

Clinical and Magnetic Resonance Imaging Manifestations of Holmes Tremor

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Abstract- Holmes tremor is a rare symptomatic slow tremor in the proximal parts of the limbs. It may be present at rest or maintenance of a posture, or during the movement of the affected limb. We describe here in three patients of Holmes tremor with possible etiologies of brainstem infarction and head injury. The intervals between the causal events and the appearance of tremor range from 1 month to 12 months. Magnetic resonance imaging studies reveal hypertrophy of the inferior olivary nucleus in all of the three patients, although only one of them has palatal myoclonus. The surface electromyographic recordings reveal characteristic slow oscillation with frequencies of 3.5 to 4.2 Hz. These features suggest that perturbation of the dentato-rubral-olivary circuitry may play a pivotal role for the generation of Holmes tremor. However, no tight correlation is observed between the presence of inferior olivary nuclear hypertrophy and the appearance of symptomatic palatal myoclonus in the current report.

Key Words: Holmes tremor, Brainstem infarction, Head injury, Inferior olivary nuclear hypertrophy, Dentate-rubral-olivary circuitry

Acta Neurol Taiwan 2005;14:9-15

INTRODUCTION

Holmes tremor is a symptomatic tremor caused by lesions in the brainstem, cerebellum, or thalamus⁽¹⁾. The tremor is infrequently seen and has been labeled in the past as rubral tremor⁽²⁾, midbrain tremor⁽³⁾, thalamic tremor⁽⁴⁾, or myorhythmia⁽⁵⁾. Because it can develop in lesions outside the midbrain⁽⁶⁾, the term of Holmes tremor has been preferred in recent years. The tremor, which is present at rest and is enhanced by both postural

maintenance and action⁽⁷⁾, has been described as typically of low frequency (2-5 Hz)^(1,5-8) and large amplitude⁽⁷⁾ with tendency to involve proximal parts of the limbs⁽¹⁾. A variety of conditions including stroke^(9,10), trauma^(11,12), multiple sclerosis⁽¹³⁾, midbrain abscess⁽¹⁴⁾, and cavernous angioma⁽⁷⁾ had been reported as the possible etiology of this tremor. Here we described three patients of Holmes tremor with probable causal link to ischemic stroke and head injury. Findings of neurological examination, tremor recording, and brain magnetic resonance imaging

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Received September 21, 2004. Revised December 1, 2004.
Accepted January 21, 2005.

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(MRI) were documented in detail for all these patients to depict the spectrum of this rare disorder.

MATERIALS AND METHODS

Subjects (Table)

Patient 1

The 52-year-old male developed sudden onset of dysarthria, swallowing disturbance and gait unsteadiness on 20th May, 2001. A diagnosis of brainstem infarction was made based on the clinical manifestations and neuroimaging findings in a local hospital. In September 2001, another event of sudden-onset right leg weakness happened without concomitant new neurological deficits in the other body parts. Insidious onset of resting and postural tremor developed in the right hand about 6.5 months later following the first event. On examination, he was well oriented but appeared chronically ill. Cranial nerve examination revealed left medial longitudinal fasciculus syndrome in association with gag hyporeflexia, dysarthria as well as dysphagia. The limbs were asymmetrically weak with grade 4 muscle power in the right and 4+ on the left limbs. His gait was ataxic and wide-based. Finger-to-nose test revealed right hand dysmetria. The deep tendon reflexes were systematically diminished and the plantar responses were flexor. Most interestingly, there was a slow resting and postural tremor over the right shoulder, arm, and forearm. The tremor was exacerbated by right hand motion.

Patient 2

The 24-year-old male suffered severe head injury from a traffic accident in April 2001. He was comatose for 4 days and was initially treated in the intensive care unit of a local hospital. Thereafter he was transferred to regular ward for another 26 days. Retrograde amnesia was observed at that moment. Meanwhile, diplopia in association with numbness and weakness of the right hand were noted. About 1 month after the head trauma, he developed gradual onset of right upper limb tremor, which affected the right arm at first and then the right shoulder as well as forearm. The tremor was minimal at rest, but would become vigorous on postural maintenance or on targeting an object.

