Letter to the Editor

# Hypertrophic olivary degeneration: a description of four cases of and a literature analysis

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## Introduction

Hypertrophic olivary degeneration (HOD) is a transsynaptic degeneration of the nervous system caused by lesions of the dentato-rubro-olivary pathway (DROP) (1). Typically, HOD occurs when disease in the midbrain, pons, or cerebellum interrupts the connection between the inferior olivary nucleus (ION) and the dentate or red nucleus. Bleeding, infarction, tumors, trauma, and demyelination can all lead to an occurrence of the connection between the dentate nucleus or red nucleus and the ION is interrupted (2). However, the exact mechanism of HOD has yet to be clarified.

In most cases of unilateral HOD, the etiology can be investigated, but more than half of cases of bilateral HOD have no obvious cause. Current studies have found that mitochondrial dysfunction may form the basis of the pathogenesis of bilateral HOD. HOD has characteristic clinical manifestations, which include palatal tremor, Holmes tremor, nystagmus, and cerebellar ataxia (3). If these symptoms occur in patients with midbrain, pons, or cerebellar injuries during treatment or, after a period of improvement, the possibility of HOD should be considered.

Because HOD has characteristic imaging findings, magnetic resonance imaging (MRI) can be used to confirm the clinical impression. MRI is therefore the preferred imaging method for this disease and can show signal changes in the ION. To date, there have been a limited number of reports on HOD, despite many clinical/imaging findings. However, it is not difficult to diagnose HOD based on the characteristic imaging manifestations of the condition and the clinical manifestations of the patient. In this paper, four cases of HOD diagnosed in The Second Hospital of Hebei Medical University are analyzed, with a view to improving our understanding of the condition. Furthermore, several challenges remain in the treatment of HOD, for which approaches are limited to symptom relief. In this paper, four cases of HOD diagnosed in our hospital are analyzed with a view to improving our understanding of HOD and exploring potential new treatments for the disease.

## Case presentation

Case 1, a 75-year-old female, was admitted to our hospital on July 29, 2020, with "sluggishness, tremor of the right hand for 3 years, and aggravated involuntary movement of the mouth and tongue for 6 months". The patient had previously been treated at another hospital in 2013 for brainstem bleeding, which left her with dizziness. The patient also had a history of arterial hypertension and coronary heart disease regularly uses drugs to treat hypertension and coronary heart disease. In 2015, the patient developed bradycardia with "rubbing pill-like" shaking of the right hand with no obvious cause. She gradually acquired a stiff facial expression, taking the first step and turning are difficult, and decreased speech fluency, although she reported no abnormal sensation. The patient visited another hospital and was diagnosed with Parkinson's disease. She was treated with oral administration of levodopa and benserazide hydrochloride tablets, benzhexol

hydrochloride tablets, and oxiracetam capsules as a long-term treatment, and the management of her condition was acceptable. However, in July 2017, aggravation of the above symptoms occurred and was accompanied by involuntary movements of the mouth and tongue, at a frequency of 4–6 Hz. The patient felt no stiffness in her limbs and did not pay attention to these symptoms. In the subsequent 6 months, the involuntary mouth and tongue movements worsened, and the patient began to experience coughing while drinking water. She received further diagnosis and treatment in January 2018. A head MRI scan conducted at this time (*Figure 1*) revealed multiple cavernous malformations in the right dorsal pons, the right deep cerebellum, and the junction between the left middle cerebellar peduncle and the cerebellum (*Figure 1A*). The patient received an anti-Parkinson's disease treatment of levodopa, benserazide hydrochloride tablets, and benzhexol hydrochloride tablets, plus other comprehensive treatments, such as nerve nutrition. Her symptoms subsequently improved. However, in July 2020, her symptoms of dizziness and a choking cough while drinking water became aggravated once again. A physical examination of the patient's nervous system showed persistent, involuntary, and rhythmic tremors in her palate and pharynx. The result of a depression drinking water test was level 3, with horizontal and oscillating nystagmus. An MRI scan of the head and neck revealed round-like different intensities signals in the pons, the right cerebellar hemisphere, and the bilateral middle cerebellar peduncles; further, the ION of the medulla oblongata was slightly enlarged with slightly hyperintense T2 and fluid-attenuated inversion recovery (FLAIR) signals (*Figure 1B*,*1D*). A subsequent diagnosis of HOD was made. After consideration of her medical history, the patient was given dobarazid tablets and benhyisol hydrochloride tablets orally. This approach nurtured the patient's nerves and improved the dizziness she had been experiencing. On discharge, physical examination showed that the nystagmus swing of the patient was smaller than that on admission, and the result of the drinking water test of the depression field was level 2 at this time. The nystagmus amplitude lessened, and the patient's liquid swallowing score improved.

