory nerve at the neck by the same agent, abolished the jerks, but slight rhythmic contractions could then be seen in pectoralis (video segment 2). One hundred units of botulinum toxin (Btx type A Botox) was injected in the left middle trapezius. At approximately 10 days after the injection, the jerks disappeared. They were still absent

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at 2 months (video segment 3) and remained absent for a total of 4 months. Then the jerks reappeared progressively, and at 6 months they were almost as intense as before the injection.

### Discussion

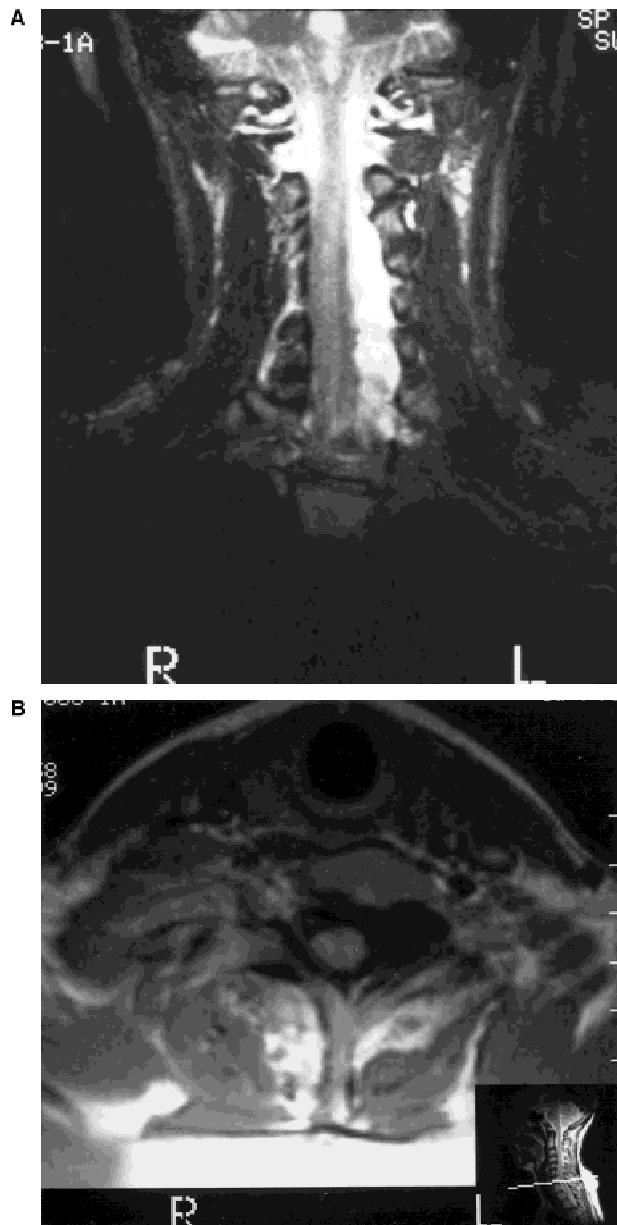
In our patient the segmental myoclonus occurred 32 years after a left brachial plexus injury and just after an additional minor trauma which could have precipitated the occurrence of the myoclonus. Rare cases of segmental myoclonus have been reported after lesions of the peripheral nerves.<sup>5-8</sup> A long delay between the trauma and the myoclonus has been reported in the case of a young man who sustained an upper brachial plexus injury during his infancy and who developed intermittent myoclonic jerks at the age of 18. In this case the jerks disappeared after the surgical treatment of a posttraumatic arachnoid cyst.<sup>9</sup> In the case of our patient, the MRI showed a pseudomeningocele compressing the cervical spinal cord, and the results of the SSEPs were consistent with cervical cord involvement.

The jerks were triggered by auditory, exteroceptive, and proprioceptive stimulation, and abolished by specific voluntary and passive movements but without the electrophysiological signs of upward activation of brain stem innervated muscles, thus eliminating reticular myoclonus. These findings were in accordance with the diagnosis of stimulus-sensitive SSM. Spinal myoclonus is classically less affected by sensory stimulations than reticular and cortical myoclonus. However, in some cases of spinal myoclonus, voluntary movements, tapping the tendons, vibrations, auditory stimuli, or mental stress precipitated or exacerbated the myoclonus.<sup>1-4</sup>

Bursts were not found in our patient's most denervated muscles, which is consistent with the need of relatively preserved motor units for occurrence of myoclonus. Anatomopathologic<sup>1</sup> and electrophysiological<sup>10</sup> studies have suggested that in spinal myoclonus abnormal discharges could be the result of a loss of inhibition (normally provided by the intercalated neurons of the dorsal horn) with the release of abnormal excitatory connections within interneuronal circuits in the spinal cord.

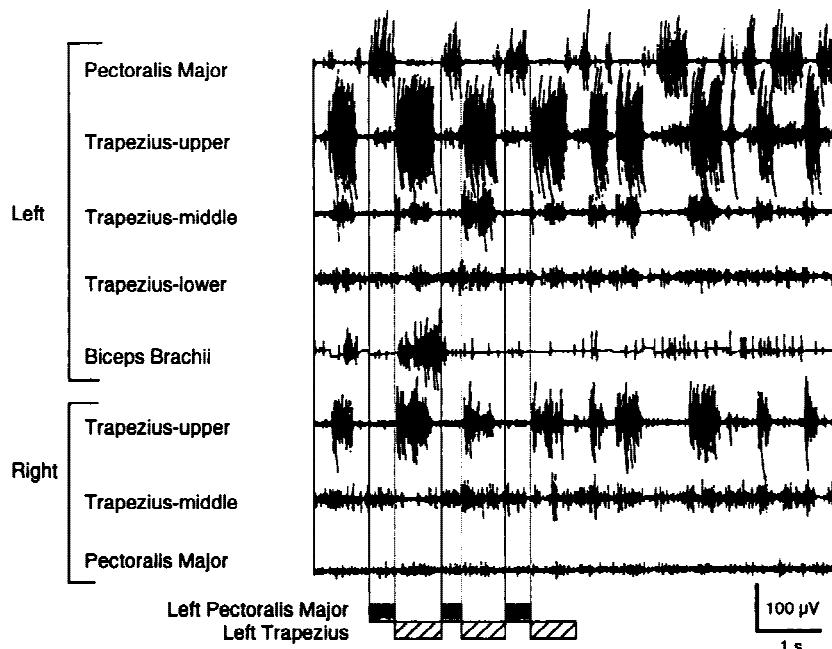
In our patient the synchronous recruitment of the trapezius alternated with the left pectoralis. Based on the concept of a central pattern generator implicated in the generation of rhythmic alternating movements, the SSM could result from discharge in one of the spinal generators distributed along the spinal cord.<sup>11</sup> The jerks were triggered and possibly abolished by activation of peripheral afferent inputs. Thus, the network generating the spinal segmental myoclonus could be considered a closed loop system which is positively or negatively influenced by peripheral afferent inputs.<sup>12</sup> The delay between the start of the afferent volleys following the electrical stimulations and the onset of the first burst of the myoclonic jerks recorded from the middle trapezius was more than 100 msec. The long latencies suggest slow conducting polysynaptic pathways with additional delays for temporal integration. Also, in our patient the voluntary movements of the left arm were usually the triggering factor of myoclonus but not always. That suggests a longer period of modulation of the rhythmic activity of the presumed generator.<sup>13</sup>

