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

Author(s):
Kevin Yen, MD, FRCPC1; Amanda Yaworski, MD, FRCPC2; Miguel Bussiere, MD, PhD, FRCPC1; Fang Ba, MD, PhD, FRCPC3

Corresponding Author:
Fang Ba, fb@ualberta.ca

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes. Videos, if applicable, will be available when the article is published in its final form.

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
Affiliation Information for All Authors: 1. Division of Neurology, Department of Medicine University of Alberta 7-112 Clinical Sciences Building, 11350 - 83 Avenue Edmonton, Alberta, Canada; 2. Division of Neurology, Department of Pediatrics University of Alberta 11405-87 Avenue Edmonton, Alberta, Canada

Equal Author Contribution:
Dr. Kevin Yen and Dr. Amanda Yaworski contributed equally to this work.

Contributions:
Kevin Yen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Amanda Yaworski: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Miguel Bussiere: Major role in the acquisition of data
Fang Ba: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Figure Count:
2

Table Count:
0

Search Terms:

Acknowledgment:
We acknowledge Dr. Francois Ducray, and Dr. Stephane Thobois from Pierre Wertheimer Hospital, France, for their contribution in the work-up of the case, and the initiation of the treatment.

Study Funding:
No targeted funding reported.

Disclosures:
The authors report no relevant disclosures.

Preprint DOI:

Received Date:
2021-12-14

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
Abstract

Holmes tremor (HT), also known as midbrain, rubral, or cerebellar pathway outflow tremor, occurs due to disturbances of the cerebellothalamic pathway. This tremor is usually related to lesions in the midbrain peduncular region involving the superior cerebellar peduncle, 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 male 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 Parkinson’s disease patient. 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 due to midbrain peduncular lesion. The striatal dopaminergic function imaging may have a role in assessing pre-synaptic dopamine dysfunction and guiding treatment.

Pearls:
• Interruption of the nigrostriatal pathway can occur and cause Holmes tremor due to midbrain peduncular lesion.
• Investigation of 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 interrupts the cerebellothalamic loop can all cause similar tremor.
• While not all tremors from midbrain lesions are related to pre-synaptic striatal denervation, if present, the degree of pre-synaptic denervation is usually more marked than in Parkinson’s patients.
• Treatment with dopaminergic agents should be trialed for patients with pre-synaptic 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 past history being hypertension, and was on low dose Amlodipine. He had no hepatic disease. His family history and social history were non-contributory. Within three years of onset, he gradually developed left arm and leg large amplitude low frequency proximal tremor that was present during rest but worsened with postural-holding and action. He subsequently developed sensory symptoms of his left hemibody. The tremor progressed over the next four years significantly impacting his daily function. Additionally, 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 2-3Hz 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 low frequency rest, postural, and intention tremor is most consistent with Holmes tremor (HT). 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 four extremities, even though the patient subjectively reported left hemibody weakness. Gait was unremarkable. Sensory examination showed decreased pin prick 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, e.g., Benedikt syndrome, which encompasses the unilateral red nucleus, 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 degree, 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 demyelination, infections, neurodegeneration, congenital, or toxic metabolic conditions.

