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Tremor and Other Hyperkinetic Movements

Case Reports

Holmes Tremor Partially Responsive to Topiramate: A Case Report

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Abstract

Background: Holmes tremor is a rare symptomatic movement disorder, characterized by a combination of resting, postural, and intention tremor. It is usually caused by lesions in the brainstem, thalamus, and cerebellum. Despite pharmacological advances, its treatment remains a challenge; many medications have been used with various degrees of effectiveness. Stereotactic thalamotomy and deep brain stimulation in the ventralis intermedius nucleus have been effective surgical procedures in cases refractory to medical treatment.

Case Report: Here we report a young woman with topiramate-responsive Holmes tremor secondary to a brainstem cavernoma.

Discussion: Herein we report a Holmes tremor responsive to Topiramate.

Keywords: Holmes tremor, topiramate

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Introduction

Holmes tremor (HT) is characterized by a combination of resting, postural, and intention tremor and is usually caused by injuries involving the brainstem, thalamus, cerebellum, or their connections.[1]

The current definition is derived from the consensus statement of the Movement Disorder Society on Tremor from 2018.[2] It is described as a syndrome of rest, postural, and intention tremor that usually appears from proximal and distal rhythmic muscle contraction at low frequency (<5 Hz). The etiology is frequently an acquired lesion in the brainstem in the vicinity of the red nucleus. The different etiologies include ischemic or hemorrhagic cerebrovascular disorders, bleeding because of vascular malformations, head trauma, tumors, demyelination, or infections.[3–5]

Tremor commonly develops between 1 and 24 months after a central nervous system insult. This delayed onset might be due to neuronal plastic changes.[6–9] HT usually occurs with other localizing signs, but is rarely isolated.[10]

As it is a symptomatic tremor, imaging studies are usually abnormal, although in some cases no lesion at all can be demonstrated.[11–14]

The treatment is often challenging and only few cases of treatment-responsive HT have been reported in the literature.[15] Here, we report a patient diagnosed with a brainstem cavernoma who developed HT responsive to topiramate (TPM).

Case report

A 33-year-old right-handed female, without any relevant medical history, suffered a sudden left hemiparesis on January 2016. Brain magnetic resonance imaging (MRI) showed a brainstem hemorrhage, involving the right mesencephalon, secondary to an extensive cavernous angioma, with diencephalic and thalamic extension (Figures 1 and 2). Repeated hemorrhages lead to a space-occupying lesion. She underwent surgery for the hematoma evacuation, but complete resection was not possible. A few weeks later, she developed a rest tremor, worsening with posture and additionally intensified with action involving her left arm. The tremor seriously affected the patient's daily activities and quality of life. Several drugs were tried, including pramipexole extended release 3 mg once a day, levodopa/carbidopa 250/25 mg four times a day, valproic acid 500 mg twice a day, levetiracetam 1 g twice a day,