Case 2 was a 35-year-old female patient. In February 2019, she presented with "unstable walking, slurred speech, ataxia, involuntary head and upper body tremor." Computed tomography (CT) scans in a local hospital indicated brainstem space-occupying lesions. In May 2019, the patient visited Beijing Tiantan Hospital, Capital Medical University. After relevant examinations had been carried out, a pons and midbrain glioma resection was performed, with postoperative pathology results showing astrocytoma. More than 2 months later, the patient received further treatment in The Second Hospital of Hebei Medical University. Neurological examination showed that the patient spoke slowly, the head and upper body shook involuntarily, the left eyeball slightly clustered, abduction difficulties, walking instability, left hand finger-nose test instability, poor alternating movement test. In addition, her alternating movement test result was negative. After consultation with family members, the decision was made to treat the patient with radiotherapy and concurrent chemotherapy, both of which were completed successfully. At the end of the treatment, the involuntary shaking of the patient's head and upper body continued, her walking coordination was poor, and she was unable to walk normally. However, the patient did not develop any new symptoms between the end of the treatment and her next examination in the outpatient department of our hospital on May 8, 2020, when an MRI of the head and neck revealed a symmetrical, slightly hyperintense T2 shadow in the medulla oblongata, but no obvious enhancement was observed (*Figure 2*).

Case 3 was a 50-year-old male patient. He had been treated in a local hospital due to a sudden brainstem hemorrhage 2 years previously (November 2018), which resulted in dyskinesia of the limbs on the left side and slurred speech. Seven months later (June 2019), the patient's left-limb weakness worsened. His walking was unsteady, and he experienced coughing while drinking fluids and complained of oscillopsia. A neurological examination showed vertical nystagmus. A head MRI scan revealed that the right part of midbrain-pons changed after hemorrhage; The volume of ION in the right part of medulla oblongata increased, showing T2 hyperintense and FLAIR hyperintense (*Figure 3*). A combined treatment of tiapride hydrochloride and clonazepam appeared to lessen the intensity of the nystagmus, and residual nystagmus was noted only in upgaze.

Case 4, a 57-year-old male, was admitted to the Second Hospital of Hebei Medical University on April 26, 2020, after experiencing progressive dizziness over a 5-year period and an unsteady gait of recent (1 month) onset. Six years earlier, the patient had had an ischemic brainstem stroke. Following the event, the patient was initially stable, but 3 years later, he developed new weakness and blurred vision. A neurological examination revealed left finger-nose test

 

