Presentation of clinical cases

Post-traumatic hypertrophic olivary degeneration associated with Holmes tremor: Clinical-imaging correlation

Degeneración olivar hipertrófica postraumática asociada a temblor de Holmes: correlación clínico-imagenológica

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ABSTRACT

Hypertrophic olivary degeneration is a disease secondary to damage to the neuronal circuit of the Guillain Mollaret Triangle, generating symptoms as varied as Holmes tremor. This article describes the case of a 52-year-old man with a history of head trauma in 2016, without mediate sequelae, who progressively presented tremors associated five years later with headache requiring emergency assistance, where studies were carried out, and pharmacological therapy was instituted. Finally, it is concluded that post-traumatic lesions in the Guillain Mollaret Triangle can generate movement disorders secondary to hypertrophic olivary degeneration as sequelae, an entity that is rarely diagnosed.

RESUMEN

La degeneración olivar hipertrófica, es una enfermedad secundaria al daño en el circuito neuronal del Triángulo de Guillain Mollaret lo que genera síntomas tan variados como el temblor de Holmes. El presente artículo describe el caso de un hombre de 52 años, con antecedente de trauma craneoencefálico en 2016, sin secuelas mediatas, quién de manera progresiva presentó temblor, y se asoció cinco años después a cefalea lo que requirió asistencia a urgencias, allí realizaron estudios e instauraron terapia farmacológica. Finalmente se concluye, que lesiones postraumáticas en el Triángulo de Guillain Mollaret, pueden generar como secuelas trastornos del movimiento secundarios a degeneración olivar hipertrófica, una entidad poco diagnosticada.
INTRODUCTION

Hypertrophic olivary degeneration (HOD) is a rare disease of unknown incidence, resulting from damage to the neuronal circuit that relates ipsilaterally to the red nucleus and inferior olivary nucleus with the contralateral dentate nucleus, comprising the Guillain Mollaret Triangle (TMG). See (Figure 1. The lesion causes synaptic degeneration of the inferior olivary nucleus, which loses its afferent inhibition of the circuit, becoming hypertrophic due to the resulting neuronal hyperactivity. Its most frequent causes correspond to unilateral or bilateral noxa in the brainstem or cerebellum, such as hemorrhage, ischemia, neoplasia, or trauma, which can be identified in the Brain Magnetic Resonance (BMR). HOD implies great variability of clinical presentations, from asymptomatic pictures to palatal tremor, ocular myoclonus, dystonia, dentato-rubral, or Holmes tremor (TH). This work aimed to describe the clinical and imaging manifestations of a man with movement disorder associated with HOD.

Figure 1. Schematic representation of the TGM with its nuclei and connection pathways in CMR in a Coronal cut in T2, taken in the Case Patient.

CLINICAL CASE

A 52-year-old male from Cali-Valle del Cauca-Colombia, with no significant clinical history until 2016, who, under a state of intoxication, fell from the stairs at an undetermined height, with subsequent severe head trauma (TCE) and injury diffuse axonal pathology, required management in an intensive care unit, prolonged orotracheal intubation and tracheostomy, without the need for neurosurgical management. He gradually recovered one month after the event without presenting apparent mediate sequelae.

After six months of the TBI, he refers to the progressive appearance of a distal to proximal tremor at rest with a frequency of 4 to 6 Hz, low amplitude, symmetrical, predominantly left in the upper limbs, gradually worsening with the anti-gravity posture and intention. No neurological medical approach was reported until April 2021, when he consulted the emergency department for a clinical picture of two days of evolution consisting of a left hemicranial headache without irradiation, progressive increase in intensity, without Valsalva effect, associated with decreased visual acuity: dysarthria, and worsening tremor pattern.

The anamnesis describes arterial hypertension managed with amlodipine 5 mg orally (PO) every 24 hours and losartan 50 mg PO every 12 hours; ex-smoker since 2016 and occasional consumption of alcohol until drunkenness.

Myotendinous reflexes in the lower limbs and standard in the upper limbs, he presented abnormal movements: tremor in the upper limbs, predominantly on the left, at rest with increased changes in posture and intention to move, taxis was not evaluable, without rigidity or bradykinesia, slightly ataxic gait—no alteration in other systems.

Simple brain tomography revealed incidental findings of a diffuse increase in density in the left suprasellar and parasellar region without hemorrhage, ischemia, or hydrocephalus. Serum studies: complete blood count, renal function, ionogram, blood glucose, coagulation times, prolactin, morning serum cortisol, morning ACTH, TSH, LH, FSH, and typical arterial blood gases, with GH (14.2 ng/mL) increased, and somatomedin C (887 ng/mL) increased. Simple cranial magnetic resonance imaging revealed a 14x10 mm macropituitary adenoma, foci of microhemorrhages in the frontal and left parietal region at a subcortical level, probably sequelae of diffuse axonal injury and...
old hemorrhage in the left midbrain at the level of the tectum and tegmentum on T2 weighting in both coronal and axial section (Figure 2). In addition to hyperintensity in the left inferior olivary nucleus and hypointensity ipsilateral periaqueductal (Figure 3).