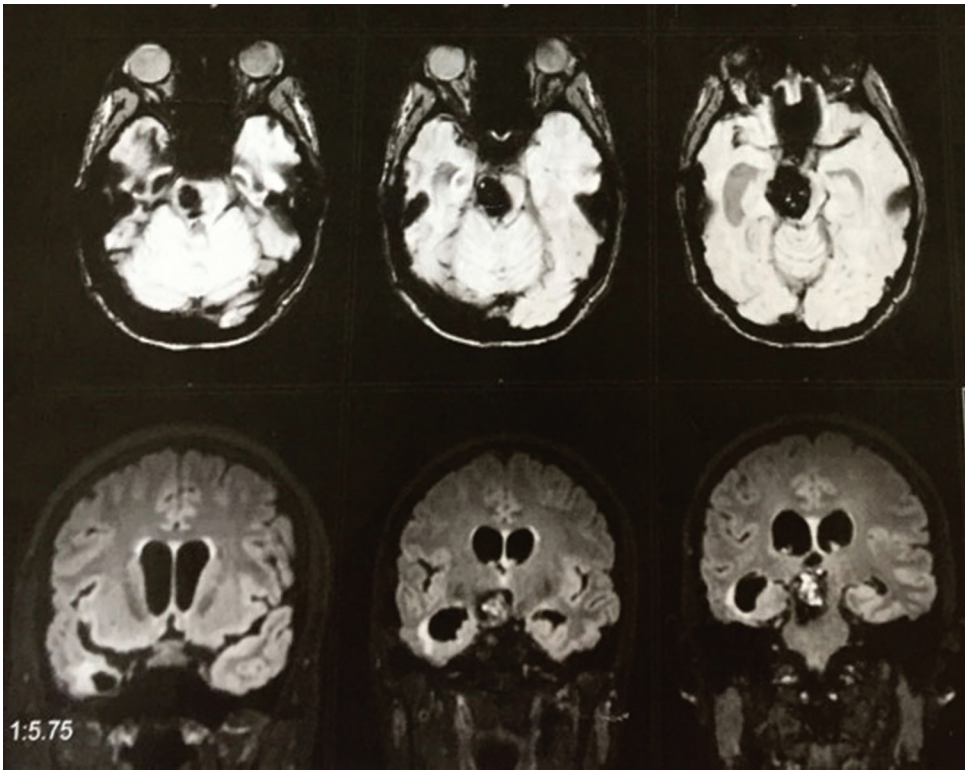


Figure 1. **Brain MRI.** ADC (Apparent diffusion coefficient) and FLAIR (fluid-attenuated inversion recovery) sequences showing a right lesion located at the mesencephalon with diencephalic extension.

quetiapine 50 mg twice a day, gabapentin 600 mg twice a day, clonazepam 2 mg twice a day, and agomelatine 50 mg once a day, all of them titrated to maximum doses, without tremor improvement. Deep brain stimulation (DBS) and thalamotomy were excluded because of the high risk of procedure-related complications. On September 2017, she was admitted to our center; neurological examination showed a left spastic hemiparesis with brisk deep tendon reflexes and a left severe resting, postural, and intention tremor. The patient's consent was obtained prior to recording the video (Video 1). The basal Fahn–Tolosa–Marin Tremor Rating Scale scored 76 points (range, parts A + B + C = 0–156). She marked the intensity of tremor as 9 out of 10 using the visual analog scale (VAS).

After other drugs were discontinued, TPM was started at a dose of 25 mg and titrated to 100 mg (50 mg twice a day). A tremor improvement was observed at the highest dose (Video 2), allowing her to be partially independent in the daily living activities, with no negative impact on the emotional or cognitive sphere. At these doses, the Fahn–Tolosa–Marin Tremor Rating Scale scored 41 points (53% improvement) and 5 out of 10 on VAS.

Discussion

HT, midbrain tremor, or rubral tremor was first described in 1904 by Gordon Holmes. It is a symptomatic, low frequency (<4.5 Hz) tremor that predominantly affects the proximal limbs. Some authors hypothesized that the delayed tremor onset after lesion could be explained by a rearrangement of central pathways in the brain or an aberrant result of plasticity.[16] The HT treatment is a challenge with moderate or poor response.[17–20] Benzodiazepines, propranolol, anticholinergics, channel-blockers, anticonvulsants (lamotrigine, levetiracetam, valproic acid, zonisamide, gabapentin, carbamazepine), atypical neuroleptics (quetiapine, clozapine), baclofen, dopamine agonists (bromocriptine, pramipexole, piribedil), and L-dopa are among the drugs with a variable success.[21] Although, the number of cases reported in the literature is small, L-dopa was the leading one with a substantial outcome.[22–24] This observation is in order with the proposed functional deficit of nigrostriatal dopaminergic pathway.[25,26]

However, satisfactory clinical improvement following treatment with L-dopa is not achieved in some patients, as in our case, and other oral medications, botulinum toxin injections,[27,28] or several surgical procedures are required.[29,30]

TPM, an antiepileptic drug that was originally designed as an oral hypoglycemic and subsequently approved as an anticonvulsant, is also effective in reducing essential tremor (ET).

TPM blocks sodium channels and potentiates gamma-aminobutyric acid activity, decreasing the thalamic output and cortex hyperexcitability.[31,32]

To the best of our knowledge, the present case is the first report of TPM-responsive HT. After an extensive search in the literature, we found the use of TPM in one HT patient of a series reported by

