Bilateral Hypertrophic Olivary Degeneration after Pontine Hemorrhage: A Case Report

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Author contributions: Zheng B, Wang J, Huang XQ and Gu GF reviewed the literature and contributed to manuscript drafting; Chen Z analyzed and interpreted the imaging findings; Luo XJ was responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Supported by: Scientific Research Project of Sichuan Hospital Management and Development

Abstract

BACKGROUND
Hemorrhage lesions may lead to bilateral hypertrophic olivary degeneration (HOD) through interruption of the dentato-rubral-olivary pathway. The pathological features of HOD are unusual neuronal trans-synaptic degenerative changes.

CASE SUMMARY
A 56-year-old female was admitted to our hospital because her lower extremities and left upper ones were unable to move for 3 mo, and the swelling of her right lower extremities became worse 3 days ago. She had a hypertension history. Her characteristic clinical manifestations are palatal myoclonus and nystagmus. The patient’s magnetic resonance imaging (MRI) results showed that she had bilateral HOD after an acute pontine hemorrhage. She was given symptomatic and supportive treatment. The gabapentin, the memantine and the trihexyphenidyl were taken twice a day each. The rehabilitation and psychotherapy were implemented. After 3 months of treatment, her eye symptoms improved.

CONCLUSION
Bilateral HOD is a rare phenomenon after pontine hemorrhage. The key to diagnosis lies in the clinical manifestations and MRI results.

Key Words: Hypertrophic olivary degeneration; Pontine hemorrhage; Dentato-rubral-olivary pathway; Magnetic resonance imaging; Quadriplegia; Case report

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Core Tip: Bilateral hypertrophic olivary degeneration (HOD) after pontine hemorrhage is rare. The clinical manifestations and MRI results of HOD are varied, which make it important to monitor the patient and identify the changes in MRI results. Generally speaking, the mechanism leading to HOD is still unclear, and the effect of symptomatic treatment for some patients is not satisfactory.

Citation: Zheng B, Wang J, Huang XQ, Chen Z, Gu GF, Luo XJ. Bilateral Hypertrophic Olivary Degeneration after Pontine Hemorrhage: A Case Report. World J Clin Cases 2022; 10(1): 289-295
URL: https://www.wjgnet.com/2307-8960/full/v10/i1/289.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i1.289

INTRODUCTION
Hypertrophic olivary degeneration (HOD) is an unusual neuronal trans-synaptic degenerative disease because the olive initially becomes hypertrophic rather than atrophic. It is the result of the imbalance of the Guillain-Mollaret triangle, which is the dentato-rubral-olivary pathway (DROP) [1]. HOD diagnosis rate could be increased through the hyperintensity and enlargement of the inferior olivary nuclei on T2-weighted magnetic resonance imaging (MRI), and through the pathognomonic symptoms including palatal myoclonus and nystagmus [2]. In general, the incidence of bilateral HOD is low, so here we report a patient suffering from pontine hemorrhage with palatal myoclonus and pendular nystagmus, whose MRI showed bilateral HOD.

CASE PRESENTATION
Chief complaints
A 56-year-old female patient admitted to our hospital complained that her lower extremities and left upper ones could not move for more than 3 mo and the swelling of her lower right extremities got worse 3 days ago.

History of present illness
The patient’s symptoms lasted for more than 3 mo, and swelling of her lower right extremities had worsened over 3 days. There were no obvious symptoms of dyspnea, headache, dizziness, disturbance of consciousness and movement disturbance of other parts.

History of past illness
This patient had a history of hypertension for more than 15 years. She took oral compound reserpine tablets intermittently. Three months ago, she was diagnosed with pontine hemorrhage by a local community hospital and had been rehabilitated there. She had no history of liver or kidney disease or malignant tumor.

Personal and family history
The patient lost 6 kg (baseline body weight: 58 kg) of body weight within the last 3 mo. Her family had no other previous medical history.