On examination, a slow and rhythmic tremor over the right arm and shoulder girdle was detected. The tremor could be barely detected at rest and was enhanced by outstretching the right hand or by right hand motion. Although there is no limitation in gross eye movement, he complained of diplopia on looking to the right. There were also right hand dysmetria in the finger-to-nose test and mild dysarthria. The muscle strength and deep tendon reflexes were normal and the plantar responses were flexor.

Patient 3

The 50-year-old male with a history of mitral regurgitation suffered an event of subacute bacterial endocarditis (SBE) in 1992. Part of the clinical manifesta-

Table. Demographic data of three patients with Holmes tremor

Patients	1	2	3
Age at tremor onset (years)	52	24	50
Interval between the neurological event and the appearance of tremor	6.5 months	1 month	12 months
Etiology	Brainstem infarction	Head trauma	Brainstem septic emboli
Tremor behavior	Rest, postural, and action	Rest, postural, and action	Rest, postural, and action
Tremor site	Right upper limb	Right upper limb	Bilateral upper limbs
Symptomatic palatal	-	-	+
Myoclonus			
Tremor frequency	4.1 Hz	4.2 Hz	3.5 Hz
Brain MRI finding	Left IONH (22 months)*	Left IONH (14 months)	Bilateral IONH (3.5 years)

*Duration in the parenthesis indicates interval between the neurological insult and the brain MRI, IONH: inferior olivary nuclear hypertrophy.

tions of this patient had been illustrated in our previous report⁽¹⁵⁾. In brief, he developed sudden onset of consciousness disturbance ten days later despite administration of appropriate antibiotics in a local hospital. In addition to the clinical features of SBE, eyeball divergence and bilateral lid ptosis were noted. Occlusion at the top of the basilar artery by septic emboli was diagnosed at that moment. One year following the event, the patient developed tremor over proximal part of the left upper limb, followed by tremor of the contralateral upper limb several months later. Symptomatic palatal myoclonus (SPM) was also detected 6 months later after the brain-stem stroke. We will focus on his SPM in this report.

METHODS

Tremor recording was conducted with electrodes taped to the muscles of the active tremor regions. The EMG signals were amplified by Digitimer 360 (Welwyn Garden City, Hertfordshire, England), bandpass filtered

(10 Hz to 2.5 KHz), digitized, and stored in a computer. The data were processed off-line with EMG rectification, smoothing, creation of 1024-point epochs, inspection of most active EMG activation, Fast Fourier Transform (FFT), and finally frequency analysis. The MR imaging sequences were spin-echo T1-weighted (TR/TE 466.6-500/12.3-14) in the axial and coronal planes, and T2-weighted (TR/TE 2800-4400/75-100) in the axial, sagittal, and coronal planes. Fluid-attenuated inversion recovery (FLAIR) (TR/TE 9002/142-142.5) in the axial plane was also performed. No contrast medium was given.

RESULTS

Patient 1

The results showed rhythmic EMG bursts in frequency of 4.1 Hz during both resting and outstretching of the right hand (Figs. 1 A-B). The brain MRI conducted on 19th February, 2003 was shown in Fig. 2A.

