Postischemic Delayed Holmes' Tremor Responding to Low-Dose Cabergoline

Holmes' tremor is an unusual combination of rest, postural, and kinetic tremor of extremities. It is usually caused by a focal neurological disease of midbrain.[1] In general, tremor disorders affect quality of life by impending simple motor tasks and activities of daily living. Unfortunately, symptomatic medical treatment of Holmes' tremor is often unsuccessful. The use of levodopa, clonazepam, a combination of propranolol and valproate, glutethimide, benztropine, bromocriptine, and amantadine has occasionally led to satisfactory clinical benefits.[2] Here we report on a case with postischemic delayed Holmes' tremor dramatically responding to low dose cabergoline treatment.

A 57-year-old man with history of hypertension and smoking suddenly developed unsteadiness and dropping of right upper eyelid. Neurological examination revealed dysarthria, a total right occulomotor nerve paralysis, and left-sided mild hemiparesis. Magnetic resonance imaging (MRI) showed an acute midbrain infarction involving right red nucleus and substantia nigra regions (Fig. 1). During follow-up extending to 4 years, right occulomotor nerve involvement only slightly improved and left-sided spasticity developed. Five years after the ischemic episode, the patient was referred again because of a tremor affecting left extremities. On examination, a severe-intensity, slow, large-amplitude resting tremor was observed on the left side. Tremor was also present during posture and action and was worsened by emotional distress and attempts to inhibit the tremor. There was no associated rigidity. Gait was almost impossible because of leg action tremor and the patient could not perform activities of daily living without assistance. MRI demonstrated no other pathology except chronic midbrain infarction. He was started on levodopa–carbidopa 250/25 mg three times a day and no response was observed during 1 month. Then, he was given cabergoline 1 mg/day. At the end of 1 month, he was able to walk independently and carry out most of daily activities by himself. However, the improvement of tremor was not satisfactory and cabergoline dose was increased to 2 mg/day. One month later, improvement of tremor was dramatic with complete alleviation of all components.

Holmes' tremor is a symptomatic tremor occurring after different lesions centered to the brain stem with damage to the neighboring cerebellothalamic and nigrostriatal fiber tracts. Involvement of these two systems accounts for static, postural, and kinetic features of Holmes' tremor.[1] Remy and colleagues[3] demonstrated that fluorodopa uptake of the striatum of patients with Holmes' tremor was too low ipsilateral to the midbrain lesion. MRI location of the midbrain lesion in our case indicates that substantia nigra, nigrostriatal dopaminergic fibers, or both are involved.

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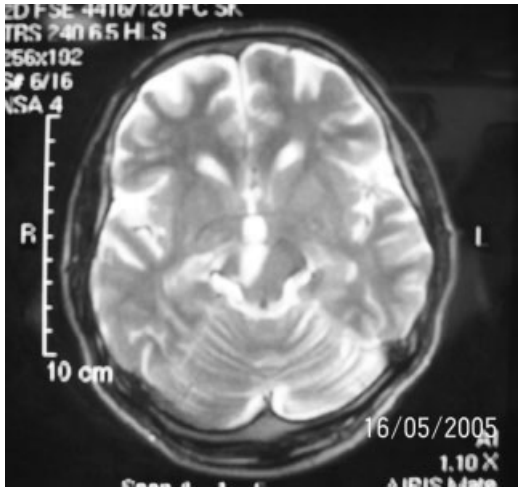

FIG. 1. Acute midbrain infarction involving right red nucleus and substantia nigra regions.

The pathophysiology of Holmes' tremor probably involves compensatory changes in nervous system function.[1] Resultant symptomatology of Holmes' tremor is a combination of dopaminergic and nondopaminergic components of tremor. Two main systems, the dopaminergic nigrostriatal system and the cerebellothalamic system, may be involved disproportionally among different patients and, furthermore, compensatory changes over time may go against the nigrostriatal dopaminergic system as in our case. This hypothesis may account for the response variability of Holmes' tremor to pharmacotherapy.

Interestingly, our case displays a contrast between a dramatic response to cabergoline and lacking response to levodopa. In some cases of Holmes' tremor, the dopaminergic neurons in the substantia nigra might be destroyed to such an extent that the presynaptic part of the dopaminergic connections in the striatum are hardly present anymore. This would be in contrast to the degenerative disease and could be an explanation for the lack of response to levodopa.

D2 dopamine receptors are mainly distributed in striatum.[4] Cabergoline is a highly selective D2 receptor agonist[5] and it has been shown that it has a higher efficacy and safety than other dopamine agonists.[6,7] Our patient is the first case in literature showing dramatic response to low-dose cabergoline treatment. Although treatment of Holmes' tremor has been disappointing, cabergoline may be an effective treatment choice with its higher dopaminergic selectivity.