Physical examination
The general condition of the patient was fair, but she could not walk. She was conscious, a bit thin and her vital signs were stable. The thyroid appearance and palpation were normal. No obvious vascular murmur was heard in the neck. She had a sinus rhythm, and his heart sounds were normal. The respiratory movement was in the normal range. On auscultation, the breath sounds in both lungs were slightly coarse. Both breasts were symmetrical. The abdomen was felt flat and soft, and there was no tenderness, no muscle tension and rebound pain. We palpated the lower abdomen without obvious lumps and other abnormalities. The spinal movement was normal right, and the upper extremities could move normally. The other extremities
did not move actively, and the right lower extremity was mild edema. There were no clinical symptoms of enlarged superficial lymph nodes. The neurological examination showed that her pupils were of equal circle size and sensitive to light reflection. Her pendular nystagmus had some horizontal and torsional movements under a prominently vertical component (three cycles per second). The patient also had rhythmic involuntary contractions of the soft palate and pharyngopalatine arch (two to three cycles per second). Her bilateral frontal lines and nasolabial were shallow, and her tongue was slightly leftward. The other cranial nerve examinations were normal. She could feel the sense of touch and temperature change, but her response was slightly slow to painful stimuli. Her examinations in sense of entity, positioning, and figure were all normal. Both her superficial and deep nerve reflections existed. The pathological signs were positive, including the Babinski sign, Chaddock sign and Oppenheim sign, etc. Her neck muscles had no resistance. The skin scratch test was negative. The Patient did not undergo the other nerve function examinations due to inconvenience. The neuromuscular examination displayed that her muscle tone increased. The left upper extremities muscle tone was level 1, the right upper one was level 3 and the lower one was level 2. The lower and left upper extremities muscle strength was level 0, and the right upper one was level 2. She had dysarthria, and the finger-nose test was negative. She refused to do the other coordination movement examinations due to inconvenience.

**Laboratory examinations**

Blood test, biochemical test, urine test, stool test, myocardial enzyme test and coagulation test were conducted, and the results of the examinations were listed in Table 1.

**Imaging examinations**

Figure 1A showed that hemorrhage was covered throughout the length of the pontine tegmentum by non-contrast computed tomography 3 mo ago. The results of brain MRI upon admission showed residual hemosiderin in the area of the hemorrhage (Figure 1B) and bilateral symmetrical hypertrophy in the bilateral inferior olivary nuclei. On a T1-weighted MRI, signal intensity was hypointense in these lesions (Figure 1C), which increased on a T2-weighted and a fluid-attenuated inversion recovery sequence MRI (Figure 1D-1F). No obvious thrombus was observed on vascular ultrasound.

**FINAL DIAGNOSIS**

Pontine hemorrhage; Bilateral HOD; Hypertension.

**TREATMENT**

We consulted with doctors from departments of neurosurgery, vascular surgery, nutrition, rehabilitation and pharmacy. The patient was given symptomatic and supportive treatment. She was treated with enteral nutrition by nasal feeding, gabapentin (300 mg, two times per day), memantine (10 mg, two times per day) and trihexyphenidyl (10 mg, two times per day) orally. We asked the nurses to turn the patient over and pat on her back to prevent complications. By consultation with physiatrists, rehabilitation physiotherapy, such as the joint movement by the passive aids machine, body massage for 3 times a day, was added to the treatment plan. At the same time, we worked with the patient’s family to carry out psychotherapy and were concerned about her changes. She had established confidence in treatment.

**OUTCOME AND FOLLOW-UP**

The patient was discharged from the hospital when her symptoms improved, and the edema of the right lower limb had disappeared. Hereafter, we maintained telephone communication with her, and we asked her to take medication and rehabilitation on time. Despite therapy for three months, the patient’s tremor only improved a little, while her extremities symptoms remained unchanged. Four months later, she had difficulty reading and felt dizzy. Since then, she felt depressed and useless, responded
### Table 1 The laboratory examinations results

| Measurement level | Normal level       |
|-------------------|--------------------|
| **Blood test**    |                    |
| WBC (×10⁹/L)      | 5.47               |
| RBC (×10¹²/L)     | 3.32               |
| Hb (g/L)          | 117                |
| PLT (×10⁹/L)      | 443                |
| NEUT (%)          | 65.40              |
| **Biochemical test** |                |
| K⁺ (mmol/L)       | 3.84               |
| Na⁺ (mmol/L)      | 140.20             |
| BUN (mmol/L)      | 2.90               |
| Cr (μmol/L)       | 31.0               |
| UA (μmol/L)       | 192.60             |
| hs-CRP (mg/L)     | 13.85              |
| GLU (mmol/L)      | 6.21               |
| TP (g/L)          | 60.30              |
| ALB (g/L)         | 35.0               |
| TB (μmol/L)       | 7.20               |
| DB (μmol/L)       | 2.50               |
| IB (μmol/L)       | 4.70               |
| AST (IU/L)        | 90.60              |
| ALT (IU/L)        | 107.10             |
| TC (mmol/L)       | 5.28               |
| TG (mmol/L)       | 1.55               |
| HDL-C (mmol/L)    | 0.82               |
| LDL-C (mmol/L)    | 3.78               |
| HCY (μmol/L)      | 8.61               |
| **Urine test**    |                    |
| SG                | 1.025              |
| PH                | 7                  |
| PRO (g/L)         | Negative           |
| GLU (mmol/L)      | Negative           |
| KET (mg/L)        | Negative           |
| BIL (μmol/L)      | Negative           |
| **Stool test**    |                    |
| RBC (piece/HP)    | 0                  |
| OBT               | Negative           |
| WBC (piece/HP)    | 0                  |
| **Myocardial enzyme test** |            |
| CK-MB (μg/L)      | < 0.001            |
| Mb (pg/L)         | 18.55              |
| cTnl (pg/L)       | 0.009              |
|                   | 0 - 18.0           |
|                   | 10.0 - 70.0        |
|                   | < 0.04             |

