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Tremor and Other Hyperkinetic Movements

Case Reports

Levodopa-responsive Holmes' Tremor Caused by a Single Inflammatory Demyelinating Lesion

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Abstract

Background: Holmes' tremor is characterized by a combination of rest, postural, and kinetic tremor that is presumably caused by interruption of cerebello-thalamo-cortical and nigrostriatal pathways. Medical treatment remains unsatisfactory.

Case Report: A 16-year-old girl presented with Holmes' tremor caused by a transient midbrain abnormality on magnetic resonance imaging (MRI). To explore the discrepancy between persistent tremor and resolved MRI changes, we performed dopamine transporter single-photon emission computed tomography (DaT-SPECT) with a 123I-ioflupane that revealed nearly absent DaT binding in the right striatum. Levodopa dramatically improved the tremor.

Discussion: This is only the second report of a transient midbrain MRI abnormality disrupting nigrostriatal pathways. The case highlights the sometimes limited sensitivity of morphologic imaging for identifying the functional consequences of tissue damage and confirms that DaT imaging may serve as a predictor for levodopa responsiveness in Holmes' tremor.

Keywords: Holmes' Tremor, midbrain lesion, remitting MRI abnormalities, abnormal DaT-SPECT, Levodopa responsiveness

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Ethics Statement: The results reported here were collected during routine clinical care, based on which the authors' ethics review board granted an exemption.

Introduction

Holmes' tremor, also known as rubral or midbrain tremor, is characterized by a low-frequency rest tremor that is accentuated by posture and movement.[1] Clinical and neuroimaging findings suggest interruption of cerebello-thalamo-cortical and dopaminergic nigrostriatal pathways as underlying mechanisms.[2,3] Knowledge about Holmes' tremor and its therapeutic response is based on case reports of patients with brain lesions following stroke,[4,5] vascular malformation,[6] tumor,[7] multiple sclerosis,[8] or infection.[9,10]

Case report

Here we present the case of a 16-year-old female who was admitted in February 2013 with left-sided stiffness and shaking of her left hand. Three months earlier she had been infected with the Epstein–Barr virus and had viral flu just before symptom onset. Magnetic resonance imaging (MRI) of the brain revealed a single gadolinium-enhancing lesion in the right upper cerebral peduncle extending rostrally to the thalamus, which led to an inflammatory demyelinating process being suspected (Figure 1A). Whole-spine MRI findings and an

