Tremor and Other Hyperkinetic Movements

Holmes Tremor as the Initial Manifestation of Multiple Sclerosis: A Diagnostic Pitfall in a Patient with Psychiatric History

CASE REPORTS

AREZOU ASHTARI
SEYEDEH FATEMEH ASGARI
MARZIE ABUTORABI-ZARCHI
*Author affiliations can be found in the back matter of this article

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ABSTRACT

Introduction: Tremor is a common neurological symptom with diverse etiologies. In psychiatric patients, it is often misattributed to medications. However, tremor asymmetry and phenomenology can provide important diagnostic clues.

Case Presentation: A 39-year-old woman who had a history of antipsychotic drug use presented with a persistent left upper limb tremor for one year, which was initially considered drug-induced. The tremor had rest, postural, and wing-beating components (rest < postural < wing-beating), accompanied by intention tremor. A week before referral to neurology, she developed gait disturbance. Neurological examination revealed left-sided limb ataxia, left upper limb intention tremor, gait ataxia, and generalized hyperreflexia. Brain magnetic resonance imaging (MRI) showed demyelinating lesions consistent with multiple sclerosis (MS).

Conclusion: Not all tremors in psychiatric patients are drug-induced. Holmes tremor warrants thorough evaluation and may indicate an underlying demyelinating disease.

HIGHLIGHTS

This case illustrates Holmes tremor as the first clinical manifestation of multiple sclerosis in a patient with a psychiatric history, underscoring the risk of misdiagnosis and the importance of considering demyelinating disease in atypical tremor presentations.

CORRESPONDING AUTHOR:
Marzie Abutorabi-Zarchi, MD
Associate professor of neurology and MS fellowship, Yazd, Iran
marzie.ab@gmail.com

KEYWORDS:
Multiple sclerosis; Holmes tremor; drug-induced tremor; cerebellar signs; tremor differential diagnosis

TO CITE THIS ARTICLE:
Ashtari A, Asgari SF, Abutorabi-Zarchi M. Holmes Tremor as the Initial Manifestation of Multiple Sclerosis: A Diagnostic Pitfall in a Patient with Psychiatric History. *Tremor and Other Hyperkinetic Movements.* 2026; 16(1): 65, pp. 1–6. DOI: https://doi.org/10.5334/tohm.1268

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disorder of the central nervous system that often presents with heterogeneous clinical manifestations [1]. Tremor, one such manifestation, is among the most prevalent movement disorders in MS [2] and affects approximately 25–58% of patients and may significantly impair daily functioning and quality of life. The most common tremor phenotypes in MS are postural and intention tremor, whereas rest tremor (only 1%) and Holmes tremor are extremely uncommon in patients with MS [2].

Tremor itself has a broad differential diagnosis, including essential tremor, Parkinson's disease, cerebellar disorders, drug-induced causes, and demyelinating diseases such as MS [3]. In patients with underlying psychiatric conditions, tremor is frequently misattributed to antipsychotic or antidepressant medications, often resulting in delayed or incorrect diagnosis. However, certain clinical characteristics and tremor type can provide critical diagnostic clues [4, 5]. Holmes tremor is a rare tremor with rest, intention, and postural components, characterized by high-amplitude and low-frequency. The pathophysiology of this tremor involves impairment of cerebello-thalamo-cortical or dentato-rubro-olivary pathways. The etiologies of this tremor include cerebrovascular events, tumors, demyelination and infections [6] and are usually caused by lesions involving upper brainstem, thalamus, and cerebellum [7, 8]. Another tremor that overlaps with Holmes tremor is wing-beating tremor, which typically arises from lesions involving the dentato-rubro-thalamic tract (DRTT) and is classically associated with Wilson's disease, though it may also be seen in demyelinating disorders affecting cerebellar outflow tracts [5, 9]. While action tremor is relatively common in MS, resting or wing-beating tremors are rare and typically reflect cerebellar or brainstem involvement [10]. This case is unique because the presence of a psychiatric history and exposure to haloperidol initially masked the diagnosis of MS, highlighting the importance of recognizing atypical tremor phenomenology to avoid diagnostic delay.

2. CASE PRESENTATION

A 39-year-old woman with a history of psychiatric illness was referred to our neurology clinic with a one-year history of persistent left upper limb tremor and newly developed gait disturbance that had started approximately one week prior to presentation. She had been receiving treatment with haloperidol and citalopram. Based on the clinical suspicion of drug-induced tremor, haloperidol was gradually tapered and eventually discontinued.

