ABSTRACT

BACKGROUND AND PURPOSE
Hypertrophic olivary degeneration (HOD) is an uncommon type of transneuronal degeneration. Case reports and case series described in the literature provide a foundation of our current knowledge of HOD. These reports have described HOD most frequently to be unilateral and occurring in association with lesions in the dentato-rubro-olivary pathway. Our purpose was to evaluate the rate of bilateral versus unilateral HOD in a large case series.

METHODS
A retrospective review was performed to identify patients in which the phrase “hypertrophic olivary degeneration” occurred in the radiology report. A diagnosis of HOD was confirmed on imaging if there was focal hyperintensity on T2-weighted images confined to either or both inferior olivary nuclei.

RESULTS
A total of 102 patients had findings consistent with HOD. Of these, 76% had findings bilaterally. In 44%, a lesion could not be identified to explain HOD. Bilateral HOD was common in both lesional and nonlesional group, though more common in the nonlesional group.

CONCLUSION
This study demonstrates that HOD is frequently bilateral. In slightly over 50% of patients with HOD, a lesion can be identified. In just under 50% patients with HOD, a lesion could not be identified and in these cases HOD was present bilaterally in the majority.

Background and Purpose
Hypertrophic olivary degeneration (HOD) was first described in 1887 by Oppenheim who observed pathological enlargement of the inferior olivary nucleus (ION) at postmortem examination.\(^1\) Subsequently in 1931, Guillain and Mollaret reported an associated pathway composed of the ipsilateral ION, the dentate nucleus of the contralateral cerebellum, and the ipsilateral red nucleus (Guillain-Mollaret triangle).\(^2\) A lesion occurring in this dentato-rubro-olivary pathway (DROP) can result in HOD (Fig 1).\(^2,3\) A variety of causative lesions have been described including infarction, toxic, trauma or surgery, tumor, vascular malformations or hemorrhage.\(^3-11\) Unilateral cases have been reported to significantly outnumber bilateral cases, perhaps due to the fact that previously reported cases of HOD in the literature have focused on identifying HOD secondary to a structural lesion in the DROP.\(^3,12\) Idiopathic cases of HOD have been infrequently described and are felt to be rare with only a single case report in the English literature.\(^9\)

HOD is thought to occur due to transneuronal degeneration when there is loss of synaptic, afferent input to a cell. This is a unique type of degeneration which results initially in hypertrophy of affected neurons. However, over time the hypertrophy resolves and results in subsequent atrophy often with residual hyperintensity on T2-weighted images. Classically, patients present with symptomatic palatal tremor (PT), previously known as palatal myoclonus. This movement disorder can either be present in isolation or in association with progressive ataxia and palatal tremor (PAPT).

Single case reports and smaller case series have been described in the literature and is the foundation of our current knowledge of HOD. As such, the current understanding of HOD is viewed as usually a unilateral process due to lesional involvement in the DROP. Anecdotally, we believe that HOD occurs bilaterally at a higher rate than reflected in the literature. The intent of this study was to evaluate the rate of bilateral versus unilateral HOD in a large case series of patients with HOD.
The dentato-rubro-olivary pathway (Guillain-Mollaret triangle) had findings of HOD bilaterally in 39/45, 87%; mean age 26 years, 68.4%. The dentato-rubro-olivary pathway arises from the dentate nucleus or the superior cerebellar peduncle. In this lesional scheme, bilateral HOD would occur when lesions involve both the red nucleus or the central tegmental tract with involvement of the dentate nucleus or the superior cerebellar peduncle. A lesion in the red nucleus or central tegmental tract would cause ipsilateral HOD. Contralateral HOD occurs when the lesion disrupts the superior cerebellar peduncle or dentate nucleus. In this lesional scheme, bilateral HOD would occur when lesions involve both the red nucleus or the central tegmental tract with involvement of the dentate nucleus or the superior cerebellar peduncle.