Injection of lidocaine at the motor point of the left middle trapezius abolished the jerks. The action of lidocaine may have occurred through the efferent output to the trapezius and by reducing afferent input from the trapezius to the spinal cord. The injection of BTx A in the middle trapezius was followed by



**FIG. 1.** Magnetic resonance imaging of the spinal cord. (A) T2-weighted image shows a large cyst with intensity as high as in the cerebrospinal fluid extending along the left side of the spinal cord from C4 to C7 consistent with a posttraumatic pseudomeningocele. (B) T1 image shows the cyst with a low intensity extending through the intervertebral foramen and compressing the spinal cord to the right.

a dramatic improvement lasting 4 months. Effectiveness of BTx A in limb myoclonus has already been reported.<sup>14</sup> BTx A blocks the cholinergic transmission of the extrafusal fibers. The remarkable effect of BTx in the stimulus-sensitive SSM of our patient could suggest additional modalities of action of BTx such as by blocking the cholinergic transmission of the fusimotor fibers,<sup>15</sup> and more putatively by raising the level of excitability of the motor neurons through a retrograde transport and transneuronal effect as demonstrated in experimental studies.<sup>16</sup>



**FIG. 2.** Surface EMG activity recorded during myoclonic jerks triggered by tapping a tendon. Note that the bursts in the trapezius alternate with the bursts in the pectoralis (horizontal bar = 1 sec, vertical bar = 100  $\mu$ V).

### Legends to the Videotape

**Segment 1:** The standing patient triggers the myoclonus by lifting her left arm. Violent rhythmic jerks of retropulsion and adduction of the scapula and lesser jerks of elevation of the shoulder can be seen. The jerks could be greatly reduced when the patient held her left arm in hyperadduction behind her back with her right hand. The examiner can abolish the jerks by pressing and stretching the middle trapezius along the inner border of the scapula. Pseudorhythmic contractions of the trapezius are apparent when the patient is flat on her face.

**Segment 2:** After blockade of the left accessory nerve at the neck by lidocaine, the jerks of the scapula are no longer present but slight rhythmic contractions at the pectoralis can now be seen.

**Segment 3:** Two months after injection of 100 U Botox in the left middle trapezius, the myoclonus is no longer triggered by voluntary movements of the left arm.

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## Pathologic Laughter Resulting From a Large Midbrain Arteriovenous Malformation



Laughter is described as pathologic when it is uncontrollable, inappropriate, prolonged, or induces an abnormal facial expression (forced). It has been reported in association with a wide range of focal and generalized intracranial conditions such as vascular lesions, motor neurone disease, toxic brain damage, brain stem tumors, hypothalamic hamartomas, and clival chordomas.<sup>1-9</sup> Pathologic laughter (PL) can also occur in Angelman's syndrome and cataplexy.<sup>10</sup>

The stimulus provoking pathologic laughter can be subtle and is often non-humorous. PL has been reported to occur in response to emotions of many kinds such as anger, sadness, or that induced by the receipt of bad news.<sup>11</sup> It has also been observed to be triggered by specific stimuli such as horizontal eye movements, funduscopy, commencement of speech, and goal-directed movement of an arm.<sup>11-13</sup> The underlying pathophysiology is complex and remains poorly understood, although the prefrontal areas, temporal lobes, limbic system, and upper brain stem are all thought to be involved in the emotional expression and laughter.

We present a patient in whom pathologic laughter had been present for many years before the diagnosis of a large midbrain arteriovenous malformation was made. The laughter was provoked by a variety of non-humorous stimuli, particularly funduscopy and stimuli applied to the right side of her body. The patient is also notable because she developed other signs including an L-dopa-responsive (Holmes') tremor of the right arm.

### Case Report

This 33-year-old woman presented in January 1996 with a 12-month history of dysarthria, incoordination, and intermittent urinary incontinence. However, her sister-in-law (a social worker) was concerned because the patient was laughing inappropriately and uncontrollably, a situation that in retrospect had been present and gradually worsening from the age of 13. The patient was not aware that her laughter was abnormal and she could not identify specific triggers for it. The sister-in-law also noted that the patient's mood appeared to be low.

Initial examination revealed a woman who kept bursting into laughter when approached by the examiner. Her laughter was particularly prominent during assessment of her visual acuities, fields, eye movements, and fundi. Her facio-expiratory move-

ments during laughter were normal and her laughter generated mirth. She had a nasal dysarthria with depressed palatal movements. The jaw jerk and gag reflex were present but not brisk. No fasciculation or wasting of the tongue was present. There was mild right arm incoordination and gait ataxia. The examination was otherwise unremarkable.

A computed tomography (CT) scan of the head showed a large midbrain arteriovenous malformation (AVM) which was subsequently confirmed by a cerebral angiogram (Fig. 1). The latter showed a well-defined AVM that fed through small branches of the basilar tip (Fig. 1). There was no flow aneurysm and the lesion was unsuitable for neurosurgery or embolization. The patient was therefore referred for stereotactic neuroradiosurgery.

In July 1996, while waiting for the radiosurgery, she was admitted with a history of sudden-onset severe occipital headache with confusion and blurred vision. An acute intraventricular hemorrhage from the AVM was demonstrated on a CT scan (Fig. 2). She was managed with intravenous fluids, analgesia, and nimodipine. She made a partial recovery from the acute bleed but was left with a bilateral internuclear ophthalmoplegia, impaired upward gaze, and her dysarthria, right arm incoordination, and gait ataxia were worse. However, the bursts of laughter were subdued for a few weeks after the bleed. Stereotactic radiosurgery to the AVM was carried out in November 1996 and her symptoms slowly improved except for the pathologic laughter which had become prominent again. A cerebral magnetic resonance imaging scan 5 months after radiosurgery showed that the AVM was still patent (Fig. 3).