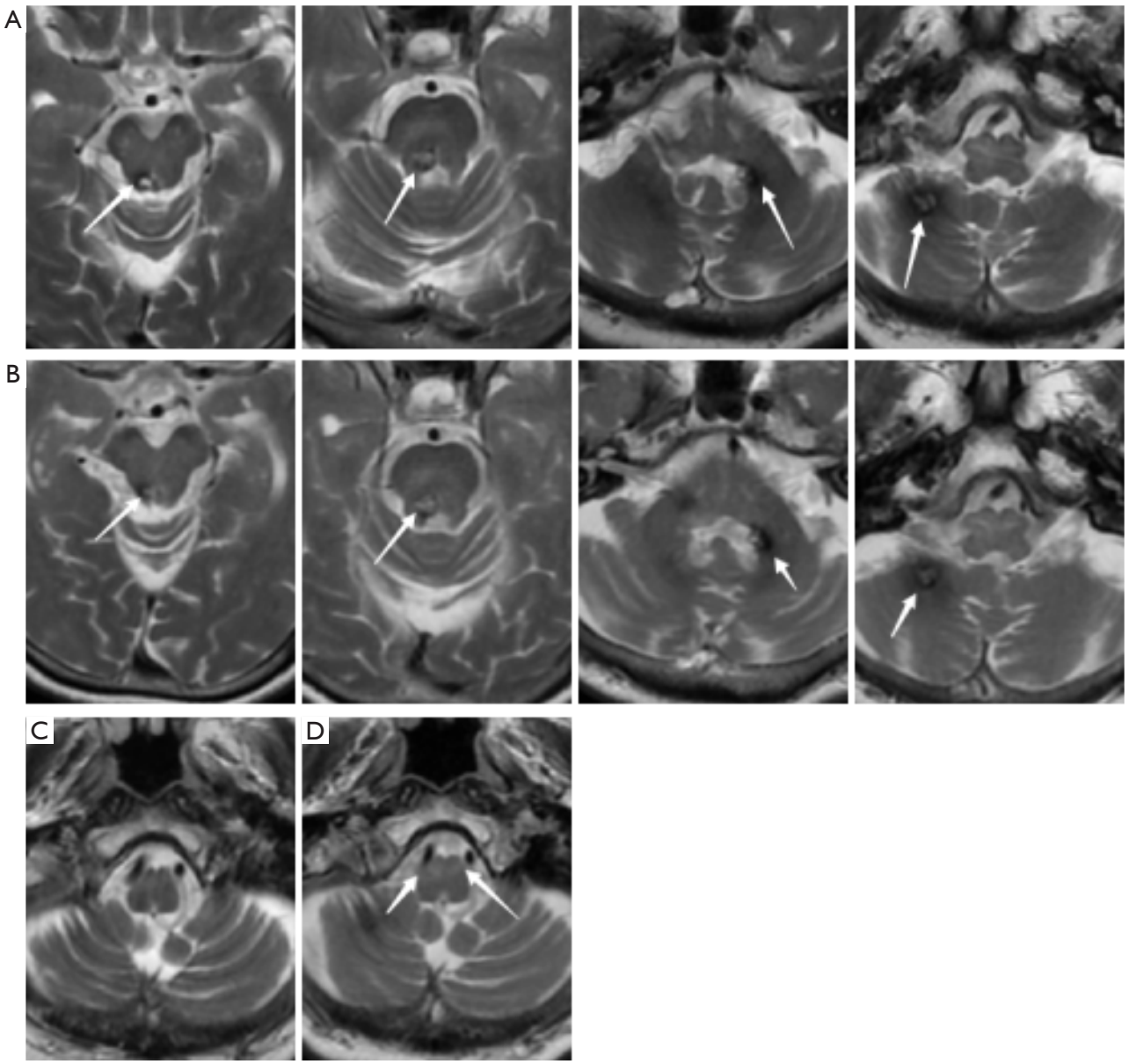


**Figure 1** Imaging data of case 1. (A) MRI scan from January 26, 2018, showing multiple cavernous malformations (arrows) in the pons and cerebellum. (B) MRI scan from July 30, 2020, showing multiple cavernous malformations (arrows) in the pons and cerebellum. (C) MRI scan from January 26, 2018, showing no abnormalities in the ION. (D) MRI scan from July 30, 2020, showing a slight enlargement (arrows) of both sides of the ION with hyperintense T2 signals. MRI, magnetic resonance imaging; ION, inferior olivary nucleus.

and heel-knee-tibia test were unstable, Romberg sign was positive. MRI showed hypertrophy of the inferior olive (*Figure 4*). The patient was treated with circulation support; his condition improved slightly, and he was subsequently discharged. Following the patient's discharge from the hospital, his instability while walking was slightly improved, but his movement coordination remained poor. Over time, his unsteadiness worsened, and the inferior olive signal intensity on MRI increased (2018); surprisingly, a 2020 MRI showed a decrease in inferior olive volume (*Figure 4*).

