Pearls & Oy-sters: A Case Report of Holmes Tremor Due to Nigrostriatal Dopamine Disruption That Responded to Dopamine Replacement Therapy

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Neurology® 2022;99:480-483. doi:10.1212/WNL.0000000000201000

Abstract

Holmes tremor (HT), also known as midbrain, rubral, or cerebellar pathway outflow tremor, occurs because of disturbances of the cerebellothalamic pathway. This tremor is usually related to lesions in the midbrain peduncular region involving the superior cerebellar peduncle, the red nucleus, and possibly the nigrostriatal circuitry. Common etiologies resulting in HT include tumor, ischemia, and demyelination. We report a case of progressive left-sided HT in an otherwise healthy man with additional symptoms of parkinsonism, hypoesthesia, right oculomotor nerve palsy, cognitive dysfunction, and hypersomnolence. Imaging investigations revealed a right-sided thalamic and midbrain glioma. Dopamine transport imaging demonstrated significant dopaminergic denervation in the right caudate and putamen. The degree of striatal dopamine transporter deficiency was more severe than expected in a patient with Parkinson disease. A trial of dopaminergic agent resulted in significant improvement of the tremor and associated symptoms. Interruption of the nigrostriatal pathway can occur in cases of HT because of midbrain peduncular lesion. The striatal dopaminergic function imaging may have a role in assessing presynaptic dopamine dysfunction and guiding treatment.

MORE ONLINE

Video

Pearls

- Interruption of the nigrostriatal pathway can occur and cause Holmes tremor because of midbrain peduncular lesion.
- Investigation of the dopaminergic system, especially with dopamine transporter imaging, can be considered.
- Holmes tremor can improve with dopaminergic agents.

Oy-sters

- Holmes tremor is often called rubral tremor, but the implied clinicoanatomical correlation does not always exist.
- Lesions in the thalamus, brainstem, or cerebellum that interrupt the cerebellothalamic loop can all cause similar tremor.
- Although not all tremors from midbrain lesions are related to presynaptic striatal denervation, if present, the degree of presynaptic denervation is usually more marked than in patients with Parkinson disease.
- Treatment with dopaminergic agents should be trialed for patients with presynaptic denervation.

Case Report

A 48-year-old man presented with mild left arm and hand incoordination and mild subjective weakness 11 years ago. He was previously healthy with the only history being hypertension and

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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was on low-dose amlodipine. He had no hepatic disease. His family history and social history were noncontributory. Within 3 years of onset, he gradually developed large-amplitude low-frequency proximal tremor in the left arm and leg that was present during rest but worsened with postural holding and action. He subsequently developed sensory symptoms in his left hemibody. The tremor progressed over the next 4 years significantly affecting his daily function. In addition, he developed symptoms of cognitive decline and excessive daytime drowsiness, sleeping up to 16 hours per day.

Initial examination showed impaired attention span, right oculomotor nerve palsy with exotropia, and horizontal diplopia on right gaze. He had a 2 to 3 Hz tremor of the left upper extremity with postural holding, most prominent in the wing-beating position. Tremor was present in the lower extremities as well. The tremor was worse with action, particularly with goal-directed movements, but minimal at rest. Such a low-frequency rest, postural, and intention tremor is most consistent with Holmes tremor (HT).[1] Ratings on the Clinical Tremor Rating Scale (CTRS) were the following: at rest = 1, with posture = 3, and with action = 4. Bradykinesia, dysmetria, and dysdiadochokinesia were also observed in the left upper and lower extremities. Strength examination was unremarkable and symmetrical in all 4 extremities, although the patient subjectively reported left hemibody weakness. Gait was unremarkable. Sensory examination showed decreased pinprick of the left hemibody.

The combination of symptoms of ipsilateral oculomotor nerve palsy, contralateral tremor, and subjective contralateral limb weakness may resemble a ventral midbrain syndrome, for example, Benedikt syndrome, which encompasses the unilateral red nucleus, the third nerve fascicle, and the cerebral peduncle. However, in our patient, his symptoms could not be explained by a midbrain lesion alone. A larger lesion in the midbrain that extends rostrally and posteriorly affecting the superior cerebellar peduncle and reticular activating system while also disrupting the substantia nigra and the dopaminergic tract can explain the HT, parkinsonism, and hypersomnolence. Multifocal localizations, involving the ipsilateral midbrain, thalamus, cerebellum, and basal ganglia to various degrees, could also be a consideration, although less likely. The differential diagnoses for a HT are wide. The underlying etiologies include demyelination, infection, stroke, neoplasm, or vasculitis. The time course for the patient's presentation was slow and insidious without fluctuation and acute deterioration, which makes vascular and demyelinating pathologies less likely. A slow infiltrative process such as infection or tumor is possible, but infections are less likely given the lack of systemic involvement. The significant unilateral presentation also argues against a diffuse process, such as demyelination, infections, neurodegeneration, congenital, or toxic metabolic conditions.

