HYPERTROPHIC OLIVARY DEGENERATION - A CASE SERIES

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ABSTRACT Hypertrophic olivary degeneration (HOD) is a rare neurological condition resulting from the trans-neuronal damage of the dentato-rubral-olivary pathway. It is more commonly seen secondary to ischemia, haemorrhage, tumour, trauma, infection, or any inflammatory condition, though few rare cases of idiopathic nature have been reported. MRI findings may be seen as early as four months after the initial insult, which may later be accompanied by classic symptoms of palatal tremors, dentatorubral tremors, ocular myoclonus, or ataxia. Prior knowledge of this condition is required to prevent some misdirected interventions. We aim to discuss the relevant anatomy, various patterns, and MRI findings and differential diagnosis of HOD through this case series.

KEYWORDS olivary degeneration, dentatorubral tremors, Holmes tremor, MRI findings

Introduction

Hypertrophic olivary degeneration (HOD) is a rare trans-synaptic degeneration that occurs as a result of damage to the neuronal fibres of the dentato-rubral-olivary pathway (DRO) pathway. It is a circuit connecting the dentate nucleus in the cerebellum of one side to the red nucleus and the inferior olivary nucleus in the midbrain and medulla of the contralateral side, respectively. In 1931, French physicians Georges Guillain and Pierre Mollaret first found out the trilateral connection between these three nuclei, and it is also known as the triangle of Guillain-Mollaret.[1] There are two such triangles in each posterior fossa – the superior end of which is formed by the red nucleus, the inferior end by the inferior olivary nucleus, and the middle end by the contralateral dentate nucleus.

A set of afferent and efferent pathways connect these three nuclei, which are named according to the structure they connect: the dentato-rubral (afferent), the rubro-olivary pathway (afferent), and the indirect olivo-cerebellar pathway (efferent). The dentato-rubral path-way originates in the contralateral dentate nucleus and connects to the ipsilateral red nucleus via the superior cerebellar peduncle. Continuing inferiorly through the midbrain and pons is the rubro-olivary pathway, located in the central tegmental and connects the ipsilateral red nucleus with the ipsilateral inferior olivary nucleus. Finally, indirect efferent fibres from the ipsilateral inferior olivary nucleus cross through the inferior cerebellar peduncle to join the contralateral dentate nucleus (olivary-dentate pathway).[2]

HOD is unique because the degeneration of the involved inferior olivary nucleus causes hy-pertrophy instead of atrophy. This can be explained by the fact that the dentate nucleus’s primary function is to inhibit the signals from the inferior olivary nucleus. Therefore, any lesion that causes an interruption in the DRO pathway’s afferent route will no longer impede the signal and eventually undergo hypertrophy.[3]

This pathway is associated with fine voluntary movements, and hence disruption classically causes palatal tremors. Less frequently can cause dentatorubral tremor (Holmes tremor) or ocular myoclonus. In some cases, these tremors may also involve facial muscles, diaphragm, or muscles of the tongue and larynx.[4,5] HOD commonly develops secondary to a focal lesion like haemorrhage, infarction, tumours, infection, inflammatory conditions, trauma, or post-surgical. In rare cases, HOD has been documented to be idiopathic.[6,7,8]

Three patterns of HOD can be produced depending on the location of the lesions:
1. CONTRALATERAL HOD: lesions in the dentate nucleus or the dentato-rubral tract in the superior cerebellar peduncle.

2. BILATERAL HOD: lesions in the midline or paramedian pons due to simultaneous involvement of superior cerebellar peduncle and central tegmental tract.

3. IPSILATERAL HOD: lesion in the brainstem tegmentum disrupts the rubro-olivary pathway in the central tegmental tract.

Interruption of the indirect efferent Olivo-dentate tract does not cause HOD.

Typical MRI findings make the diagnosis of HOD of increased T2 and FLAIR intensity, which may later be accompanied by the enlargement of the inferior olivary nucleus. No diffusion restriction, blooming on T2* and post-contrast enhancement is seen. The evolution of HOD has been described in four stages based on MRI findings.[9,10]

These MRI stages have been proven to coincide pathologically. Initial hyperintense signals correlate with demyelination and oedema. Olivary enlargement corresponds with the increase in the area of the cell body of astrocytes and vacuolar degeneration of the cytoplasm. However, no actual increase in the number of astrocytes has been documented. Later in the atrophic changes, a decrease in some neurons are seen.

Case series

Case 1:
A 52-year-old female with a history of stroke one year back came for a follow-up scan. She had no discomfort or any symptoms at the time of presentation. Physical examination was normal. MRI revealed multiple T2 hyperintense foci in the pons, right cerebellar peduncle and right cerebellar hemisphere showing signal drop on FLAIR representing chronic infarcts. On T2 and FLAIR imaging, there are abnormally enlarged and hyperintense bilateral inferior olivary nucleus showing no diffusion restriction or blooming on SWI.

Case 2:
A 55-year-old male with no significant past medical history presented to the emergency department with a 4 days onset of giddiness and worsening coordination. An MRI was performed, and it revealed a T2 hyperintense lesion in the right medulla, which showed no diffusion restriction suggesting Hypertrophic Olivary Degeneration. A chronic infarct was noted in the right cerebellum. No lesion was noted, particularly in the Guillian-Mollaret triangle.