Due to the lack of clinical improvement after discontinuation of haloperidol and the recent onset of gait disturbance, the patient was referred to a neurologist.

Neurological examination revealed left-sided limb ataxia, gait ataxia, generalized hyperreflexia, and Holmes tremor. A tremor was noted in the left upper limb, characterized by a low-frequency, (<5 Hz) high-amplitude rest tremor involving both distal and proximal segments that worsened when the arms were outstretched and increased more in a wing-beating position (rest < postural < wing-beating). This tremor was accompanied by intention tremor. There was no rigidity or bradykinesia and no dystonic posturing, null point, or sensory trick was observed on examination.

MRI demonstrated demyelinating lesions consistent with MS. Brain MRI showed multiple typical MS lesion in periventricular lesions with Dawson's fingers, posterior fossa (brainstem and cerebellum), cortical/juxtacortical, and cervical cord (Figure 1). The MS diagnosis was confirmed with 2024 McDonald criteria based on typical clinical and paraclinical findings. In patients with typical clinical presentations, like our patient (cerebellar symptoms and signs), the presence of typical lesions in four anatomical locations is sufficient to diagnose MS (Table 1) [7, 11].

The patient was treated with intravenous methylprednisolone (IVMP) (1 g/day for 5 days), followed by ocrelizumab (every six months) as disease-modifying therapy (DMT). Primidone was prescribed for tremor management. She was followed for six months after the initiation of treatment, during which she showed marked clinical improvement. Rest tremor markedly improved, and action tremor improved significantly (Video 1). Her ataxia also improved substantially. There was no evidence of clinical and MRI activity and improvement of tremor continued after 2 years follow up (Video 2). The timeline is shown in Table 2.

3. DISCUSSION

In patients with a psychiatric history, physicians may prematurely attribute tremor to medications, which can lead to delayed investigation of underlying neurological disorders [8, 12]. Regarding the possibility of a parkinsonian tremor, the patient had no rigidity or bradykinesia, and the tremor was less prominent at rest than during action. Therefore, the overall clinical phenomenology was not consistent with a typical parkinsonian tremor, making this diagnosis less likely. Based on the aforementioned findings, as well as the asymmetric and unilateral nature of the tremor, drug-induced parkinsonian tremor, which typically presents as a symmetrical, bilateral rest tremor, was also considered less likely [13–15]. However, the

