CLINICO-PATHOLOGICAL CASE

Received: 19 MAR 2025 | Accepted: 26 MAR 2025 | **DOI:** https://doi.org/10.57849/ulisboa.fm.jscml.0000014.2025

JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

Remission of Parkinson's Disease Rest Tremor Following Cerebellar Hemorrhage

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ABSTRACT: Parkinson's Disease (PD) is a clinical diagnosis that relies on the presence of bradykinesia and rigidity and/or rest tremor. Whereas the striatal dopamine depletion explains the characteristic PD symptoms such as bradykinesia and rigidity, the mechanism of tremor generation is not completely established. Mounting evidence suggests that resting tremor is associated with increased activity in a distinct cerebellothalamic circuit, which may explain its lower response to dopaminergic treatment.

We describe the case of a 74-year-old man with idiopathic tremor-dominant PD who experienced rest tremor remission after cerebellar hemorrhage, supporting the role of the cerebellum in rest tremor pathophysiology.

KEY WORDS: Parkinson's Disease; Rest Tremor; Cerebellar Hemorrhage

INTRODUCTION

The clinical diagnosis of PD relies on bradykinesia and rigidity and/or rest tremor.[1] Neuronal loss in the substantia nigra and intracellular inclusions containing aggregates of α-synuclein are its neuropathological hallmarks resulting in dysfunction of striato-thalamo-cortical pathways.[2] However, considering the anatomical connections between the cerebellum and basal ganglia[3] and the increased activation of the cerebellum found in individuals with PD, it has been suggested that the cerebellum may also contribute to the pathophysiology of PD symptoms, mainly tremor.[2,4,5] We describe a case of PD rest tremor remission after ipsilateral cerebellar hemorrhage, which may support the role of the cerebellum in rest tremor pathophysiology.

CASE REPORT

A 74-year-old man, right-handed, with a history of smoking and localized prostate adenocarcinoma, was followed in our neurology outpatient clinic for idiopathic tremor-dominant Parkinson's Disease with 11 years of evolution and a Hoen & Yahr scale of 2. The neurologic

examination revealed upper and lower limbs moderate rigidity and bradykinesia as well as a disabling, high amplitude, pill-rolling and flexion-extension rest tremor in the right upper limb, without postural or intentional components (UPDRS-III tremor 7), and minor gait impairment. At that time, the patient was undergoing treatment with Levodopa/Benserazide 800 mg/day, Levodopa/Benserazide CR 100 mg/day, Rasagiline 1 mg/day, and Opicapone 50 mg/day. A few months after the last follow-up visit, the patient was admitted to the emergency department (ED) with occipital headache, vomiting, and gait instability. At ED admission blood pressure was 170/89 mmHg. Neurological evaluation revealed somnolence and mild paresis on the right upper limb (NIHSS 2). A brain MRI revealed a corticosubcortical in the right cerebellar hemisphere, with a maximum dimension of 5.4 cm along its longest axis, with extension to the medial cerebellar peduncle and the superior portion of the vermis, along with a slight deviation of the fourth ventricle (Figure 1). A hypertensive etiology was assumed, and treatment with an angiotensin-converting enzyme inhibitor and a calcium channel blocker was initiated. At the follow-up visit, six months after the stroke, the resting tremor had disappeared (UPDRS-III tremor score: 0), as confirmed by both the examiner and the patient.

DISCUSSION

Resting tremor is the classic type of tremor in PD. Whereas the striatal dopamine depletion explains the characteristic PD symptoms such as bradykinesia and rigidity, increasing evidence suggests that resting tremor is associated with increased activity in a distinct cerebellothalamic circuit, justifying its lower and unpredictable response to dopaminergic treatment. [2,4,6]

Growing data support the role of the cerebellum in Parkinson's disease. A "dimmer-switch model" was proposed to explain tremor generation. According to the dimmer-switch hypothesis, tremor-related activity originates at the internal pallidal globus, which propagates to the cortex. The cortex and ventral intermediate nucleus of thalamus (VIM) form a circuit, which is possibly the base of tremor-related oscillation. The cerebellum also projects to VIM, with this projection possibly modulating amplitude of tremor, while cerebellum is modulated by cerebral cortex. Multiple neurotransmitter systems are involved, including the dopaminergic retrorubral area, noradrenergic locus coeruleus, and serotonergic raphe nuclei.[7,8,9] So, this model suggested that tremor onset involves basal ganglia circuitry, whereas tremor magnitude involves cerebellar-thalamocortical projections.