**Note:** All values are measured in their respective units as indicated.
Coagulation test

| Test   | Value  | Normal Range   |
|--------|--------|----------------|
| PT (s) | 10.20  | 10.50-14.0     |
| APTT (s) | 22.90  | 21.0-34.0     |
| TT (s)  | 18.0   | 14.0-20.0     |
| FIB (g/L) | 2.50   | 2.0-4.0     |
| INR    | 0.94   | 0.80-1.20     |

WBC: White blood cell count; RBC: Red blood cell count; Hb: Hemoglobin; PLT: Platelet; NEUT: neutrophil; K: Potassium; Na: Sodium; BUN: Urea nitrogen; Cr: Creatinine; UA: Uric acid; hs-CRP: hypersensitive C-reactive protein; GLU: Glucose; TP: Total protein; ALB: Albumin; TB: Total bilirubin; DB: Direct bilirubin; IB: Indirect bilirubin; AST: Aspartate transaminase; ALT: Alanine aminotransferase; TC: Total cholesterol; TG: Total triglycerides; HDL-C: High density lipoprotein-Cholesterol; LDL-C: Low density lipoprotein-Cholesterol; HCY: Homocystein; SG: Urine specific gravity; PH: Potential of Hydrogen; PRO: Urine protein; GLU: Urine glucose; KET: Urine ketone; BIL: Urine bilirubin; OBT: Occult blood test; HP: high power objective; CK-MB: Creatine kinase isoenzyme-MB; Mb: Myoglobin; cTnI: cardiac Troponin I; PT: Prothrombin time; FIB: Fibrinogen; APTT: Activated partial thromboplastin time; TT: Thrombin time; D-D: D-Dimer; INR: International Normalized Ratio; s: second.

Figure 1 The results of brain computed tomography 3 months ago and magnetic resonance imaging (MRI) after admission. A: The results of the brain computed tomography demonstrate an acute bilateral pontine haemorrhage; B: The results of T2-weighted axial MRI show the residual blood region after 3 months; C: The results of T1-weighted axial MRI through the medulla demonstrate expansion of the bilateral inferior olivary nucleus; D-F: The white arrow region shows hyperintense signal in the T2-weighted and fluid-attenuated inversion-recovery (FLAIR) sequence, and it displays no enhancement or restricted diffusion on others. (D: Axial T2-weighted image; E: Axial FLAIR image; F: Sagittal T2-weighted image).

DISCUSSION

Bilateral HOD after pontine hemorrhage is rarely observed in clinics. The causes of HOD can be hypertension, vascular malformation, heavy surgery, brain trauma, brainstem tumor, hemorrhagic or ischemic stroke. In addition, ischemia and demyelination can lead to the development of the disease[3-5]. According to neuroanatomical analysis, HOD is trans-synaptic degeneration at the site of DROP. Changes in slowly, and had no interest in what she used to like. We told her to go to a hospital for follow-up treatment immediately. Later, the patient couldn’t be reached by phone anymore.
neuroanatomy have played an important role in the manifestations of the disease. The DROP is composed of three structures, which are the ipsilateral inferior olive nucleus (ION), the ipsilateral red nucleus, and the contralateral dentate nucleus. The ION is connected to the contralateral dentate nucleus via the inferior cerebellar peduncle, the ipsilateral red nucleus is connected to the ION via the central tegmental tract, and the contralateral red nucleus and the dentate nucleus are connected by the superior cerebellar peduncle[1]. Many of the nerve fibers from dentate nucleus to inferior olive are primarily inhibitory. The results in loss of inhibitory control with consequent hyperactivity of the olivary neurons lead to abnormal involuntary movements. Furthermore, the main pathological features of HOD are often cytoplasmic vacuolation and the neural cell body enlargement, while the ischemia and demyelination could be occasional, which were first described by Oppenhen in 1887 [6]. A study by Dogan et al[7] showed that an unusual symptomatic tremor, which is the Holmes Tremor (HT), is characterized by the combination of rest and intention tremor. The pontine-midbrain hemorrhage may be considered to cause the HOD and HT to spread to the upper and lower extremities by influencing anatomy structure in the Guillain-Mollaret triangle. When damage occurs in the red nucleus or the central tegmental tract, the ipsilateral ION would degenerate. On the contrary, when the dentate nucleus or the superior cerebellar peduncle is affected, degeneration would happen in the contralateral ION. If the damage occurs in both the central tegmental tracts and the bilateral superior cerebellar peduncle, bilateral HOD happens[8]. In some cases, the lesion is located in the dorsal pons of the midline and the left DROP, which also causes bilateral HOD[9-11]. In general, these structures are interconnected and may influence each other functions.

