Bilateral High-Frequency Synchronous Discharges

A New Form of Tremor in Humans

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Objectives: To report bilateral high-frequency synchronous discharges in a patient with a sporadic form of olivopontocerebellar atrophy; to investigate the electromyographic pattern, the coherence and cospectral density across limbs, and the resetting effects of electrical stimulation over the posterior fossa; and to highlight the clinical, electrophysiologic, and radiologic features of this new form of tremor associated with posterior fossa disorders.

Design: Case study of a patient clinically exhibiting a sporadic form of olivopontocerebellar atrophy associated with cerebellar and brainstem atrophy.

Setting: Research unit, university hospital.

Main Outcome Measures: Electromyographic studies, coherence and cospectral density analysis, and calculation of a resetting index based on the timing of measured bursts and predicted bursts for an electrical stimulus given over the posterior fossa at increasing delays.

Results: Surface electromyographic recordings in forearm muscles revealed a low-frequency postural tremor in the upper limbs, with episodes of highly coherent tremor at a frequency of 14 Hz. Squared coherence and cospectral density was strong between agonist and antagonist muscles in the left and right upper limbs and across limbs for the high-frequency discharges. Electrical stimulation over the posterior fossa reset the explosive high-frequency bursts. The resetting index was 0.82 Hz.

Conclusions: Our results show that bilateral high-frequency synchronous discharges may be associated with the sporadic form of olivopontocerebellar atrophy. Bilateral coherent bursting and resetting of this explosive postural tremor following electrical stimulation over the posterior fossa strongly suggest that the brainstem plays a key role in the network involved in the genesis of rhythmic bursts. We suggest that the high-frequency discharges are due to repetitive discharges in the reverberating cerebello-precerebellar circuits.

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We recently described a new form of tremor in 2 patients with a posterior fossa disorder.1,2 The first patient was a 17-year-old girl with a history of hemorrhage in the brainstem due to an arteriovenous malformation. Brain magnetic resonance imaging demonstrated lesions in the mesencephalon and a marked enlargement of the fourth ventricle. The second patient was a 57-year-old man with a cerebellar form of multiple system atrophy. The first patient complained of sensations of “fast vibrations” or “automatic rhythm” (“rythme automatique”) in the upper arms. Contraction were noted 1 to 2 times per week. The second patient complained of brief episodes of “uncomfortable contractions” in the upper limbs, which occurred up to 4 times per day and were sometimes clearly triggered by fatiguing tasks, such as painting a wall. Both patients clinically exhibited brainstem and cerebellar signs. They developed episodes of explosive high-frequency synchronous tremor (15-16 Hz) of the forearm muscles when they were asked to maintain the upper limbs outstretched. No corticomuscular coherence was found, but coherence analysis of electromyographic (EMG) recordings from antagonist muscles and from muscles across limbs suggested a common generator. Stimulation over the posterior fossa reset these bilateral high-frequency synchronous discharges (BHFSs), indicating an oscillator in the posterior fossa.3,4 The rate of tremor was unaffected by loading the limbs or by peripheral electrical stimulation (ES), suggesting a central oscillator.5,6

We report a third case of this type of tremor in humans. We underline the main clinical, electrophysiologic, and radiologic features.
features of this new form of high-frequency tremor. A scheme of the circuitry generating the tremor is proposed.

REPORT OF A CASE

A 65-year-old right-handed woman had a 5-year history of gait difficulties. She complained of clumsiness in her upper limbs, which was associated with episodes occurring from 2 to 3 times per week to several times per day. She had no history of urinary incontinence. There was no family history of neurologic disease. There was no postural hypotension. Her Mini-Mental State Examination score was 28/30. A neurologic examination showed a gaze-evoked nystagmus and scanning speech. The finger-to-nose test and heel-to-knee test revealed marked ataxia. Fine finger movements were very irregular. She exhibited a postural and kinetic tremor in her upper limbs. No rest tremor was observed. Sensory examination results were normal. Tendon reflexes were brisk in 4 limbs. Plantar reflexes were extensor. Gait was based and ataxic, requiring one aid. Tandem gait was impossible. The following blood analyses revealed normal results: erythrocyte sedimentation rate, complete blood cell count, liver and renal function tests, thyroid function tests, vitamin E level, and levels of anti–glutamic acid decarboxylase, antithyroid, antiangiadenine, and antinuclear antibodies. A search for spinocerebellar ataxia type 1, 2, 3, and 6 was negative. Electroencephalography results were normal. A needle EMG showed normal motor units in 4 limbs. A sphincter EMG did not reveal signs of denervation. Sensory and motor conduction velocities were normal in the upper and lower limbs. No increased H-reflex responses to conditioning stimuli were observed in the upper limbs. There was no giant somatosensory evoked potential and no reflex response (C reflex) in the upper limbs after stimulation of the median nerves. Brain magnetic resonance imaging disclosed marked atrophy of the cerebellum and brainstem. Clonazepam, trihexyphenidyl, and gabapentin had no effects. A diagnosis of sporadic olivopontocerebellar atrophy was made.