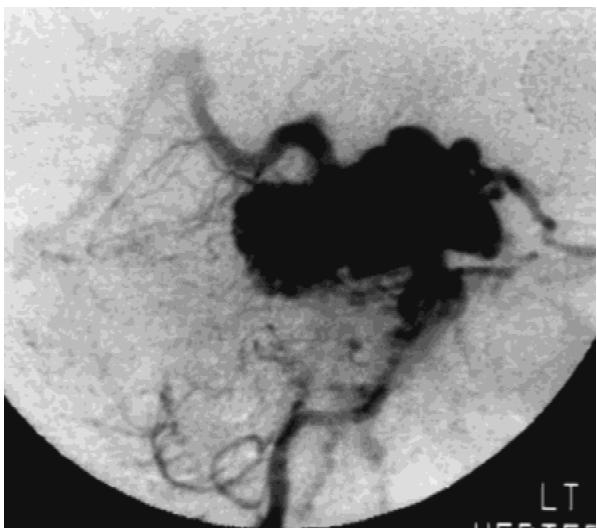
On review in August 1997, the patient reported that her diplopia, speech, incoordination, and gait ataxia were slowly getting worse. In addition, an intrusive tremor had developed in her right arm. Examination revealed a depressed woman who frequently burst into laughter. On one occasion she switched rapidly from laughter to tears. (However, her daytime caretaker noted that it was most unusual for her to cry.) The patient's laughter was not preceded by elation or excessive happiness. She was unable to suppress her laughter when she attempted to speak and during goal-directed movements of both arms. Funduscopy, eye movement examination (horizontal rather than vertical pursuit movements), tactile stimulation particularly to the right side of her face or cornea induced laughter (see videotape segment 1). Her speech was more dysarthric and the palatal movements were weak. The gag reflex and jaw jerk were present. There was a mild right hemiparesis associated with brisk, right-sided reflexes and an extensor plantar response, and a wide-based ataxic gait. Tremor of the right arm was seen at rest and was provoked by counting (grade 3-4 of 10). It was most evident at the wrist, although there was also a more proximal component. The tremor almost disappeared on posture when mild dystonia was evident and reappeared during the finger-nose-finger test when past-pointing and intention tremor (grade 2-3 of 10) occurred. Orthoptic assessment revealed a bilateral internuclear ophthalmoplegia and failure of convergence on downward gaze. A selective serotonin reuptake inhibitor antidepressant (venlafaxine) was administered for her affective state and co-beneldopa (Madopar CR three times a day) provided good symptomatic control of her resting tremor but not the intention component of the tremor which responded much less.

In September 1997, the patient was readmitted as an emergency having had another abrupt deterioration. She had also

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**FIG. 1.** Cerebral angiogram: a lateral view of the vertebral artery injection demonstrating a well-defined high flow midbrain AVM. The blood supply is through multiple small branches arising from the basilar tip and the venous drainage is predominantly through the lateral mesencephalic veins to the straight sinus. The nidus of the AVM measures 2 cm in diameter.

started to have seizures in the preceding 48 hours which were short-lived and consisted of jerking of the arms accompanied by head retraction without loss of consciousness and which were abolished by gabapentin. Re-examination revealed worsening of the ataxia, right hemiparesis, dysarthria, and swallowing. The patient's affect was still low but had improved with antidepressant treatment. However, the pathologic laughter had ceased (see videotape segment 2). A CT scan excluded another intracranial hemorrhage. A formal psychiatric assessment revealed that she did not have major biologic depression or mania.

### Discussion

We present a patient who has an unusual form of pathologic laughter and an underlying AVM arising from the basilar artery. There are three main reasons to conclude that this patient's pathologic laughter was caused by her AVM. First, her PL ceased when the AVM bled. Secondly, the PL returned during her recovery. Third, sensory stimuli to the right side of her face and body produced laughter more often than stimuli applied to her left side which would be consistent with the left of center location of her midbrain AVM. To our knowledge, there have been only two reported cases of brain stem vascular malformation causing pathologic laughter<sup>14,15</sup> and only one producing an L-dopa-responsive tremor.<sup>16</sup>

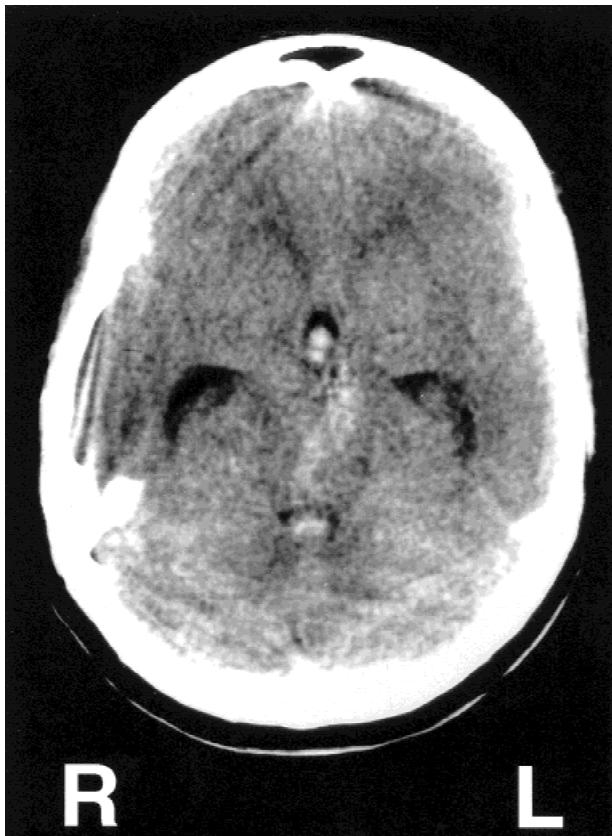
Our patient did not have tremor at the time of presentation but developed a Holmes' (previously termed "midbrain" or "rubral") tremor approximately 9 months after her intraventricular bleed. Because an L-dopa-responsive rubral tremor arising from a brain stem angioma had been described previously, co-beneldopa (Madopar CR) was administered to beneficial effect; the rest tremor was markedly attenuated but the intention component persisted (see videotape segments 1 and 2, respectively, filmed while off and on Madopar CR).<sup>16</sup>