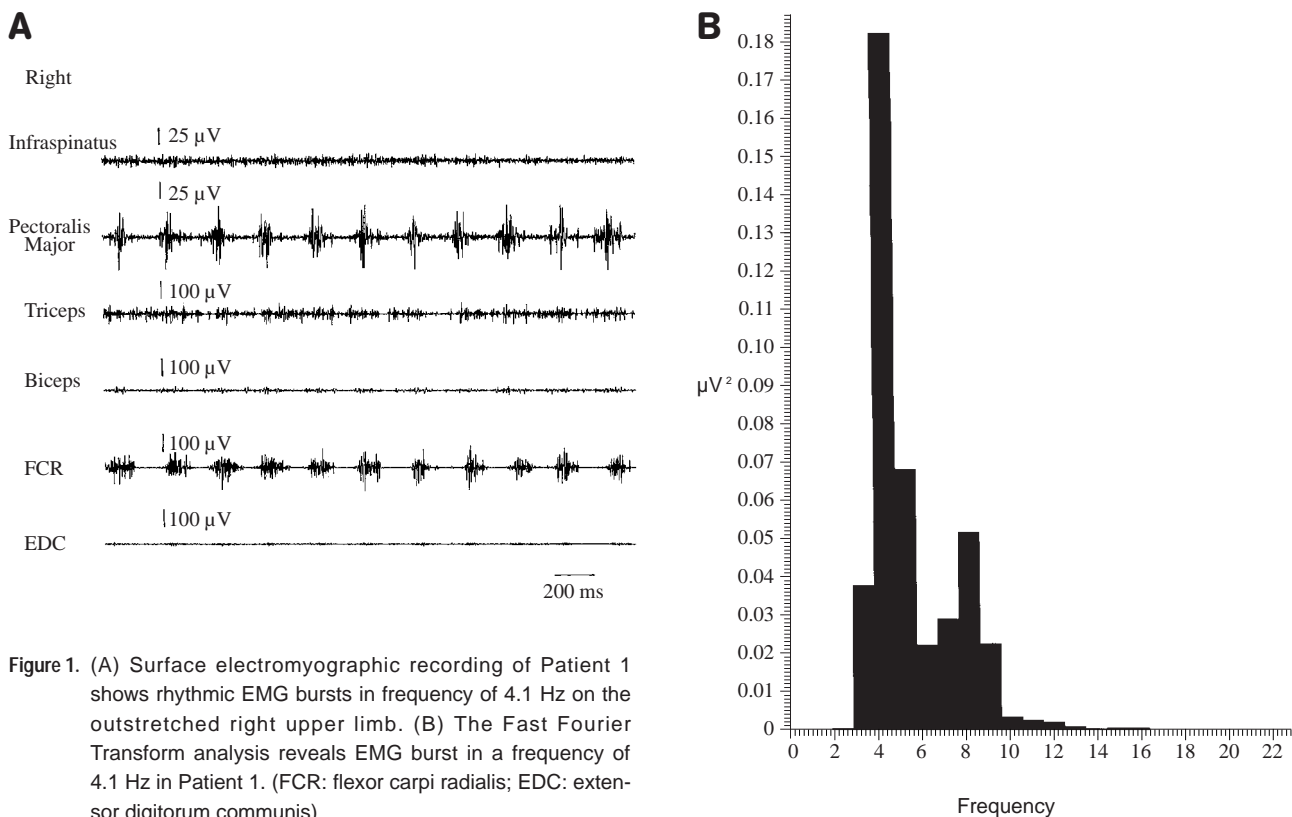


Figure 1. (A) Surface electromyographic recording of Patient 1 shows rhythmic EMG bursts in frequency of 4.1 Hz on the outstretched right upper limb. (B) The Fast Fourier Transform analysis reveals EMG burst in a frequency of 4.1 Hz in Patient 1. (FCR: flexor carpi radialis; EDC: extensor digitorum communis)