The baseline data of the four patients are shown in *Table 1*.

This study was conducted with approval from the Ethics Committee of Shunyi Teaching Hospital of Capital Medical University. All procedures performed in this study were in

 

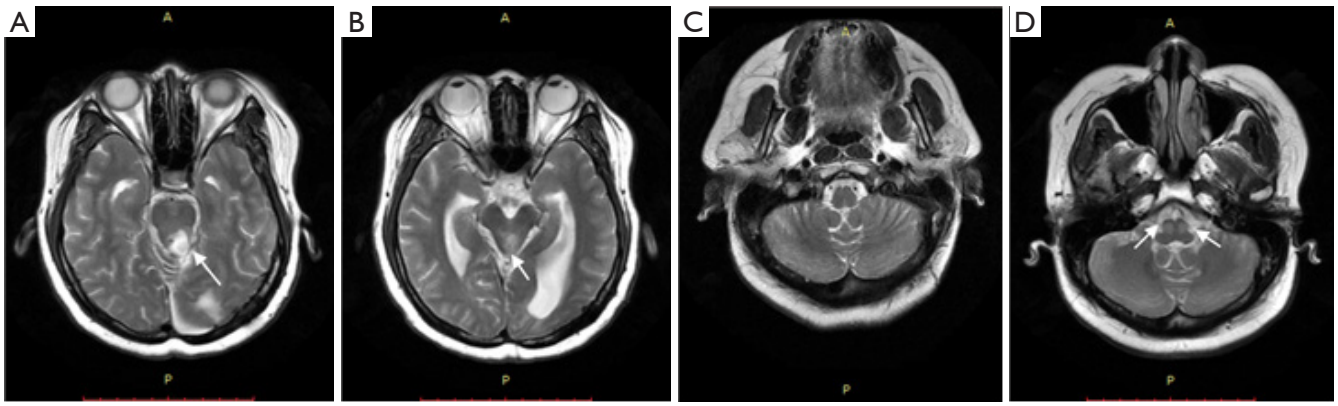


**Figure 2** Imaging data of case 2. (A,B) MRI scans from May 8, 2020, showing changes in the pons and midbrain (arrows) following surgery involving the bilateral red nucleus and the central tegmental tract. (C) MRI scan from July 18, 2019, showing no abnormality in the ION. (D) MRI scan from May 8, 2020, showing enlargement (arrows) of both sides of the ION and hyperintense signals on T2WI. MRI, magnetic resonance imaging; ION, inferior olivary nucleus; T2WI, T2-weighted imaging.

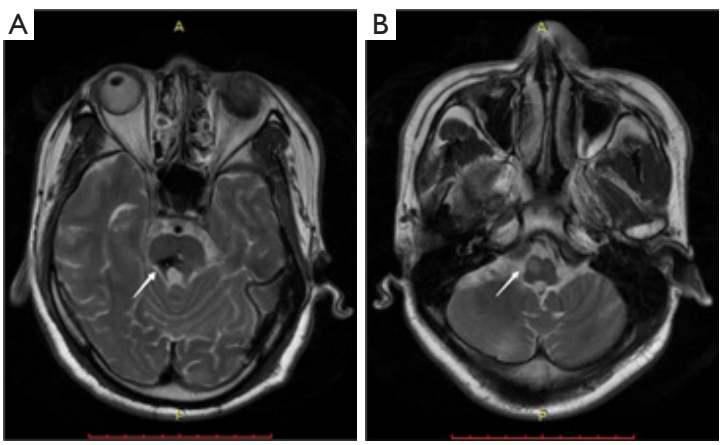


**Figure 3** Imaging data of case 3. (A) Changes following a pontine hemorrhage (arrow) in the right-central tegmental tract. (B) Enlargement (arrows) of the right ION and hyperintense signals on T2WI. ION, inferior olivary nucleus; T2WI, T2-weighted imaging.