Methods
This retrospective study was reviewed and approved by the Institutional Review Board at our institution which is a tertiary referral center. The departmental radiology report database for all head MRI reports performed between 7/1/2002 and 7/1/2011 was queried for cases in which either the phrase “hyperpneuropathy” or “HOD” occurred in both adult and pediatric patients. Given the size of our referral center, the reports of 151,895 patients who underwent clinical head MRIs were initially read and dictated by board certified subspecialty neuroradiologists who practice neuroradiology exclusively. These patients had been scanned on either a 1.5 or 3.0 Tesla closed MRI scanner.

The search of the database returned 123 patients. Fifteen patients were subsequently excluded when review of the report revealed negative results for HOD, that is, when a phrase such as “no evidence of HOD” was used. A neuroradiology fellow and a board certified neuroradiologist reviewed the MR images of the remaining 108 patients for imaging features consistent with HOD as defined below. Based on consensus review, HOD was confirmed if there was focal rounded hyperintensity on T2-weighted images confined to either or both inferior olivary nuclei (ION) which is the diagnostic imaging criteria for HOD that has been reported in the literature. FLAIR images were also reviewed in conjunction with the T2-weighted images. The presence of a lesion in the triangle of Guillain-Mollaret, presence or absence of enhancement and unilateral versus bilateral involvement were recorded. In addition, patients were to be excluded if there was lesion extension into the ION as this would suggest the T2 hyperintensity could be related to the lesion rather than representing true HOD.

A total of 6 patients were excluded after the review. One patient was excluded as a large cavernoma was immediately adjacent to the ION and there appeared to be T2 hyperintensity directly extending into the ION. Two patients were excluded due to the T2 hyperintensity being in the medullary pyramids rather than the ION. Three patients were excluded on the basis of equivocal findings. In these last 3 patients, the reports had raised the diagnostic possibility of HOD but there was subtle if any T2 hyperintensity without any definite enlargement or any lesion in the DROP. Although these could potentially represent HOD during the late atrophic phase, these were excluded since the findings were very subtle and a diagnosis could not be confidently made. After these patients were excluded, there were a total of 166 MRI’s from 102 patients with a diagnosis of HOD made by the initial neuroradiologist and subsequently confirmed that were then included in the study.

Each patient’s electronic medical record was reviewed by a neuroradiology fellow for any documented history of PT or PAPT (either at the time of the MRI or subsequently) that was performed by a neurologist as well as for basic demographic information.

Results
A total of 102 patients (60 males; age range 11-92 years; mean 54 ± 19.1 years) had head MRI examinations meeting the inclusion criteria. A total of 166 MRI’s from these 102 patients were reviewed. The majority of patient’s (68) had a single MRI exam available for review.

Seventy-eight patients (76%; mean age 57.7 years [range 11-92]; male = 44 [56.4%]) had findings of HOD bilaterally presenting both symmetric and asymmetric in size and signal. Two patients with clearly unilateral HOD on the initial MRI developed bilateral asymmetric findings on subsequent exams, 8 months and 5 years after initial MRI, respectively (Fig 2). Neither of these patient’s had an identifiable lesion within the DROP. The T2 hyperintensity and inferior olive hypertrophy was greatest on the originally involved side with asymmetric development of contralateral findings. Of note, in the second patient, they initially had unilateral PT which subsequently became bilateral when the follow-up MRI demonstrated bilateral findings of HOD.

Bilateral HOD findings were common in both the group of patients with a lesion (“lesional”) (n = 39/57, 68%; mean age 45.1 years [range 11-81]; female = 20 [51.3%]) (Figs 3, 4, and 5) and the nonlesional (n = 39/45, 87%; mean age 61.9 years [range 15-82]; male = 26 [68.4%]) group (Figs 2 and 6), though more commonly seen in the group of patients without a lesion (“nonlesional”) in the DROP (P < .03) (Table 1). Overall, HOD was most frequently seen in conjunction with a discrete lesion within the DROP and a lesion was...
Fig 2. MR images of a 44-year-old female without an identifiable lesion in the DROP. (A) Axial spin echo T2-weighted MR image from the initial scan demonstrates enlargement and T2 hyperintensity of the right ION (arrow) and a normal appearance to the left ION. (B) Eight months later on follow-up imaging, axial spin echo T2-weighted MR image demonstrates involvement of the left ION (dashed arrow) but the configuration is asymmetric with the right ION (arrow) larger and having greater T2 hyperintensity. No lesion was visualized within the DROP on any of the patient’s MRIs.

