# Cerebrovascular Manifestations of Adult-Onset Varicella Zoster Virus Infection in the Central Nervous System: A Literature Review

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**Research**

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## Abstract

# Background

Cerebrovascular complications after adult-onset varicella-zoster virus (VZV) infection have been increasingly recognized. The aim of this study was to analyze clinical and neuroimaging findings, treatment and outcome of these patients.

# Methods

Systematic literature review from January 2000 to December 2019.

# Results

We analyzed 31 articles with a total of adult-onset 34 cases, including 25 (73.53%) cases of ischemic stroke (median age 52 years), 6 of intracerebral hemorrhage (median age 70.5 years) and 3 with venous sinus thrombosis. The incidence in men was higher than in women in ischemia (72% and 28%) or venous sinus thrombosis groups (100% for men). There was median time with 42.8 days from herpes zoster infection to hospital in patients with ischemic stroke. Cognitive impairment was the most common symptoms either in the ischemic group (56%) or hemorrhagic group (83.33%). The lesions after VZV-associated cerebral infarction or hemorrhage were mutifocal and was most common in the parietal lobe. Venous sinus thrombosis was common in the transverse sinus (100%). Lesions in large vessels (48%) were common, followed by small vessels (36%) in ischemic group and multiple beaded stenosis (16.67%) were showed in hemorrhagic group by digital subtraction angiography or magnetic resonance angiography. 60.87% of the patients with antiviral treatment in the ischemic group had favorable prognosis. All patients with anticoagulant therapy in venous sinus thrombosis group improved well (100%), however, 60% of the patients with intracerebral hemorrhage had a poor prognosis or died.

# Conclusion

We found ischemic stroke related with VZV encephalitis is common and mainly affects the middle-aged. In general, the young patients with venous sinus thrombosis improve completely, however, the old patients with intracerebral hemorrhage have poor prognosis. When the patient represents with some neurological symptoms within 2 months after VZV infection, and multiple lesions probably induced by vasculitis showed in neuroimaging, cerebral complications related with VZV infection should be considered even though the existence of some vascular risk factors for atherosclerosis.

## Background

The varicella-zoster virus (VZV) is a double-stranded DNA neurotropic alpha-herpesvirus belonging to human herpesvirus type 3. After the initial infection with chickenpox, the virus may retrograde to the sensory neuron body of the ganglion through replicating T cell toxemia, thus forming a latent infection[1]. When virus replication is reactivated, it can reach the skin via anterograde axon transport, causing herpes zoster. Activated VZV is also one of the important causes of acute viral encephalitis. It has been reported herpes simplex virus (HSV) accounts for 50–75% of confirmed cases of viral encephalitis, and VZV and enteroviruses account for the majority of the remaining cases[2].

VZV can spread to the arteries of the central nervous system(CNS), eventually leading to bleeding or ischemic complications[3]. Baudouin et al. first identified stroke associated with VZV in 1896. A study consisting of pediatric patients showed the mortality rate of cerebrovascular diseases associated with VZV infection is as high as 35% in the 1970s[4]. In a population-based study, the stroke risk of older adults with herpes zoster infection within 3 months was reportedly increased 1.53-fold [5].

In recent years, with the increasing number of infective cerebrovascular lesions, it has been gradually recognized that the reactivation of VZV is associated with subsequent cerebral hemorrhage or infarction. However, most of the researches are case reports with only several cases or involved with children. Here, we review the literature with a total of adult-onset 34 cases to demonstrate clinical presentations, imaging features, possible pathogenesis, treatment and outcome in VZV-related cerebral vascular lesions. It may be helpful for early recognition, accurate diagnosis and therapeutic options.

## Methods

### literature search and selection

We performed a literature search to identify all published cases of cerebral vascular manifestations of VZV from January 2000 to December 2019 using MEDLINE/PubMed, Web of Science. There were no language restrictions. The case reports of children and not getting full text articles were excluded. Search terms used were “varicella-zoster virus,” “encephalitis,” “meningitis,” or “meningoencephalitis” and one of the following terms: “ischemia,” “infarction,” “stroke,” “hemorrhage,” “venous sinus thrombosis,” or “vasculopathy.” We reviewed full text and additional cases were identified by reviewing the reference section of the retrieved articles. Each article was evaluated by two independently investigators to determine inclusion in the final review.

