



## A Patient with Bilateral Tremors Secondary to a Unilateral Brainstem Lesion: The Utility of Mollaret's Triangle

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### Abstract

A unilateral tremor developed in a patient's left arm after a right midbrain hemorrhage. Thirteen years later, a re-bleed into that same area caused an additional right arm tremor. He now had bilateral arm tremors from a unilateral midbrain hemorrhage. The tremor was refractory to medications (propranolol, primidone, clonazepam, and levodopa). MRI brain showed bilateral hypertrophic olivary degeneration (HOD) from this unilateral midbrain hemorrhage. Although HOD has been associated with unilateral midbrain "rubral" tremor, it has not been described for bilateral intentional tremor. This case report illustrates how overlapping Mollaret's triangles can explain this patient's bilateral clinical findings.

**Keywords:** Intentional tremor; Mollaret's triangle; Midbrain tremor; Rubral tremor; Midbrain hemorrhage; Hypertrophic olivary degeneration

### Introduction

Guillain-Mollaret's triangle (GMT) is a commonly described anatomic model in association with palatal myoclonus [1]. It is also useful in the localization of tremor. The triangle consists of the dentate nucleus of the cerebellum, the red nucleus in the midbrain and the inferior olivary nucleus in the medulla. The central tegmental tract connects the red nucleus with the ipsilateral inferior olivary nucleus, while the superior cerebellar peduncle connects the dentate nucleus with the contralateral red nucleus. The contralateral dentate nucleus and inferior olivary nucleus are connected via the inferior cerebellar peduncle. Any focal lesions involving the dentato-rubro-olivary pathway (superior cerebellar peduncle, dentate nucleus or central tegmental tract) result in degeneration of the inferior olivary nucleus and pseudohypertrophy of the inferior olive. This process is called "Hypertrophic Olivary Degeneration" (HOD) [2]. Here we present a unique case of a unilateral hemorrhage causing bilateral tremor and HOD with interesting imaging findings.

### Case Presentation

A 42-year-old man developed a left sided 2-3 Hz postural tremor that worsened with intention one year after a right midbrain hemorrhage from a cavernous malformation. He was also dysarthric, diplopic with bilateral oculomotor nerve palsy, and hemiparetic on the left side with hemiparesthesia, but he was able to walk with a hemi-walker using his right arm. Thirteen years later, he developed a right-sided intentional tremor after a rebleed from the same right midbrain cavernous malformation (Figure 1A). He now had bilateral arm tremors with truncal ataxia, lower limb ataxia, bilateral dysmetria and dysdiadochokinesia. He became wheelchair-bound and developed autonomic dysfunction (syncope, central sleep apnea, gastroparesis, urinary incontinence). The tremors were coarse, slightly irregular, large amplitude, and most prominent proximally with a slow frequency of 2-3Hz. The tremors were present with posture and increased with intentional movements. Interestingly, there were no rest tremors in either arm. There was no ocular or palatal myoclonus. The tremors were refractory to medications (propranolol, primidone, clonazepam, and levodopa). MRI brain, at the time of the second hemorrhage, revealed a right midbrain tegmental lesion affecting the right cerebellar peduncle, the right substantia nigra, and the right red nucleus (Figure 1A and B, Figure 2).

The first hemorrhage into the right red nucleus/midbrain area caused a contralateral left-sided tremor. This hemorrhage, which disrupted the central tegmental tract, illustrates the contralateral GMT (green triangle, Figure 1). The second hemorrhage extended the damage into the right superior cerebellar peduncle resulting in a right-sided tremor, illustrating the involvement of a second GMT