### Normal Laughter

Laughter is normally accompanied by a feeling of amusement and joy. The stimulus to laugh may proceed from our thoughts or through visual, auditory, and cutaneous (tickling) stimuli and the resultant laughter is usually proportional to the stimulus in degree and duration.<sup>17</sup> Natural laughter consists of two parts, a more voluntary movement causing a smiling facial expression and a more automatic laryngeal and respiratory response.<sup>17</sup> In 1924 Wilson postulated a supranuclear pontobulbar laughter center that controlled input to the facial nucleus, nucleus ambiguus, and the region of the upper cervical cord that controls the phrenic nerve. He also postulated that there is an integrative mechanism involving the medial thalamus, hypothalamus, and subthalamus that is under voluntary and involuntary control from the cerebral cortex.<sup>1</sup> The involvement of the anterior cingulate, anterior thalamus, hypothalamus, and globus pallidus in the production of laughter have been supported by electrical or mechanical stimulation studies in people.<sup>18-21</sup>

### Pathologic Laughter

Attempts to classify pathologic laughter have yielded inconsistent results. Black<sup>11</sup> proposed three specific forms of PL: (1) forced laughter, which is seen in pseudobulbar palsy; (2) laugh-



**FIG. 2.** Cerebral CT scan: an unenhanced scan showing blood in the third and fourth ventricles with hyperdensity within the midbrain implying hemorrhage within the AVM and extension into the ventricular system.

ter fits (gelastic epilepsy); and (3) laughter secondary to psychiatric conditions. Grumet<sup>22</sup> included a fourth type, excessive or "low-threshold" laughter, which he considered to be the result of physiological impairment of cortical inhibitory influences. However, neither of these classification schemes accommodates the laughter apparent in our patient.

Shaibani and colleagues proposed the following three features to distinguish PL from normal laughter<sup>23</sup>: first, it is inappropriate in that it occurs spontaneously or in response to nonhumorous stimuli; secondly, it is involuntary; and third, it is unmotivated in that the laughter is incongruous with the person's mood. Our patient's laughter fulfilled two of these criteria. It was not under voluntary control and was triggered by various motor acts and nonhumorous sensory stimuli. However, her laughter produced mirth although her mood before the onset of the PL was not elated or expansive (see videotape segment 1).

This form of PL can be distinguished from pseudobulbar laughter, laughter resulting from gelastic seizures, and that which occurs in psychiatric disorders.

### Pseudobulbar Laughter

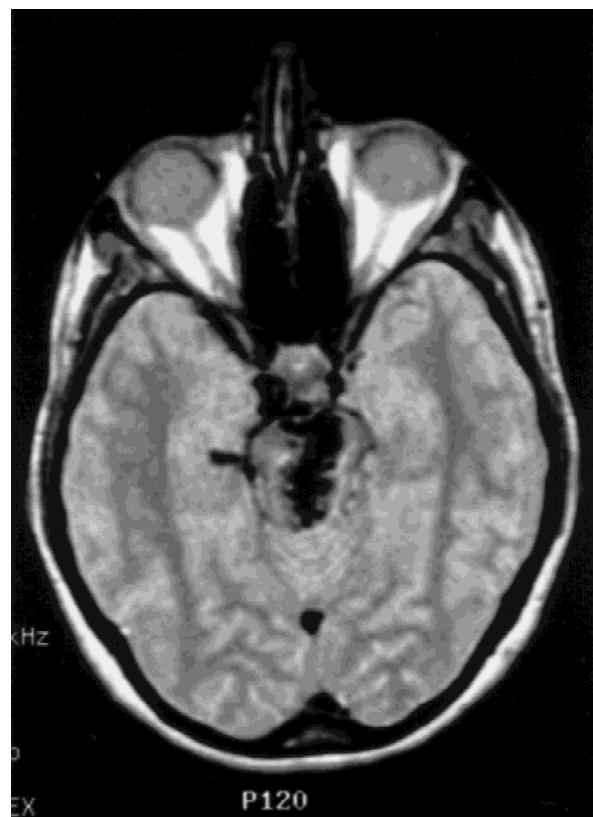
Despite developing a partial pseudobulbar palsy, our patient did not show the characteristic features of pseudobulbar (forced) laughter in which there is usually an exaggerated response to stimuli that would be expected to trigger laughter. Crying may be triggered as well as laughing, giving rise to emotional lability. Although our patient was once observed in the clinic to switch rapidly from laughing to crying, this was not true emotional lability because the laughter (unlike the crying) had no appropriate trigger and because this pattern of emotional response was not sustained. Another distinction between our patient's laughter and pseudobulbar laughter is that whereas our patient's facial expression during laughter was normal, pseudobulbar laughter produces an abnormal facio-respiratory pattern with waxing and waning of contractions of the facial musculature.<sup>11</sup> The corticobulbar pathways are interrupted resulting in supranuclear denervation of bulbar and pontine nuclei and consequently impaired voluntary facio-respiratory movements that nevertheless contract reflexly, albeit abnormally, during laughter. The resultant laughter spells can be exhausting, distressing, and socially embarrassing.<sup>11,17</sup>

### Laughter Fits (Gelastic Epilepsy)

Our patient did not have gelastic epilepsy, which usually results in laughter episodes that are, or form part of, a stereotyped motor phenomenon for which there is usually no humorous trigger.<sup>21</sup> However, she did eventually develop seizures, which were successfully treated with gabapentin.

### Laughter Secondary to Abnormal Mental States

Disinhibited frontal laughter spells are part of an extreme state of elation. In 1954 Kramer described compulsive laughter that has no apparent cause in association with continuous merriment in patients who have had a frontal lobotomy. The laughter spells in these patients were said to be meaningless, non-contagious, and were accompanied by a distortion of their facial expression.<sup>24</sup> These patients were also overactive, overtalkative, and disinhibited.<sup>24</sup> A similar presentation is possible during manic episodes or during mixed affective states in



**FIG. 3.** MRI brain scan: axial proton density-weighted MR image through the midbrain taken 5 months after radiosurgery demonstrating that the AVM remains patent.

which such features coexist with features of depression. In our patient, there was no evidence of any of these presentations. Similarly, inappropriate laughter can occur in schizophrenia but then it is usually shallow, fatuous, and without mirth.

### Fou rire prodromique

Fou rire prodromique is a rare syndrome in which pathologic laughter occurs at the onset of an apoplectic event.<sup>25-28</sup> Ischemic stroke affecting the basalis pontis, hemorrhage into both thalamus and internal capsules, and rupture of an aneurysm that was pressing on the upper brain stem, posterior part of the third ventricle, and mammillary bodies have all been recorded as causing this syndrome.<sup>25-28</sup> Clearly the temporal pattern of our patient's PL distinguishes it from fou rire prodromique.