Case 3:
A 35-year-old male with a previous history of stroke now presented to the emergency department with a complaint of occasional palatal tremors for 15 days. No limb weakness or ophthalmoplegia was seen on physical examination. MRI revealed multiple non-hemorrhagic infarcts in the central portion of the pons and bilateral cerebellar hemispheres in addition to bilateral almost symmetrical T2 high signal at the anterior olivary nuclei without restricted diffusion or blooming on T2* representing bilateral hypertrophic olivary degeneration. Only this patient had palatal myoclonus in our case series and was managed conservatively with oral carbamazepine and was relieved of symptoms.

Case 4:
A 47-year-old female with a history of cerebrovascular events three years back presented with chief complaints of recurrent headaches for 30 days. On physical examination, no significant
Table 1

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<tr>
<th>NAME AND DURATION</th>
<th>MRI FINDINGS</th>
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<tr>
<td>STAGE 1 Early acute (0-1month)</td>
<td>No olivary changes</td>
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<tr>
<td>STAGE 2 Acute stage (1-6months)</td>
<td>Increased T2 flair signal intensity of the olivary nucleus</td>
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<tr>
<td>STAGE 3 Intermediate (6months-4years)</td>
<td>Increased T2 flair signal + Hypertrophy of the olivary nucleus</td>
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<tr>
<td>STAGE 4 Chronic (3-4 years)</td>
<td>Increased signal intensity persists while the nucleus size may normalize.</td>
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abnormality was seen. MRI revealed multiple T2 hyperintense foci with a hypointense rim in mid pons, expressing blooming on T2* WI suggestive of chronic haemorrhage. Also noted were a T2 and FLAIR hyperintense non-enhancing lesion in the right medulla showing no restriction on diffusion-weighted images or blooming on SWI suggestive of Hypertrophic Olivary Degeneration.

![Figure 4](image)

Discussion

Hypertrophic olivary degeneration is a rare, unique kind of transsynaptic degeneration which occurs due to the damage to the nerve fibres in the triangle of Guillain and Mollaret. Only the lesions affecting the afferent pathway will cause HOD since the efferent fibres are indirect fibres that first relay to the cerebellar cortex via the olivo-cerebellar tract and then relay to the dentate nucleus.

Varied causes of HOD have been described ranging from infarcts, haemorrhages to tumours of which bilateral HOD is more common.[11] Sanverdi et al., Van Etvelde R et al. have re-reported cases where no lesion along the GM pathway was found, suggesting an idiopathic origin. Two recent extensive studies by Gu et al. and Carr et al. concluded that no lesion was detected in up to 44% of cases in the Guillain-Mollaret-triangle. Although a clear explanation is not given, the study assumes that either lesion outside the Guillain-Mollaret-triangle is involved or that the causative lesions in the Guillain-Mollaret-triangle are too small to be detected with MRI. In their study, most patients without a DROP lesion had bilateral HOD, and two-thirds were male, unlike our study, where we had one male patient of unilateral HOD of unknown cause. The other three patients in our discussion had a history of old brain insults, including old hematoma(1 patient) and old infarcts (2 patients). HOD has also been reported following metronidazole intoxication and associated with Dandy-Walker malformations.[14]

Three patterns of hypertrophic olivary degeneration have been described, as discussed earlier. Lesions involving the dentato-rubral-pathway will cause contralateral HOD, and damage to the rubro-olivary pathway will cause ipsilateral HOD. Midline pons lesions were said to cause bilateral HOD, which was not in contradiction to our case 4, where chronic bleed in the cen-tral pons leads to unilateral HOD. The explanation for this is not identified.

Although all of our patients were adults, similar patterns have been described in the pediatric age group.[7] Prior studies have shown that the typical MRI hyperintensities associated with HOD initially appear about one month after the inciting injury, which may later also lead to hypertrophy of the inferior olivary nucleus after about 3–5 months [10]. This was in concordance with our study, where all three patients of secondary nature were diagnosed at least one year after the initial insult.

The diagnostic imaging criteria used were hyperintensity on T2 and FLAIR with iso to mildly hyperintense signals on T1 with average/increased size of an inferior olivary nucleus. No post-contrast enhancement, diffusion restriction, or blooming on T2* was another essential criterion.

Any T2/FLAIR hyperintense lesion in the anterior pontomedullary region will be a differential for HOD, including infarction, haemorrhage, infection (tuberculosis, sarcoid), demyelination, tumour, or any inflammatory process.[15]

Thus, signal changes confined to the olivary nucleus or nuclei (with or without enlargement of the ION), lack of contrast enhancement or diffusion restriction in addition to the presence of an inciting lesion in the brain stem or cerebellum should point toward the diagnosis of HOD.

Correct identification of HOD is essential in preventing the mistaken identification of this benign condition with more sinister pathology. HOD usually has a symptomatic treatment. Palatal myoclonus may respond to medications such as valproic acid, carbamazepine, and clonazepam. Botulinum toxin injections into the tensor veli palatine muscle are reserved to severe cases of palatal myoclonus.[15]

Conclusion

HOD is a rare neurological condition that occurs as a result of delayed insult to fibres of the dentato-rubral-olivary pathway presenting with characteristic symptoms. MRI changes can be noticed as early as 1 month after the initial insult, which can be either secondary to a variety of causes. The absence of any lesion in the DRO pathway does not rule out HOD. MRI changes
include hyperintensity on T2 and FLAIR with the increased size of the inferior olivary nucleus with no restricted diffusion, post-contrast enhancement or blooming. The distinction between left, right, and bilateral HOD serves as a clue to the location of the primary lesion. An accurate diagnosis is necessary since it mainly has a symptomatic management and does not require special intervention.

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**Conflict of interest**

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**References**