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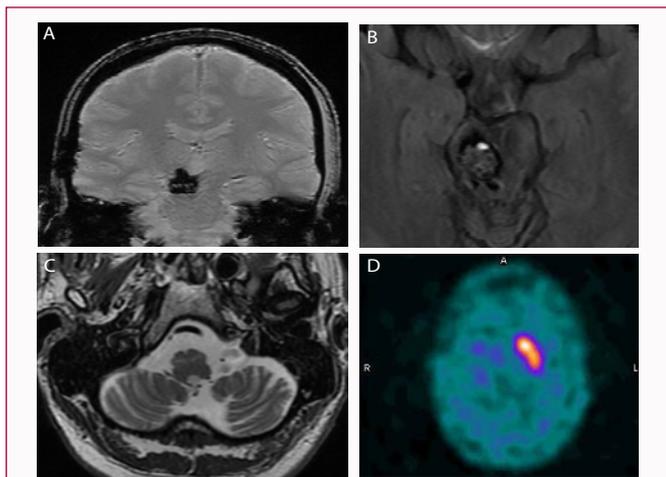
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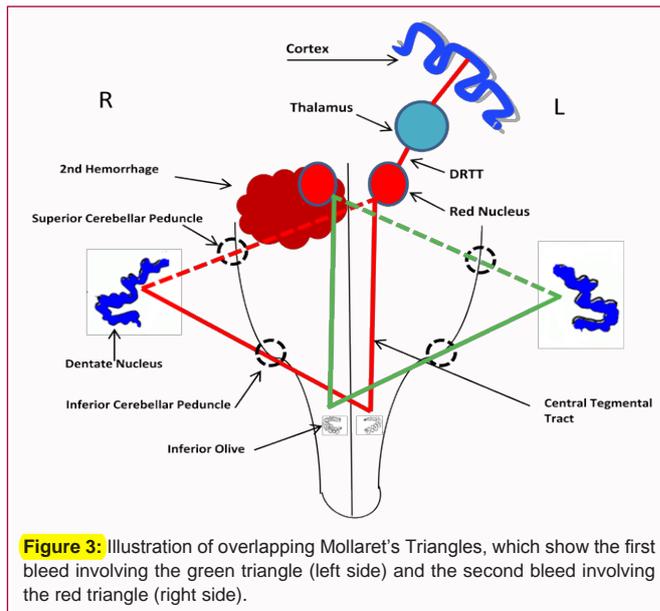
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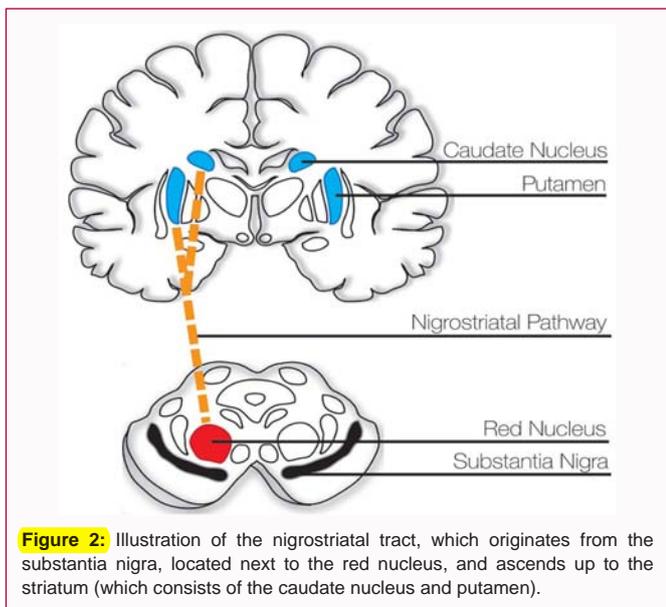
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**Figure 1:** **A:** T2 weighted gradient echo showing hemosiderin-laden cavernous malformation in the right midbrain. **B:** FLAIR sequence showing cavernous malformation of the right midbrain tegmentum, involving the red nucleus and substantia nigra. **C:** Bilateral hypertrophic olivary degeneration is shown on this T2 axial section through the medulla. Subtle T2 hyperintensity is noted within the bilateral inferior olives. **D:** DAT scan showing absent uptake in the right caudate and putamen.



**Figure 3:** Illustration of overlapping Mollaret's Triangles, which show the first bleed involving the green triangle (left side) and the second bleed involving the red triangle (right side).



**Figure 2:** Illustration of the nigrostriatal tract, which originates from the substantia nigra, located next to the red nucleus, and ascends up to the striatum (which consists of the caudate nucleus and putamen).

on the ipsilateral side (red triangle, Figure 1). T2-weighted MRI one year after the second hemorrhage showed bilateral hypertrophy of the inferior olivary nucleus suggesting that bilateral pathways of GMT were involved (Figure 1C, Figure 2 and 3).