### Mirth

The relationship between mirth and laughter is complex. Normally mirthful laughter can be elicited by external stimuli (visual, auditory, and somatosensory) or internal stimuli (thought) pertaining to ironic or absurd situations.<sup>21,22</sup> Mirthful laughter can also occur without a perception of incongruity as in tickling or a euphoric state; the latter are thought to be less cognitively processed and related to socialization. Mirthless laughter is also seen in response to embarrassment or fear.<sup>21</sup>

The majority of pathologic laughter cases are thought to be mirthless, which in consequence has been called "sham mirth"

by some authors.<sup>21</sup> However, there have been five reported cases of pathologic laughter in patients with gelastic epilepsy in whom there was a feeling of mirth at seizure onset. The lesions in these patients were of temporal, frontal, or hypothalamic origin.<sup>21</sup>

According to the theory of laughter proposed by Arroyo et al. in 1993, the cingulate gyrus is of primary importance in the motor aspects of laughter, whereas the temporal cortex is involved in the processing of humor. These two areas were thought to interrelate with each other and other cortical and subcortical areas to produce laughter,<sup>21</sup> which is emitted from the limbic system, including the cingulum, to the effector brain stem neurones involved in the expression of emotion.<sup>21</sup>

Although our patient appeared joyful and elated during her laughter bursts, she reported the absence of mirth before them and had no signs or behavior to indicate a manic disorder. However, laughing made her feel happy (see videotape segment 1), suggesting that feedback was occurring from the brain stem to the limbic system. This situation is different from true emotional lability in which patients have a readiness or a lowered threshold to laugh or cry. This case therefore supports the notion that the motor act of laughter may bring out the emotion associated with it, which is thought to be a result of the reciprocal association between the executive and the affective systems.<sup>21</sup>

## Mechanisms

Matsuoka et al., from their studies on tumors causing pathologic laughter, emphasized that lesions in a number of areas of the brain cause emotional activity, which can arise at three levels: a low level (brain stem), an intermediate level (diencephalic or limbic), and a high level (anterior hypothalamic, frontal and temporal cortex).<sup>7</sup> These three anatomic levels were thought to have different roles in the expression of emotions. The cortical level was considered to be responsible for controlling the emotional response, the effector level used the bulbar nuclei at the brain stem to evoke the physiological manifestations of laughter, and the synkinetic (intermediate) level integrated both the cortical and bulbar responses.<sup>11</sup>

In 1977 Leopold reported horizontal gaze-induced pathologic laughter in a patient with osteochondroma displacing the midbrain and pons. He postulated that the tumor in his patient had compromised the cortico-fugal fibers which synapse in the cortico-tegmental tract or the lower brain stem (cortico-tegmental tract).<sup>12</sup> The clinical features of our patient support his observation, although it is not clear to us why horizontal but not vertical ocular-pursuit movements should provoke laughter in these patients. Perhaps horizontal eye movements are intrinsically funnier than vertical ones, as in our culture upgaze indicates exasperation and downgaze fear or depression. Alternatively, there might have been differential treatment of the retinal input from a horizontally moving target and background compared with a vertically moving one.

An explanation is also required for the provocation of laughter by funduscopic and while the pupil responses or corneal reflexes were elicited or during light touch to her face (particularly the right). Again it is not clear why this should have happened because these different sensory stimuli input at different CNS levels ranging from the pons to the thalamus. In addition, voluntary goal-directed movements of her arms precipitated laughter but maintaining a posture (arms outstretched) did not (see video segment 1).

Hartman et al. emphasized the important role in emotional expression of afferent sensory fiber input into the thalamus.<sup>1</sup> Perhaps a midbrain defect could disinhibit the thalamus so sensory input leads to the release of emotional activity without prior engagement of higher cortical centers. This hypothesis may provide a good explanation for the provocation of our patient's laughter by tactile as well as by visual stimuli, speech, and specific limb movements, although it does not explain the differential response to horizontal compared with vertical ocular pursuits. As far as we are aware, the induction of mirth by laughter, as demonstrated in our patient, has not previously been described. This suggests the possibility that the motor act of laughing may itself influence mood by upward feedback to the limbic system.

## Conclusion

We have described a patient with a midbrain AVM who exhibits an unusual form of laughter. Her laughter is pathologic, because it is induced by a variety of non-emotional stimuli but has a natural form of facio-respiratory expression and generates mirth. The patient is also unusual in that she has a Holmes' tremor which responds partially to L-dopa treatment.

## Legends to the Videotape

**Segment 1:** August 1997: The patient can be seen laughing: (a) spontaneously and during articulation; (b) during horizontal but not vertical ocular-pursuit movements (a rest tremor of the right hand is also evident); (c) while the right but not the left corneal reflex is elicited; (d) during the finger-nose-finger test performed with either arm; (e) but not while holding her arms outstretched; (f) during funduscopic and while the pupil responses are elicited.

**Segment 2:** September 1997: The patient is no longer laughing spontaneously and not during (saccadic) eye movements, speech, and the finger-nose test. The patient is on Madopar CR three times a day. There is no rest tremor but an intention tremor persists but to a lesser degree.

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## Delayed Onset of Hand Tremor Related to Cerebellar Hemorrhage

Tremor is a rhythmic oscillatory movement. Although it is the most common movement disorder clinically, the pathophysiological mechanism of this hyperkinesia is still uncertain. Recently, a study of positron emission tomography (PET) in patients with essential tremor revealed increased cerebellar activity and indicated that the cerebellum may contribute to the generation of tremor.<sup>1</sup> We report a patient with delayed onset of kinetic tremor caused by an ipsilateral cerebellar hemorrhage. This case clinically supports the concept that cerebellar dysfunction may contribute to the pathogenesis of kinetic tremor.

