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Levodopa-responsive Holmes Tremor in a Young Patient with Hypertrophic Olivary Degeneration

Hipertrofik Olivar Dejenerasyonu Olan Genç Bir Hastada Levodopa Yanıtlı Holmes Tremoru

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Anahtar Kelimeler: Holmes tremoru, hipertrofik olivar dejenerasyon, Guillain-Mollaret üçgeni, beyinsapı lezyonu

Dear editor,

Holmes tremor (HT), previously also known as rubral or midbrain tremor, was first described by Holmes (1) in 1904. It is a rare movement disorder, characterized by slow-frequency (<4.5 Hz) resting, postural, and action tremor combinations; it can also be associated with other neurological signs (2). There are different HT etiologies, including trauma, ischemic or hemorrhagic cerebrovascular disorders, vascular malformations, neoplasms, and infections. Symptoms may begin months to years after the etiological diagnosis (3). Pharmacological treatment is generally unsuccessful, and some cases require surgery (4). Both the lesion location and the affected circuit determine the medical and surgical treatment response; it is also important whether or not the Guillain–Mollaret triangle (GMT) is affected.

Case History

The present case was a 20-year-old right-handed male who underwent third ventricular colloid cyst surgery in January 2018. Five months after the surgery, the patient underwent a second operation due to increased intracranial pressure. Two months later, he underwent a shunt operation due to hydrocephalus. Two years after the first surgery, the patient was diagnosed with right focal epileptic seizures and was maintained on a treatment plan with levetiracetam 3,000 mg/day, lacosamide 300 mg/day, and phenytoin 150 mg/day following the diagnosis. One year later, he experienced abnormal hand movements that were unlike his previous seizures.

A neurological examination showed that the patient had right hemiparesis, dysarthria, slow-frequency postural and resting tremor, and dystonic posture in the right hand. The tremor was worsened by movement and disappeared during sleep. Routine laboratory test results were normal; however, the brain magnetic resonance imaging (MRI) revealed a small porencephalic cyst in the left mesencephalon continuous with third ventricle and hypertrophic olivary degeneration (HOD), which had not been present in a previous brain MRI (Figure 1A). Tremor monitoring and frequency analysis was performed via electromyography (EMG). The tremor was recorded from the right forearm during rest, posture with and without weight loading and kinetic action, with a surface electrode overlying the flexor and extensor muscles. The analysis showed a 3–4 Hz, large amplitude, mostly synchronous, and irregular tremor activity with resting, postural, and kinetic components. The tremor increased with movement and was not affected by weight. The EMG recording was consistent with HT (Figure 1B). The EEG video revealed a left frontal epileptic focus and a clinical right focal seizure suppressed by diazepam (Videos 1, 2).

The antiepileptic-resistant movements in the patient's right hand were not considered a seizure; rather, it was concluded that these movements were HT, and lacosamide and phenytoin treatments were gradually reduced before being stopped completely. The levetiracetam dose was reduced, and levodopa/benderizine was chosen for treatment instead. The patient's

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symptoms improved considerably, and no tremor was detected in the second tremor recording (Figure 1C).

Pharmacological treatment of HT is generally disappointing, and surgical procedures are commonly required. The present case suggests that levodopa may be a useful treatment for HT, which is secondary to brainstem lesions and should be assessed prior to surgery.

Discussion

HT is characterized by <4.5 Hz resting, postural, and action tremor combinations and exacerbated by movement (2). The tremor is a result of a lesion in the cerebello–thalamo–cortical or dentato–rubro–olivary pathways, with superimposed nigrostriatal dysfunction. The mesencephalon is the most affected area, where these two systems can be affected together. The role of the nigrostriatal system may explain the resting component of the tremor (5).

Dysfunction of the cerebellothalamic and nigrostriatal systems is considered in the pathophysiology of HT due to the coexistence of resting and kinetic tremors (5). A midbrain lesion, as in the above cases, can interrupt the nigrostriatal pathway or cerebellothalamic tract, causing HT. The first above patient had a brain stem lesion, leading to injury of the nigrostriatal and GMT pathways.

Hypertrophic olivary degeneration may be secondary to head trauma, vascular diseases, tumors, and demyelinating/degenerative diseases, as well as surgery in patients with lesions affecting the dentatorubral or central tegmental pathways. The hallmark of HOD is hypertrophy of the olivary nucleus with increased T2 signal intensity on the brain MRI. There have been several cases of an MRI revealing HT accompanying olivary nucleus hypertrophy in the literature (3,6,7,8,9). In most cases, palatal tremor is accompanied by HOD; however, not all cases of HOD are accompanied by palatal tremor, and HT without palatal tremor after HOD is rare (8). The authors of the present study believe that both HT and HOD may be caused by the same brainstem lesion via disturbance of the GMT.