All the patients met the diagnostic criteria reported as follows [6, 7]: (1) VZV vascular lesions (ischemic stroke, hemorrhage, venous sinus thrombosis, or vasculitis) were confirmed by imaging findings of computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance angiography

(MRV), or digital subtraction angiography (DSA), (2) cerebrospinal fluid(CSF) results of VZV infection were confirmed according to diagnostic criteria by a consensus article[8], and (3) exclusion of other causes for cerebral vascular disease.

### Data extraction

Two investigators collected data from the selected articles. The following information were extracted: last name of the first author, demographics, clinical symptoms, etiology, CSF examination, time from onset of Herpes zoster infection to hospital, imaging data, therapy and outcome. Clinical symptoms include headache, fever, cognitive abnormalities, hemiplegia, peripheral facial palsy, aphasia, seizure or ataxia. Diagnostic tests of CNS VZV infection were polymerase chain reaction (PCR), anti-VZV IgG antibody and viral culture. Cerebrovascular lesions were identified by CT, MRI or MRV. Large and small vessels, and evidence of vasculitis were assessed by DSA or MRA. The Large arteries were the internal carotid artery, the anterior cerebral artery and the middle cerebral artery in the anterior circulation, and the posterior cerebral artery, the vertebral artery and basilar artery in the posterior circulation. Small vessels included the small penetrating arteries. We also recorded the use of antiviral therapy, corticosteroids and anti-platelet or anticoagulant medication. In clinical trials, the Modified Rankin Scale (mRS) was commonly used scales to assess outcome. The definition of poor outcome was mRS greater than or equal to 3 points while good outcome defined as a mRS score of 0–2 points [9].

All statistical analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY, USA).

## Results

# Systematic review

From January 2000 to December 2019, through a preliminary electronic literature search and manual literature search, we finally analyzed 31 articles with a total of 34 cases. There were 25 cases(25/34, 73.53%) with ischemic stroke [10–32], 6 cases(6/34, 17.65%) with intracerebral hemorrhage [33–38], and 3 patients(3/34, 8.82%) with venous sinus thrombosis [39–41].

# Ischemic Stroke

The age of onset varied between 24 and 85 years old with a median age of 52. Eighteen patients were males (18/25, 72%) with an 18:7 of male to female ratio. 40% (10/25) of the patients had no previous history of varicella zoster infection. 40% (10/25) of the patients developed ischemic manifestations within one month after zoster infection, while 12% (3/25) of the patients demonstrated ischemic symptoms within 2–3 months. The longest interval of onset was seven months after the existence of zoster with a median time of 42.8 days. Initial clinical presentations of patients included cognitive impairment (14/25, 56%), lalopathy (10/25, 40%), headache (9/25, 36%), hemiplegia (8/25, 32%), fever (6/25, 24%), ataxia (4/25, 16%), epilepsy (4/25, 16%) and peripheral facial paralysis (3/25, 12%).

CSF VZV-DNA positive was confirmed by PCR in 10 patients (10/25, 40%), and there were 9 cases (9/25, 36%) with positive anti-VZV IgG in CSF test. Both VZV DNA and anti-VZV IgG in CSF were positive in 5 cases (5/25, 20%). Anti-VZV IgG positive for both VZV CSF and serum was in one case (1/25, 4%). VZV was confirmed in one patient by viral culture. Multiple ischemic lesions were found in 52% (13/25) distributed most commonly in both anterior and posterior circulations simultaneously, which is different from cerebrovascular disease caused by common atherosclerosis. The parietal and occipital lobes, as well as brainstem were the main sites of ischemic stroke after VZV infection. The remaining locations were basal ganglia, temporal and frontal lobes and cerebellum in sequence. Evidence of vasculitis was found in 40% (10/25) of patients. Large vessel lesions were found in 48% (12/25) patients, and small vessel lesions in 36% (9/25) on MRA or DSA images.

All patients (100%, 24/24) received Intravenous acyclovir at the early stage except one patient whose treatment was not mentioned, among them 60.87% (14/23) (not mention of prognosis in one patient) had 0–2 mRs. There was no significant difference in either mortality (22.22% vs 21.43%) or favorable prognosis (77.78% vs 50%) between antiviral drug therapy alone and antiviral drug combined with steroid. One patient recovered well on the combination of antiviral, steroid and anti-platelet treatment.

Demographics, clinical features, imaging abnormalities, and outcome were presented separately for patients with ischemic stroke in Table 1. The characteristics of the included cases were presented in Table 2.

