The Pathophysiological Basis for Hypertrophic Olivary Degeneration (HOD) Following Brainstem Insult

Peter Bouz, Rafeek OJ Woods, and Kamal RM Woods*
Department of Neurological Surgery, Loma Linda University Medical Center, USA

Abstract
Primary lesion of the dentatorubral-olivary pathway may lead to secondary degeneration of the inferior olivary nucleus (ION), resulting in a rare but clinically relevant condition called hypertrophic olivary degeneration (HOD). Patients with HOD often present with palatal myoclonus, ataxia, tremor, dysarthria and/or hemiparesis. Early MRI shows T2 lengthening in the dentate nucleus, superior cerebellar peduncle, red nucleus, or pontine tegmentum. By 6 months, hypertrophy of the ION is usually apparent. HOD is a self-limiting pathology and only symptomatic management is recommended.

ABBREVIATIONS
GMT: Triangle of Guillain and Mollaret; ION: Inferior Olivary Nucleus; HOD: Hypertrophic Olivary Degeneration, DTI: Diffusion Tensor Imaging

INTRODUCTION
Hypertrophic olivary degeneration (HOD) was first reported in 1887 by Oppenheim;[1] however, it was not until the early 20th century that the etiology was elucidated. In 1926, Foex et al. described a process referred to as "transsynaptic degeneration" where neurons undergo neuronal loss and reactive gliosis after losing synaptic input from injury to their afferent fibers [2]. This "deafferentation syndrome" is a unique form of degeneration because it results in enlargement of the affected structure rather than atrophy. Transsynaptic degeneration can occur in various locations in the central nervous system. For example, it has been well described in the lateral geniculate body after lesions in the eye, retina, optic nerve or optic tract. Similarly, HOD is regarded to be the result of transsynaptic degeneration of the inferior olivary nucleus (ION) following injury to the dentatorubral-olivary pathway. This pathway was first described by Guillain and Mollaret in 1931 as the anatomical basis for palatal myoclonus, a common clinical feature associated with HOD. The triangle comprises connections between the ION, the red nucleus and the contralateral dentate nucleus and is referred to as the "triangle of Guillain and Mollaret" (GMT) [3].

CASE PRESENTATIONS
Case 1
A 16-year-old female presented with progressive gait ataxia, vertigo, and nausea. Investigational imaging revealed a large posterior fossa mass. At the time of surgical resection of this mass, it was found to be adherent to floor of the fourth ventricle and the brain stem. Pathology demonstrated a low-grade astrocytoma (WHO grade 2). MRI done 6 months post-operatively showed T2-lengthening of the ION bilaterally (Figure 1). At 12 months post-operatively, the patient developed debilitating palatal myoclonus. Interestingly, this finding was not appreciated during...
the first 12 months after surgery. Two years after surgery, the palatal myoclonus persisted and is being managed successfully with repeated Botox injections. The most recent MRI, which was done 19 months after surgery, showed interval mild enlargement of the ION bilaterally and persistence of T2 lengthening (Figure 2).

Case 2

A 37 year-old male diagnosed with trigeminal neuralgia underwent open right-sided microvascular decompression (MVD). Due to unsatisfactory outcome, he was retreated with gamma knife surgery a few months after the MVD. Three years later, his trigeminal neuralgia still had not improved, and he underwent endoscopic MVD. This endoscopic procedure was complicated by right posterior inferior cerebellar stroke (Figure 3). Two years later, the patient presented to our institution with complaints of dysphasia and slurred speech. Physical examination demonstrated pendular nystagmus, and palatal myoclonus. MRI of the brain showed a hypertrophic lesion in the right medulla, consistent with HOD (Figure 4). The patient's dysphagia, slurred speech, and nystagmus all slowly improved. Three years after the stroke, these essentially resolved. The palatal myoclonus, however, persisted but is improved with carbamazepine. The most recent MRI, which was done 3 years from the time of insult, still shows HOD (Figure 5).

**DISCUSSION**

HOD is a unique form of degeneration because it results in enlargement of the affected structure rather than atrophy [4,5]. The mechanism underlying these unique pathologic changes is still not well understood. What has been clearly demonstrated is that HOD represents the end-result of a lesion that damages the neuronal connections between the dentate nucleus of the cerebellum, the red nucleus, and the inferior olivary nucleus. The condition carries a wide differential diagnosis that includes infarction, demyelination, primary tumor, metastasis, and infection. Even though the imaging characteristics of hypertrophic olivary degeneration resolve, the clinical hallmarks such as palatal myoclonus persist [6,7]. These clinical symptoms presumably reflect loss of inhibitory control that is transmitted through the dentatorubral pathway. Makoto et al. showed that palatal myoclonus, and other involuntary movements, appear prior to the peak in olivary hypertrophy and persist after the hypertrophy resolves. It appears that initial symptomatology is caused by hyperactivity of the olivary neurons, as these neurons are released from inhibitory inputs, until the peak of olivary hypertrophy. However, the persistence of the symptoms after the
resolution of hypertrophy is probably due to both the disturbance of natural rhythmicity, and the lack of feedback [8].

