Case report

Holmes tremor in multiple sclerosis: clinical characterization as a diagnostic tool

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Carolina Beatriz Zepeda Salazar[1]*, Jorge David Clavel Arbizú[2], Wilber Alexander Ortiz Guerra[3]

1-3. Department of Neurology, Rosales National Hospital, San Salvador, El Salvador.

*Correspondence
dracbzs@gmail.com

1. 0009-0007-0366-8320
2. 0009-0007-5093-0395
3. 0009-0000-3645-3755

Abstract

Case presentation. A 32-year-old man who presented with four years of tremor with predominance in pelvic limbs, activated by standing and walking, improving at rest and in decubitus. In the course of his disease, he developed intention tremor, ataxic dysarthria, and gait ataxia. Physical examination revealed ataxic dysarthria, quadriparesis, pelvic hyperreflexia, bilateral dysmetria and dysdiadochinesia, as well as dystonic tremor at rest, posture, and intention, predominantly right. **Treatment.** Symptomatic treatment of tremor started with one milligram of clonazepam every 12 hours and gabapentin 300 milligrams at night, with symptomatic improvement. Electromyography confirms tremor of 9 Hertz in quadriceps, 7 Hertz in biceps brachii; brain magnetic resonance imaging reveals hyperintense lesions in T2 and Fluid-Attenuated Inversion Recovery with involvement in cerebellar outflow tracts, and cortico-subcortical regions suggestive of multiple sclerosis type demyelinating disease. Clinical evolution. After establishing the diagnosis, treatment of the acute flare was initiated, with significant improvement in tremor and motor coordination, reinforcing the link between demyelinating inflammatory activity and the clinical expression of tremor. This case highlights the relevance of a phenomenological characterization of tremor in multiple sclerosis, including atypical presentations such as Holmes tremor, whose identification improves clinical-radiological correlation and therapeutic approach.

Keywords
Tremor, Intention Tremor, Multiple Sclerosis, Ataxia.

Resumen

Presentación del caso. Hombre de 32 años que debuta con cuatro años de temblor con predominio en miembros pélvicos activado por bipedestación y marcha, mejoría al reposo y en decúbito. En el curso de su enfermedad desarrolla temblor de intención, disartria atáxica y ataxia de la marcha. En el examen físico se verifica disartria atáxica, cuadriparesia, hiperreflexia pélvica, dismetrías y disdiadocinesia bilaterales, además de temblor distónico en reposo, postura e intención de predominio derecho. **Intervención terapéutica.** Se inicia tratamiento sintomático de temblor con clonazepam 1 miligramo cada 12 horas y gabapentina 300 miligramos por la noche, con mejoría sintomática. Electromiografía confirma temblor de 9 Hertz en cuádriceps, 7 Hertz en bíceps braquial; resonancia magnética cerebral revela lesiones hiperintensas en T2 y FLAIR con compromiso en vías cerebelosas de salida, y regiones cortico-subcorticales sugestivas de enfermedad desmielinizante tipo esclerosis múltiple. **Evolución clínica.** Tras establecer diagnóstico, se instauró tratamiento de brote agudo, con mejoría significativa de temblor y coordinación motora, reforzando vínculo entre actividad inflamatoria desmielinizante y expresión clínica de temblor. Este caso resalta la relevancia de una caracterización fenomenológica del temblor en la esclerosis múltiple, destacando presentaciones atípicas, como el temblor de Holmes, cuya identificación mejora la correlación clínico-radiológica y el enfoque terapéutico.

Palabras clave
Temblor, Temblor de Intención, Esclerosis Múltiple, Ataxia.