Unilateral movement disorder diagnosis was difficult in an epileptic patient with focal motor seizure. Unilaterally tremor can be considered an epileptic seizure. Zonisamide, levetiracetam, gabapentin, primidone, and clonazepam have been administered in several cases of HT (4); the best results were described for levetiracetam and zonisamide (6). Despite the present patient using these drugs, his tremor persisted. Therefore, it was considered that the hand movements were not epileptic seizures.

Patients with drug-resistant focal epileptic seizures should be evaluated for HT. Since HT is a symptomatic tremor, patients should be evaluated via brain imaging studies. The present patient's postural and resting tremors were abolished with levodopa treatment; the response to levodopa can be considered evidence of nigrostriatal involvement. The abolishment of the tremor's postural component and the presence of HOD indicate that the nigrostriatal pathway may affect the dentato–rubro–cerebellar pathway.

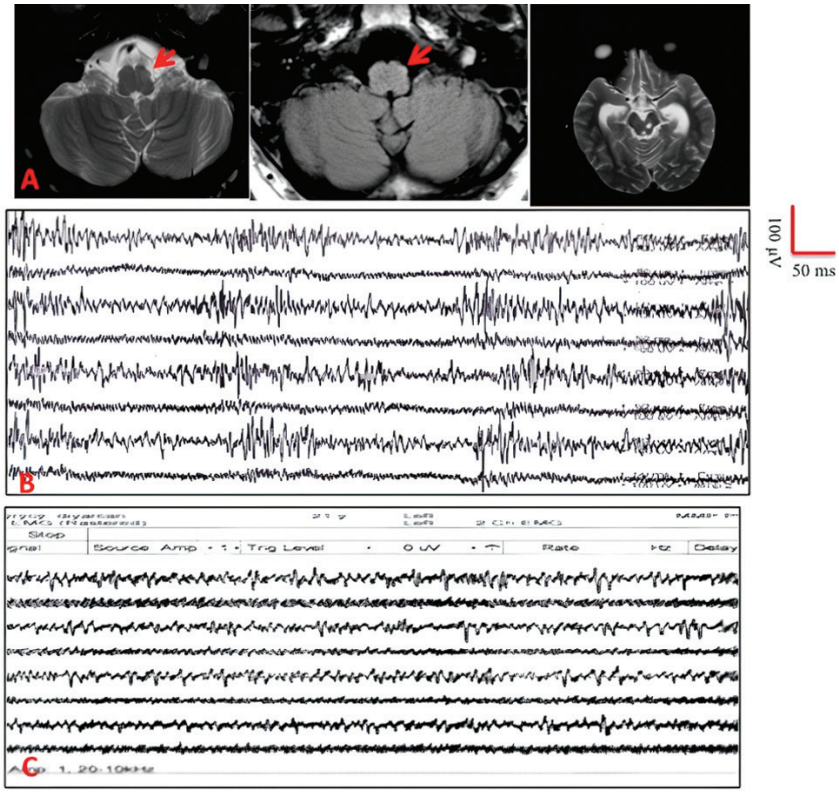

Figure 1. (A) T2 and FLAIR images show a hypertrophied olive nucleus (arrows) with an increased FLAIR T2 signal. There is a porencephalic cyst in the left mesencephalon. (B) The analysis shows a 3–4 Hz, large amplitude, mostly synchronous, irregular tremor with resting, postural, and kinetic components. (C) No tremor was detected after treatment

FLAIR: Fluid-attenuated inversion recovery

The use of levodopa and dopamine agonists has been reported as a beneficial form of treatment (8). If the major injury is in the nigrostriatal pathway, a resting tremor may improve with levodopa treatment (as in the first above case). Isolated cases with a positive response to levodopa therapy have also been reported (7,8); however, the treatment's long-term efficacy is unclear, and there is currently no gold-standard treatment for HT. Medical therapy is generally unsuccessful, but stereotactic ablative procedures (thalamotomy) and deep brain stimulation (DBS) therapy may provide benefits for medically refractory HT. The preferred targets for DBS include the ventral intermediate nucleus of the thalamus (VIM), the subthalamic nucleus (STN), and the globus pallidus interna (GPi) (9). Improvements have been reported as follows: 1) 32.3% with VIM-DBS; 2) 78.6% with GPi-DBS; 3) 16.7% with STN-DBS (8).

The patient's neurological and electrophysiological examinations, as well as their radiologic findings, were consistent with HT. The authors of this study emphasized that HT should be considered, especially in young patients presenting with delayed tremors caused by midbrain lesions.

Ethics

Informed Consent: Patient consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Z.T., Y.S., Ş.A., Design: Z.T., Y.S., Ş.A., Analysis or Interpretation: Z.T., Y.S., Ş.A., M.F.G., Literature Search: Z.T., Y.S., Ş.A., M.F.G., Writing: Z.T., Y.S., Ş.A., M.F.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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Video 1. Slow frequency resting tremor with a dystonic posture of the right hand was observed

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Video 2. The patient's symptoms improved after levodopa/benserazide treatment

https://www.doi.org/10.4274/tnd.2023.52721-video-2

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