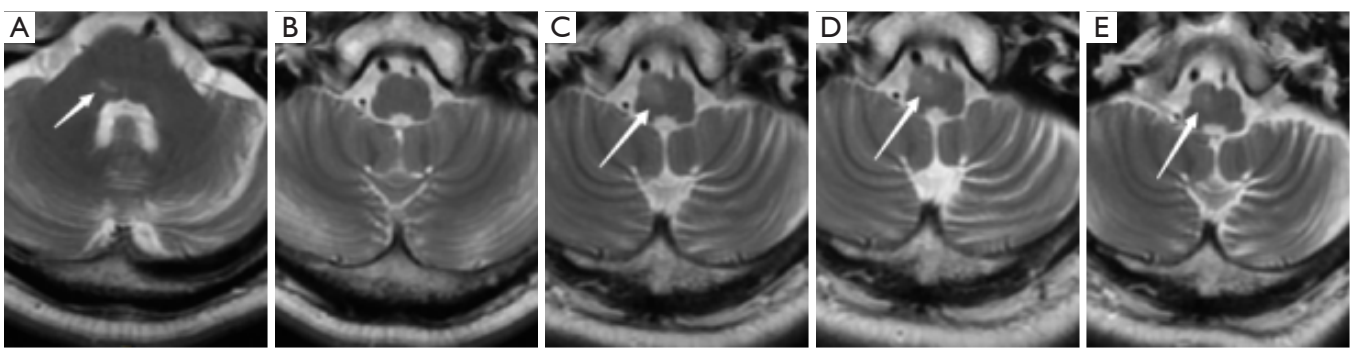


**Figure 4** Imaging data of case 4. (A,B) MRI scans from September 8, 2014, showing right pontine infarction (arrows); no abnormality was found on any side of the ION. (C) MRI scans from November 3, 2017. (D) MRI scan from May 4, 2018. (E) MRI scan from April 27, 2020, showing enlargement of the left ION with hyperintense T2 signals (arrow). MRI, magnetic resonance imaging; ION, inferior olivary nucleus.

 

**Table 1** Baseline data of the 4 patients

| No. | Gender | Age, years | Protopathy | Time from primary onset to symptom onset, months | Clinical feature |
|---|---|---|---|---|---|
| 1 | Female | 75 | Cavernous hemangioma of the brain stem | 30 | Palatal nystagmus |
| 2 | Female | 35 | Brainstem glioma | 12 | Ataxia, tremor of limbs |
| 3 | Male | 50 | Intracerebral hemorrhage in brain stem | 7 | Dizziness, ataxia |
| 4 | Male | 57 | Cerebral stem infarction | 38 | Dizziness, ataxia |

accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of their case reports and any accompanying images. A copy of the written consent form is available for review by the editorial office of this journal.

## Discussion

HOD is a unique form of transsynaptic degeneration that occurs secondary to damage to the DROP. This neuron-contact pathway was first described by Guillain and Mollaret in 1931 and is consequently referred to as the Guillain-Mollaret Triangle (GMT). On one side, the dentate nucleus crosses the ipsilateral superior cerebellar peduncle at the midbrain level to the contralateral red nucleus. It then connects with the ipsilateral ION through the central tegmental tract. The fibers from the ION run to the contralateral inferior cerebellar peduncle, project onto the corresponding cerebellar hemisphere cortex, and then connect to the dentate nucleus. This pathway is considered to be the pathological basis of HOD (4). The clinical manifestations of HOD vary, but it has characteristic imaging features. In 2000, Goyal *et al.* (5) summarized the changes of in HOD MRI findings by conducting a meta-analysis. This present study analyzed four cases of HOD diagnosed in the Second Hospital of Hebei Medical University. The clinical manifestations and imaging features of these cases were consistent with those previously reported.