Table 1
Demographics, clinical features, imaging abnormalities, and outcome are presented for patients with ischemic stroke

| **Demographics** | |
|---|---|
| *n* | 25 |
| Median age, years | 52(24–85) |
| Male gender | 72% (18/25) |
| Days from Herpes zoster infection to the occurrence of neurologic symptoms (median), *n* = 15 | 42.8(4-210) |
| Clinical features | |
| Headache | 36% (9/25) |
| Fever | 24% (6/25) |
| Cognitive impairment | 56% (14/25) |
| Hemiplegia | 32% (8/25) |
| Peripheral facial palsy | 12% (3/25) |
| Lalopathy (aphasia or dysarthria) | 40% (10/25) |
| Seizure | 16% (4/25) |
| Ataxia | 16% (4/25) |
| Diagnostic testing | |
| PCR positive for VZV(CSF) only | 40% (10/25) |
| anti-VZV IgG positive for VZV(CSF) only | 36% (9/25) |
| Both PCR and anti-VZV IgG positive for VZV(CSF) | 20% (5/25) |
| Both anti-VZV IgG positive for VZV CSF and serum | 4% (1/25) |
| Viral culture positive for VZV(CSF) | 4% (1/25) |
| Neuroimaging | |
| Evidence for vasculitis | 40% (10/25) |
| Affected vessels | |
| Small-sized | 36% (9/25) |
| Large-sized | 48% (12/25) |
| Not done | 16% (4/25) |
| Affected areas of circulation | |
| Anterior | 36% (9/25) |
| Posterior | 24% (6/25) |
| Mixed | 40% (10/25) |
| Distribution of lesions | |
| Single | 48% (12/25) |
| Multiple | 52% (13/25) |
| Treatment | |
| Acyclovir treatment | 100% (24/24) |
| Steroid treatment | 62.50% (15/24) |
| Anti-platelet medication | 4.17% (1/24) |
| Outcome | |
| Good outcome (mRS 0–2) | 60.87% (14/23) |
| Unfavorable outcome (mRS 3–5) | 17.39% (4/23) |
| Death | 21.74% (5/23) |

Table 2
The characteristics of twenty-five ischemic stroke cases

| Case | Reference | Sex, age(years) | Clinical features | Diagnosis test | Time from Herpes zoster infection | Affected brain region | Treatment | Outcome (mRS) |
|---|---|---|---|---|---|---|---|---|
| 1 | David et al.2015 | Male,51 | Fever, chills, confusion herpes zoster, lethargic disoriented | CSF, anti-VZV IgG(+) | 2 weeks | Bilateral gray-white matter | acyclovir Dexamethasone | Complete recovery(0) |
| 2 | Jeroen et al.2014 | Male,72 | Herpes zoster, cognitive abnormalities, the left-sided facial paresis, difficulty retrieving some words, | CSF, PCR VZV(+) | 6 weeks | Right internal capsule | Acyclovir | Paresis of the left arm and left-sided facial paresis(1) |
| 3 | Tiago et al.2014 | Male,72 | Headache, anorexia, nausea, zoster, memory deficit, incoherent speech | CSF, PCR VZV(+) | 11 days | Posterior ischemic optic neuropathy | Prednisolone Acyclovir | Not reported |
| 4 | Francisco et al.2014 | Male,26 | Zoster, VZV meningitis | CSF, PCR VZV(+) | 4 months | Right occipital lobe | Not reported | Not reported |
| 5 | Francesca et al.2014 | Female,67 | Rash, left peripheral facial palsy, gait instability, cerebellar ataxia | CSF,PCR(+)and anti-VZV IgG in CSF | 2 weeks | Left pons, left midbrain, right periventricular area | Acyclovir Carbamazepine | Complete recovery(0) |
| 6 | Brian et al.2012 | Male,69 | Vision loss, word-finding difficulties, dysarthria, short-term memory loss, ataxia, dizziness ,expressive language difficulties, unable to identify any elements of date or location | CSF, anti-VZV IgG (+) | No history of zoster experienced | Left corona radiata, basal ganglia ,right basal ganglia, both thalam, periventricular white matter, right superior cerebellum | Cyclophosphamide Rednisone; Acyclovir | Complete recovery(0) |
| 7 | Yu-Miyazaki et al.2008 | Male,66 | Headache, fever, and altered mental status, zoster rash consciousness and stiff neck | CSF,VZV-IgG antibody and VZV-DNA (+) | Not reported | Brainstem, vermis of cerebellum and cerebral white matter | Acyclovir Methylprednisolone | Death |
| 8 | O.Outteryck et al.2004 | Male,57 | Fever, headache, abnormal behavior, mental retardation | CSF ,PCR VZV (+) | Not reported | Amygdala, cerebellum, brainstem, deep white matter | Acyclovir | Death |
| 9 | Manuel et al.2002 | Female,68 | Mental retardation, difficulty walking, right hemiplegia, aphasia, rash | CSF ,PCR VZV (+) | Not reported | Left internal capsule | Acyclovir | Death |
| 10 | Nasir et al.2003 | Male,52 | Chicken pox, headache, nausea, vomit, and photophobia, confusion | CSF, viral culture VZV(+) | 5 weeks | Left frontal, left parietal, right medial temporal, and right occipital lobes | Ceftriaxone Methylprednisolone Acyclovir | Right-side hemiparesis persisted(2) |