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Temblor de Holmes en esclerosis múltiple: caracterización clínica como herramienta diagnóstica

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Introduction

The International Parkinson and Movement Disorder Society (IPMDS) working group defines tremor as an involuntary, rhythmic, oscillatory movement of one or more parts of the body.[1] It is one of the most common reasons for consultation at specialized neurological clinics for abnormal movements. Tremor can be classified according to the condition that triggers it, either at rest or during movement, and may occur in isolation or in combination with both components.[1]

Holmes tremor (HT) was originally described in 1904 by Dr. Gordon Morgan Holmes as a low-frequency tremor (< 4.5 Hz), characterized by the combination of three components: presence at rest, exacerbation in posture, and intensification in action[2]. HT mainly affects the proximal extremities and arises due to lesions located in the upper brainstem, thalamus, and cerebellum. The lesions specifically involve the cerebello-thalamocortical and dentatorubro-olivary pathways.[3] Due to the involvement of multiple networks and structures of the central nervous system, HT often coexists with other neurological manifestations such as bradykinesia, spasticity, ataxia, dystonia, and ophthalmoplegia.[4] Symptoms generally appear between one month and 24 months after the brain injury.[2] This latency interval can be explained by pathological reorganization processes.[3] Its etiological cause is very diverse, ranging from ischemic or hemorrhagic cerebrovascular disorders, which together account for 50 % (48-55 %) of cases,[5] to traumatic injuries (17 %), infections (10 %), or demyelinating lesions (10 %).[4] This case documents an uncommon presentation of HT as an initial symptom of multiple sclerosis (MS) with confirmation deferred eight years later. The description aims to provide evidence for the clinical variability of tremor in this disease and highlight the importance of recognizing atypical presentations to avoid diagnostic delays.

Case presentation

A 32-year-old man, Salvadoran, unemployed, occasional drinker approximately once a month, user of multiple illicit drugs including cocaine, crack, and marijuana, who reports having stopped three years ago.

Four years ago, he began to experience an insidious tremor, predominantly in his pelvic limbs, which was activated when standing and walking, and increased with strong emotions, making daily activities difficult. In addition, he reported that three years ago he began experiencing changes in prosody, with the tremor progressing to his right thoracic limb, making it difficult to pick up objects and write. For the past year, the patient has explained that the generalized tremor contributed to multiple arrests by police officers for appearing to be intoxicated.

Finally, for the past three months, he has been unable to perform daily activities such as eating, dressing, and walking. For this reason, he was evaluated at a secondary hospital, where he was referred to the neurology department of a tertiary care hospital.

Physical examination

He was admitted to the tertiary care hospital for evaluation at the abnormal movements' clinic, neurological examination reported ataxic dysarthria; proximal and distal quadriparesis 4/5 according to the modified Medical Research Council muscle strength scale. Also, the patient had bilateral patellar and Achilles muscle stretch reflexes 3+; bilateral dysdiadochokinesia predominantly on the right side, bilateral hypermetric dysmetria predominantly on the right side; ataxic gait, but no trunk ataxia, scoring a total of 22 points on the scale for assessment and rating of ataxia (SARA).[6]

We evaluated the patient using the essential tremor evaluation and rating scale (TETRAS).[7] He had rest, postural an intention tremor in upper limbs (3.5 points); rest, postural and intention tremor in lower limbs (four points); Archimedes' spiral (four points); two-point approximation (3.5 points); tremor when standing (four points). He obtained 23.5 points on the functioning subscale and 35 points on the activities of daily living scale. It is important to note that TETRAS scale is validated only for essential tremor; however, it was used in this case for descriptive purposes, to quantify the parameters of postural and action tremor, given that there is currently no specific scale for HT (supplementary material 1).

Clinical diagnosis

The patient was admitted to the neurology department with a diagnosis of orthostatic tremor. We found no abnormalities on blood biometry, blood chemistry, vitamin B12 levels, thyroid profile, and neurophysiological studies (electroencephalogram and four-limb nerve conduction). Electromyography of the pelvic limbs reported a frequency of 9 Hz when standing and 7 Hz in the thoracic limbs during activation (Figure 1 and Figure 2).

Treatment

Treatment was initiated with gabapentin 300 mg at night and clonazepam 1 mg every 12 hours, with improvement in tremor when standing (supplementary material 2). A brain magnetic resonance imaging revealed multiple hyperintense lesions in T2 weighted and Fluid-Attenuated Inversion Recovery (FLAIR) sequences with multifocal and random distribution in both cerebral hemispheres in cortical, juxtacortical, and subcortical locations perpendicular to the ventricular system (Dawson's fingers), similar lesions in the thalamus, brainstem (pons), and spinal cord segments C1-C3 (Figure 3).