## Case Report

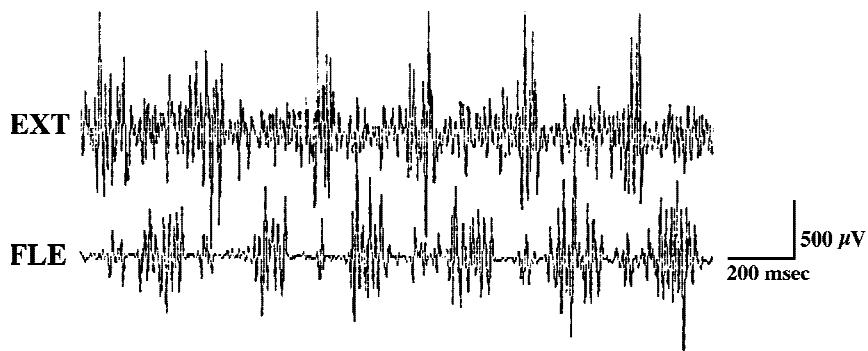
This 54-year-old, right-handed, hypertensive man had an acute onset of gait disturbance in January 1996. Dysarthria of his speech and ataxia of his right extremities were also noted. However, the function of motor and sensory systems was preserved. A computed tomography (CT) scan of the brain was performed and revealed a focal hemorrhage in the right cerebellum. He then was admitted to a hospital where he received conservative treatment. Seven days after onset of the cerebellar hemorrhage, an insidious-onset tremulous movement of his right fingers was noted when he was holding a pen or other light object in his right hand. Although the cerebellar dysfunction was gradually improved, the hyperkinetic movement was still obvious and caused some difficulty in his daily activity.

Four months later, he visited the movement disorders clinic of our hospital because the kinetic tremor in his right hand still remained. On neurologic examination, he was alert and oriented but a mild dysarthria was noted. The function of motor and sensory systems was normal. There was mild impairment of a rapid alternating movement of the right hand and agility of the right leg. The finger-to-nose test revealed mild dysmetria of his right arm but there was no intentional tremor. Moreover, there was a tremor characterized by flexion-extension movements of his right third, fourth, and fifth fingers at the right metacarpophalangeal joints when he was holding a pen in his hand, but there was no tremulous movement when he wrote. There was also no tremor while he was at rest or when he was outstretching his right arm. An electromyogram using surface electrodes recorded a rhythmic tremor burst with frequency of 3–4 Hz alternating between extensors and flexors of the right forearm while he was holding a pen in his right hand (Fig. 1). However, there was no tremor burst during the finger-to-nose test.

The magnetic resonance image (MRI) of the brain revealed a focal lesion consistent with a recent hemorrhage located in

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**FIG. 1.** Electromyography recording (surface electrodes) from extension (upper trace) and flexion (lower trace) of muscles in the patient depicted a regular continuous and alternative 3-Hz tremor burst while the patient's right forearm was outstretching and the hand was holding a pen. FLE, flexors of the right forearm; EXT, extensors of the right forearm.

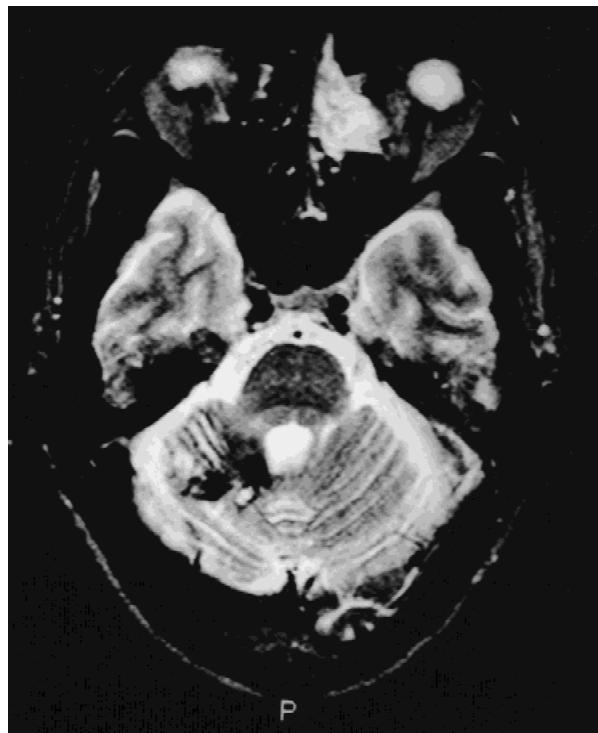
the right cerebellar area (Fig. 2). He was first treated with propantheline but this was ineffective. However, medication with clonazepam and trihexyphenidyl gradually improved the tremor. A 6-month follow up of his condition showed that his tremor nearly remitted.

### Discussion

Some kinetic tremors of the extremities may occur in patients who have, or will later develop, other neurologic conditions.<sup>2</sup> In our patient, his tremor was characterized by a low tremor frequency (3–4 Hz) and only occurred when he was holding a pen. Moreover, the tremor did not appear in writing, resting, or finger-to-nose test. We, therefore, thought the nature of his tremor was position-dependent tremor. In this study, there was a gradual development of kinetic tremor after the

onset of the cerebellar hemorrhage, and this hyperkinesia was gradually restored after treatment using medication. Because there was no pre-existing lesion in the brain and a lack of any precipitating factors (such as ingestion of drugs), we think there is a causal relationship between kinetic tremor of hand and ipsilateral cerebellar hemorrhage. Furthermore, there was a 7-day gap between the onset of stroke and initiation of the tremor. This is compatible with previous reports that tremor related to a vascular insult often has a delayed onset.<sup>3–5</sup>

Cerebellar disease may result in either a postural or kinetic tremor.<sup>6</sup> An animal study by Carrea and Mettler revealed that selective lesions in various parts of the branchium conjunctivum can selectively result in tremor.<sup>7</sup> An animal study has revealed that the process of regeneration with neof ormation of synapses of the cerebellofugal projection after transection of the superior cerebellar peduncle can occur within hours to days and can become functionally active.<sup>8</sup> Therefore, the neural plasticity in the central nervous system involving the cerebellum may contribute to the pathogenesis of the delayed-onset kinetic tremor caused by the cerebellar lesion. Recently, a study by Singer et al. revealed that there was a 50% abnormality in tandem gait of patients with essential tremor.<sup>9</sup> This result indicated that cerebellar dysfunction may contribute to the pathophysiology of tremor. Furthermore, Wills et al. applied PET to study patients with essential tremor, and revealed that there was a significant increase in the bilateral cerebellar blood flow during arm extension as well as at rest.<sup>1</sup> This study was compelling evidence that the cerebellum plays an important role in the pathophysiological mechanism of tremor. Therefore, our patient presenting with kinetic tremor after onset of cerebellar hemorrhage gives clinical evidence to support the preceding studies that the cerebellum may be a generator of oscillatory movement of patients with kinetic tremor.



**FIG. 2.** Axial T2-weighted (TR/TE; 3000/90) magnetic resonance scan shows dark signals of old blood product (hematosiderin) in the right cerebellar hemisphere and surface of folia.