TREMOR ANALYSIS

When asked to maintain the upper limbs outstretched, the patient demonstrated a low-frequency postural tremor of the forearms that was irregular and asynchronous. Occasionally, episodes of BHFSs were recorded in the forearm muscles (Figure 1). The synchronous discharges lasted several hundred milliseconds. They ended with a forceful contraction of the wrists. After a brief silent period, the low-frequency tremor resumed. These explosive bursts were absent in paraspinal muscles and in lower limb muscles during prolonged standing. Coherence between EMG activities in antagonist muscles and between opposite forearm muscles was very high during episodes of high-frequency bursts (Figure 2). Coher-

Figure 1. Raw electromyographic (EMG) data recorded from the right and left flexor carpi radialis (FCR) and the right and left extensor carpi radialis (ECR). This recording presents the characteristic EMG pattern observed while the patient maintained the upper limbs outstretched. The patient displayed an irregular and asynchronous 3- to 4-Hz tremor, such as that in the first segment of the recording, throughout the performance of the postural task. Approximately every 1 or 2 minutes, there was a sudden shift of the EMG activity to highly regular 14-Hz bursts, shown in the second segment of the recording. Hyperflexion of the wrists caused the high-frequency burst episodes to cease, and a very brief period of silence followed. After the silence, the irregular low-frequency tremor resumed.
ence was low for the low-frequency tremor. Transcranial magnetic stimulation over the motor cortex did not reset the high-frequency discharges, in contrast with ES over the posterior fossa (see below). Analysis of the syn-

Figure 2. Spectral analysis of the low- and high-frequency tremor episodes. For the low-frequency tremor, the power spectrum for each of the 4 muscles shows a strong rhythmic component between 3 and 4 Hz. The squared coherency between the right and left flexor carpi radialis (FCR) and the squared coherency between the right and left extensor carpi radialis (ECR) show no strong peaks and values significantly less than 0.6 at this frequency. This result suggests that the low-frequency tremor is not coherent across limbs. The relatively small cospectral density peaks observed for the low-frequency tremor help to support this finding. For the high-frequency tremor, the power spectrum for each of the 4 muscles shows a strong rhythmic component at approximately 14 Hz. The squared coherency between the right and left FCR and the squared coherency between the right and left ECR show strong peaks at this frequency, with values greater than 0.6 Hz. This result suggests that the high-frequency tremor is coherent across limbs. The relatively large cospectral density peaks observed for the high-frequency tremor help to support this finding. PSD indicates power spectral density.
chronization of the electroencephalogram was not performed. The rate of tremor was unchanged by loading the limbs or by stimulating peripheral nerves with electrical shocks.

**RESETTING OF THE EXPLOSIVE TREMOR**

To investigate the resetting phenomenon, ES was delivered through electrodes over each mastoid process using a Digitimer stimulator (DS7; Digitimer, Hertfordshire, England) (pulse width, 100 microseconds; intensity, 40-50 mA generating discomfort). Five delays between recording onset of EMG activity and ES were determined on the basis of a reference recording. For this reference recording, the peak time of successive bursts of tremor was measured. The average cycle length was computed by averaging the interpeak intervals. Electrical stimuli were given after the sixth tremor cycle at the following delays: 25%, 30%, 40%, 50%, and 60% of the average cycle length. The resetting index was evaluated according to the method reported by Lee and Stein. The peak time of the tremor bursts preceding ES was determined (Figure 3). The mean cycle length (A) was defined as the mean value of the intervals between peaks (T1, T2, T3, T4). The averaged value A is subsequently used to estimate the timing of predicted bursts. Differences between times of measured peaks of bursts and times of predicted peaks of bursts are calculated. These differences are called d1, d2, d3, d4, and d5 for the 5 bursts following ES. Each of these differences will be plotted as a function of the time of the stimulus expressed in percentage of the average cycle length.