Suspicion of MS-type demyelinating disease is complemented by oligoclonal bands present in the cerebrospinal fluid study. Treatment was started with intravenous steroids at 1 g per day for five days, followed by an evaluation of tremor and movement coordination, quantifying 48.5 points (29+19.5) on TETRAS, 19 points on the SARA, and 6.5 points on the Kurtzke Disability Status Scale (EDSS).[8] Treatment with azathioprine immunosuppressants was started, as no disease-modifying drugs were available, at a dose of 1 mg/kg of weight, and the dose of gabapentin was increased to 600 mg at night plus clonazepam every 12 hours, to optimize symptomatic treatment of tremor, which was the most disabling symptom in the patient. He was discharged from the hospital with follow-up for monitoring in one month.

Clinical evolution

A follow-up evaluation was performed one month later, with a total of 50 points (30+20) on the TETRAS scale, 17.5 points on the SARA scale, and 6.5 points on the EDSS scale (Table 1).

From the clinical axis, it was considered a thermogenic syndrome with additional neurological signs, Holmes' tremor subtype; while, from the etiological axis, a demyelinating disease of the central nervous system, primary progressive MS type.

Discussion

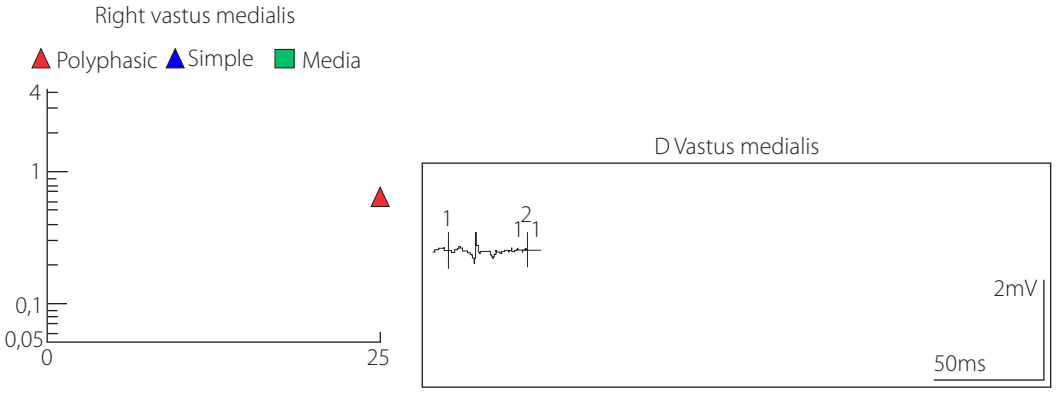
Multiple sclerosis is an immune-mediated demyelinating disease that affects the central nervous system in people aged 20 to 40 years, and is the leading cause of disability in the economically active population. Among the most common symptoms is tremor, with a prevalence of 25 to 58 % of cases, one of the three main characteristics, along with nystagmus and ataxic dysarthria, described by Charcot in 1877.[9]

The prevalence is around 45 to 46.8 % according to data from the largest North American population database of patients with MS (NARCOMS), with a predominance of action tremor (postural and kinetic) distributed in order of frequency in the upper limbs (dominant extremity), voice, head, trunk, and lower limbs.[10] Action tremor accounts for 18-64 % of cases; intention tremor occurs in 12 44 % of cases, rest tremor in 30 %, postural tremor in 20 %, and HT in less than 10 % of cases.[11] It is important to take these data into account, as they are among the most disabling motor manifestations.[11-12]

Holmes tremor, also known as rubral tremor, is a form of low-frequency tremor (2-4 Hz) that combines resting, postural, and intentional components, and whose pathophysiology involves simultaneous lesions of the cerebellothalamic, nigrostriatal, and rubrothalamic pathways. Classically, it is associated with structural lesions in the midbrain, thalamus, and perirubral region; however, vascular events (infarcts and hemorrhages) are the most commonly reported causes in clinical series and systematic reviews.[8]