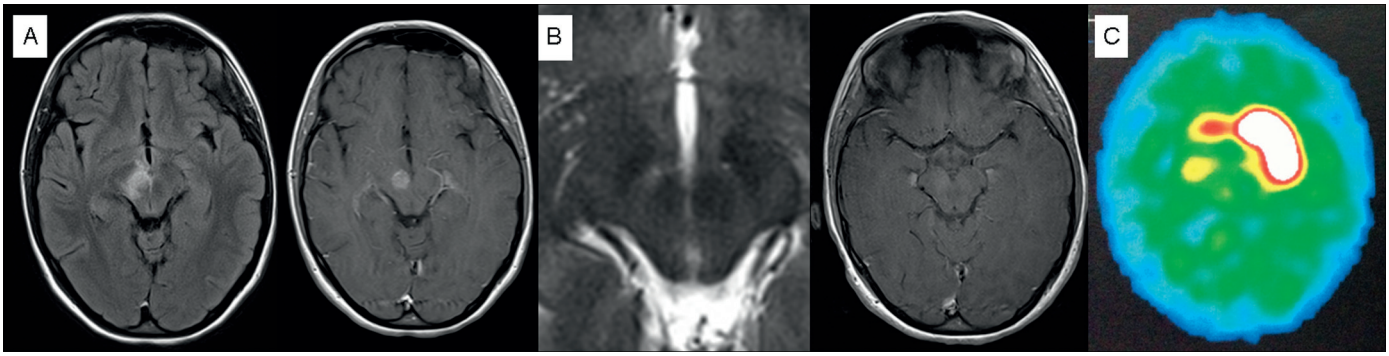


Figure 1. **MRI Findings.** (A) Baseline: left, transversal FLAIR image; right, transverse T1-weighted image. A 1.1 × 0.9 × 1.0-cm gadolinium-enhancing lesion in the right upper cerebral peduncle with perifocal edema is shown. (B) Follow-up MRI after 4 months: left, only a slightly smaller right red nucleus compared to the left, and a small hyperintensity in the area of the right substantia nigra indicating discrete residual changes on T2-weighted imaging; right, complete remission on contrast-enhanced T1-weighted MRI. (C) DaT-SPECT 5 months after symptom onset shows nearly absent DaT binding in the right striatum. Abbreviations: DaT-SPECT, Dopamine Transporter Single-photon Emission Computed Tomography; FLAIR, Fluid-attenuated Inversion Recovery; MRI, Magnetic Resonance Imaging.

ophthalmological assessment were unremarkable. Cerebrospinal fluid examination showed two oligoclonal bands. Cell count, glucose, total protein, and lactate were normal. Methylprednisolone (1000 mg/day) was administered for 3 days without clear clinical benefit, although a marked improvement was noted on MRI. One month later she was readmitted with a combination of marked rest, postural, and action tremor; mild dystonic posturing of the left hand; moderately increased left-sided muscle tone and brisk reflexes; and a spastic gait (Video Segment 1). Another trial of methylprednisolone (1,000 mg/day) was administered for 5 days without clinical benefit. Symptomatic treatment for the disabling tremor was refused.

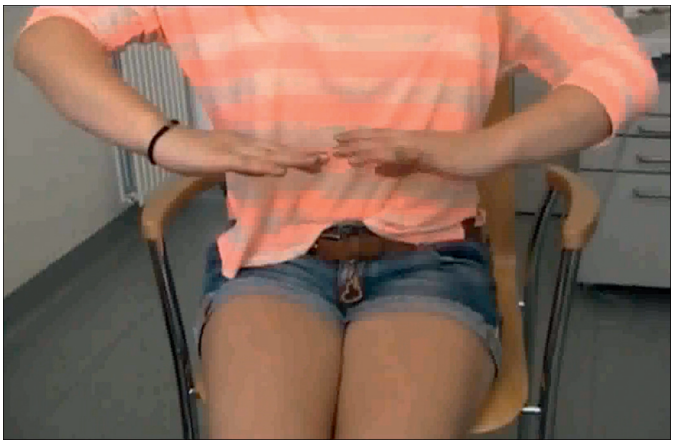
She presented as clinically unchanged to our movement disorders clinic in July 2013. Follow-up MRI taken 1 month earlier (Figure 1B) had shown almost complete remission of the lesion; a slightly smaller red nucleus on the right side and a small hyperintense area in the right substantia nigra were the only discrete residual changes on T2-weighted imaging. Propranolol was started (up to 80 mg/day) with only mild benefit. To further explore the discrepancy between her persistent clinical symptoms and nearly normal MRI, we performed dopamine transporter single-photon emission computed tomography (DaT-SPECT) with 123I-ioflupane and found nearly absent DaT binding in the right striatum compatible with ipsilateral nigrostriatal pathway disconnection (Figure 1C). Levodopa was introduced (up to 300 mg/day) and substantially improved all tremor components (Video Segment 2). Her symptoms further improved in the following 6 months, with tremor only mildly present during movement (Video Segment 3). Her gait was normalized except for reduced arm swing on the left, and a neurological status assessment revealed mildly increased muscle tone and brisk reflexes on the left side. Levodopa was slowly reduced to 150 mg/day. Brain MRI 11 months after symptom onset was unchanged with no new visible lesions.