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## Rubral Tremor Associated With Cavernous Angioma of the Midbrain



Rubral or midbrain tremor was first described<sup>1</sup> as typically of low frequency (3-5 Hz) and large amplitude. It is present at rest, enhanced by both posture and action, and disappears during sleep. There is a lack of voluntary control and any volition to inhibit the tremor often results in its enhancement.

This tremor has been associated with a variety of conditions including cerebral hemorrhage,<sup>2,3</sup> trauma,<sup>4,5</sup> neuroleptic exposure,<sup>6</sup> multiple sclerosis,<sup>7</sup> midbrain abscess,<sup>8</sup> and inborn metabolic disorder.<sup>9</sup> There is, however, no general agreement on whether the tremor should be regarded as a separate clinical and pathologic entity. The term "rubral" tremor somewhat denotes involvement of the red nucleus,<sup>10</sup> but there is little evidence that lesions of the red nucleus are essential for the development of the tremor.<sup>11</sup> We report a case of rubral tremor associated with a cavernous angioma situated over the contralateral tegmentum.

### Case History

A 42-year-old, right-handed, Chinese man presented in May 1992 with gradual onset of left upper limb tremor, which initially affected the left forearm but later progressed to involve successively the left upper arm and the left shoulder. The tremor increased in severity over the course of 6 months, became continuous, and disappeared only during sleep. There was

A videotape accompanies this article.

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no headache or dizziness. He has a history of well-controlled non-insulin-dependent diabetes mellitus for 5 years and carcinoma of the nasopharynx. The latter was treated with external irradiation and had remained in clinical remission for 4 years. He has no history of head injury or family history of tremor.

On examination, the patient has a slow resting tremor involving the left upper limb (see the videotape). The tremor was continuous at rest, enhanced in posture, and grossly exacerbated with action and intention. There were marked ipsilateral cerebellar signs and purposeful movement of the left hand was impossible. Muscular tone, power and tendon reflexes were preserved. Sensation and speech were normal. He has a partial right-sided third nerve palsy with symmetric pupils and preserved pupillary reflexes (see the videotape). There was a downward gaze palsy of his right eye. Other cranial nerves were intact. The rest of the body was unaffected. Palatal myoclonus and ptosis were not present.

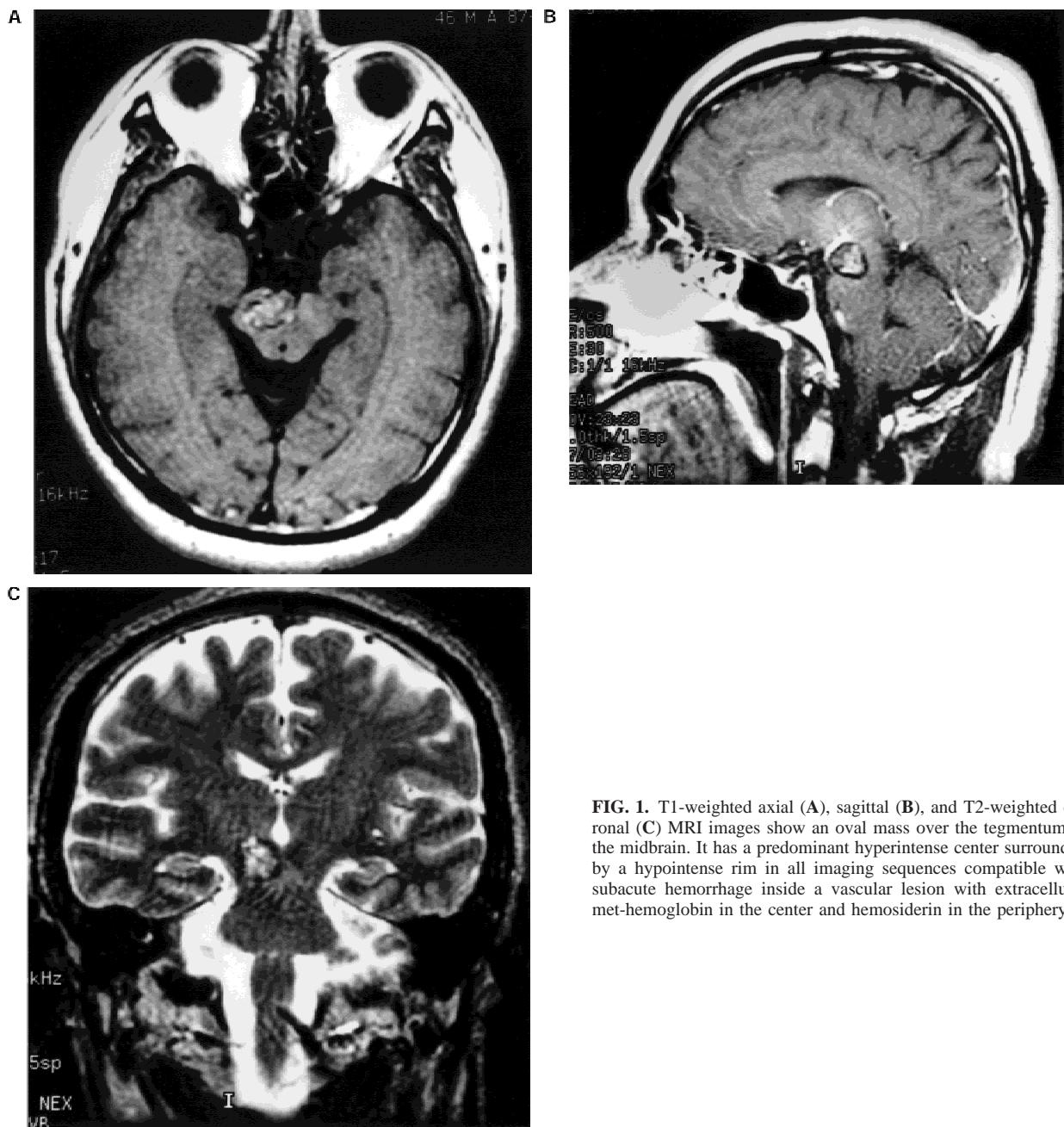
Subsequent investigations with magnetic resonance imaging (MRI) revealed an oval mass (1.5 cm in diameter) over the tegmentum in the midbrain, including the red nucleus (Fig. 1). Superiorly, the lesion extended to the lower aspect of the right thalamus, and inferiorly the upper aspect of the right pons. There was a predominant hyperintense center surrounded by a hypointense rim in all imaging sequences. No significant mass effect or perifocal edema was detected. The findings were compatible with subacute hemorrhage inside a vascular lesion with extracellular met-hemoglobin in the center and hemosiderin in the periphery. No vascular malformation or abnormal vessels were identifiable on magnetic resonance angiography (MRA) and digital subtraction cerebral angiography. The overall picture was consistent with a cavernous angioma.