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An Open-Label Trial of Levetiracetam for Treatment of Cervical Dystonia

Levetiracetam is a novel antiepileptic drug approved for treatment of partial seizures. Its mechanism of action is uncertain. It does not interact with inhibitory or excitatory brain neurotransmitters. It appears to prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity and has been effective in suppressing paroxysmal dystonia in a hamster model[1] and levodopa dyskinesia in MPTP-lesioned marmoset monkeys.[2] In clinical reports, levetiracetam improved myoclonus,[3,4] L-dopa dyskinesia,[5] tardive dyskinesia,[6] and paroxysmal kinesiogenic choreoathetosis,[7] although essential tremor was unaffected.[8] The dose range used in these studies was 500 to 3,000 mg/day. One patient with blepharospasm, oromandibular dystonia, and mild cervical dystonia was successfully treated with levetiracetam, 1,500 mg/day, suggesting that it might also be helpful in the treatment of dystonia.[9] We carried out an open-label pilot study of levetiracetam in the treatment of cervical dystonia.

The protocol was approved by the Institutional Review Board, and informed consent was obtained from all patients. Ten patients with primary idiopathic cervical dystonia (CD) attending our dystonia botulinum toxin outpatient clinic were recruited for participation in an open-label clinical trial of levetiracetam. Patients were offered participation in the trial regardless of their response to botulinum toxin. Patients with primary and stable CD with duration of at least 3 years were eligible. Patients with secondary forms of torticollis, epilepsy, active psychiatric disorder, treatment with other anticonvulsant medications, previous sensitivity to levetiracetam, and pregnancy were excluded. There were 5 women and 5 men. Mean age was 54.1 ± 12.4 years; mean duration of CD was 9.6 ± 7.4 years. Four patients had rotational torticollis, 2 had laterocollis, 1 had retrocollis, and 3 had a mixed pattern. Five patients had dystonic head tremor. Responses to botulinum toxin were excellent in 5 patients and moderate in 5 patients. Two patients had developed immune-mediated resistance to Botox and Myobloc and were no longer receiving botulinum toxin. Patients were enrolled into a 7-week, open-label trial that began at least 14 weeks after the last administration of botulinum toxin. Patients were examined at weeks 0, 1, 3, 5, and 7 weeks, with telephone contact at weeks 2 and 4. After an initial baseline visit (week 0), levetiracetam 250 mg b.i.d. was initiated at week 1. Dose was increased to 500 mg b.i.d. at week 2 and 1,000 mg b.i.d. at week 3. Dose was maintained at 1,000 mg b.i.d. until the medication was discontinued at week 5. A post-treatment evaluation was carried out at week 7. Inquiry was made regarding adverse effects at each contact. Depending on severity, if adverse effects were reported, the dose was either kept unchanged or reduced to the previous level. Severity of CD was assessed with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) at each visit,[10] and a standardized video recording was recorded at baseline and week 5. The primary outcome measure was change in the TWSTRS scores from baseline to final visit on medication (week 5). Secondary outcomes were improvement in CD as determined by review of the video recordings and the patient's global impression of change.

Five of the 10 patients completed the trial. Four reached 1,000 mg b.i.d., and 1 reached 250 mg b.i.d. Two dropout patients reached 1,000 mg b.i.d. One dropped out at week 5 due to vomiting; the other dropped out at week 5 due to lack of improvement. One patient dropped out at week 2 on 250 mg b.i.d. due to drowsiness, and one dropped out at week 3 on 500 mg b.i.d. due to drowsiness and myalgias. All dropout patients were assessed at the time of study termination and last observation carried forward (LOCF) was used for analysis. One patient dropped out at visit 1 before beginning treatment and is not included in the analysis. TWSTRS scores at baseline and final visit were compared in the 5 patients who completed the trial and the 2 patients who dropped out at week 5 but reached the target dose of 1,000 mg b.i.d. with LOCF. There was no significant change in TWSTRS total score (37.4 ± 9.6 vs. 35.7 ± 11.1); TWSTRS severity subscore (16.7 ± 6.1 vs. 17.0 ± 6.5); TWSTRS disability subscore (11.0 ± 4.5 vs. 11.3 ± 6.0); or TWSTRS pain subscore (9.7 ± 2.3 vs. 8.3 ± 3.1). No patient reported subjective improvement in symptoms of CD. There was also no improvement in dystonic head tremor in the 5 patients with this manifestation. Comparison of video recordings and patient global impression of change before and after treatment also showed no change. Adverse effects were drowsiness with fatigue in 8 patients; gastrointestinal symptoms in 4 patients (vomiting, heartburn, abdominal cramps, tongue burning); dizziness, headache, and increased neck pain in 3 patients each; central nervous system symptoms in 3 patients (depersonalization, insomnia, impaired concentration); upper respiratory symptoms in 3 patients; and paresthesias, myalgias, hypotension, and urinary frequency in 1 patient each.

Although preclinical studies and case reports have suggested that levetiracetam may be helpful in the treatment of several dyskinetic and dystonic movement disorders,[5–7] this open-label trial found no improvement in CD and a high drop-out rate. Similar to previous clinical trials with levetiracetam,[5,8] drowsiness with fatigue was the most common troublesome adverse effect in this group of patients. No patient reported improve-

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