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## Letter to the Editor: New Observation

# Repeated Vertebrobasilar Strokes Caused by Varicella Zoster Virus Vasculopathy

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Varicella zoster virus (VZV) vasculopathy is an uncommon complication of VZV reactivation but is regarded as a significant cause of ischemic stroke and transient ischemic attacks (TIAs). Recent studies of VZV vasculopathy using high-resolution magnetic resonance imaging (MRI) revealed multifocal intracranial vasculitis and stenosis mostly in 'anterior circulation'.[1] Restricted posterior circulation involvement was seldom reported, and in such circumstances, VZV vasculopathy is barely diagnosed if there is no preceding zosteriform rash.[2,3] Here, we report a case of VZV vasculopathy solely involving posterior circulation without preceding rash or vertebrobasilar arterial stenosis.

A 56-year-old man, with hypertension and dyslipidemia, experienced throbbing pain at the right aspect of neck along with the right temporal region and pin-and-needle feelings at the entire scalp for 2 weeks without skin rash or blisters. After that, he started to have a few episodes of transient neurological deficits, including weakness of the left leg, clumsiness of the left hand, and vertigo accompanied by diplopia in the following 1 month. Eventually, he developed persistent weakness of the left limbs and visited our Emergency Department (ED). Upon examination, he showed mild left hemiparesis and dysmetria. Routine brain MRI revealed multifocal recent infarcts involving the right paramedian pons and the right upper medulla oblongata on day 2 after ED visit (Figure 1A). The patient was treated with daily clopidogrel and hospitalized on day 3 for motor fluctuation.

Regarding work-up for stroke etiology, there was no cardiac arrhythmia or coagulopathy. Computerized tomography (CT) angiography did not show any evidence of stenosis or dissection in bilateral cervical or intracranial vertebrobasilar arteries. Concerning preceding headache and multiple brainstem TIAs and infarcts, he then underwent lumbar puncture for potential basal meningitis on day 6. The cerebrospinal fluid (CSF) results showed mildly elevated opening pressure (210 mm$H_2O$, normal <200 mm$H_2O$), lymphocyte predominant pleocytosis (white blood cell, 35; lymphocyte to neutrophil ratio, 29/6) (normal 0–5 × $10^9$cells/L), and elevated protein level (103 mg/dL, normal 15–45 mg/dL). While polymerase chain reaction (PCR) of CSF samples showed negative for cryptococcus and tuberculosis, VZV PCR turned out positive on the next day. The results of VZV IgG in both serum and CSF were also positive (unfortunately no quantitative titers available). The high-resolution vessel wall MRI (HRVW-MRI) on day 8 showed a new right paramedian pontine infarct (compatible with motor deterioration on day 3) and, notably, abnormal enhancing wall thickening in bilateral distal vertebral arteries and proximal basilar artery, as well as scattered leptomeningeal enhancing foci around brainstem (Figure 1B–1F), indicating vertebrobasilar vasculitis and basal meningitis, respectively.

On day 9, he developed acute onset of room tilt illusion, dysarthria, and dysphagia with multi-directional nystagmus. Accordingly, acyclovir and short-term prednisolone (1 mg/kg) were started to treat VZV meningitis and vasculopathy. After then, there were no more stroke-like events. A repeated MRI on day 20 showed compatible new infarcted foci at right lateral pons and dorsal midbrain. He received acyclovir treatment for 5 weeks and also intravenous immunoglobulin (IVIG) in the fifth week after hospitalization for very slow normalization of pleocytosis (white blood cells, 73, 21, and 16 on days 12, 22, and 43, respectively) and still elevated protein levels (81, 82, and 80 mg/dl) in CSF. Follow-up MRI studies at 1.5 and 8 months posthospitalization showed partial resolution of both vessel wall enhancement at the vertebrobasilar arteries and meningeal enhancement around brainstem (Figure 1G–1L). He was able to return to work at 5 months posthospitalization.

The present study demonstrates a case of VZV vasculopathy exclusively affecting the vertebrobasilar system, causing multifocal brainstem infarcts. Despite no preceding skin zoster, the presence of VZV DNA and VZV IgG in CSF further confirmed the stroke etiology as VZV vasculopathy.

Direct VZV infiltration to the vessel walls via transaxonal spread is thought to be the mechanism of VZV vasculopathy.[4] The anterior and middle cerebral arteries are innervated by nerve fibers originating from the trigeminal ganglia, while the vertebrobasilar arteries and their tributaries are innervated additionally by those from the upper cervical dorsal root ganglia.[5] Although uncommon, it had been reported that zoster eruption in cervical dermatone may precede brainstem infarct.[2,6] The mechanism was believed to be direct viral invasion via cervical nerve innervation