Brain MRI with and without contrast showed a 3.5 to 4 cm right paramedian thalamic/midbrain mass without contrast enhancement, most consistent with a low-grade primary glioma (Figure 1). [^{123}I]FP-CIT (^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl]nortropane) SPECT (DaTscan) demonstrated severe right-sided dopaminergic denervation in the caudate and putamen (Figure 2). The degree of striatal dopamine transporter deficiency was more severe than expected in a patient with Parkinson disease. The patient was offered a trial with a dopaminergic agent with levodopa or dopamine agonist. He opted to take the long-lasting pramipexole (1.5 mg/d) and appreciated significant improvement in motor and cognitive symptoms. Repeat examination showed normal cognition. He scored 28/30 on the Montreal Cognitive Assessment. He lost 1 point in delayed recall and abstract thinking each. Tremor improved markedly (1–2/4 on CTRS) (Video). However, his right-side oculomotor nerve palsy and diplopia persisted.

The tumor has remained stable for the past 7 years on MRI. The patient has no functional limitations on the same dose of pramipexole and is actively followed by neurosurgery and neurology team jointly, with regular brain MRI every 6 months. Given the localization of the lesion and the imaging features suggesting low-grade tumor and a stable course, it was deemed that biopsy or resection can potentially be more harmful than beneficial. If there is progression clinically or with MRI surveillance, biopsy and referral to radiation oncology will be considered.

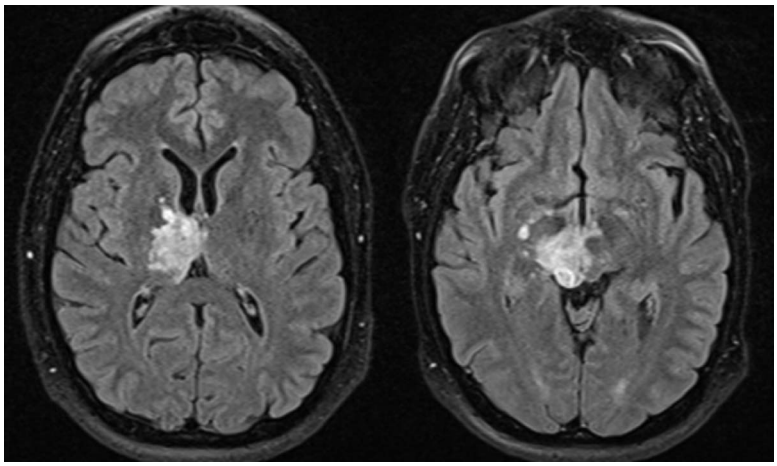
Discussion

Our patient presented with a constellation of symptoms including prominent left-sided HT, parkinsonism, hypoesthesia, right oculomotor nerve palsy, cognitive dysfunction, and hypersomnolence. The large glioma revealed by MRI supports the above localization of a midbrain lesion with extension up into the thalamus to explain the cognitive complaints. The involvement of the nigrostriatal pathway may also partially explain the changes in attention. The slow and insidious progression with a lack of systemic involvement is also consistent with the slow and stable course of a glioma.

The phenomenology of the movements is in keeping with HT with parkinsonism. The revised 2018 consensus of the classification of tremors by the International Parkinson and Movement Disorder Society describes HT as "a syndrome of rest, postural, and intention tremor that usually emerges from proximal and distal rhythmic muscles contractions at low frequency (<5 Hz)."[1] The consensus emphasized that acquired lesions within the brainstem and thalamic region should be investigated for HT.[1,2] The common etiologies include infections, multiple sclerosis, tumor, stroke, trauma, and vascular malformation.[2,3] This predominantly unilateral, irregular, and low-frequency tremor is frequently associated with other neurologic signs, such as ataxia and ophthalmoplegia.[4]

HT is often referred to as rubral tremor suggesting an involvement of red nucleus, but the clinicoanatomical correlation does not always exist. The localization or anatomical correlation