![Figure 3](image-url)

**Figure 3.** The method used to analyze the resetting index following electrical stimulation (ES). T1, T2, T3, and T4 correspond to measured cycle lengths prior to ES. The 4 values are averaged. The averaged value A is subsequently used to estimate the timing of predicted bursts. Differences between times of measured peaks of bursts and times of predicted peaks of bursts are calculated. These differences are d1, d2, d3, d4, and d5 for the 5 bursts following ES. Each of these differences will be plotted as a function of the time of the stimulus expressed in percentage of the average cycle length.

The resetting index was defined as the average slope of the regression lines. A value of 0 indicates no resetting, whereas a value of 1 indicates total resetting. The ratio of the slope of the regression line obtained for d1 was divided by the slope of the regression line obtained for d5 (1st/5th ratio) to distinguish a transient resetting from a steady-state resetting. A ratio of 1 would mean steady-state resetting, while a much higher ratio would indicate a transient phenomenon.

**RESETING INDEX IN OUR PATIENT**

Electrical stimulation over the posterior fossa did not change the frequency of the tremor. Electromyographic bursts were transiently suppressed by ES. Regardless of the delay length to stimulation, EMG bursts occurred after a constant interval following the stimulus. Figure 4 shows the rela-
tionships between stimulus delay and mean differences in timing between predicted bursts and measured bursts for each of the 5 bursts following ES. Regression analysis demonstrated that this relationship was linear for d1, d2, d3, d4, and d5. Slopes of regression lines were strongly in favor of a resetting, with an average slope of 0.82. The ratios of the slope of the regression line obtained for d1 divided by the slope of the regression line obtained for d5 (1st/5th ratio) was 1.04, suggesting a steady-state resetting.

This is the third case of this type of explosive tremor that we have seen. The main clinical, electrophysiologic, and radiologic characteristics of BHFSD are presented in the Table. The generator is active in patients who exhibit a disorder predominating in the posterior fossa. Patients complain of episodes of involuntary vibrations or contractions in their upper limbs, which may be uncomfortable. In our experience, other patients with sporadic cerebellar degeneration or hereditary cerebellar ataxias do not describe these symptoms. Stretch of forearm extensors is associated with a termination of the high-frequency discharges, but peripheral stimulation with electrical shocks has no effect on tremor. Bilateral coherent discharges and resetting of the explosive bursts following stimulation over the posterior fossa are key neurophysiologic features. Imaging techniques demonstrate lesions affecting mainly the structures located in the posterior fossa (brainstem and cerebellum in the 3 cases).

Tremor spectral analysis and coherence studies are not routinely used in clinical neurophysiologic laboratories. The estimation of the spectra from the data is usually done by averaging the squared modulus of the Fourier transformation of segments of data. Data-driven adaptive methods able to deal with the whole variety of real tremor dynamics have also been suggested. Tremor frequency and signal-noise ratio are 2 important tremor parameters. Additional tremor characteristics describing interactions between groups of muscles can be derived using cross-spectral analysis. For 2 stochastic processes, x(t) and y(t), the coherency function measures the extent to which y(t) may be predicted from x(t) by an optimum linear least squares relationship. Coherency is thus interpreted as a measure of linear predictability. The coherence between 2 signals is defined by:

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\text{Coherence}(x(t), y(t)) = \frac{(\text{CSD}[x(t), y(t)]^2/(\text{Power}[x(t)] \times \text{Power}[y(t)]))}{\text{Coherency values should not be interpreted by themselves. For instance, when the spectral density estimates in both series are very small, large coherency values may result, although there are no strong cyclical components in either series at the respective frequencies. A better picture of underlying periodicities often emerges when examining the spectral and cospectral densities, that is, the frequency regions these consist of many adjacent frequencies, which contribute most to the overall periodic behavior in series. The spectral and cospectral density estimates are computed by smoothing the periodogram values with a weighted moving average. In our study, we considered a lower bound of 0.6 for the coherency, as recommended by Boose et al. A high intermuscular coherency, observed, for instance, in orthostatic tremor (OT) and sometimes in enhanced physiologic tremor, indicates the existence of either a unique oscillator that generates tremor in all involved muscles on both sides of the body or a linking mechanism at a supraspinal level. By contrast, poor side-to-side coherence in essential and parkinsonian tremors suggests distinct bilateral oscillators. In these patients, a considerable number of muscle combinations may oscillate at virtually the same frequency but without showing a significant coherence. In a recent study, 1 of 22 patients with Parkinson disease had essential tremor, and of 28 patients with essential tremor, none showed significant coherencies between muscles from different limbs. However, significant coherencies between muscles within the same arm or leg were found in 70% of patients with Parkinson disease and 90% of patients with essential tremor.