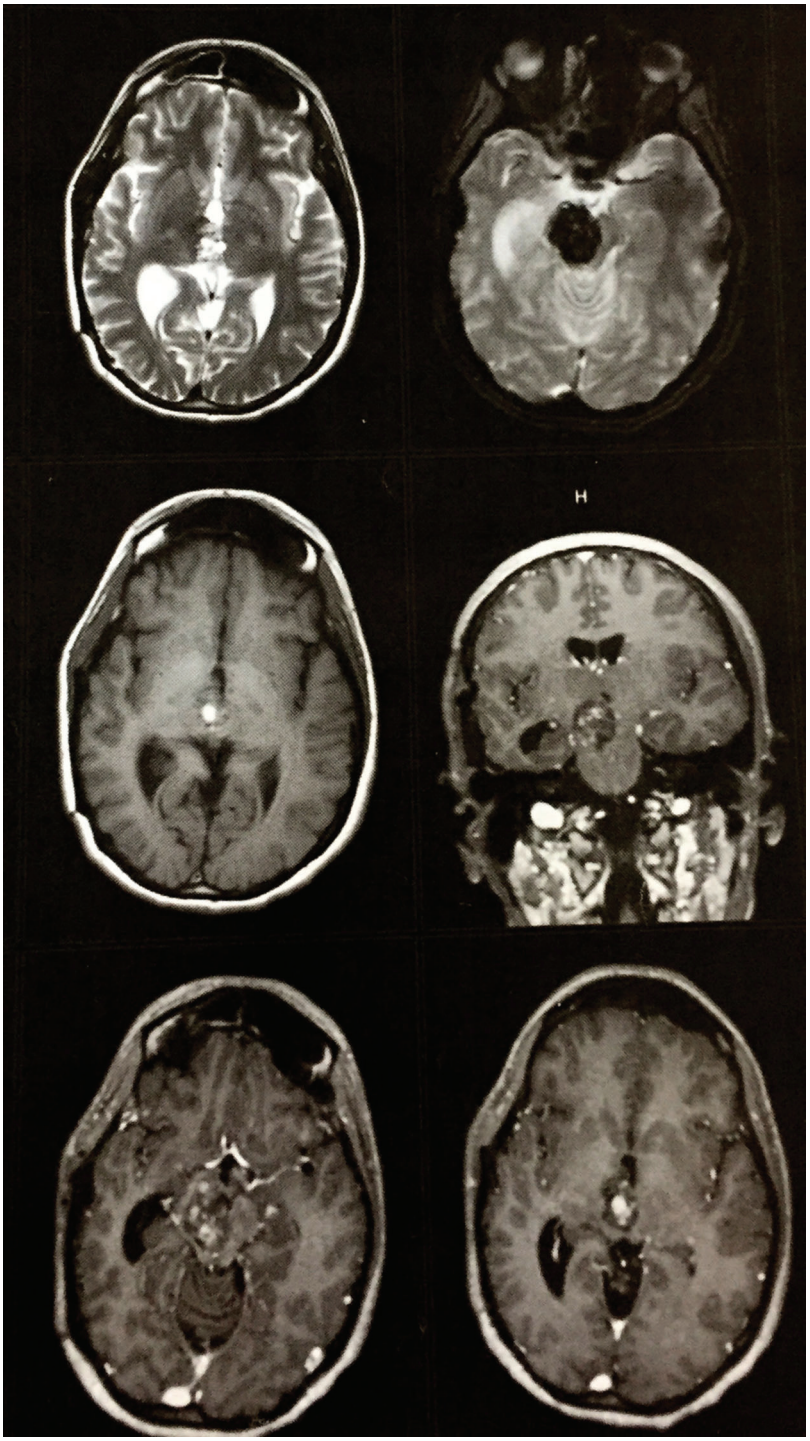
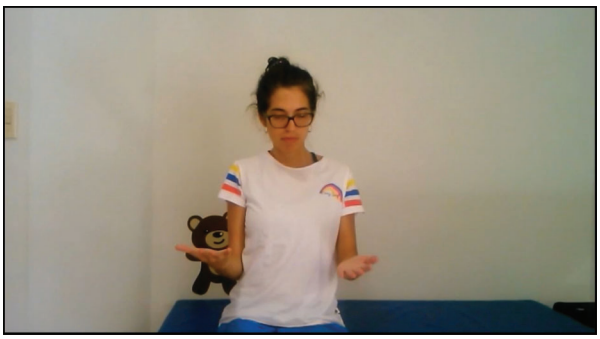


Figure 2. **Brain MRI, Post-gadolinium Images.** T2 and T1 sequences enhanced after the administration of gadolinium.

Raina et al.[33] but in this case TPM was included in the group of drugs with poor or no response. Despite these controversial findings and the lack of evidence, extensive research is still warranted to determine the effectiveness of TPM in HT.[34,35]

In summary, in this patient, with a contraindication for surgical approach[36,37] (DBS or thalamic lesion) and lack of responsiveness to various drugs, including L-dopa, TPM may be a useful drug to improve HT with moderate benefits (about 50 % of tremor scales).

Video 1. **Basal Holmes Tremor. Segment 1A.** Standing position, showing a rest tremor on the left upper limb that worsens with posture and even more with action. A right palpebral ptosis can also be seen. **Segment 1B.** Sitting position, showing how the left lower limb is also involved to a lesser extent with a rest tremor.



Video 2. **Treatment Response. Segment 2A.** Sitting position, showing a decrease in the three components of tremor with predominance of the resting and postural component. **Segment 2B.** Walking, showing a decrease in the rest component in both the upper and the lower left limbs.

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