Review Article

Treatment responsive Holmes tremor: case report and literature review

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Abstract

Holmes tremor is a rare symptomatic movement disorder, characterized by a combination of resting, postural, and action tremors. It is usually caused by lesions involving the brainstem, thalamus, and cerebellum. It is often difficult to treat, many medications have been used with varying degrees of success. It may respond to stereotactic thalamotomy and deep brain stimulation in ventralis intermedius nucleus. Here I report a case of Holmes tremor secondary to multiple sclerosis that treated with L-dopa/carpidopa and showed marked improvement. A relevant literature search was performed, using PubMed for Holmes tremor as labelled in the literature. I included all patients diagnosed with Holmes tremor who responded to medical treatment. I found 27 cases, which are summarized in this review. This report describes a patient with Holmes tremor, who responded very well to Levodopa. This outcome suggests that Levodopa should be considered in the initial management of Holmes tremor.

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Introduction

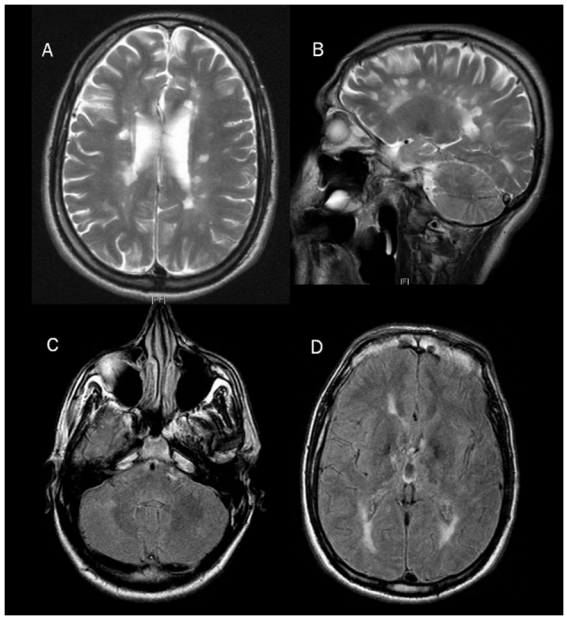
Holmes tremor (HT) is characterized by a combination of resting, postural, and action tremors and is usually caused by lesions involving brainstem, thalamus, and cerebellum. HT is an irregular, slow-frequency (<4.5 Hz) tremor that is predominantly unilateral and can be associated with other neurological signs, such as ataxia, bradykinesia, and ophthalmoplegia. [(1)] Lesions associated with HT may have different etiologies, including ischemic or hemorrhagic cerebrovascular disorders, bleeding secondary to vascular malformations, head trauma, tumors, demyelination, or infections. [(2)] Here, I report a patient diagnosed with multiple sclerosis (MS) who developed HT and was responsive to Levodopa.

Case Report

A 31-year-old, left-handed man was diagnosed with relapsing-remitting multiple sclerosis (RRMS) 10 years ago and was maintained on interferon β-1a therapy. He suffered three attacks of multiple sclerosis since diagnosis. The last attack was six months prior to presentation at our clinic. He had been in his usual state of health until he developed hyperkinetic movements that initially involved the right upper limb, followed seven weeks later by the right lower limb. On neurological examination, the patient was alert and fully oriented, with bilateral internuclear ophthalmoplegia and tremor that was rhythmic, irregular, slow in frequency (~3Hz), marked in amplitude and present most of the time during rest, posture and kinetic in the right hemibody, it was worsened by emotional distress or attempts to inhibit the tremor, and disappeared during sleep. No associated rigidity or bradykinesia was found. Levels of serum electrolytes, urea, creatinine, bicarbonate, liver enzymes, free T4, and thyroid stimulating hormone were normal. Magnetic resonance imaging revealed multiple periventricular T2-hyperintense non-enhancing white matter lesions, together with small, bilateral cerebellar lesions and bilateral thalamic foci of tissue loss (figure 1). He was started on L-dopa/carbidopa that incremented gradually to 250/25 mg four times daily. Treatment resulted in marked improvement in resting, postural and kinetic tremors. The patient tolerated the treatment well and was discharged with a diagnosis of L-dopa-responsive Holmes tremor secondary to relapsing-remitting multiple sclerosis. The treatment effect persisted after 3 months of follow-up.