The involvement of the right substantia nigra in the second hemorrhage prompted a dopamine transporter SPECT (DAT) scan, which revealed a complete loss of dopamine uptake in the right striatum (Figure 1D). A trial of levodopa resulted in no improvement in the left-sided tremor. Remarkably, the patient had no rest tremor that is classic of rubral tremor or clinical signs of Parkinson disease, despite involvement of the substantia nigra and absence of dopamine uptake in the right striatum.

**Discussion**

Holmes tremor is a low frequency rest tremor (3-4Hz) that

worsens with posture and action. It was first described in 1904 by Gordon Holmes [3]. Holmes tremor is also known as rubral, midbrain or thalamic tremor. The tremor on average develops about 2 months after a CNS insult [4].

Any GMT lesion can result in HOD, which can clinically manifest as Holmes tremor [5]. Midbrain and thalamic vascular lesions are leading causes of Holmes tremor [4].

Our patient did not develop palatal myoclonus, which is commonly associated with HOD. Most patients who have palatal myoclonus from a brainstem injury also have HOD, but not all patients with HOD develop palatal myoclonus [6].

The GMT contains part of the dentato-rubro thalamic tract (DRTT). The DRTT coordinates the initiation, planning and time of movements. The DRTT originates from the dentate nucleus in the cerebellum, ascends up the superior cerebellar peduncle, decussates to the contralateral red nucleus and ends in the ventrolateral nucleus (VL) of the thalamus (Figure 1). A lesion of the DRTT gives rise to tremors, ataxia and dystonia. Our patient with disruption to the DRTT has bilateral postural and intentional tremor with ataxia. The VL in the Hirai system corresponds to the ventral intermediate nucleus (VIM) in the Hassler system. Deep brain stimulation (DBS) of the VIM thalamus has been reported to alleviate Holmes tremor [4]. VIM DBS for our patient was not advised by the DBS committee due to new symptoms of autonomic dysfunction and dysphagia in this patient. It is common to have autonomic involvement with brainstem lesions due to the interruption of the dorsal longitudinal fasciculus and the medial forebrain bundle, which are the output and input, respectively, to the hypothalamus. These two tracts run the length of the brainstem [7].

The midbrain hemorrhage extends from the red nucleus to involve the right substantia nigra causing interruption to the nigrostriatal pathway. The dopaminergic neurons in the nigrostriatal pathway project from the substantia nigra pars compacta to the striatum (Figure 3). Thus, a right midbrain lesion to the nigrostriatal pathway in this patient resulted in a unilateral loss of dopamine in the right striatum as confirmed by the DAT scan (Figure 1D). The implication of the loss of dopamine is yet to be understood. It is thought that

perhaps the loss of dopamine in the nigrostriatal system (i.e. due to the involvement of the substantia nigra) may account for the rest tremor component of Holmes tremor [8]. However, our patient did not have a rest tremor, despite having absent dopamine uptake on the DAT scan. He did have a low frequency postural and action tremor, suggestive of a Holmes tremor. Levodopa has been reported to provide benefit in some cases where there is a loss of dopamine [9-12]; however, this was not the case in our patient. The right sided loss of dopamine did not produce left sided Parkinsonian symptoms, such as left sided rest tremor, rigidity or bradykinesia in our patient.

Hypertrophic degeneration of olivary complex (HOD) can be differentiated into three types. The first type is a lesion involving the central tegmental tract, resulting in ipsilateral degeneration of the olive. The second type is a lesion involving the superior cerebellar peduncle or dentate nucleus causing contralateral degeneration of the olive. The third type is bilateral degeneration that occurs with involvement of both pathways [11-14]. In our patient, T2-weighted MRI one year after the second hemorrhage showed bilateral hypertrophy of the inferior olivary nucleus suggesting that bilateral pathways of the Mollaret's triangle were involved (Figure 1C, Figure 2 and 3). The concept of two overlapping GMTs offers an explanation of how a unilateral midbrain lesion can cause bilateral tremors.

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