Resetting of Orthostatic Tremor Associated With Cerebellar Cortical Atrophy by Transcranial Magnetic Stimulation

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Objectives: To investigate the resetting effects of transcranial magnetic stimulation over motor cortex on orthostatic tremor, characterized by high-frequency electromyographic discharges in weight-bearing muscles, particularly orthostatic tremor (OT) associated with cerebellar cortical atrophy; and to compare our results with those obtained in primary OT, for which transcranial magnetic stimulation does not reset tremor.

Design: Study of 3 patients who clinically exhibited a sporadic pancerebellar syndrome associated with isolated cerebellar atrophy and features of OT.

Setting: Research hospital.

Main Outcome Measures: Electromyograms and transcranial magnetic stimulation studies with a resetting index calculated on the basis of the timing of measured bursts and predicted bursts for a magnetic stimulus given at increasing delays.

Results: Surface electromyographic recordings in weight-bearing muscles showed tremor with a frequency of 14, 15, and 14 Hz in the 3 patients. Transcranial magnetic stimulus was able to reset OT. Resetting index was 0.72.

Conclusions: Transcranial magnetic stimulus resets OT associated with cerebellar cortical atrophy, emphasizing the role of motor cortex in the genesis of OT associated with a cerebellar dysfunction. Our results argue in favor of a distinct pathophysiological mechanism of primary OT and OT associated with cerebellar cortical atrophy.

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Orthostatic tremor (OT) is characterized by high-frequency burst firing of 13 to 18 Hz in weight-bearing muscles, with synchronous discharges between homologous muscles. Recently, the high-frequency tremor pattern has also been observed in cranial muscles during isometric contractions. Patients typically complain of unsteadiness when standing still in association with a fear of falling. A rapid postural upper limb tremor of 14 to 16 Hz has also been observed in patients with OT. The pathophysiological characteristics of OT are poorly understood. Orthostatic tremor may be primary or may occur in association with cerebral lesions. In particular, OT can be associated with cerebellar cortical atrophy (CCA) and with pontine lesions disrupting crossed pontocerebellar afferences. When OT is associated with CCA, patients complain not only of unsteadiness when standing, but also of gait difficulties. The broad-based ataxic character of gait observed in these patients is a feature not encountered in primary OT. Furthermore, response to drugs is distinct. In particular, response to clonazepam in patients with OT associated with CCA is poor or slight, in contrast to primary OT, which is characterized by a moderate to good response to this drug. In addition, drinking alcohol worsens the feeling of unsteadiness in OT associated with CCA, but either does not change or slightly improves primary OT.

It has been shown previously that transcranial magnetic stimulation (TMS) over motor cortex does not reset primary OT, indicating that motor cortex is not implicated in a central oscillator that generates or modulates primary OT. Given the distinct clinical, radiological, and pharmacological characteristics of primary OT and OT associated with CCA, we tested the hypothesis that TMS might reset OT associated with CCA.

RESULTS

Surface EMG recordings in lumbar paraspinal muscles, in quadriceps femoris...
PATIENTS AND METHODS

PATIENTS

Clinical features of the 3 patients included in the present study have been described previously. Briefly, patients were 1 man and 2 women (aged 49, 62, and 64 years) with a duration of disease of 7, 8, and 6 years, respectively. All complained of a sensation of imbalance when standing, with relief by sitting. They also reported gait difficulties. There was no family history of tremor, and alcohol intake worsened symptoms. They exhibited a cerebellar syndrome including gaze-evoked nystagmus, dysmetria of saccades, scanning speech, intention tremor in 4 limbs, and broad-based ataxic gait. None had postural hypotension. Results of blood studies, including erythrocyte sedimentation rate, blood cell count, renal and liver function tests, thyroid function tests, and ceruloplasmin level, were normal. The following investigations gave unremarkable results: electroencephalogram, sensory evoked potentials in upper and lower limbs, magnetic resonance imaging of the brain disclosed a pancerebellar atrophy. Feeling of unsteadiness was slightly improved with clonazepam in patient 1 and was unchanged in patients 2 and 3. There was no response to ß-blockers.

METHODS

Electromyographic Recordings and TMS

Patients were studied while standing. We analyzed tremor by using surface electrodes taped 3 cm apart over lumbar paraspinal muscles, quadriceps femoris muscles, and tibialis anterior muscles bilaterally. Electromyographic (EMG) activities were amplified, filtered (30-1000 Hz), rectified, and averaged by means of an analog/digital converter (Cambridge Electronic Design, Cambridge, England). Fast Fourier transform frequency analysis of 40 repeated 10-second epochs was also performed.

