Treatment of Ballism and Pseudobulbar Affect With Sertraline

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Background: The pathogenesis of ballism is uncertain and may involve more than one mechanism; treatment is not always efficacious.

Objective: To provide evidence of a nondopaminergic mechanism and the potential for a prompt and nearly complete response to a serotonergic agent.

Methods: Report of 2 separate trials of sertraline hydrochloride in a single patient.

Results: Complete remission of symptoms within 48 hours of each drug trial.

Conclusion: Sertraline may offer an alternative with a better adverse effect profile than dopamine receptor blockers in the treatment of patients with ballism.

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The mechanism of ballism is uncertain, and its response to treatment with neuroleptics is frequently slow, fraught with adverse effects, and occasionally so unsatisfactory as to motivate surgical treatment. We report a case that suggests that an alternative treatment, sertraline hydrochloride, may be rapidly effective and associated with few adverse effects. This and other reported cases also suggest that the mechanism of ballism may be complex and susceptible to different treatments in different patients.

Report of a Case

A 73-year-old, previously healthy right-handed man had a 10-day history of right-sided weakness, unpredictable jerking of his right upper extremity and, to a lesser extent, his right lower extremity, and uncontrollable crying spells. He also complained of recent difficulty with short-term memory, mild slurring of speech, an inability to see objects on his right side, and a several-month history of intermittent palpitations. He had no double vision, dysphagia, dizziness, or sensory symptoms. He had a history of hypertension and type 2 diabetes mellitus that was diet controlled, and he had undergone coronary artery bypass surgery. There was no history of stroke. He had a 60-pack-year smoking history but had not smoked in 25 years. He was a former railroad worker now practicing television evangelism.

Although the patient's vital signs were normal, he had an irregularly irregular heartbeat. He recalled none of 3 objects after several minutes of distraction, and he had an anomic aphasia. He had a depressed mood and flattened affect, and he frequently exhibited pseudobulbar crying. When asked, he denied that he was sad on these occasions. Cranial nerve examination results were normal with the exception of an incongruous right homonymous hemianopia, saccadic breakdown of ocular smooth pursuit movements, and a mild right supranuclear palsy of the seventh cranial nerve. During a motor examination, there was facilitatory paratonia in the right upper and lower extremities, a mild right hemiparesis (4/5 in the deltoid, distal upper extremity muscles, and hip flexors), and pronation drift of the right upper extremity. At rest he exhibited frequent, irregular, high-amplitude ballistic movements of his proximal right upper extremity. Adventitious movements of the right lower extremity were of much lower amplitude. These movements were worse during intentional activity, including finger-to-chin and toe-to-target maneuvers and ambulation. He also had mild, nearly continuous choreiform movements of the right upper and lower extremities, both at rest and with intentional activity, that were
present between the episodes of ballistic movement. There was mild, symmetric impairment in all sensory modalities extending to the ankles, and there was a decrease in pinprick and temperature sensation in the right upper and lower extremities. Cerebellar function was intact. Reflexes were slightly more brisk on the right, and plantar responses were equivocal.

The results of a complete blood cell count, measures of electrolytes, a metabolic profile, and liver function studies were normal. An electrocardiogram revealed atrial fibrillation. An echocardiogram revealed an ejection fraction of 25%. A 4-hour electroencephalogram did not reveal any epileptiform activity, even during the patient's involuntary movements and pseudobulbar episodes. Goldmann perimetry of the left eye demonstrated a right hemianopia detectable only with the smallest, least intense target. Perimetry of the right eye revealed a dense right superior quadrantanopia extending inferiorly as far as the 330° radian in the right inferior quadrant.

The lesion was mapped using axial 3-mm sections from a magnetic resonance imaging (MRI) study of the brain (Figure) onto plates from the Schaltenbrand and Bailey atlas with a modified camera lucida technique. The lesion involved posterior portions of the posterior limb of the internal capsule, posterolateral portions of the pulvinar, portions of the body and tail of the caudate, portions of the lateral geniculate nucleus, the hippocampus and adjacent parahippocampal gyrus, and posteroinferior portions of the amygdala and periamygdaloid cortex. There was a small region of hemorrhage in the area of infarction. The locus and extent of the lesion were entirely consistent with a left anterior choroidal artery distribution infarct even though involvement of the entire territory of the artery was not evident. No other lesions appeared on the MRI.

A dose of 50 mg/d of sertraline was initiated 10 days after the onset of symptoms. Marked improvement in depression, pseudobulbar symptoms, and ballism was noted within 24 hours, and these problems had completely resolved following 48 hours of treatment. The only residual movement disorder was a subtle, intermittent chorea of the arm at rest that increased during walking. The sertraline was then stopped, and within 48 hours the patient again became morose, exhibited uncontrollable crying episodes, and experienced a return of the ballism. Symptoms resolved within 48 hours of resumption of treatment.