Figure 1 Brain MRI

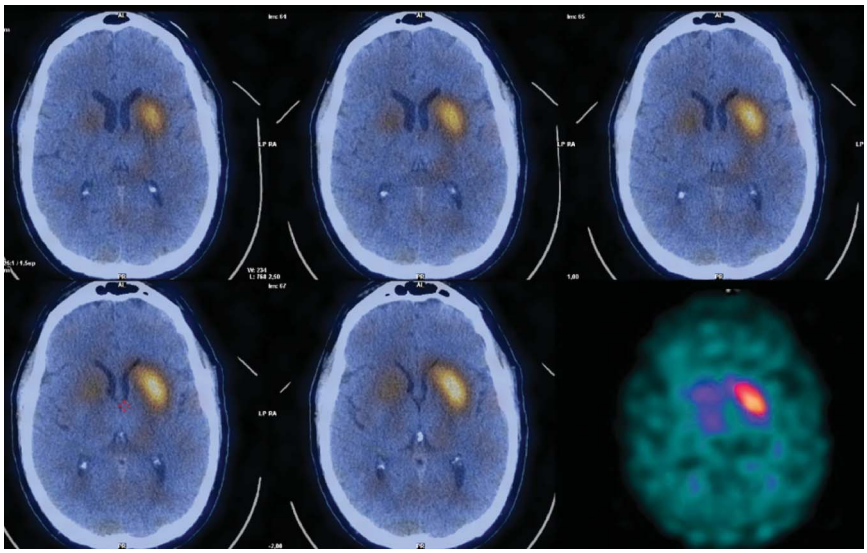


MRI axial FLAIR sequence showed a hyperintense right paramedian thalamic/midbrain mass, which was consistent with a low-grade primary glioma.

for HT is likely due to combined cerebellothalamic and dopaminergic nigrostriatal pathways.[4,5] The track connecting the dentate nucleus of the cerebellum with the contralateral thalamus plays a major role in the pathogenesis of tremor and is believed to result in the kinetic and intention tremor in patients with HT.[6] Within the dentatothalamic pathway, a predecussational lesion may cause an ipsilateral tremor; a postdecussational lesion would result in contralateral tremor as in this case.[7-9] Regarding the interruption of the nigrostriatal pathways, a previous PET study[10] demonstrated asymmetry of ^{18}F-fluorodopa uptake without any asymmetry of postsynaptic D_2 receptor binding in patients with HT. Dopaminergic therapy has been shown to be effective in case reports and case series, supporting the hypothesis that the nigrostriatal pathway is involved.[2,5,10]

The glioma in our patient, located at the posterior thalamus and midbrain, can interrupt both the nigrostriatal pathway and the cerebellothalamic loop. His DaTscan shows a severe striatal dopaminergic denervation pattern in both the caudate and the putamen. The pattern on the DaTscan is similar to the ^{18}F-fluorodopa PET from a previous PET study.[10] The DaTscan in conjunction with the MRI demonstrated the anatomical and functional status of the presynaptic nigrostriatal dopaminergic system, reflecting severe striatal dopaminergic denervation. In this case, the glioma spared the striatum. The denervation is not directly resulted from damage to the striatum

Figure 2 Dopamine Transporter Imaging



DaTscan demonstrated marked decreased uptake in the right caudate and putamen with normal uptake in the left basal ganglia. The pattern is more pronounced than the typical pattern seen in Parkinson disease. DaTscan, [^{123}I]FP-CIT (123I-N-ω-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl]nortropane) SPECT.

itself; it can instead result from damage to the ipsilateral substantia nigra and/or the nigrostriatal fibers.

In patients with HT, dopaminergic treatment does not always provide significant benefit in all patients. Therefore, one should be aware that although patients may present with tremor disorders of similar phenomenology, different neurocircuitries can be involved. An imaging study[11] assessed 3 patients with HT using DaTscan and I^{123}-iodobenzamide (IBZM) and did not observe asymmetry of DaTscan and IBZM binding in the striatum of all patients. This observation raises the question whether presynaptic dopaminergic involvement always occurs in HT.

In this case, our patient's symptoms responded to the dopamine agonist very well. Other treatments that can be considered for HT include a variety of pharmacologic agents, including levodopa, levetiracetam, propranolol, topiramate, trihexyphenidyl, and benzodiazepine.[5,12] Thalamotomy and deep brain stimulation can also be applied to refractory tremors.[5]

Our patient responded very well to pramipexole from a cognitive perspective. There is a significant relationship between nigrostriatal dopaminergic denervation and cognitive dysfunction in Parkinson disease.[13,14] Experimental data revealed involvement of dopamine in regulating attention.[15] The same phenomena may apply especially given the severity of the dopaminergic denervation.

As shown in this case, dopaminergic treatment can provide benefit in tremor control when the presynaptic nigrostriatal pathway is interrupted. Given the neurocircuitry of nigrostriatal pathway involvement in HT, it is reasonable to start a trial dopaminergic treatment, and in clinical practice, it is widely accepted.[5] If no evident benefit, the DaTscan or other dopamine transporter imaging can be considered to determine the function of nigrostriatal pathway to further guide treatment.

Acknowledgment

The authors acknowledge Dr. Francois Ducray and Dr. Stephane Thobois from Pierre Wertheimer Hospital, France, for their contribution in the workup of the case and the initiation of the treatment.

Study Funding

No targeted funding reported.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* December 14, 2021. Accepted in final form June 8, 2022. Submitted and externally peer reviewed. The handling editor was Roy Strowd III, MD, Med, MS.

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Neurology 2022;99;480-483 Published Online before print July 8, 2022
DOI 10.1212/WNL.0000000000201000