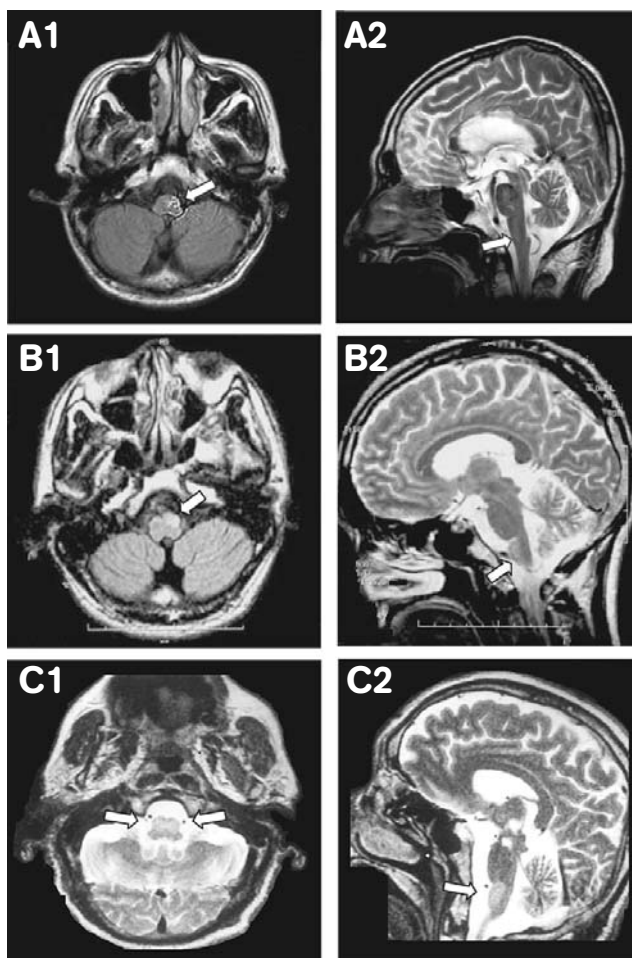


Figure 2. (A) Patient 1. (B) Patient 2. (C) Patient 3. (A1) axial FLAIR and (A2) sagittal (T2-weighted) views of magnetic resonance images show left inferior olivary nuclear hypertrophy (arrow). Several spots of infarction are also noted within the midbrain and pons in A2. (B1) axial (FLAIR) and (B2) sagittal (T2-weighted) views of magnetic resonance images show left inferior olivary nuclear hypertrophy (arrow). (C1) axial (T2-weighted) and (C2) sagittal (T2-weighted) views of magnetic resonance images show bilateral inferior olivary nuclear hypertrophy (arrows). Infarctions in the midbrain are also noted in (C2).

Patient 2

Multi-channel surface EMG recording with electrodes taped to the right supraspinatus, pectoris major, deltoid, and flexor carpi radialis revealed a tremor frequency of 4.2 Hz. The brainstem MRI conducted on 16th July, 2002 was shown in Fig. 2B. Levodopa in a daily dose of 200 mg was administrated initially and did

not show any benefit to his problem. He was then treated with buspirone (30 mg/day) and amantadine (300 mg/day), and the tremor was partially ameliorated.

Patient 3

The result of brainstem MRI conducted 3.5 years after the embolic stroke was shown in Fig. 2C. Surface EMG recording over the muscles with active tremor revealed 3.5 Hz rhythmic discharges both at rest and during postural maintenance of the hands. The SPM was recorded with video (not shown).

DISCUSSION

The diagnosis of Holmes tremor was evident in our patients as based on the clinical findings and tremor recording. The demographic data were summarized in Table. All these patients had a slow, coarse, large amplitude tremor during both rest and postural maintenance. The tremor was predominantly observed in the proximal parts of the upper limb. It was caused by brainstem ischemic stroke in two patients and by head injury in the third one. The lag between the neurological insult and the appearance of the tremor was from 1 month to 12 months. The tremor frequency of the three patients ranged from 3.5 to 4.2 Hz and was consistent with the results of previous reports⁽⁷⁾. Brain MRI revealed IONH in all these patients. In patient 3, in whom palatal myoclonus was concomitantly present with limb tremor, the inferior olivary nuclei were involved bilaterally. Although the pathogenesis of Holmes tremor is not fully understood, some authors proposed that interruption of both the nigrostriatal pathway and the dentato-rubral-olivary circuitry, the Guillain-Mollaret triangle, could cause the tremor^(2,16,17). The former perturbation may be related to the 'resting' component of the tremor, whereas the latter may be responsible for the development of the 'postural and kinetic' components of the tremor as well as the appearance of inferior olivary nuclear hypertrophy (IONH)⁽⁷⁾. Guillain-Mollaret triangle is composed of the contralateral dentate nucleus, the ipsilateral red nucleus and the ipsilateral inferior olivary nucleus. The inferior olivary nucleus is the major source of climbing fibers. It