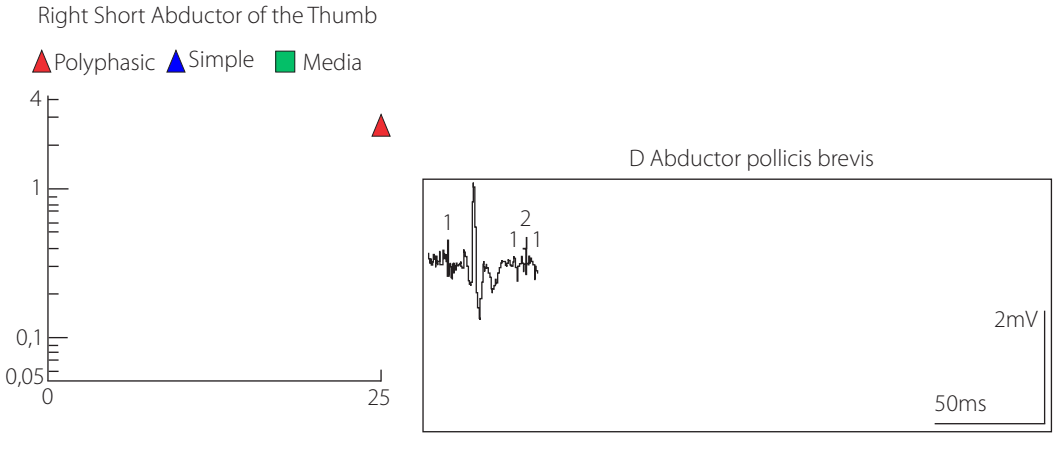
In the described patient, the clinical presentation was initially interpreted as orthostatic tremor due to marked difficulty in standing and walking. However, according to the definition of the International Parkinson and Movement Disorder Society (IPMDS 2018), orthostatic tremor is defined as the "subjective sensation of instability during standing and, in severe cases, during walking, which improves when sitting or lying down, confirmed by an electromyographic pattern of 13 to 18 Hz."[1] It is a subjective feeling of instability secondary to high-frequency tremor; the clinical manifestation is imperceptible and can only be measured by electromyography. In contrast, the case presented shows clinically visible, low-frequency tremor (upper limb tremor 7 Hz; inferior limb tremor 9 Hz), present at rest, in posture, and on intention, with increased activity when standing and walking, allowing it to be reclassified as HT.

The observed phenomenology was accompanied by spooning-type dystonic postures of the hands, suggesting the coexistence of a dystonic component.[14] Magnetic resonance imaging revealed lesions in the cerebellar outflow and probable nigrostriatal involvement, neuroanatomical findings consistent with the pathophysiology described for HT. Damaged synapses tend to degenerate, reinnervate, and reorganize in order to restore functional neuronal connections. In the case of HT, the process occurs in a disorganized, incomplete manner, leading to maladaptive synaptic reorganization, ineffective neuronal connectivity, and reduced neurotransmitter release, which contribute to the onset of tremor and the characteristic delay between the initial lesion and clinical manifestation. The underlying mechanisms are not yet fully understood.[3] Furthermore, although tremor has classically been described as predominantly affecting the upper limbs, there are reports of its extension to the lower limbs,[15] a phenomenon that, in this case, contributed to the inability to walk due to the distribution of the tremor in the patient.



Muscle:	Scans	Amplitude µV	Duration ms	# Phases	#Turns	Thickness	Frequency Hz
Right vastus medialis							
Average ALL		631	36.0	8	12	2.49	9
Total MUPs	1	-	-	-	-	-	-
% Polyphasic	100 %	-	-	-	-	-	-
1.1	40	631	36.0	8	12	2.49	9

Figure 1. Summary of motor action potentials. The frequency recorded in the vastus medialis for lower limb-tremor is shown while the patient is standing.