It is likely that the neuronal networks, including the cerebellar nuclei and their brainstem connections, play an important role in the pathogenesis of high-frequency synchronous discharges. There are abundant connections between the cerebellar nuclei and brainstem nuclei, which are implicated in tremorgenesis. In their experimental studies of the dynamic properties of reverberating circuits in the mammalian brain, Tsukahara and colleagues have shown that when cerebellar nuclei were released from the inhibitory control of Purkinje neurons following injection of picrotoxin, prolonged depolarization and explosive repetitive discharges appeared in brainstem nuclei. Surgical ablation of the intermediate cerebellar cortex in the anterior lobe was also associated with prolonged depolarization in the nucleus interpositus. This prolonged depolarization was abolished after cooling the inferior and middle cerebellar peduncles and persisted following ablation of the cerebral sensorimotor cortex. These findings supported the hypothesis that prolonged depolarization was due to impulse reverberation along the interpositus-precerebellar loop circuits (Figure 5A). Repeated discharges of interpositus neurons produced tonic bombardment of brainstem nuclei. Neurons returned to the resting state after several hundred milliseconds. Elec-
trical stimulation may excite preferentially myelinated fibers running parallel to the direction of the flow of the current. Stimulation between the mastoids in our patients could depolarize the axons of the pontocerebellar tracts and the efferents from the nucleus reticularis tegmenti pontis toward the cerebellar cortex and nuclei. This would mimic the effects observed by Tsukahara et al16,17 after cooling the middle cerebellar peduncles. We suggest that the high-frequency discharges found in our patients were due to repetitive discharges in the cerebellar-precerebellar circuits.

Is there a peripheral influence on the central generator in our patients? It must be pointed out that peripheral and central mechanisms are not mutually exclusive. In our patients, the absence of the effects of peripheral ES argues against the hypothesis of a peripheral influence and suggests that voluntary wrist flexion influences the oscillator by virtue of the command for voluntary movement. However, electrical pulses cannot mimic the stretch of muscles in some circumstances. Studies in monkeys have shown that cerebellar tremor may be synchronized to a torque pulse. Tremor occurring when attempting to hold the arm in a position may be driven by stretch-evoked peripheral feedback. Muscle tendon vibration is another technique used for proprioceptive stimulation. In one of our patients, we found that vibratory proprioceptive stimulation applied between the belly and tendon of flexor carpi radialis and extensor carpi radialis muscles at a frequency of 80 Hz reduced tremor intensity, suggesting an interaction between proprioceptive inflow and tremor drive outflow. The dense projections of Ia/Ib/II afferents from the upper limbs to the anterior lobe of the cerebellum, conveyed via the cuneo-
cerebellar tract and the rostral spinocerebellar tract (Figure 5B), and the responses of interpositus nuclei to muscle stretch, could participate in the terminal phase of the repetitive explosive bursts, abolishing the reverberation. Stretch or contraction of muscles greatly intensifies the discharges along the Ia/Ib fibers of cuneocerebellar and spinocerebellar tracts, evoking a mossy fiber response in the anterior lobe. The focus of this response is sharpened by the Golgi cell inhibition of all feebly excited granule cells. A wide inhibitory effect results. This inhibition could participate in the return to the resting state following stretch of the forearm extensors in our patients. The cuneocerebellar tract is a good candidate to explain the inhibitory effect of wrist flexion on high-frequency bursts because its receptive fields are small and each muscle is somatotopically represented. Neurons in the main cuneate nucleus transmit predominantly dynamic information to the cerebellum, and perturbations of joint position result in vigorous central responses.

High-frequency bursts are known to occur in OT. Recently, it was demonstrated that primary OT is also reset by ES over the posterior fossa but is not reset by transcranial magnetic stimulation over the motor cortex. In addition, secondary OT has been associated with lesions of the pontocerebellar tracts and the cerebellum. In particular, secondary OT may occur in association with a sporadic pan cerebellar syndrome associated with isolated cerebellar atrophy. However, while primary OT and secondary OT affect primarily weight-bearing muscles, BHFSs are not observed in paraspinal and lower limbs. In addition, a major discrepancy between OT and BHFS is the explosive character, which is in favor of distinct pathophys-
ologic characteristics. Another tremor characterized by bilateral coherent bursting has been reported recently. The clinical and neurophysiologic characteristics are also distinct from BHFS: (a) the tremor resembles enhanced physiologic tremor, involves all limbs, and may involve the face or jaw; (b) the rhythmic activity is not explosive and the frequency of bursts is between 6 and 13 Hz. Therefore, BHFS seems to be distinct from other forms of tremor described so far.

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