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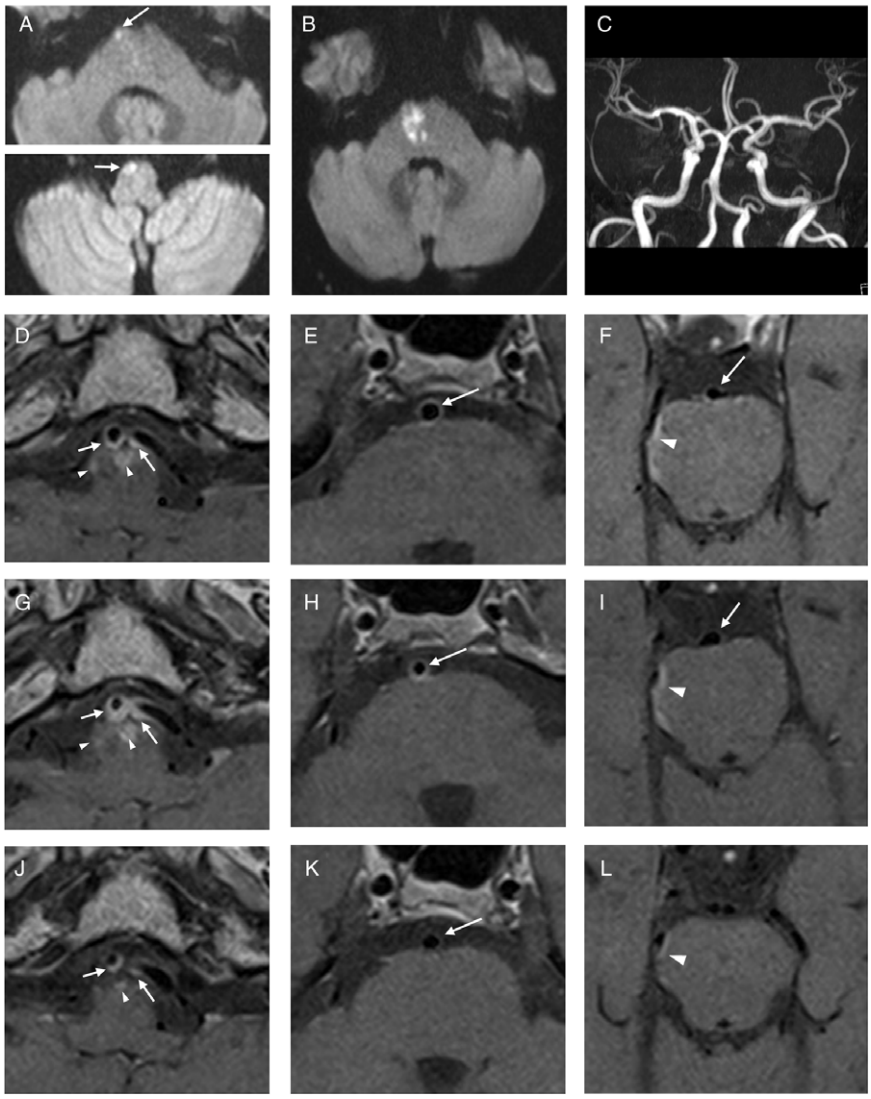


**Figure 1:** Multifocal brainstem infarct secondary to varicella zoster virus vasculopathy involving bilateral vertebral and basilar arteries. Lesions with abnormal diffusion restriction on MRI were seen in right anterior medulla oblongata (bottom) and right medial pons (top) on day 2 after Emergency visit (A), and a new lesion was seen in right paramedian pons on day 8 (B). Magnetic resonance angiography showed no definite stenosis of intracranial vessels (C). Gadolinium enhanced high-resolution vessel wall MRI showed vessel wall enhancement in bilateral distal vertebral arteries (D, arrow), middle basilar artery (E, arrow) and faintly in distal basilar artery (F, arrow), as well as focal leptomeningeal enhancement in medulla and pons (D, F, arrowhead) on day 8. The wall enhancement became thickened in vertebral arteries (G), remained stationary in middle basilar artery (H), and resolved in distal basilar artery (I) on day 49. On day 256, the vertebral artery wall enhancement partially remitted (J), the middle basilar artery enhancement completely resolved (K), and the leptomeningeal enhancement became faint (J, L).

of the vertebral arteries.[6] Our case did not show a preceding typical zosteriform rash, but he did experience cervical pain and scalp numbness, suggestive of possible VZV reactivation in cervical dermatomes 2 weeks before the development of neurological symptoms. Therefore, in stroke patients having neck pain, VZV vasculopathy is another differential diagnosis in addition to arterial dissection.

VZV vasculopathy usually presents with unifocal, multifocal, or diffuse intracranial arterial stenosis.[1,7] In contrast to that, this case demonstrated no evidence of arterial stenosis, making clinicians easily overlook underlying vasculopathy. Using HRVW-MRI, vertebrobasilar vasculitis was noticed, showing concentric thickening with contrast enhancement of the vessel walls. Vertebrobasilar arteries feature numerous penetrating perforators supplying the brainstem. Therefore, vasculitis of large vessels even without severe stenosis may affect adjacent small perforators, causing multifocal brainstem infarcts.

Regarding treatment for VZV vasculopathy, acyclovir and steroid therapy were suggested to contain the virus and ameliorate the inflammatory response of vessel wall.[4] In our case, the recurrent ischemic events did not end until the initiation of antiviral and steroid treatment. Additionally, our patient further received empirical IVIG for persistent pleocytosis and high CSF protein levels, which possibly indicated unresolved inflammation/infection. Further follow-up MRI studies demonstrated gradual resolution of both vessel wall and meningeal enhancement. Previous study has shown that adjuvant IVIG treatment is able to reduce serum viral load.[8] Nevertheless, the optimal treatment for VZV vasculopathy remained to be determined. As depicted in this case, it is noteworthy to point out the far slower laboratory and radiological resolution compared to the clinical course.

In conclusion, this case illustrates the importance of recognizing VZV vasculopathy in patients with multifocal recurrent brainstem infarcts, masquerading as vasculitis and/or basal meningitis. CSF studies for VZV DNA and IgG should be examined in such circumstances even without preceding zosteriform rash or intracranial arterial stenosis. HRVW-MRI is helpful to uncover subtle vasculitis. Early prompt treatment effectively halts the disease progression, if VZV vasculitis is recognized early.

**Statement of Authorship.** PFH: Data collection and manuscript drafting. LKT: Patient's main physician, review of the manuscript.

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