Muscle:	Scans	Amplitude µV	Duration ms	# Phases	#Turns	Thickness	Frequency Hz
Right short abductor of the thumb							
Media TODAS	-	2454	36,0	17	45	3,05	7
Total de MUPs	1	-	-	-	-	-	-
% Polyphasic	100 %	-	-	-	-	-	-
1,1	20	2454	36,0	17	45	3,05	7

Figure 2. Summary of motor action potentials showing frequencies recorded in the abductor pollicis brevis muscle for upper limb tremors, with limbs at rest.

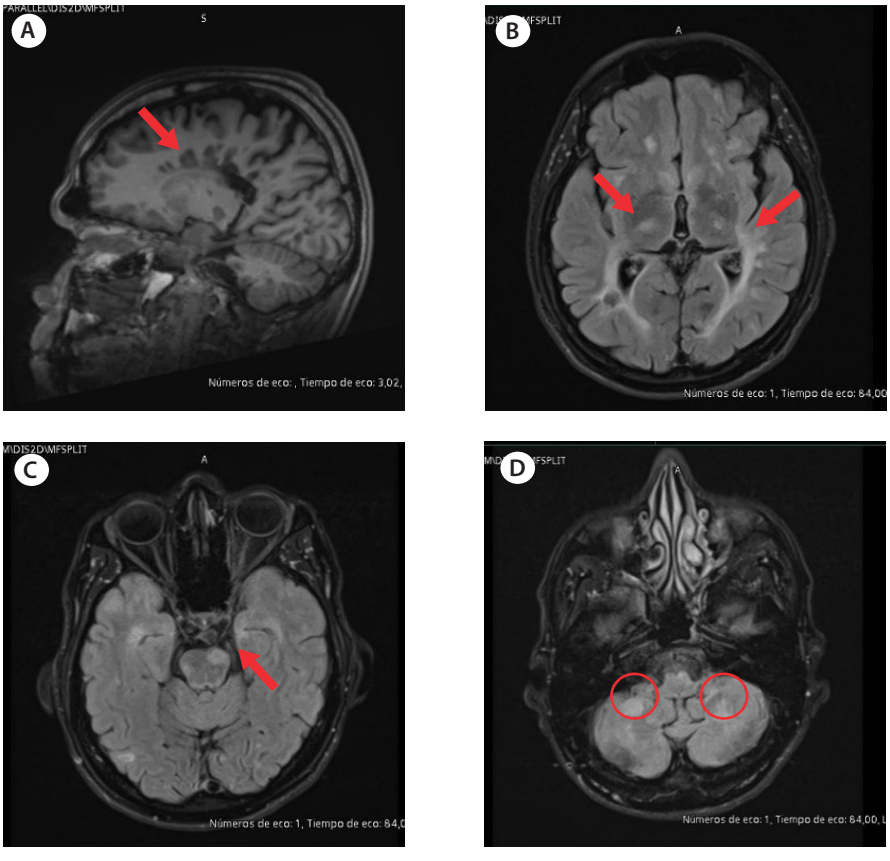


Figure 3. Brain magnetic resonance imaging using Avanto 1.5 Tesla equipment, T1-weighted and FLAIR sequences. (A) Sagittal T1-weighted section showing hypointense lesions at the margin of the corpus callosum (callosal-septal interface) and some with a perpendicular arrangement to the ventricular system. (B) Axial slice, FLAIR sequence, showing hyperintense cortical, juxtacortical, subcortical (bilateral thalamus), and confluent periventricular lesions in contact with the ependymal surface. (C) Axial section, FLAIR sequence, bilateral parieto-occipital cortical hyperintense lesions, bilateral hippocampal juxtacortical lesions, and infratentorial lesions in the pons. (D) Axial section, FLAIR sequence, hyperintense lesions in both cerebellar hemispheres. None of the lesions showed post-contrast enhancement or diffusion restriction.

Table 1. The scales for assessing strength, ataxia, and tremor in their postural, intentional, and specific-task modalities are described for objective assessment during physical examination.