MRI brain with and without contrast showed a 3.5-4cm right paramedian thalamic/midbrain mass without contrast enhancement, most consistent with a low-grade primary glioma (Figure 1). $^{[123]}\text{I}]\text{FP-CIT}$ ($^{123}\text{I-N-\(\omega\)-fluoropropyl-2\(\beta\)-carbomethoxy-3\(\beta\)-[4-iodophenyl]nortropane}$) SPECT (DaTscan) demonstrated severe right sided dopaminergic denervation in caudate and putamen (Figure 2). The degree of striatal dopamine transporter deficiency was more severe than expected in a Parkinson’s disease patient. The patient was offered a trial with a dopaminergic agent with Levodopa or dopamine agonist. He opted to take the long lasting Pramipexole (1.5mg/day) 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 one 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 seven 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 six 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 (<5Hz).” ¹ The consensus emphasized that acquired lesions within the
The brainstem and thalamic region should be investigated for HT.\textsuperscript{1,2} The common etiologies include infections, multiple sclerosis, tumor, stroke, trauma, vascular malformation, etc.\textsuperscript{2} This predominantly unilateral, irregular, and low frequency tremor is frequently associated with other neurologic signs, such as ataxia and ophthalmoplegia.\textsuperscript{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 correlate for HT is likely due to combined cerebellothalamic and dopaminergic nigrostriatal pathways.\textsuperscript{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 thought to result in the kinetic and intention tremor in patients with Holmes tremor.\textsuperscript{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.\textsuperscript{7-9} In regard to the interruption of the nigrostriatal pathways, Remy et al. demonstrated asymmetry of \textsuperscript{18}F-fluorodopa uptake without any asymmetry of post-synaptic D\textsubscript{2} receptor binding in patients with Holmes tremor.\textsuperscript{10} Dopaminergic therapy has been shown to be effective in case reports and case series, supporting the hypothesis that the nigrostriatal pathway is involved.\textsuperscript{2,5,10}

The glioma in our patient, located at the posterior thalamus and midbrain, can interrupt both the nigrostriatal pathway and cerebellothalamic loop. His DaTscan shows severe striatal dopaminergic denervation pattern in both the caudate and putamen. The pattern on the DaTscan is similar to the \textsuperscript{18}F-fluorodopa PET from Remy et al.’s study.\textsuperscript{10} The
DaTscan in conjunction with the MRI demonstrated the anatomic and functional status of the pre-synaptic 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 itself; it can instead result from damage to the ipsilateral substantial nigra, and/or the nigrostriatal fibers.

In cases 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 neuro-circuitry can be involved. Gajos et al. assessed three patients with HT using DaTscan and I\textsuperscript{123}-iodobenzamide (IBZM), and did not observe asymmetry of DaTscan and IBZM binding in the striatum of all subjects.\textsuperscript{11} This observation raises the question whether pre-synaptic dopaminergic involvement always occurs in HT.

In this case, our patient’s symptoms responded to dopamine agonist very well. Other treatments that can be considered for HT include a variety of pharmacological agents, including levodopa, levetiracetam, propranolol, topiramate, trihexyphenidyl, and benzodiazepine.\textsuperscript{5,12} Thalamotomy and deep brain stimulation can also be applied to refractory tremors.\textsuperscript{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’s disease.\textsuperscript{13,14} Experimental data revealed involvement of
dopamine in regulating attention.\textsuperscript{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 pre-synaptic 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.\textsuperscript{5} If no evident benefit, DaTscan or other dopamine transporter imaging can be considered to determine the function of nigrostriatal pathway to further guide treatment.

**Video 1 - [http://links.lww.com/WNL/C190](http://links.lww.com/WNL/C190)**

**References:**


Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited


Figures:

**Figure 1: MRI brain imaging.** MRI axial FLAIR sequence showed a hyperintense right paramedian thalamic/midbrain mass which was consistent with low-grade primary glioma.

![MRI brain imaging](image1)

**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’s disease. DaTscan, $[^{123}\text{I}]$FP-CIT ($^{123}\text{I}$-N-o-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl]nortropane) SPECT.

![Dopamine transporter imaging](image2)
Pearls & Oy-sters: A Case Report of Holmes Tremor Due to Nigrostriatal Dopamine Disruption that Responded to Dopamine Replacement Therapy

Kevin Yen, Amanda Yaworski, Miguel Bussiere, et al.

Neurology published online July 8, 2022
DOI 10.1212/WNL.00000000000201000

This information is current as of July 8, 2022

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/early/2022/07/08/WNL.00000000000201000.full

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Parkinson's disease/Parkinsonism
http://n.neurology.org/cgi/collection/parkinsons_disease_parkinsonism
Primary brain tumor
http://n.neurology.org/cgi/collection/primary_brain_tumor
Tremor
http://n.neurology.org/cgi/collection/tremor

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise

Neurology © is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2022 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.