Another study confirmed that a 31-year-old female developed HOD after pontine cavernoma surgery. She had the most classic symptom and MRI results of HOD[12]. Our case had a similar situation. The patient had the pontine hemorrhage, and her lower extremities dyskinesia and the swelling of the right leg were complications caused by the pontine hemorrhage. The characteristic clinical manifestations of HOD include palatal myoclonus and nystagmus, which may be the reason for a loss of inhibitory control of DROP. The hyperactivity of the olivary neurons then leads to rhythmic involuntary movements. We found these positive signs through careful physical examination in this case. Patients with HOD may develop ataxia, diplopia, dysarthria, and diplopia dento torubral tremor in the upper extremities, but not all patients have these symptoms[2,7]. Palatal myoclonus as a typical sign of this disease does not always exist[9,13]. Some patients’ tremors may only be observed in physical examinations, which makes it critical to monitor the occurrence of tremor phenomenology, even months after the initial insult[14]. An analysis by Suner et al[15] confirmed that brief weekly measurements with an eye-tracker may allow early detection of HOD. To sum up, when encountered with these abovementioned clinical manifestations, we need to consider HOD. In the meantime, the key to the diagnosis of HOD is the recognition of the results of the head MRI. Research has demonstrated that HOD was detected following primary neurologic insult, but no change in clinical symptoms was observed within a mean of 7.2 mo[16]. The feature is the enlargement of the ION without any contrast enhancement and T2 hyperintensity. In addition, another study has clarified that pontine-midbrain hemorrhage may cause delayed onset of HT thus delaying the appearance of HOD. In such cases, MRI should be referred to[7]. Some researchers have analyzed the results of MRI and offered three phases. Phase 1: the signal of the ION in T2-weighted does not change in 6 mo, but it increases after 3 wk in other regions; Phase 2: the signal of ION hypertrophy and hyperintensity persists for approximately 3–4 years on T2-weighted; and phase 3: the signal increases on T2-weighted for a long time with the disappearance of ION hypertrophy[1]. All in all, the diagnosis of HOD is difficult sometimes, which makes it important to monitor the clinical manifestations and identify the changes in MRI results. In our case, the patient’s MRI result conformed to the first phase of HOD, and her ION had hypertrophy degeneration bilaterally.

The treatment of HOD is generally the use of gabapentin, memantine, botulinum toxin injections, and deep brain stimulation. Psychotherapy is also a good treatment option for people with long-term illnesses. However, some patients showed self-limiting recovery, and excessive treatments are not necessary in such cases. Suffering from palatal or oculopalatal tremor usually last for life, but a few patients may have improved symptoms after many years[5]. Because of the uncertainty of the pathological mechanism of HOD, the treatment effect is not satisfactory. Our patient underwent pontine hemorrhage rehabilitation at the same time with the treatment of HOD, which turned out to be beneficial for the HOD treatment. So far, the pathological mechanism of HOD is still unclear, and more studies need to be done.
about bilateral HOD after pontine hemorrhage.

CONCLUSION

Overall, bilateral HOD is a rare phenomenon after pontine hemorrhage. In order to diagnose HOD as soon as possible, it is critical to monitor the patient’s clinical manifestations and the MRI results. The comprehensive treatment of HOD is based on the symptoms. The drugs, rehabilitation and psychotherapy are most commonly used. Further research is required to clarify the pathological mechanism of HOD.

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