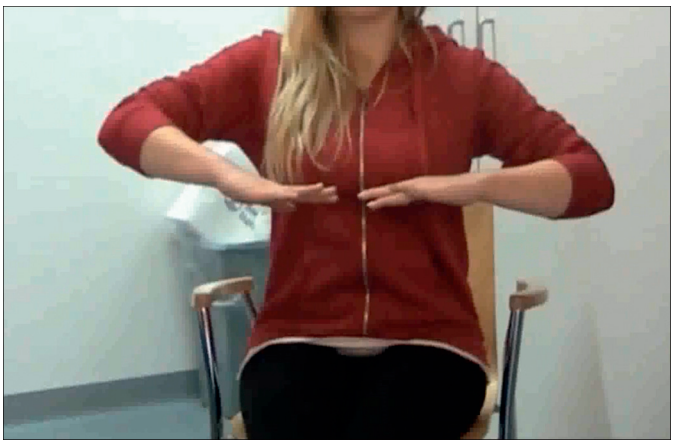
Discussion

Holmes' tremor is a symptomatic tremor that typically appears after a variable delay following midbrain or thalamic lesioning. There is no evidence of spontaneous remission in patients with static lesions, and pharmacological treatment is usually unsatisfactory. The pathophysiologic basis seems to be interruption of the nigrostriatal and cerebello-thalamic pathways combined with maladaptive neuroplasticity. This complex mechanism may account for the variable treatment responses to pharmacotherapy. Several functional neuroimaging techniques have revealed neurochemical abnormalities of the nigrostriatal system in some but not all patients. Abnormal 18F-fluorodopa uptake was reported in six patients who developed contralateral tremor after experiencing upper peduncular lesions.[11] Reduced or abolished DaT binding was found in patients with Holmes' tremor following pontine and mesencephalic hemorrhaging caused by cavernoma,[2] midbrain stroke,[4] cerebral toxoplasmosis,[9] or an ependymoma.[12] Bilateral DaT binding reduction was found in a patient with Holmes' tremor after thalamic hemorrhage; increased tracer uptake 3 years later was interpreted as partial regeneration of the nigrostriatal system and corresponded with clinical improvement.[13]

In our patient, abolished DaT binding in the right striatum was found despite an almost complete resolution of the midbrain MRI abnormality. This indicates a profound disruption of the nigrostriatal pathways despite apparent tissue regeneration, similar to the description of abnormal DaT-SPECT in a patient who developed Holmes' tremor following a regressive midbrain lesion due to cerebral toxoplasmosis.[9] This highlights the sometimes limited sensitivity of morphologic imaging in detecting the functional consequences of tissue damage.

Levodopa responsiveness has been suggested as a marker of nigrostriatal involvement, and DaT imaging findings may predict levodopa responsiveness in patients with Holmes' tremor.[14] In accordance with this hypothesis, the introduction of levodopa led to significant clinical improvement. This is only the second report of a transient midbrain MRI abnormality disrupting nigrostriatal pathways.[9] One may speculate that in such instances, nigrostriatal pathways may regenerate or functionally recover to some extent. This may explain why the patient's tremor continued to improve





Video **Segment 1.** Before the introduction of levodopa: subtle dystonic post uring, moderate rest and postural tremor, and severe kinetic tremor of the left arm during finger nose testing and while drawing a spiral. **Segment 2.** Two weeks after the introduction of levodopa: only mild rest and postural tremors and moderate kinetic tremor of the left arm during finger nose testing were observed. **Segment 3.** Six months after the introduction of levodopa: no rest tremor, subtle postural tremor, and mild kinetic tremor of the left arm during finger nose testing and while drawing a spira. Note: The patient provided signed informed consent to be videotaped and for the content to be viewed for educational purposes.

despite a levodopa dosage reduction. However, in the only comparable case described in the literature, discontinuation of the dopaminergic agent after 1 year was followed by tremor reappearance.[9] Follow-up DaT-SPECT would have shed light on this but was refused by our patient.

In a case series of six patients with Holmes' tremor, only one showed mild interhemispheric differences regarding DaT uptake and responded moderately to levodopa.[14] It therefore remains debatable whether nigrostriatal damage is crucial for the phenomenology of this tremor type. Holmes' tremor may cover a heterogeneous spectrum of tremors with similar phenomenologies but different pathophysiologies. It is thus unlikely that clinical grounds alone are sufficient for predicting responsiveness to levodopa; the case reported here confirms that functional imaging studies should be considered in the clinical work-up of these patients.[14]

It therefore appear that nigrostriatal damage is not crucial for the phenomenology of Holmes' tremor. This tremor syndrome has multiple etiologies and variable pathophysiology; it does not always involve a nigrostriatal dopaminergic deficiency. Holmes' tremor frequently does not respond to levodopa or other dopaminergic agonists, and the case reported here lends further support to the notion that striatal dopaminergic imaging studies may identify patients who are more likely to respond.[13]

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