Fig 3. Fifty-year-old male with multiple surgeries for recurrent midbrain epidermoid cyst. (A) and (B) Axial fast spin echo T2 and FLAIR MR images obtained 1 year after two partial resections of a recurrent midbrain epidermoid cyst demonstrate marked abnormal increased signal and enlargement of the ION bilaterally.

identified in 56% (57/102; mean age 47.7 years [range 11-81]; male = 30 [52.6%]) of patients. Review of these lesions demonstrated a wide variety of causes for disruption of the DROP and subsequent HOD. The most common lesions resulting in HOD include surgery/trauma in 32% (18/57), a vascular malformation in 21% (12/57), and infarction in 16% (9/57) of cases (Figs 4 and 5 and Table 2). The remaining 31% (18/57) of the lesional cases had a spectrum of causes including demyelination, tumor, or hemorrhage without MR imaging evidence for a vascular lesion. In 44% (45/102) of the patients with MRI findings of HOD, a definite lesion could not be identified within the DROP to explain the HOD (Figs 2 and 6). None of the cases of HOD demonstrated enhancement.
The presence of PT was more common in the nonlesional group occurring in 49% (22/45) compared with 23% (13/57) of patients with a lesion within the DROP ($P < .004$). In the patients without a demonstrable lesion, progressive ataxia and palatal tremor (PAPT) was the most common clinical diagnosis in 22% (10/45) of patients (Fig 6). Of note, all of the cases of PAPT demonstrated bilateral findings of HOD. In addition, of the bilateral nonlesional cases there was a single diagnosis of multiple system atrophy and of olivopontocerebellar atrophy.

**Discussion**
As initially described by Guillain and Mollaret, the connections of the DROP run between the contralateral dentate nucleus of the cerebellum, the ipsilateral red nucleus of the midbrain, and the ipsilateral ION of the medulla. The afferent connection from the dentate nucleus to the contralateral red nucleus is made via the superior cerebellar peduncle. At this point these fibers then decussate within the brachium conjunctivum and enter the red nucleus. The afferent fibers from the red nucleus pass through the central tegmental tract and into the ION. The efferent connection between the ION and the contralateral dentate nucleus is made via the inferior cerebellar peduncle. HOD is thought to occur when there is a disruption of the afferent pathways to the ION (dentate nucleus to red nucleus and red nucleus to ION) and results in transneuronal degeneration. A lesion in the efferent pathway between the ION and dentate nucleus via the inferior cerebellar peduncle...
Seventy-year-old female who presented with progressive ataxia and palatal myoclonus diagnosed with PAPT syndrome, sporadic type. (A) and (B) Axial spin echo T2 and FLAIR MR images, respectively, demonstrate increased signal and enlargement of both ION. The conspicuity of the increased T2 signal is better visualized on spin echo T2 rather than FLAIR. No lesion was identified in the DROP.

Increased prevalence of bilateral HOD in this series may be due to a referral bias at a tertiary referral center or a population otherwise skewed toward patients with PAPT which is typically a bilateral process. Increased prevalence of bilateral HOD in this series may be due to a referral bias at a tertiary referral center or a population otherwise skewed toward patients with PAPT which is typically a bilateral process. Included in referral bias is passage of additional time for signs, symptoms, and imaging findings to progress into a more coherent picture. Small symmetric lesions may escape detection due to technical and human factors issues including posterior fossa MRI artifacts of CSF flow pulsation and field inhomogeneity shading, location of the abnormality on the first or last images in a series, and the reliance on asymmetry to prompt recognition of a potential abnormality.

