

# A case of varicella zoster encephalitis with glossopharyngeal and vagus nerve injury as primary manifestation combined with medulla lesion

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## Abstract

Varicella zoster virus (VZV) can invade the brainstem or brain via the glossopharyngeal, vagus, or facial nerve, resulting in brainstem inflammation or encephalitis. We report the case of a 66-year-old male patient with a primary manifestation of medulla injury of the glossopharyngeal and vagus nerves, combined with a medulla lesion, who was misdiagnosed with lateral medullary syndrome. Facial nerve injury and earache subsequently occurred and human herpes virus 3 (VZV) was detected by second-generation sequencing of the cerebrospinal fluid. The final diagnosis was varicella zoster encephalitis, which improved after antiviral therapy.

## Keywords

Glossopharyngeal nerve, vagus nerve, varicella zoster encephalitis, lateral medullary syndrome, facial nerve, diffusion-weighted imaging, cerebrospinal fluid

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## Introduction

Classical Hunt syndrome refers to unilateral facioplegia combined with external auditory canal herpes, usually accompanied by vestibulocochlear nerve injury.<sup>1</sup> However, the V, VI, IX, X, XI, and XII pairs of

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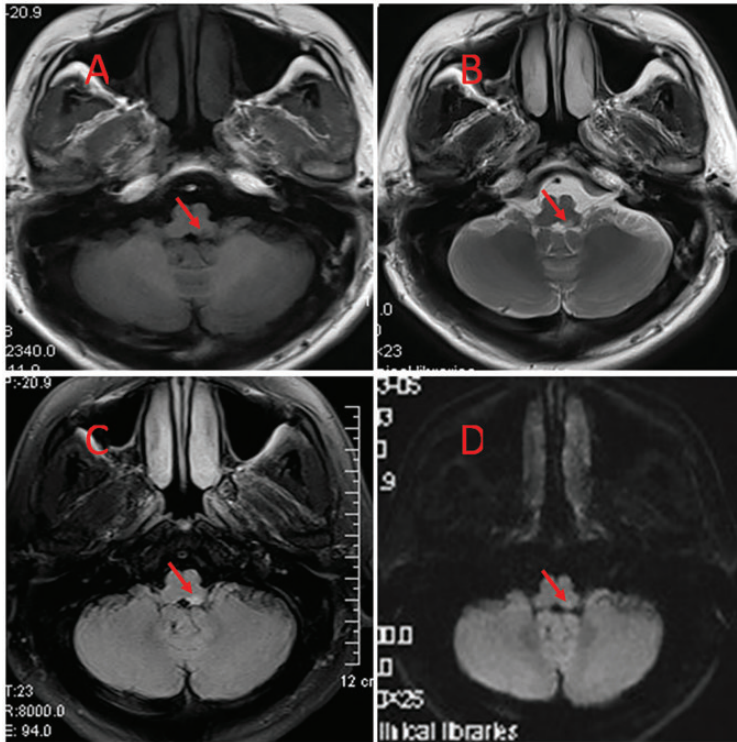


cranial nerves can occasionally be similarly affected, with corresponding clinical manifestations.<sup>2-4</sup> Varicella zoster virus (VZV) can enter the skull by retrograde transport along these cranial nerves, invading the brain stem and causing brain stem inflammation or encephalitis.<sup>5</sup> We report on a patient with VZV and a dorsolateral medulla oblongata lesion caused by VZV infection, with a primary manifestation of swallowing difficulty and hoarse voice, who was misdiagnosed with lateral medullary syndrome (LMS). This case should improve clinicians' understanding of central and peripheral nerve injuries caused by VZV-related brainstem inflammation.