The anterior choroidal artery supplies anterior regions of the medial temporal lobe (most consistently including the anterior hippocampus), dorsomedial portions of the lateral geniculate nucleus and adjacent optic tract and radiations, ventral and retrolenticular portions of the posterior limb of the internal capsule, the medial globus pallidus, dorsal portions of the subthalamic nucleus, the H2 field of Forel, the zona incerta, and in some cases, the middle portion of the cerebral peduncle and adjacent substantia nigra.2,3 On MRI studies of our patient, infarction was not visible through the entire territory of the artery, presumably because of the limited sensitivity of MRI in detecting ischemic damage short of complete infarction.4 Nevertheless, it may reasonably be inferred that the memory deficits seen in our patient reflect involvement of mesial temporal structures; the hemianopia reflects involvement of the optic tract, lateral geniculate nucleus, or proximal portions of the geniculocalcarine tract; the language deficits, characteristic of thalamic aphasia, reflect damage to thalamocortical pathways by the internal capsule lesion;5 and the ballism reflects disruption of the subthalamopallidal pathway or damage to the subthalamic nucleus. The origin of the depression and pseudobulbar affect is uncertain. The territory of the anterior choroidal artery extends sufficiently medially below the thalamus to include the ascending noradrenergic and serotonergic pathways traveling in the median forebrain bundle.5,6 Thus, the depression and pseudobulbar affect could reflect depletion of norepinephrine and serotonin in the mesolimbic structures.

The treatment of pseudobulbar affect with selective serotonin reuptake inhibitors (SSRIs) such as sertraline is well established in the literature,6 although there is some uncertainty about the mechanism underlying its effects. Patients typically respond rapidly and to low doses.

Magnetic resonance imaging study (fluid-attenuated inversion recovery sequences) obtained 15 days after the onset of symptoms.

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The favorable response of pseudobulbar affect to sertraline in our case may reflect the effect of this SSRI on serotonin levels in the limbic system, the nucleus accumbens, or the cerebral cortex on the involved side.

Neuroleptics have been the mainstay of treatment for hemiballism. However, approximately 16% of affected patients fail to respond to these or other antiparkinsonian drugs or to clonazepam, and the mean delay to response in one series was 15 days. In some patients, the disorder is so severe and refractory that it motivates surgical approaches. Thus, there is a need for alternative pharmacological approaches. The response to sertraline in our patient was both dramatic and prompt. It is conceivable that the improvement reflected a placebo effect, but this seems unlikely because we told the patient that we were targeting only the emotional incontinence. It is unlikely that the improvement reflected spontaneous resolution because symptoms recurred following discontinuation of sertraline.

This may represent the first report of successful treatment of ballism with sertraline. It is not the first report of a favorable response to a drug that potentiates serotonergic activity. Lenton et al described successful treatment with valproate sodium in 1981. The mechanism underlying the beneficial effect of sertraline is uncertain, but there are several possibilities. First, serotoner is known to play a role in modulating the presynaptic release of several neurotransmitters via its action on serotonin (5-HT) receptors, and SSRIs have been shown to reduce dopamine release in the striatum. By this mechanism, sertraline could have emulated the beneficial effects of dopamine receptor blockers in the treatment of ballism. This same effect may account for the occasional development of extrapyramidal features in patients given SSRIs, including sertraline, and in patients given sumatriptan succinate, a specific 5-HT antagonist. These characteristics most often consist of akathisia or dystonia but may include more classical parkinsonian features.

Second, postsynaptic serotonergic effects of sertraline may have increased the firing rate of neurons within the subthalamic nucleus that, via the globus pallidus pars interna, affected neurons of the pars oralis of the ventral lateral thalamic nucleus (VLo) projecting to the supplementary motor area and area 4. This also would have reduced the effects of the ischemic lesion.

Finally, the potentiation by sertraline of interstitial serotonin levels within VLo or the cerebral cortex could have compensated for the apparent imbalance between the direct and indirect basal ganglia pathways caused by the lesion.

Some patients with ballism resistant to haloperidol have improved following treatment with risperidone, an atypical dopamine receptor blocker that is also a 5-HT receptor blocker. These observations coupled with our report, as well as evidence of the variable efficacy of valproate, suggest that there may be more than one mechanism for ballism. Treatment with sertraline may provide an alternative to haloperidol by virtue of its fast onset of action and better adverse effect profile (low risk of parkinsonian effects or tardive dyskinesia), or it could provide an alternative for patients in whom the mechanism of ballism makes the disorder susceptible to treatment that potentiates serotonergic activity. Because we did not test the merits of sertraline relative to typical or atypical D2 (dopamine) receptor blockers, we can draw no conclusions regarding these possibilities.

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