| Case | Reference | Sex, age(years) | Clinical features | Diagnosis test | Time from Herpes zoster infection | Affected brain region | Treatment | Outcome (mRS) |
|---|---|---|---|---|---|---|---|---|
| 11 | John et al.2012 | Male,50 | Chicken pox, seizure and coma, rash, deeply comatose | CSF ,PCR VZV (+) | 4 days | Posterolateral medulla | Levetiracetam Acyclovir Prednisone | Awake and oriented with significant psychomotor slowing and persistent quadriparesis(4) |
| 12 | Mckelvie et al.2002 | Female,67 | Nausea, tiredness, hyperaesthesia, fever, disorientation to time, place, verbal response. | CSF,PCR VZV (+) | 2 weeks | Bilateral cerebellum | Dexamethasone Acyclovir | Death |
| 13 | Katchanov et al.2010 | Male,36 | Locked-in syndrome | CSF, ,PCR VZV (+) | Not reported | Bilateral pons and midbrain | Acylovir, Methylprednisolone | Severe (5) |
| 14 | Katchanov et al.2010 | Male,32 | Global aphasia, right hemiplegia | CSF, VZV-IgG antibody(+) | Not reported | Left MCA territory, left PCA territory | Acylovir, Methylprednisolone | Severe (5) |
| 15 | Gilden et al.2002 | Male,71 | Zoster, headache, mild confusion, foot numbness, unsteady gait, difficulty finding words, numbness of the left hand, weakness of the left leg | CSF, VZV-IgG antibody(+) | 4 weeks | Right pericallosal, occlusion of the anterior cerebral artery on the right side and stenosis on the left side | Acyclovir | Complete recovery(0) |
| 16 | Gilden et al.2002 | Male,76 | Zoster, headache, lost all vision in the left eye | CSF, VZV-IgG antibody(+) | 7 months | Posterior ischemic optic neuropathy | Acyclovir | Complete recovery(0) |
| 17 | Richard et al.2011 | Male,80 | zoster, sudden painless loss of vision in the left eye | CSF, VZV-IgG and VZV-IgM antibody(+) | One month | Occlusion of the left ophthalmic artery | Methylprednisolone, Prednisone Acyclovir | Visual acuity had improved to 20/50(2) |
| 18 | Andreas et al.2002 | Male,28 | HIV+,HCV+, progressive dizziness, left-side weakness | CSF, VZV DNA and IgG antibody(+) | Not reported | Right occipitotemporal, parieto-occipital cortices | Acyclovir | Complete recovery(0) |
| 19 | Andrew et al.2003 | Female,51 | Confusion, disorientation, vertigo, decreased right hearing, right-sided clumsiness left leg weakness, seizure, | CSF, VZV IgG antibody(+) | Not reported | Right facial nerve, brainstem, thalamus, caudate nucleus, internal capsule, left temporal lobe,parietal and occipital lobes, hippocampus, insula, periventricular white matter | Acyclovir Methylprednisolone | Decreased arousal, spastic quadriparesis, severe dysphagia, tracheostomy dependence(5) |
| 20 | Takeshi et al.2006 | Male,36 | HIV+, fever, convulsions, herpes zoster, neck stiffness | CSF, VZV DNA and IgG antibody(+) Serum, VZV IgG antibody(+) | 9 days | A stenotic lesion in the left middle cerebral artery, higher-intensity perivascular areas within subcortical regions | Acyclovir Prednisolone | Complete recovery(0) |