Lewis et al, 2011, also investigated the role of the cerebellum in PD by studying functional differences between PD subtypes using fMRI, suggesting that the primary dysfunction in the cerebellar-thalamo-cortical circuit, particularly in the vermis and paravermis, could be responsible for the generation of resting tremor [10]. Wu et al. (2013) contributed to this understanding by using neuroimaging to demonstrate altered cerebellar activation in Parkinson's disease patients during motor execution, motor learning, and at rest, suggesting a significant role of the cerebellum in the pathophysiology of PD.[2] This was enhanced by Liu et al., 2013, who found disrupted connectivity of the dentate nucleus in

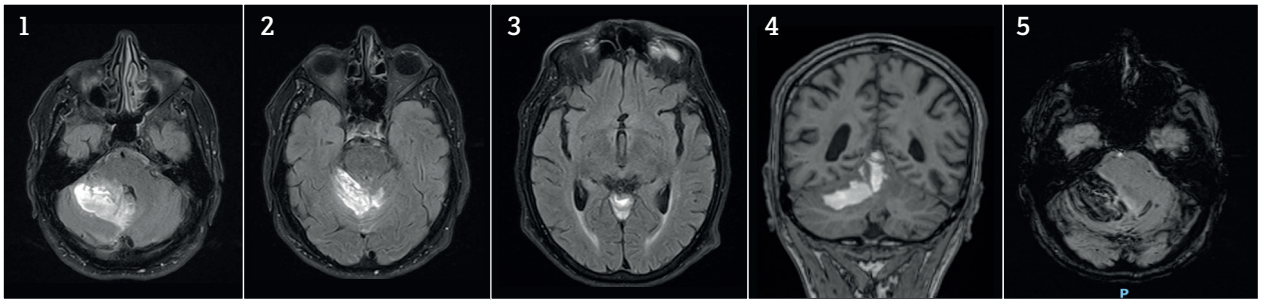

FIGURE 1. Brain MRI (1,2,3: Axial Flair, 4: Coronal T1, 5: SWI): Corticosubcortical hemorrhage in the right cerebellar hemisphere with extension to the right medial cerebellar peduncle and superior portion of vermis.

PD compared with healthy controls [11]. Bostan et al., 2013 reinforced this relation, demonstrating reciprocal connections between the basal ganglia and cerebellum via the thalamus and pontine nucleus, identifying projections between the cerebellar cortex and subthalamic nucleus via the pontine nucleus, and between the dentate nucleus and striatum via the thalamus.[3]

Lewis et al., 2013, pointed the oscillatory bursting at tremor frequencies in the VIM in PD patients consistent with its role in tremor genesis and/or propagation, with the VIM mainly receiving cerebellar inputs; and the improvement of tremor after surgical lesions or long-term stimulation of the VIM but not of bradykinesia and/or rigidity.[12] Lefaivre et al., 2016, through a repetitive transcranial magnetic stimulation protocol, demonstrated that the severity of resting tremor was reduced in individuals with tremor-dominant PD regardless of whether stimulation was applied over the medial or lateral cerebellum, suggesting involvement of the cerebellum in the generation of resting tremor.[5]

Recently, pathological changes in cerebellum have been found in PD patients. The cerebellum is affected by α-synuclein-formed Lewy bodies and by iron accumulation, which may induce white matter damage and structural and functional change. PD patients with rest tremor presented decreased gray matter volume mainly in quadrangular lobe and declive, and tremor-dominant PD patients had decreased gray matter volume in left cerebellar lobule VIIIa compared with akinesia/rigidity-dominant PD patients. Furthermore, larger volume of cerebellar lobule IV is associated with more severe resting tremor in all PD patients. These findings suggest a possible relation between these cerebellar regions and tremor in PD. Functional changes were also proved, being the functional connectivity between dentate nuclei and the cerebellar posterior lobe positively correlated with tremor severity. It seems that dentate nuclei plays a key role in cerebellum-related tremor regulation. It is possible that the activation of dentate nuclei or increase of dentate nuclei-cerebellar cortex interaction may enhance tremor. Moreover, cerebellar lobules may be involved in the mechanism of tremor in PD via its influence on dentate nuclei activity. [8]

Although the mechanism of tremor generation it is not completely established and some of the existing studies are controversial about the role of cerebellum, the majority supports a relation between tremor in PD and cerebellum, which is reinforced by our clinical report.

A deeper understanding of increased cerebellar activity, its mechanisms and effects in PD may provide a wider range of therapeutic targets, mainly for symptoms less responsive to dopaminergic treatments as tremor.

CONFLICT OF INTEREST: *None of the authors have conflict of interest related to this manuscript. The authors received no specific funding for this work. Joaquim J. Ferreira has provided consultancy and received speaker fees from BIAL, Biogen, AbbVie, Sunovion Pharmaceuticals, Infucure, Zambon, Roche, Stada, ONO Pharma, Britannia, Neuroderm, SK Chemicals and Organon and has received grants from AbbVie, BIAL, Medtronic, and Angelini.*

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