Correct identification of HOD is essential in preventing misdirected interventions. In fact, Case #2 was referred to our institution for biopsy of a presumed “medullary glioma” After careful review of the case, the diagnosis of HOD was made. Fortunately, as described above, the patient’s clinical course showed slow but steady improvement.

Neurosurgeons and other clinicians must include HOD in the differential diagnosis for enlarged medullary lesions, especially in the setting of previous posterior fossa insult. The differential diagnosis should also include: tumor, multiple sclerosis or other demyelinating disorder, and stroke. The nearly pathognomonic feature of palatal myoclonus should heighten clinical suspicion for HOD.

Fortunately, HOD is a self-limiting pathology and requires only symptomatic management. Palatal myoclonus has been shown to respond to medications such as clonazepam, valproic acid, and carbamazepine. More severe cases of palatal myoclonus have been successfully treated with botulinum toxin injections into the tensor veli palatine muscle.

Anatomy of the guillain-mollaret triangle

The ION is located in the anterolateral medulla and plays a role in coordination. It receives afferent fibers from the ipsilateral red nucleus in the midbrain via the central tegmental tract, which traverses the central brainstem tegmentum. Next, the red nucleus receives afferent fibers from the contralateral dentate nucleus of the cerebellum through cerebellorubral fibers, specifically the dentatorubral tract. The dentatorubral tract leaves the cerebellum via the superior cerebellar peduncle and decussates in the inferior colliculus of the lower midbrain, before synapsing in the contralateral red nucleus. This pathway participates in a reflex arc that controls fine voluntary motor movements. Finally, completing the triangle are the efferent fibers from the ION to the cerebellum, which cross midline through the medial lemniscus and enter the cerebellum through the contralateral inferior cerebellar peduncle to synapse on the contralateral dentate nucleus (Figure 6).

The fibers from the ION do not project directly to the dentate nucleus; instead, they first synapse in the cerebellar cortex via the olivo-cerebellar tract then project to the dentate nucleus [9]. This is of clinical significance because it has been shown that isolated lesions of the inferior cerebellar peduncle (olivodentate tract) do not cause palatal myoclonus or HOD, which has been postulated to be due to the lack of direct connections between the ION and the dentate nucleus [10]. Additionally, the olivodentate tract is an efferent tract and the pathophysiologic basis of HOD is deafferentation of the ION. Nonetheless, the olivodentate tract is believed to play role in maintaining the cerebellar hemispheres, and lesions of this pathway have been reported to cause cerebellar atrophy [11].

Lesions in the brainstem involving the central tegmental tract cause ipsilateral HOD, while lesions in the cerebellum (dentate nucleus and superior cerebellar peduncle) cause contralateral HOD. Bilateral HOD has also been reported from lesions that involve both the central tegmental tract and the superior olivary nucleus [12]. In this paper, we presented examples of HOD related to a posterior fossa tumor and following brainstem stroke. Other mechanisms described in the literature include: head trauma, posterior fossa surgery, stroke, vascular lesions, and idiopathic.

Radiological progression of HOD

HOD appears in a delayed fashion after insult to the dentatorubral-olivary pathway. The radiologic hallmark of the condition is T2 lengthening on MRI. The T2-hyperintense lesion can be evident anywhere along the GMT: in the dentate nucleus, superior cerebellar peduncle, red nucleus, or pontine tegmentum. According to metaanalysis of the evolution of MR findings, the increased olivary signal on T2-weighted images can appear as early as 1 month post-insult, and persisted for at least 3-4 years.

Olivary hypertrophy is another characteristic finding of this entity on MRI. Olivary hypertrophy is a later finding, with initial development around 6 month and resolving at around 3-4 years (Figure 7). This resolution appears as a result of olivary atrophy. Another new modality that can be utilized for evaluation of HOD
is diffusion tensor imaging (DTI). DTI may reveal increased radial diffusivity representing demyelination, and an increase in axial diffusivity that is reflective of neuronal hypertrophy. [16] Characteristic deviation, deformation and interruption were not observed during the DTI in HOD as would be expected with brainstem tumors. [17]

**Pathological progression of HOD**

It has been implicated that the initial signal hyperintensity relates to the early phases of gliosis due to demyelination and increased water content.[18] The hypertrophy of olivary nucleus, therefore, is the stage of pathological changes that leads to cell death of both neurons and astrocytes. This process eventually results in atrophy, and olivary shrinkage.

Neuronal hypertrophy begins 20–30 days after the onset of the causative lesion, and reaches maximum size, accompanied by prominent astrocytosis and synaptic and axonal remodeling, 6–7 months later. Early hypertrophic changes correlate with neuronal ballooning and the presence of increased numbers of protoplasmatic astrocytes. At 6 months, there is further olivary enlargement with the presence of vacuoles in the ballooned neurons, as well as prominence of gemistocytic astrocytes. The hypertrophic changes decrease with time in association with atrophy. At 2 years, there is a decrease in the number of neurons. In patients surviving >6 years after the insult, there is >90% reduction in the normal number of neurons.

**CONCLUSION**

HOD is a rare pathological entity that presents with a spectrum of physical manifestations. It appears to be the end-result of insult to a variety of structures along the GMT. Accurate and timely diagnosis is essential to prevent untoward and misdirected interventions.

**REFERENCES**


Cite this article