Neurosurgery performed surgical management by transsphenoidal route without complications. On the other hand, after the evolution since 2016, he presented a progression of abnormal movements that limited his daily activities, and neuroimaging lesions were evidenced in the TGM. For that reason, the TH neurology service considered it secondary to post-traumatic HOD, not fulfilling parkinsonism criteria; pharmacological treatment with biperiden 2 mg PO every 24 hours was started, and a therapeutic trial with levodopa/carbidopa 25 mg/250 mg po titrated, half a tablet four times a day, obtaining progressive clinical improvement with subsequent post-surgical outpatient controls for neurosurgery and neurology.

**Statement on ethical aspects**

In the present case, the patient signed an informed consent to authorize the publication, guaranteeing confidentiality, privacy, and anonymity.

**DISCUSSION**

HOD, as a clinical condition of low prevalence, is more frequent in male adults; among the leading causes include cerebrovascular attack (CVA), TCE, toxins and neoplasms, entities that generate partial lesions between the connections of the components of the TGM (excluding lesions of the olivodentate tract as these lead to cerebellar atrophy), causing transsynaptic degeneration and interruption of...
afferent input to the inferior olivary nucleus, generating loss of inhibition within the circuit and subsequently prolonged nuclear hypertrophy, which in the long term culminating in nuclear atrophy, all of the above can be correlated with the post-traumatic etiology of HOD described in the present case and is related to the findings of reviews and case series established in the literature, who together describe clinical imaging correlation as diagnostic criteria 10–14, as will be described below.

Regarding the characteristic neuroimaging signs of HOD, up to now, no definitive Gold Standard diagnostic consensus has been described 13,15, so most authors propose CMR as part of the arsenal to define the radiological criteria, which are usually defined as a pattern of unilateral and ipsilateral imaging damage to the causative noxa located predominantly in the brainstem on T2 sequences, specifically in the course of the central segmental tract of the TGM, with increased inferior olivary hyperintensity on T2 or FLAIR, as a result of hypertrophy nuclear that is usually revealed 4 to 6 months after the establishment of the etiological agent 8,12,14,16–18. Several of these aspects previously mentioned in the literature, are coupled to the case in the description since the cranial magnetic resonance of the patient showed disruption of the TGM, given by the association of a hypointense midbrain lesion on T2 of the hemorrhagic type ipsilaterally distanced from the hyperintense inferior olivary nucleus affected by HOD, in the same imaging sequence.

Although the clinical presentation of HOD corresponds to a complex movement disorder with various underlying causes and presentations, clinical suspicion criteria can help identify this pathology, such as palatal tremor, ocular myoclonus with nystagmus, or as appropriate. In this case, debut with LT 4,19,20 makes it necessary to rule out structural damage, identify the etiology and offer the best treatment to affected patients. Even though reports of HT associated with HOD due to damage to the dentorubro-olivary pathway are scarce 5,21, the possibility that the diagnosis of this condition is being overlooked is not ruled out, as commented in a recent review of 2023 22 on the clinical syndromes associated with injuries in the TGM.

A fundamental contribution of this clinical case to the literature is the semiological description of a rarely diagnosed entity, such as LT. The patient in question met the definition criteria for this movement disorder, established in the latest consensus on the Classification of tremors of 201823 (1. Onset at rest, postural and intentional, 2. Proximal and distal rhythmic muscle contraction, 3. Low frequency (<5 Hz)). From the IPMDS (International Parkinson and Movement Disorder Society). Pyrgelis et al24 proposed that the diagnosis should be based mainly on a careful clinical examination, together with neurophysiological and imaging studies, proposing cranial magnetic resonance imaging as the test of choice for initial evaluation. He also describes how this tremor is frequently associated with additional neurological signs, which in the corresponding case were dysarthria and alterations in gait and balance.

Regarding the therapeutic approach of HT associated with HOD, the main objective is to improve the quality of life of patients; since there is currently no cure for this disorder, the options to improve symptoms usually include levetiracetam, levodopa/carbidopa and other non-pharmacological measures such as deep brain stimulation 24, interventions which have shown benefits in treated patients. In the present case, there was a progressive favorable response to an alternative readily available in our environment, such as levodopa/carbidopa, controlling a large part of the tremor and the patient's functionality. Finally, the prognosis of HOD depends on the causative agent, so some cases may reveal marked progressive disability, such as those related to stroke 22, while others, such as the present case, remain stable over time with symptomatic treatment.

CONCLUSIONS

From functional neuroanatomy, it is vital to consider that post-traumatic lesions in the Guillain Mollaret Triangle can generate movement disorders secondary to HOD as sequelae, a rarely diagnosed entity, the knowledge of which could avoid erroneous diagnoses and prevent unnecessary interventions in affected patients.

DECLARATION ON CONFLICTS OF INTEREST

The authors declare that they have no interest conflict.

AUTHORS' CONTRIBUTION

First author: Writing the manuscript and structuring the case.
Second author: Reviewing medical board of the case, and review, analysis.

Third author: Reviewing medical case board, and review, analysis.

Fourth author: Reviewing case medical board, manuscript writing, and review analysis.

Fifth author: Reviewing the analysis, review, and final approval.

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