Scale	Assessment	First assessment (06/13/2024)	Post-treatment of acute MS flare-up (07/29/2024)	Follow-up Monthly (08/29/2024)
Muscle strength *Medical Research Council*		4+	4+	4+
Assessment and ataxia rating (SARA)	Total	**23 points**	**19 points**	**17.5 points**
	Components			
	-March	7	6	5
	-Posture	6	5	5
	-Seating	0	0	0
	-Speaks	2	2	2
	-Finger tracking	1.5	1.5	1
	-Finger- nose	3.5	1.5	1.5
	-Movements alternating	2.5	1.5	1.5
	-Heel-to-knee	2.5	1.5	1.5
Evaluation and rating of essential tremor (TETRAS)	Total	**58.5 points**	**48.5 points**	**50 points**
	Subscales			
	-Activities of daily living daily	35	29	30
	-Operation	23.5	19.5*	20*
State of Kurtzke disability (EDSS)	Ambulation	-	**6,5 points**	**6,5 points**
	Systemic			
		-	6,5	6,5
		-	6 a 6.5	6 a 6.5

* The improvement was in the upper limb tremor, inferior limb tremor and in standing.

Tabla 2. Comparative summary of clinical entities that may be considered as differential diagnoses in the phenomenological evaluation of lower limb tremor, emphasizing that only Holmes tremor and cerebellar tremor have been consistently described in MS.

Entity	Frequency	Main clinical characteristics	Differential diagnosis
Holmes tremor	2–5 Hz	Rest + posture + intention; large amplitude; associated with cerebellar/nigrostriatal lesion	Magnetic resonance imaging correlation
Cerebellar tremor	3–5 Hz	Intentional, irregular, associated with ataxia	Pure cerebellar lesion
Classic orthostatic tremor	13–18 Hz	Feeling of instability, clinically imperceptible, improves with walking	EMG confirmation
Slow orthostatic tremor	3–8 Hz	Visible tremor when standing, instability, wide amplitude	More rarely, it can be confused with cerebellar
Orthostatic myoclonus	> 9 Hz (variable)	Rapid, irregular jerks, instability when standing	Partial response to clonazepam
Segmental myoclonus	Variable	Rhythmic contractions, limited to a muscle group or segment	Not always suppressed by action
Myorhythmia	1–3 Hz	Slow, rhythmic, continuous movements	Associated with trunk lesions
Wing-beating tremor	2–4 Hz	Abduction of arms → large-amplitude proximal tremor	Mesodiencephalic lesions
Functional tremor	Variable	Distractibility, clinical inconsistency	Inconsistent findings on examination

As for the attribution of clinical improvement in tremor and ataxia following management of the acute flare-up with intravenous steroids, supplemented with immunosuppression with azathioprine, the only immunosuppressant available at the time, this should be considered with caution, given that neuroimaging already showed chronic lesions at the time of diagnosis. However, the observed evolution can be explained by modulation of residual inflammation and optimization of symptomatic management, demonstrating that even in advanced stages of the disease, it is possible to achieve clinically relevant functional benefits.

This case highlights several relevant aspects. First, HT may constitute an initial presentation of MS, which is uncommon;[11-12] secondly, that phenomenology is essential in movement disorders, as it allows misdiagnosis to be avoided, especially in cases of atypical tremor; thirdly, that the clinical-radiological correlation is a fundamental pillar in the correct classification of tremor in MS; fourthly and finally, that early intervention with immunomodulatory therapies can significantly modify the trajectory of disability and quality of life in these patients.

Finally, it is essential to consider differential diagnoses of lower-extremity tremor in the context of MS. These include entities such as segmental myoclonus, orthostatic myoclonus, myorhythmia, HT, cerebellar tremor, functional tremor, as well as classic orthostatic tremor and its low-frequency variants (Table 2).[14] Correct differentiation between these conditions requires clinical phenomenological integration, neurophysiological recording, and radiological findings, which allow for accurate classification and better therapeutic guidance.

Ethical aspects

This manuscript complies with the Declaration of Helsinki and international ethical guidelines. The patient's informed consent was included.

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Supplementary material

The online version contains supplementary material available at:

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