Legends for the Figure segments:

Brain Magnetic resonance imaging revealed multiple periventricular T2-hyperintense non-enhancing white matter lesions, together with small, bilateral cerebellar lesions and bilateral thalamic foci of tissue loss



Discussion

In 1904, Gordon Holmes first described a syndrome characterized by a low-frequency resting tremor accentuated by posture and intentional movement. [(1)] Holmes tremor, also called midbrain tremor, is a symptomatic, lowe-frequency (<4.5-Hz) tremor that predominantly affects the proximal limbs. Oscillations are present at rest but worsen during movements and goal-directed tasks. A delay of between 4 weeks to 2 years is commonly observed between lesion onset and the occurrence of tremor, suggesting a rearrangement of central pathways in the brain or an aberrant result of plasticity. [(1, 3, 4)] Most of lesions that cause this kind of tremor often located in the upper brainstem, thalamus, and cerebellum. Lesions

in these locations interrupt the pathways in the midbrain tegmentum and brainstem telencephalic fibers. [6, 7] Despite its name, a rubral tremor is generally not caused by lesions confined to the red nucleus. Instead evidence suggests that damage to the cerebellothalamic or nigrostriatal fibers must also be present. [5] Because more cases of rubral tremor have been described in literatures with lesions outside the red neclues, the term 'Holmes tremor', named for Gordon Holmes, is used as an alternative name for the disorder. [1] Holmes tremor is often difficult to treat. Many medications have been used, including benzodiazepines, propranolol, anticholinergcs, bromocriptine, and levodopa, with varying degrees of success. [6] Holmes tremor may respond to stereotactic thalamotomy and deep brain stimulation in ventralis intermedius nucleus. [7] I searched PubMed for all reports of patients diagnosed with HT who responded to medical treatment. I found 27 such cases, which are summarized in Table 1. Central nervous system hemorrhage was the most common cause include post trauma [6 cases], hemorrhagic infarction [5 cases], cavernoma [3 cases], AVM [3 cases], hemangioma [1 case], and SAH [1 case]. Ischemic stroke was the cause of holmes tremor in 4 cases [14.8%]. Toxoplasmosis abscess was the cause in 2 HIV+ patients.

Levopoda was used in the treatment of 21 patients [77%] either as monotherapy or in combination with other medication, levetiracetam was used in 2 cases. Other agents used to treat individual cases include cabergoline, piribedil and zonisamide. The use of other agents following L-dopa treatment failure was associated with remarkable response rates. In a single case, holmes tremor with an ischemic midbrain lesion associated with chronic hydrocephalus responded to cerebrospinal fluid release. [17]

Table 1. Patients with Treatment-Responsive Holmes Tremor

Patient	Sex/Age (Yrs)	Site of Lesion	Etiology	Medications Used	Reference Number
1	M/51	Interpeduncular fossa	AVM "Bleeding"	Levodopa	7
2	M/21	Midbrain	Posttraumatic hemorrhage	Levodopa	8
3	F/36	Midbrain and thalamus	Posttraumatic hemorrhage	Levodopa and carbamazepine	9
4	F/30	Midbrain and thalamus	Posttraumatic hemorrhage	Levodopa	10
5	M/25	Midbrain	AVM "Bleeding"	Levodopa	11
6	F/31	Midbrain and thalamus	Posttraumatic hemorrhage	Levodopa	12
7	M/41	Midbrain	Bullet	Levodopa and piribedil	12
8	M/46	Midbrain and thalamus	Hemorrhagic infarction	Levodopa	12
9	M/25	Midbrain and thalamus	AVM "Bleeding"	Levodopa and piribedil	12
10	M/54	Midbrain and thalamus	Hemorrhagic infarction	Levodopa	12
11	M/32	Midbrain and thalamus	Posttraumatic hemorrhage	Levodopa and bromocriptine	12
12	F/28	Midbrain	Hemangioma "Bleeding"	Levodopa	13
13	M/25	Midbrain	Hemorrhagic infarction	Levodopa	14

14	M/46	Midbrain and thalamus	Toxoplasma abscess	Levodopa and INH	15
15	M/57	Midbrain	Ischemic infarction	Cabergoline	16
16	M/61	Cerebellum	Hemorrhagic Infarction	Levetiracetam	18
17	F/53	Midbrain	Cavernoma "Bleeding"	Levodopa	19
18	F/30	Pons	Posttraumatic hemorrhage	Levodopa	19
19	M/51	Midbrain	Toxoplasma abscess	Pramipexole	20
20	M/19	Midbrain	Posttraumatic contusion	Levetiracetam	21
21	F/16	Midbrain and pons	Cavernoma "Bleeding"	Levodopa	22
22	F/81	Cerebellum	Ischemic infarction	Levodopa	24
23	F/54	Midbrain, thalamus and cerebellum	Ischemic infarction	Piribedil	23
24	M/32	Midbrain and cerebellum	Cavernoma "Bleeding"	Levodopa and piribedil	25
25	M/84	Pons and cerebellum	Ischemic infarction	Levodopa and propranolol	25
26	F/68	Midbrain	Aneurismal subarachnoid hemorrhage	Zonisamide	26
27	F/70	brachium pontis to the dorsal midbrain	Hemorrhagic Infarction	Levodopa	27

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