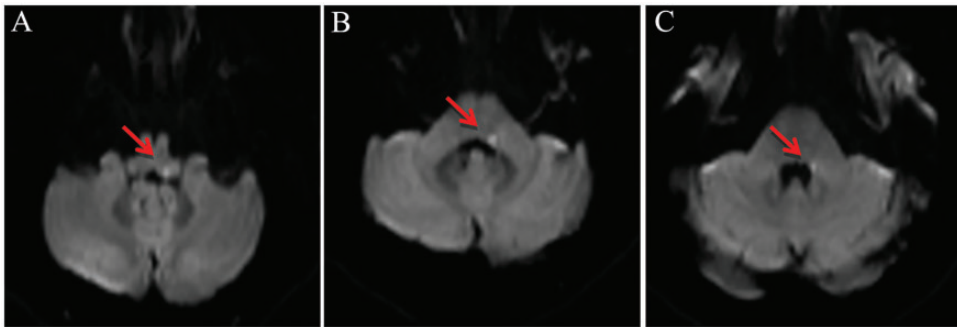
## Case report

A 66-year-old man was admitted to hospital with a 3-day history of hoarseness and swallowing difficulty, with no obvious cause. He had discomfort in the laryngeal part of the pharynx, but no dizziness, vomiting, or limb activity disorder. He had a >20-year history of hypertension. He had complained of 'post-sternal pain' for the past month, which was most obvious after eating. Physical examination upon admission revealed that the patient was conscious, but his articulation was unclear, his pharyngeal reflex was slow, and the lift of his left soft palate demonstrated inertia. Physical examination of the remaining nervous system showed no abnormality. Skull computed tomography revealed multiple lacunar infarctions. No obvious blood, urine, or stool abnormalities were detected by routine observations and blood biochemical tests. No abnormalities were found in the preoperative results for hepatitis B (HB) surface antigen, HB surface antibody, HB e antigen, HB e antibody, HB core antibody, human immunodeficiency virus antibody, thymostimulin, or hepatitis C virus antibody. His autoantibody spectrum and immune functions were normal. Head

magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) showed a patch-shaped long T1, long T2 signal in the left lateral medulla oblongata, fluid-attenuated inversion recovery (FLAIR) showed a high signal, and diffusion-weighted imaging (DWI) showed a high signal shadow, indicating the possibility of an infarct (Figure 1). Head MRA showed mild intracranial arteriosclerosis. Carotid artery ultrasound showed a left carotid plaque (single occurrence) and right subclavian artery plaque. Gastroscopy showed multiple esophageal ulcers, likely due to virus infection, and chronic non-atrophic gastritis. Laryngoscopy showed left vocal cord paralysis. The primary diagnosis was cerebral infarction (LMS). Seven days after admission, the corner of the patient's mouth was skewed towards the right, with left ear pain accompanied by dizziness. Physical examination showed left peripheral facioplegia, and horizontal nystagmus could be observed in the left and right views, with the fundus undetectable. There were no obvious changes in the results of physical examinations compared with the previous examinations. Reexamination of his head MRI showed patch-shaped long T1 and long T2 signals in the left medulla and left brachium pontis, FLAIR showed high signal, and DWI showed a high signal shadow (Figure 2). There was no abnormality on audiometry, but video electronystagmography showed an abnormality of the vestibular nerve center. Lumbar puncture showed a pressure of 160 mmH<sub>2</sub>O, white blood cell count  $32 \times 10^6/L$ , protein 0.68 g/L, and normal glucose and chloride. Cerebrospinal fluid (CSF) cytology showed that the cells were mainly activated lymph cells. Human herpes virus 3 (VZV) was detected by second-generation sequencing of the CSF. The revised diagnosis was VZV encephalitis, which was treated with acyclovir 0.2 every 8 hours for 21 days,



**Figure 1.** First cranial MRI. (a) T1, (b) T2, (c) FLAIR, and (d) DWI. Patch-shaped long T1 and long T2 signal could be observed in left lateral medulla oblongata; FLAIR and DWI showed high signals (red arrow).



**Figure 2.** Second MRI. (a) DWI sequence showed a high signal in left lateral medulla oblongata (red arrow), (b) DWI sequence showed a high signal in the left brachium pontis (red arrow) and (c) DWI sequence showed a high signal in the exterior portion of the facial colliculus (red arrow).

intravenous immunoglobulin (0.4 g/kg, for 5 days), and methylprednisolone sodium succinate (120 mg, for 5 days) to alleviate the inflammation. Repeat lumbar puncture

after antiviral therapy for 21 days showed that the pressure had fallen to 110 mmH<sub>2</sub>O, the white blood cell count to  $4 \times 10^6/L$ , and protein to 0.32 g/L. Both glucose and

chloride remained normal. The nasogastric feeding tube was removed before discharge and the patient was able to consume a liquid diet through his mouth. Left peripheral facioplegia was the remnant syndrome. The total period of hospitalization was 24 days. Ethical approval for this study was provided by Harrison International Peace Hospital, and the patient provided written informed for publication of this case report.