To investigate the resetting phenomenon, we recorded the activity of the right quadriceps femoris muscle. The TMS was applied by means of an angled figure-eight coil for lower limbs, which was positioned over vertex (Digitimer D190; Digitimer Ltd, Hertfordshire, England). Stimulus intensity was 20% above motor threshold, which was defined as the lowest stimulus intensity needed to produce motor evoked potential of at least 50 µV peak to peak by at least 5 stimuli in a series of 10. Five delays between recording onset of EMG activity and magnetic stimulus were determined on the basis of a reference recording. For this reference recording, peak time of maximal amplitude of each of 40 successive bursts of tremor was measured. The interpeak intervals were then averaged to obtain average cycle length. Magnetic stimuli were given just after the fifth tremor cycle at one of 5 delays: 25%, 30%, 40%, 50%, and 60% of average cycle length. An intensity level of EMG signal of 0.15 mV was used to trigger recordings.

Resetting Index

For each of the 5 delays, 10 individual EMG signals were averaged. The resetting index was evaluated according to the method described by Lee and Stein. Peak time of the 5 tremor bursts preceding TMS was determined (Figure 1). The mean cycle length was defined as the average value of the intervals between peaks. Mean cycle length was subsequently used to calculate predicted timing of peaks of tremor bursts after TMS. Differences in timing between predicted peak bursts and actual peak bursts were calculated for the 5 bursts after stimulus. These differences were called d1, d2, d3, d4, and d5, respectively, and were averaged for the 3 patients. Average values were plotted against the 5 delays for TMS (25%, 30%, 40%, 50%, and 60% of average cycle length). Five linear regressions were determined with Sigma Plot software (Jandel Scientific, Erkrath, Germany), one for each of the first 5 bursts after magnetic stimulus. The resetting index was defined as the average slope of the regression lines. A resetting index of 0 indicates absence of resetting, while a value of 1 means total resetting. Moreover, to distinguish a transient resetting from a steady-state resetting, the slope of regression line obtained for d1 was divided by the slope of regression line obtained for d5 (first-fifth ratio). A ratio of 1 would mean steady-state resetting, while a ratio much higher would indicate a transient phenomenon.

We demonstrated resetting of OT associated with CCA by means of TMS. Our neurophysiological results suggest a distinct pathophysiological mechanism for primary OT and OT associated with a cerebellar degeneration. Indeed, the resetting phenomenon after motor cortex stimulation in our patients argues for an important role of cortical structures in modulating the activity of the neuronal network generating tremor, while rhythmic prog-
In primary OT, the rapid postural upper limb tremor has been demonstrated to be associated with abnormal bilateral cerebellar and contralateral lentiform and thalamic activation, suggesting that cerebellum plays a role in genesis of primary OT. Since our patients exhibited a clinical picture of cerebellar cortical degeneration, and since Purkinje cells exert a potent inhibitory effect on cerebellar nuclei, the target nuclei of cerebellar efferent pathways may be overactive in our cases, in particular thalamic nuclei. Such an overactivity of thalamic nuclei might explain the fact that OT associated with CCA shares with essential tremor and postural tremor of Parkinson disease the property of resetting after motor cortex stimulation. Indeed, overactivity of thalamic neurons is implicated in the genesis of essential tremor and tremor in Parkinson disease, and inhibition of thalamic nuclei has a beneficial effect on tremor in these patients. Another pathophysiological hypothesis to explain OT in our patients is the dysfunction of stretch reflexes as a consequence of cerebellar disease. Indeed, experimental evidence shows that stretch reflexes at the segmental and suprasegmental level participate to generate tremor in cerebellar ataxia. Particularly, gain of long-latency stretch reflexes is increased in patients with cerebellar ataxia dur-
ing posture in a standing position. This higher gain results in an overcompensation during tasks requiring postural adjustments, such as adaptation to displacement, and is probably involved in body oscillations associated with lesions of the cerebellar anterior lobe, which is a major site of projections of spino-cerebellar pathways. Abnormal stretch reflexes could result from the inability of cerebellum to regulate appropriately the traffic between its afferent and efferent pathways, such regulation being a critical cerebellar function.

As indicated previously, primary OT usually has a moderate to good response to pharmacological agents. So far, the most frequently used drug has been clonazepam. Other drugs have also been administered with relatively favorable results; these include primidone, barbiturates, and valproic acid. Responsiveness to these drugs in primary OT may indicate impairment of γ-aminobutyric acid (GABA)-ergic pathways. The recently described good response to gabapentin, an antiepileptic agent probably acting through potentiation of GABA inhibition, strengthens this hypothesis. Since GABA is also a major neurotransmitter for inhibitory interneurons and for Purkinje cells in cerebellar cortex, defective GABA-ergic neurotransmission might be seen as a common feature in primary OT and OT associated with CCA. However, atrophy of cerebellar cortex implies marked neuronal loss, a major difference between the 2 forms of OT discussed herein.

Considering results obtained by others, we conclude that our findings support a classification of OT into primary and secondary forms. Such a classification seems reasonable not only on the basis of distinct clinical features, pharmacological responses, and radiological features, but also on the basis of different neurophysiological features.

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