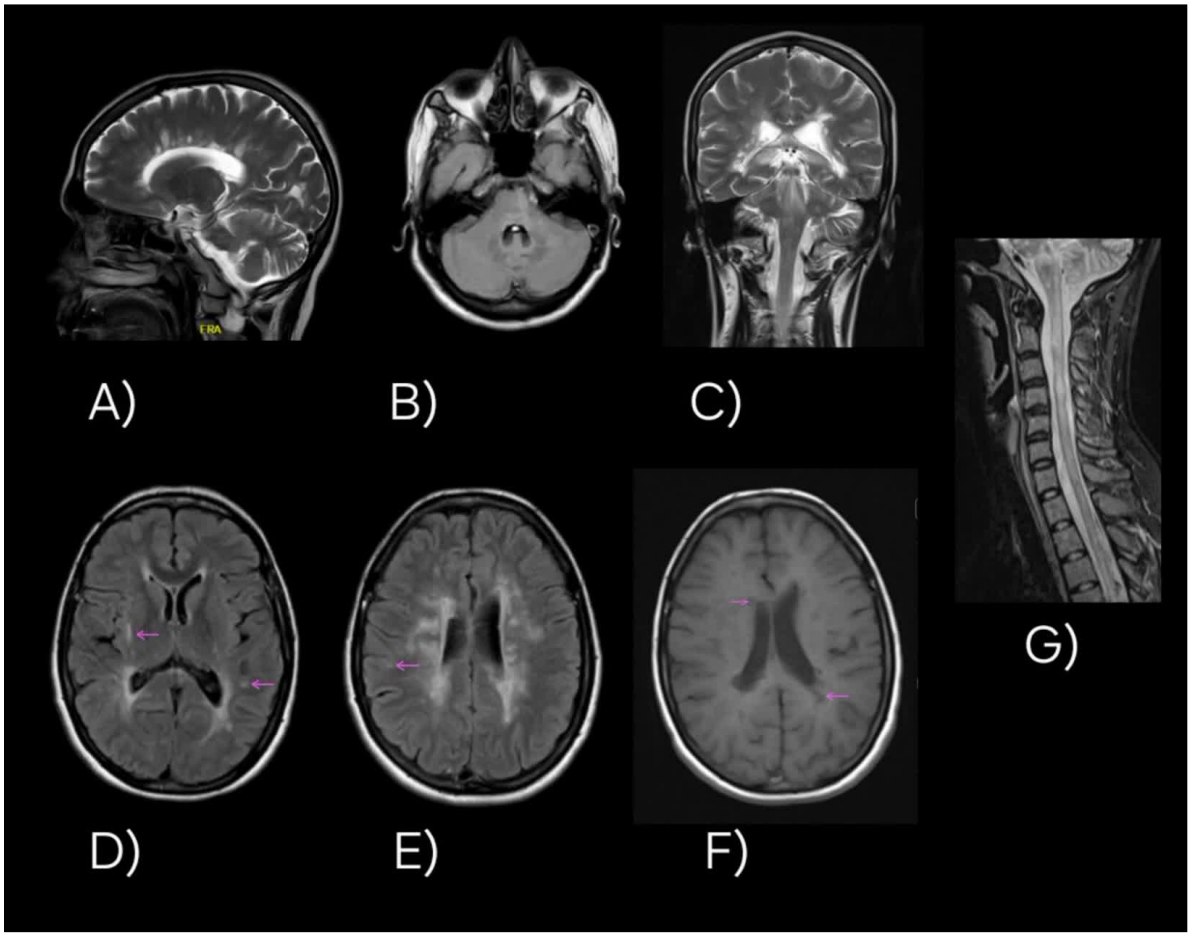


Figure 1 Brain and cervical MRI finding in the patient.

Brain MRI: Sagittal T2-weighted sequence shows multiple periventricular lesions with Dawson's fingers, a specific sign of multiple sclerosis **(A)**. Axial FLAIR and coronal T2-weighted sequence show multiple lesions in the brainstem and cerebellum (cerebellar outflow pathways) **(B,C)**. Axial FLAIR sequence shows cortical/juxtacortical lesions **(D,E)**. T1-weighted sequence shows multiple ('black holes') **(F)**. Sagittal STIR sequence of the cervical cord MRI shows multiple short segment lesions **(G)**.

CRITERIA	PATIENT FINDINGS
Dissemination in Space (≥4 of 5 typical location periventricular (P/V), juxtacortical/cortical, infratentorial, spinal cord and optic nerve)	Multiple plaques on initial MRI in 4 typical location including P/V, juxtacortical/cortical, infratentorial (brain stem and cerebellum) and spinal cord

Table 1 Application of the 2024 McDonald Criteria to the Patient.

Note: Summary of the patient's clinical and imaging findings according to the 2024 McDonald diagnostic criteria for multiple sclerosis, including dissemination in space (DIS).

Abbreviations: MS, multiple sclerosis; MRI, magnetic resonance imaging; DIS, dissemination in space.

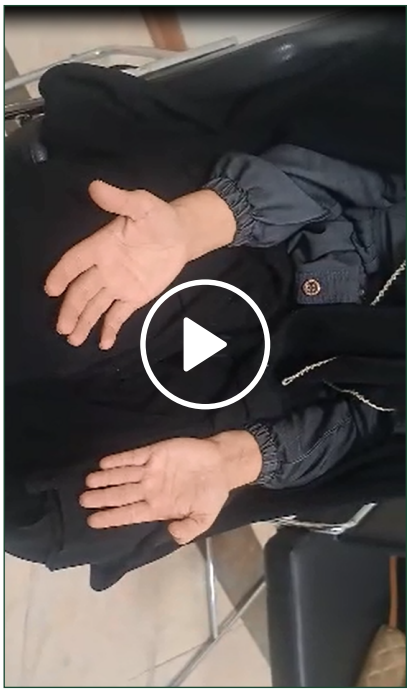
presence of asymmetric tremor, upper motor neuron signs, and cerebellar deficits, as seen in our patient, is not typical of drug-induced tremor and warrants further investigation [11, 16].

It is unlikely to be dystonic tremor because no dystonic posturing, null point, or sensory trick was observed



Video 1 Improvement of Holmes tremor following treatment.

The video demonstrates marked improvement of resting tremor and reduction of action tremor 6 months after treatment.



Video 2 Improvement of Holmes tremor following treatment.
The video demonstrates marked improvement of resting tremor and reduction of action tremor 2 years after treatment.