## Discussion

VZV is a double-stranded DNA herpesvirus that is transmitted via the respiratory tract and mainly causes varicella and herpes zoster. Chickenpox usually recovers without sequelae, but the virus remains dormant within neurons and may reactivate after decades of incubation, resulting in herpes zoster or cranial nerve palsy (such as Ramsay Hunt syndrome), without a rash. In rare cases, reactivated VZV may cause brainstem inflammation, myelitis, and cerebellitis.<sup>6</sup> The virus invades the dorsolateral medulla oblongata, making it difficult to differentiate from cerebrovascular diseases, demyelinating diseases of the central nervous system, infections, and nutritional and metabolic diseases.

The most common cerebrovascular disease involving the dorsolateral medulla is dorsolateral medulla syndrome. LMS, also known as Wallenberg syndrome or posterior inferior cerebella artery syndrome, is the most common type of brainstem infarction and a typical manifestation in patients with posterior circulatory ischemic stroke.<sup>7,8</sup> LMS is mainly caused by occlusion of the posterior inferior cerebellar artery or its branches, and presents with classical clinical manifestations including dizziness, nausea, vomiting, Horner syndrome, unilateral cerebellar ataxia, facial pain and

numbness. The current patient had difficulty swallowing, hoarse voice, cough when drinking water, taste disorder, soft palate palsy, and pharyngeal hyporeflexia. They also had reduced pain and heat sensations in the limbs. DWI sequence on MRI has been confirmed as the preferred diagnostic method for sub-cerebellar zone or acute infarction of the lateral medulla oblongata.<sup>9</sup> The current patient was an elderly man with an acute illness onset, whose primary manifestations were swallowing difficulty and hoarse voice. Together with his risk factors for cerebrovascular disease and abnormal Wallenberg signal on head MRI, the initial diagnosis was incomplete LMS. However, 7 days after hospital admission, the patient developed left peripheral facioplegia, and reexamination of his MRI showed diffusion-limited abnormal signals in the lateral medulla oblongata and the left brachium pontis, which were not in accordance with the vessel distribution, indicating the possibility of a non-vessel-related illness. The patient also complained of left ear pain, and combined with the results of his physical examination, the possibility of brainstem encephalitis caused by a herpes virus infection was considered. VZV was finally confirmed by second-generation sequencing of the CSF. Following activation of Hunt syndrome virus in the geniculate ganglion of the trigeminal nerve, it invades the geniculate ganglion in a retrograde manner and enters the skull through the inner ear canal to invade the facial and vestibulocochlear nerves. It reaches the facial, vestibular and posterior and anterior cochlear nerve nuclei, and simultaneously invades the adjacent ventral and dorsal tissue directly through fiber connections.<sup>10</sup> The primary manifestation in the current patient was involvement of the glossopharyngeal and vagus nerves. The herpes virus invasion path in this case was not clear,

but the possible pathogenic mechanism involved invasion of the glossopharyngeal and vagus nerves at the pharynx and larynx or esophagus. Gastroscope showed injury to the gastric tract mucosa, considered to be a virus-induced esophageal ulcer, though pathological biopsy of the ulcer site was not conducted. VZV may then have entered the skull retrogradely via the glossopharyngeal and vagus nerves, and extended to the nerve hillock of the lateral medulla oblongata and the dorsal surface of the brachium pontis. Alternatively, VZV may have been present in the geniculate ganglion of the trigeminal nerve, and after activation, may have invaded the glossopharyngeal and vagus nerves via connections among the facial, glossopharyngeal, and vagus nerves. According to Hunt's theory, VZV affected the facial and vestibular nerves simultaneously, i.e., via their connection in the geniculate ganglion.<sup>10</sup> There were several reasons for the misdiagnosis in the current patient. First, there was a lack of understandings of the classical clinical manifestation of LMS. The diagnosis of LMS was thus made simply on the basis of the abnormal medulla signal and glossopharyngeal/vagus nerve injury, even though the other typical clinical manifestations of LMS were absent. Second, the understanding of varicella zoster encephalitis was inadequate. Ramsay Hunt syndrome is a complication of herpes zoster virus, but brainstem involvement is rare. Finally, the doctor had excessive confidence in the DWI diffusion limited MRI signal, but did not consider that brain infarction, tumor, demyelination, and virus infection could all manifest as diffusion limitation.

This case highlights the need to be cautious when making a clinical diagnosis of LMS, and to ensure that its typical clinical manifestations are analyzed adequately. In addition, this case has widened our

understanding of the possibility of virulent brainstem inflammation caused by entry of VZV via the glossopharyngeal and vagus nerves into the skull. This information could help to reduce the incidence of missed or inaccurate diagnoses. This case also demonstrates the value of second-generation sequencing of CFS for intracranial pathogen screening.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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