The etiologies of HOD vary and include hemorrhage, infarction, tumors, trauma, demyelination, and surgery. Although other primary diseases may cause HOD, the most common cause is vasculopathy, including vascular malformations, cerebral hemorrhage, and infarction (6). In the present study, the causes of cases 1, 3, and 4 were pontine cavernous hemangioma, cerebral hemorrhage, and cerebral infarction, respectively. In case 1, the interval between the cavernous hemangioma and hypertrophy of the ION was 30 months. A comparison of the MRI results before and after January 2018 to July 2020 revealed that the shape of the cavernous hemangioma in this patient had changed dynamically. The results suggested that a medium-term hemorrhage had led to brain injury and HOD. Similarly, Rosenblum *et al.* (7) reported sudden progression of lesions in a patient with midbrain pontine cavernous hemangioma which had been stable for several years previously, which led to falls, dysarthria, and headaches. Imaging at the 10-month follow-up revealed enlargement of the left ION of the medulla oblongata with a hyperintense T2 signal and a reduction in the cavernous hemangioma. These results indicated a medium-term hemorrhage and the intermittent development of HOD. In cases 3 and 4, the GMT was damaged by a brainstem hemorrhage and infarction, respectively, and HOD occurred.

Tumors are also a major pathogeny of HOD. Posterior cranial fossae are typically located near the DROP, and tumors lesions may cause secondary neurodegeneration of the ION. The clinical symptoms of HOD occur slowly over several months and may potentially be missed in patients with progressive neuro-tumor diseases. Schaller-Paule *et al.* (8) analyzed 12 patients with nervous system tumors and HOD, all of whom had developed HOD after tumor treatment. Although the posterior cranial fossa tumors affected the DROP overall, the patients did not present with signs of HOD on MRI images until they received treatment that affected the DROP. On average, the signs of HOD could be observed on MRI 6 months after the operation. Schaller-Paule *et al.* (8) noted that therapeutic lesions in the DROP were associated with the occurrence of HOD in a group of patients with neuro-tumors. In contrast, in a series of case studies, Hirano *et al.* suggested that HOD may occur due to the tumor itself or because

 

of the treatment (9). Their study included patients with posterior cranial fossa masses of non-tumor origin, three of whom developed HOD before undergoing neurosurgery. This difference in results may be explained by the small sample size of both studies and the different (non-tumor) etiology of the cases reported by Hirano *et al.* In case 2, the patient's symptoms of "unstable walking, unclear pronunciation, ataxia, and involuntary vibration of the head and upper body" progressed slowly. However, no changes in the ION were observed in the initial imaging data, whereas at the 12-month follow-up, the MRI scans exhibited signs of HOD. This finding was consistent with those reported by Schaller-Paule *et al.* (8). In a retrospective study by Avula *et al.* (10), MRI data of 48 children undergoing resection of posterior fossa tumors were analyzed; HOD was found in 15 children, while 10 had combined postoperative pediatric cerebellar mutism (POPCMS), a recognized complication of posterior fossa tumor resection. Further analysis showed a significant association between POPCMS and bilateral HOD, both of which are related to GMT pathway injuries. Therefore, avoiding injury to the GMT structure as much as possible in posterior fossa tumor resection may play a positive role in reducing postoperative complications.

The exact mechanism of HOD remains unclear. At present, the mainstream view is that it is related to the de-inhibition of the ION. The afferent fibers of the ION are divided into two groups: the first group comprises the inhibitory nerve fibers of the dentate-olivary nucleus, while the second comprises excitatory nerve fibers, which project onto the ION and jointly regulate the normal activity of neurons. When the inhibitory afferent fibers are damaged, the excitatory afferent impulses become excessive, leading to gradual hypertrophy of neurons and glial cells (11). However, not all patients with HOD present with damage to the DROP. In two recently published large-scale studies, GMT lesions were not found in the imaging data of 44% of patients with HOD (12). Although there was no clear explanation for this finding, the researchers believed that the lesions inside or outside the GMT were too small to be detected by MRI; however, this may not be the case.