Onset of tremor	August 20 2023
Taper and discontinuation of haloperidol	May 20 2024
Refer to our clinic and request MRI	August 1 2024
Diagnosis of MS	August 24 2024
Treatment with IVMP	August 25–29 2024
Treatment with ocrelizumab Every six months that continues	September 1 2024–September 1 2026

Table 2 Timeline table.

on examination. In addition, the tremor did not show consistent directional asymmetry or a specific position-dependent pattern of exacerbation or attenuation. These findings provided no clinical evidence suggestive of dystonia and therefore argued against a diagnosis of dystonic tremor [17].

Wing-beating tremor, which is typically seen in Wilson's disease, is slow, high-amplitude, posture-induced tremor in proximal upper limbs (bilateral) that may be asymmetrical [18], it appears when the patient sustains abduction with flexed elbows and palms facing downward (wing-beating position) [9, 19]. In contrast, Holmes tremor is a rare tremor with rest, intention, and postural components, characterized by high-amplitude and low-frequency [6, 8] and caused by lesions of the thalamo-cerebellar pathways [7, 8].

Our case had unilateral rest, postural, and intention tremor both distally and proximally, in the left upper limb. Therefore, this tremor exacerbated in the wing-beating position but it's one-sidedness, the presence of rest tremor and a distinct distal part, is more suggestive of Holmes tremor.

Although psychiatric misdiagnosis preceding the recognition of MS is a recognized phenomenon in the literature, with one large registry-based study finding that 40.4% of participants reported that symptoms later attributed to MS had initially been misdiagnosed, and that this misattribution was associated with a significantly longer diagnostic delay [12, 20], our case is unique in the persistence of tremor despite complete discontinuation of haloperidol.

In this case, the diagnosis of MS was supported by brain MRI demonstrating demyelinating lesions, along with cerebellar and pyramidal signs. The presence of a unilateral tremor in a patient with no improvement after withdrawal of haloperidol pointed away from a drug-induced etiology. Furthermore, the tremor's pattern, combined rest and postural tremor, which became more pronounced in voluntary action and accompanied by intention tremor, was consistent with Holmes tremor. Holmes tremor as a presenting sign in an MS patient is a rare finding, because Holmes tremor is very uncommon in MS [3, 8] and the tremor is also typically observed in the advanced stages of disease [21]. The patient's improvement following corticosteroids, ocrelizumab supports an inflammatory-demyelinating origin, while primidone may also have been effective as a symptomatic treatment. This case emphasizes the importance of considering MS in patients presenting with atypical unilateral tremor accompanied by cerebellar or pyramidal signs, even when psychotropic medication appears to provide an alternative explanation.

A limitation of our report is the lack of video documentation during the initial visit prior to treatment.

ETHICS AND CONSENT

This case report was conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki. Written informed consent for publication of anonymized clinical details and images was obtained from the patient. All identifying information has been removed to ensure confidentiality.

ACKNOWLEDGEMENTS

The authors also acknowledge the Research Committee of the Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, for providing the ethical approval (Code:IR.SSU.REC.1404.052).

FUNDING INFORMATION

The authors received no financial support for the research, authorship, and/or publication of this article. The Article Processing Charge (APC) for this publication was waived by the journal.

COMPETING INTERESTS

The authors have no competing interests to declare. Furthermore, none of the authors are currently members of the journal's editorial team or board, nor have they held such a position within the last three years.

AUTHOR AFFILIATIONS

Arezou Ashtari orcid.org/0009-0007-4943-7886
Student Research Committee, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Seyedeh Fatemeh Asgari
Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Marzie Abutorabi-Zarchi, MD orcid.org/0000-0002-4531-2134
Associate professor of neurology and MS fellowship, Shahid Sadoughi Hospital, Shahid Sadoughi Medical School, Shahid Sadoughi University of Medical Sciences, and health services, Yazd, Iran

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TO CITE THIS ARTICLE:
Ashtari A, Asgari SF, Abutorabi-Zarchi M. Holmes Tremor as the Initial Manifestation of Multiple Sclerosis: A Diagnostic Pitfall in a Patient with Psychiatric History. *Tremor and Other Hyperkinetic Movements*. 2026; 16(1): 65, pp. 1–6. DOI: https://doi.org/10.5334/tohm.1268

Submitted: 16 July 2026 **Accepted:** 29 October 2026 **Published:** 18 November 2026

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