The cases of lesional HOD did lend support to the presence of the DROP. For example, in Figure 5, the patient had infarcts of both red nuclei. In this case, HOD is seen bilaterally, as would be inferred. Likewise, in Figure 4, the pontine cavernoma is to the right of midline which would affect the traversing CTT resulting in ipsilateral HOD of the right ION, as would be expected. In the case of the multiply recurrent midbrain epidermoid cyst (Fig 3), this was a midline lesion. HOD was seen bilaterally, as would be predicted.

In the cases of bilateral HOD, the findings in the ION were, on occasion, found to be asymmetric in size and shape. Included in this cohort were two patients whose MRI exams demonstrated hypertrophy of the ION initially unilaterally and subsequently became bilateral (Figs 4 and 5) with an asymmetric appearance. Asynchronous timing may account for other cases with an asymmetric appearance.

As this study demonstrates, imaging findings of HOD can be present without a clearly defined lesion in the above described pathway. There is only one report of idiopathic HOD within the English-language literature to our knowledge. In our series, we identified 45 patients without a visualized lesion in the DROP. Within the group of patients without a lesion in the DROP, the largest single clinical diagnosis was PAPT. The patients with the clinical diagnosis of PAPT were all found to having findings of HOD bilaterally. PAPT is a condition in which there is progressive ataxia, both sporadic and familial forms, with additional cerebellar features. These patients often develop visual disturbance, dysarthria, dysphagia, arm ataxia, and difficulty walking and standing. This syndrome is typically idiopathic. Structurally there may be brainstem and cerebellar atrophy as well as hypertrophy of the ION. Familial forms of PAPT usually have normal ION and this is thought to be a functional, rather than structural, abnormality resulting in PT.

PT is divided into two categories: essential and symptomatic PT. Essential PT is defined as occurring in the setting of a structurally normal MRI. Symptomatic PT is defined as occurring when there is a definable lesion in the brainstem or cerebellum. In patients with symptomatic PT, HOD is typically present.
However, the lack of PT does not exclude the diagnosis of HOD. In our series, only 33% of all patients with findings of HOD had PT. Of those who had a definable lesion in the DROP, only 22% had PT. Since many of these patients had other clinical issues (eg, trauma, recent neurosurgery for posterior fossa tumors, etc) it is possible that PT was not aggressively sought on physical exam and could have been overlooked since it can be a subtle physical exam finding. In our series, PT presented more commonly in patients with HOD in which there is no demonstrable lesion in the DROP. Of the 45 patients without a lesion in the DROP, 10 of these patients had the clinical diagnosis of PAPT.

Further study is warranted for the nonlesional cases, especially those without PAPT. In these cases it would be useful to determine if there are lesions outside of the triangle of Guillain-Mollaret, that could produce HOD, potentially via pathways which are either separate from or secondarily affect this triangle. Additional investigation of cases of bilateral HOD may help clarify the degree to which these occur in an asynchronous fashion and/or asymmetric pattern.

This study has several limitations. This is a retrospective review and is limited as such. Cases were identified from a cohort of patients in whom HOD had been reported as a diagnostic possibility by a neuroradiologist. Therefore, there exists the potential for having missed cases not appreciated by the initial neuroradiologist, which could include subtle cases or those without a classic history of PT. The study is also limited in that the reference standard for the diagnosis of HOD was the opinion of the neuroradiologists, based upon the MRI appearance of the ION. Although this is an imperfect method of diagnosis, a pathologic diagnosis is typically not feasible in this disorder. There may also be a referral bias since we are a tertiary care center.

**Conclusion**

This study demonstrates that HOD is frequently bilateral. HOD may present as a unilateral process or, more commonly, a bilateral process which can be asymmetric in signal and shape and may be asynchronous. In slightly over 50% of our patients with HOD a lesion was identified in the DROP. Surgery or trauma, infarction, and vascular lesions were the most common in our cohort. In just under 50% patients with HOD, no lesion was identified in the DROP; HOD was present bilaterally in the majority of these cases.

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**References**


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