There are two types of HOD: unilateral and bilateral. In most cases, the etiology of unilateral HOD can be investigated, and there is a correlation between the affected side of the ION and the location of the lesion. In contrast, there is no obvious cause for bilateral HOD in more than half of cases. Gu *et al.* similarly revealed that most patients with HOD who had no structural lesions in the DROP had bilateral HOD (12,13). These results suggest that the etiology of unilateral HOD may differ from that of some bilateral HOD cases. In general, unilateral HOD occurs secondary to a lesion involving the DROP. Three main patterns are ascribed to the syndrome: (I) ipsilateral HOD caused by a primary lesion involving the unilateral midbrain red nucleus or the central tegmental tract; (II) contralateral HOD induced by a primary lesion involving a unilateral dentate nucleus or the superior cerebellar peduncle; (III) Bilateral HOD is secondary when the disease involves bilateral red nucleus, bilateral central tegmental tract, bilateral dentate nucleus, or both central tegmental tract and superior cerebellar peduncle (3). In the present study, in case 1, hemorrhage of the cavernous hemangioma in the right cerebellar hemisphere involved the right dentate nucleus, which may have induced left HOD, and hemorrhage of the cavernous hemangioma in the right tegmental part of the pons caused ipsilateral HOD; therefore, bilateral HOD was observed on the MRI scan. In case 2, the lateral red nucleus and the central tegmental tract were involved after resection of the pons and midbrain gliomas; as a result, bilateral HOD was induced. In case 3, a pontine hemorrhage involving the right-central tegmental tract induced ipsilateral HOD. In case 4, the right pontine lacunar infarction involved the right-central tegmental tract, causing ipsilateral HOD. All four cases were consistent with the anatomical and physiological basis of HOD.

Some gene mutations have been found in patients with bilateral HOD. The polymerase gamma (POLG) gene, which encodes mitochondrial DNA polymerase, has been identified as the pathogenic gene of progressive external ophthalmoplegia (14). POLG mutations are known to lead to more heterogeneous clinical phenotypes, including bilateral HOD (15). The pathogenic gene of Leigh syndrome, a severe neurodegenerative disease, is SURF1, and bilateral HOD is a characteristic finding in patients with SURF1 mutations (16,17). The TTC19 nonsense mutation leads to a deficiency in mitochondrial respiratory chain complex III and neurodegeneration, and some patients with the TTC19 mutation show bilateral HOD on MRI scans (18). Recently, a brain MRI scan of a male patient with adult-onset mitochondrial disease associated with an AIFM1 mutation was reported to have exhibited bilateral ION hyperintense lesions (19). Given that all these genes are related to mitochondria, mitochondrial dysfunction may be the basis of the pathogenesis of bilateral HOD.

The core clinical characteristic of HOD is the recurrence of dizziness, blurred vision, nystagmus, diplopia, palatal tremor, limb tremor, ataxia, or other symptoms during

 

the treatment or improvement of the primary disease. A palatal tremor in HOD, referred to as symptomatic palatal tremor, is a sustained, involuntary, and rhythmic tremor of the soft palate, uvula, pharynx, and larynx muscles at a frequency of 1–3 Hz, which most often affects the levator veil palatini muscle. The condition can produce a clicking sound and rarely affects the larynx (20). A previous study considered palatal myoclonus as the primary core sign of HOD; however, an increasing number of clinical trials have revealed that palatal myoclonus is not found in all HOD cases, nor is it unique to HOD (6). Palatal tremor synchronous with nystagmus is known as oculopalatal tremor (OPT). PT/OPT may occur in patients with destructive lesions in the GMT, with PT/OPT and lower olivary hypertrophic degeneration occurring weeks or months after structural brainstem or cerebellar lesions. Additionally, PT/OPT and progressive cerebellar ataxia occur in patients with no structural brain stem or cerebellar lesions. This syndrome of progressive ataxia and palatal tremor may be sporadic or familial. Among the family forms without hypertrophic degeneration of lower olive, the main reported causes are Alexander's disease, polymerase γ mutation and spinocerebellar ataxia type 20. However, whether these conditions are related to the specific degeneration of the DROP remains to be determined (21).

## Patterns of ocular oscillation in OPT

Kim *et al.* (22) identified oculopalatal myoclonus as the type of nystagmus in OPT, and found that it was correlated with MRI scan changes in the ION. Mixed torsional vertical oscillating nystagmus in OPT is considered to be a marker of unilateral brainstem injury, and symmetrical vertical nystagmus is considered to be a marker of bilateral disease. Of the four cases described in this study, only case 1 developed symptomatic palatal tremor; case 2 mainly presented with ataxia and limb tremor, while cases 3 and 4 presented primarily with dizziness and ataxia. In a recently published cohort study, ataxia was the most common symptom of HOD (23).