sends efferents crossing the midline and terminating on the dendrites of the Purkinje cells, which in turn sends fibers to the dentate nucleus^(9,18) in the cerebellum. The dentate nucleus then conveys efferents to the contralateral red nucleus through superior cerebellar peduncle^(16,17). The red nucleus conveys uncrossed fibers through central tegmental tract to the dorsal lamella of the inferior olivary nucleus^(9,18). It has been proposed that lesions allocated to some parts of the triangle may cause IONH and Holmes tremor^(9,15-18). Because IONH is present in all of the three patients, the Guillain-Mollaret triangle is very likely perturbed in all of them. There is usually a lag between the neurological insult and the appearance of the Holmes tremor. This delay could be related to the time for the development of postsynaptic degeneration and release of the inferior olive after the disruption of the Guillain-Mollaret triangle by the insult⁽¹⁹⁻²¹⁾. It is intriguing to note that Holmes tremor may exist without concomitant presence of IONH^(15,22-24) and the pathogenesis for this finding remains to be elucidated. One possibility is that the lesion may involve only olivodentate fibers but not the other two limbs of the triangle. In that case IONH would not happen because olivary deafferentation is thought to be the most important causal factor for IONH⁽¹⁸⁾. Another possibility is that the structures outside but relevant to Guillain-Mollaret triangle, such as the dentatothalamic tract, was perturbed. This condition potentially may also cause tremor without IONH^(9,18).

One patient, patient 3, developed SPM 6 months after the brainstem stroke. The causal relationship between the presence of IONH and the development of SPM has long been under debate. Llina's et al. proposed that interruption of the dentate-olivary tract may culminate in hypersynchronous discharge and hyperactivity of the inferior olivary nuclear neurons to trigger SPM⁽²⁵⁾. On the other hand, Nishie et al. examined the relationship between IONH and palatal myoclonus in 8 of 16 autopsied subjects with cerebrovascular lesions of the dentate-olivary tracts, and found that the generation of SPM can not be correlated with IONH⁽²⁶⁾. They suggested that the development of SPM is ascribable to the disturbance of natural rhythm in the body and the lack of

feedback from the inferior olivary nucleus. Because only one of the three patients with IONH developed SPM, this report may be viewed as an evidence in favor of Nishie's hypothesis. It should be emphasized that SPM may be present without Holmes tremor and vice versa^(27,28). In patients with Holmes tremor without SPM, autopsy findings in general show less extensive involvement of the olive and more severely affected dentate nucleus as compared to those with SPM⁽²⁷⁾.

The treatment of Holmes tremor is usually difficult. Medications including benzodiazepines, valproic acid, beta-blockers, anticholinergics, dopamine agonists and levodopa have been reported to benefit the patients with Holmes tremor to some extent^(15,29-31). In this report, the tremor of two patients was ameliorated by the administration of amantadine. Because amantadine is an NMDA receptor blocking agent and could also help the release of dopamine from the neuronal terminals^(32,33), it is possible that these functional domains share a role in the pathogenesis of Holmes tremor. Recently, deep brain stimulation of the thalamus^(34,35) and Vim (ventrointermedius) thalamotomy⁽³⁶⁾ have been advocated for the management of Holmes tremor. These procedures may offer novel options for the treatment of the Holmes tremor which is resistant to conventional management.

Since there is a resting component of Holmes tremor, the tremor should be carefully differentiated from that of Parkinson's disease. As a rule of thumb, the tremor frequency of Holmes is usually slower than 4 Hz^(1,5,7,8) and the proximal parts of the limbs are usually involved. In contrast, Parkinson's disease is usually characterized by 4- to 6- Hz pill-rolling tremor which is most pronounced in the distal parts of the limbs⁽⁵⁾.

ACKNOWLEDGMENTS

The study was supported by grants from the National Science Council (NSC 92-2314-B-039-016) and CMRP856 (Chang Gung Memorial Hospital).

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