The patient declined surgical intervention, including stereotactic thalamotomy. Therapeutic trials with levodopa, clonazepam, propranolol, and anticholinergics were all unsuccessful. Although he continued to live independently, he could not resume his previous job as an airport supervisor.

### Discussion

The tegmentum of the midbrain contains all the ascending spinal and lower bulbar tracts, and many of the descending pathways. The function of the red nucleus within the tegmentum is primarily that of motor coordination. It receives crossed efferent fibers from the cerebellum and projects fibers to the thalamus and contralateral spinal cord through the rubrospinal tract.

The pathophysiology of rubral tremor is poorly understood. Combined lesions of the superior cerebellar peduncle and tegmental structures in experimental animal studies have been shown to result in what resembled a rubral tremor.<sup>12</sup> It has been suggested that rubral tremor may in fact represent a combination of a parkinsonian (rest) and a cerebellar (postural and kinetic) tremor.<sup>4,6</sup> The two components act synergistically and are perhaps linked by a central processor or through an as-yet undiscovered pathway.<sup>6</sup> Specific thalamic nuclei thought to be involved in the final common pathway of various tremor disorders<sup>5</sup> and lesions at various sites, including the substantia nigra, cerebellum, and cortex, may cause increased rhythmic activities in the thalamus.<sup>13</sup> Using positron emission tomography and [<sup>18</sup>F]-dopa uptake technique, Remy et al. demonstrated significant ipsilateral dopaminergic denervation in patients with rubral tremor implicating damage to the substantia nigra, the nigrostriatal fibers, or both.<sup>14</sup> The fact that levodopa some-



**FIG. 1.** T1-weighted axial (A), sagittal (B), and T2-weighted coronal (C) MRI images show an oval mass over the tegmentum in the midbrain. It has a predominant hyperintense center surrounded by a hypointense rim in all imaging sequences compatible with subacute hemorrhage inside a vascular lesion with extracellular met-hemoglobin in the center and hemosiderin in the periphery.

times provides therapeutic benefit substantiates the suggestion that the dopaminergic pathway is involved.<sup>3</sup> The postural component, on the other hand, is probably related to disruption of the cerebellar outflow pathway (for example, the dentatothalamic and dentatorubral tracts) at the superior cerebellar peduncle and the rubro-olivary tract in the central tegmentum.<sup>1,15</sup>

The finding of an associated third nerve palsy in our patient is not unique. Oculomotor palsy, ptosis, and internuclear ophthalmoplegia have been known to coexist with midbrain tremor after head injury<sup>5</sup> and pontine hemorrhage.<sup>2</sup> In 1912, Henri Claude first described a case of paramedian mesencephalic infarction presented with an ipsilateral third nerve palsy and con-

tralateral ataxia and dysmetria.<sup>16</sup> Other cases of the eponymous oculomotor fascicular syndrome have since been described.<sup>17</sup> We think the presence of the right-sided downgaze palsy in our patient indicates that the tectum as well as adjacent areas dorsal and rostral to the tegmentum may be affected.

Our patient has a cavernous angioma in the contralateral mesencephalon. Cavernous angioma is a benign, hamartomatous lesion characterized by abnormally enlarged vascular channels. Its size may range from a few millimeters to many centimeters. Typically, these vascular spaces are separated by fibrous tissue with no intervening brain parenchyma. It is well-demarcated from the surrounding brain tissue, which is often

gliotic and hemosiderin-stained.<sup>18</sup> The incidence of cavernous angioma is approximately 0.5%.<sup>19</sup> Multiple lesions may be present in up to 50% of cases and familial series have been described.<sup>20</sup>

Magnetic resonance imaging is the most sensitive and specific diagnostic method of choice for cavernous angioma.<sup>19</sup> The residual macrophages laden with hemosiderin, as a result of repeated hemorrhage, presents as an indelible tissue signature of an area of decreased signal intensity on a T2-weighted image in the periphery.<sup>20</sup> Cavernous angioma is sometimes called the "angiographically occult vascular malformation." Angiography is normal in approximately one third of cases, the most common sole positive finding being an avascular mass.<sup>21</sup> Abnormal dilated arteries, draining veins, or arteriovenous shunting, suggestive of arteriovenous or venous malformations, are absent.<sup>20</sup>

Cavernous angioma most commonly presents with seizures, hemorrhage, and progressive neurologic deficit.<sup>21</sup> Presentation as a movement disorder is unusual. Cases of cavernoma in the head of the caudate nucleus have presented as hemichorea<sup>22</sup> and in the lentiform nucleus as focal dystonia.<sup>23</sup> The lesion in our patient was situated over the right tegmentum and we think it is likely to be responsible for his tremor. Cavernoma rarely increase appreciably in size over time<sup>19</sup> and our patient's lesion did not exhibit a significant mass effect on imaging. Almost all cavernous angioma show evidence of hemorrhage, either microscopic or gross.<sup>21</sup> Cavernomas may present as subarachnoid hemorrhage associated with the development of a classic rubral tremor.<sup>3</sup> Our patient did not have any overt hemorrhage clinically. There were, however, repeated episodes of subclinical hemorrhage, as evident by the dark surrounding ring of hemosiderin on MRI. It is possible that repeated episodes of subclinical hemorrhage may have resulted in progressive dysfunction of the adjacent nigrostriatal and cerebellar outflow tracts with worsening of the tremor.

Treatment of rubral tremor is notoriously difficult. The tremor is usually intractable to medical therapy although isolated cases of either complete or partial relief have been reported with levodopa,<sup>3,4</sup> anticholinergics,<sup>6</sup> propranolol,<sup>24</sup> clonazepam,<sup>25</sup> and glutethimide.<sup>7</sup> Stereotactic thalamotomy<sup>5</sup> and thalamic stimulation<sup>2</sup> have been successfully used to alleviate rubral tremor.

### Legend to the Videotape

The low-frequency, high-amplitude tremor is present at rest, with posture, and with intention. The patient has a partial ptosis with downward gaze palsy and limited adduction of his right eye. The tremor is present when walking. His gait is normal and the rest of his body appears unaffected.

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