MRI is the preferred imaging method for HOD and can show signal changes in the ION. According to the volume of the ION and changes in the T2-weighted imaging (T2WI) signal, HOD can be divided into three stages. The first stage occurs approximately 1 month after onset, with T2WI hyperintense signals in the ION but no increase in the ION volume. The second stage occurs 4 to 6 months after an injury, with hyperintense signals present on the T2WI of the ION and an increase in the ION volume, which peaks at 8.5 months after injury. The third stage occurs 3 to 4 years after an injury, during which the ION recovers its normal volume or atrophies but maintains hyperintense signals on T2WI, which can last for several years (5,24). However, there are no quantitative criteria for evaluating this hypertrophy/atrophy. In case 1 in the present study, signs of HOD were found on MRI scans 30 months after the discovery of the cavernous hemangioma, and the medulla oblongata diameter was larger on the MRI scan conducted in 2020 than on a scan completed in 2018. The reason for the 30-month gap is that the patient's cavernous hemangioma was stable during the initial period without any signs of a brain injury. In cases 2 and 3, the HOD MRI findings were observed 12 and 7 months after the primary lesion, respectively, and in case 2, the medulla oblongata diameter was larger on the MRI scan conducted in 2020 than on the scan conducted in 2019. In case 3, the diameter of the right side of the medulla oblongata was larger than that of the left side. Case 4 developed HOD-related symptoms 31 months after the primary lesion, and the symptoms were repeatedly aggravated in the 3 years that followed. Multiple MRI examinations revealed that its diameter was 9.16 mm when the hypertrophic ION was first detected. A year later, MRI showed that the diameter of the medulla oblongata had stayed approximately the same. Three years later, the volume of the ION was still larger than that on the contralateral side, but its diameter had reduced to approximately 8.18 mm. During this period, the hypertrophic ION showed hyperintense T2 signals.

In practice, HOD needs to be distinguished from corticospinal tract degeneration caused by infarction, inflammation, tumors, or demyelination. The absence of contrast enhancement helps to distinguish HOD from tumors, infection, and inflammation, while the enlargement of the ION is helpful for distinguishing it from chronic cerebral infarction or multiple sclerosis. Typical primary diseases in the GMT and typical delayed clinical manifestations such as OPT, ataxia, and non-enhanced hyperintense T2 signals in the ION, with or without enlargement of the ION volume in an MRI scan, are the key points of HOD diagnosis.

There are still many challenges in the treatment of HOD, with current approaches being limited to symptomatic relief. In the cases described above, symptomatic treatment was often adopted to relieve symptoms. Varying degrees of symptomatic relief have been reported using different drugs such as clonazepam, levodopa, and dopaminergic agents.

 

Levetiracetam, a new antiepileptic drug that modulates the dopaminergic system, has been shown to reduce tremors, dyskinesia, and myoclonus (2). There have also been successful cases of local injection of botulinum toxin for the treatment of soft palate clonus, which is difficult to control with drugs (25-27). Moreover, one study reported that the application of deep-brain stimulation in refractory cases achieved positive results (2). Also, Hornyak *et al.* (28) reported that carbamazepine, clonazepam, and diazepam were effective in relieving the symptoms of symptomatic palatal tremor caused by HOD after surgery on brainstem cavernous hemangiomas.

## Conclusions

HOD is a rare transsynaptic degeneration that is secondary to diseases affecting the DROP and has varying clinical manifestations. The syndrome has characteristic imaging findings, which are non-enhanced hyperintense T2 signals and are often accompanied by an increase in the volume of the ION. Because a patient's clinical manifestations may be typical, clinicians and radiologists should pay attention to the imaging features of the syndrome. Clinicians need to improve their understanding of HOD to better predict and diagnose the condition. Further, more clinical studies should be carried out to provide patients with more effective treatment.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1048/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted with approval from the Ethics Committee of Shunyi Teaching Hospital of Capital Medical University. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.



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