| Case | Reference | Sex, age(years) | Clinical features | Diagnosis test | Time from Herpes zoster infection | Affected brain region | Treatment | Outcome (mRS) |
|---|---|---|---|---|---|---|---|---|
| 21 | Deepti et al.2012 | Female,48 | HIV+, rash, headache, vomit, numbness of the left half of the face and right arm | CSF, IgG antibody(+) | 7 days | Left lateral medullary | Aspirin<br>Acyclovir<br>Prednisone | Complete recovery(0) |
| 22 | Gustavo et al.2008 | Female,24 | HIV+, rash, left peripheral facial palsy, headache and mild left sided weakness, dysarthria, and dysphagia | CSF, VZV DNA(+) | 2 weeks | Acute ischemic pontine infarction<br>MRA: multiple areas of narrowing and beading in posterior and anterior circulation<br>DSA: segmental caliber narrowing in distal vertebral arteries and basilar artery. Similar changes were seen in distal left internal carotid artery (ICA), proximal left middle cerebral artery, and proximal left anterior cerebral artery | Acyclovir<br>Methylprednisolone | Complete recovery(0) |
| 23 | Kalita et al.2004 | Male,27 | Herpes zoster, numbness on his left arm and face, left hemiplegia | CSF, IgG and IgM antibody(+) | 3 months | Right middle cerebral arterial territory, complete occlusion of the right MCA | Acyclovir | Complete recovery(0) |
| 24 | Jyotsna et al.2011 | Male,35 | HIV+, left-sided body weakness and slurred speech | CSF, VZV DNA(+) | Not reported | An acute right basal ganglia infarct<br>Bilateral carotid arteries revealed occlusion | Acyclovir | Minimal residual weakness(1) |
| 25 | Eleonora et al.2008 | Female,85 | Headache, mild hyperthermia, confusion and seizures | CSF, VZV DNA and IgG antibody(+) | Not reported | Right superior temporal gyrus, left paramedian parieto-occipital cortex | Acyclovir<br>Methylprednisolone | Death |

# Intracerebral Hemorrhage

The age of onset varied between 45 and 79 years old with a median age of 70.5. The sex ratio of the patients is 1:1. One-third of the patients had a history of immunosuppression use. Clinical presentations of patients included cognitive impairment (5/6, 83.33%), headache (4/6, 66.67%), hemiplegia (4/6, 66.67%) and fever (4/6, 66.67%).

Multifocal cerebral hemorrhage was found in 66.67% located in parietal lobe (3/6, 50%), occipital lobe (2/6, 33.33%), temporal lobe (2/6, 33.33%), frontal lobe (2/6, 33.33%), cerebellum (1/6, 16.67%) and brainstem (1/6, 16.67%). There were two patients with ventricular and subarachnoid hemorrhage. Evidence of vasculitis was found in 16.67% (1/6) of patients. DSA and MRA examinations revealed multiple beaded stenosis in both the anterior and posterior circulation vessels.

100% (5/5) of the patients received antiviral therapy, and among them 40% (2/5) had used steroid at the early stage of the disease. However, 60% (3/5) of the patents had a poor prognosis or died (not mention of therapy and prognosis in one patient).

Demographics, clinical features, imaging abnormalities, and outcome were presented separately for patients with intracerebral hemorrhage in Table 3. The characteristics of the included cases were presented in Table 4.

Table 3
Demographics, clinical features, imaging abnormalities, and outcome are presented for patients with intracerebral hemorrhage

| **Demographics** | |
|---|---|
| *n* | 6 |
| Median age (IQR), years | 70.5(45–79) |
| Male gender | 50% (3/6) |
| Immunosuppression | 33.33% (2/6) |
| Clinical features | |
| Headache | 66.67% (4/6) |
| Fever | 66.67% (4/6) |
| Cognitive impairment | 83.33% (5/6) |
| Hemiplegia | 66.67% (4/6) |
| Diagnostic testing | |
| PCR positive for VZV(CSF) only | 33.33% (2/6) |
| anti-VZV IgG positive for VZV(CSF) only | 16.67% (1/6) |
| Both PCR and anti-VZV IgG positive for VZV(CSF) | 16.67% (1/6) |
| Both anti-VZV IgG positive for VZV CSF and serum | 33.33% (2/6) |
| Neuroimaging | |
| Evidence for vasculitis | 16.67% (1/6) |
| Affected areas of circulation | |
| Anterior | 0% (0/6) |
| Posterior | 16.67% (1/6) |
| Both anterior and posterior | 83.33% (5/6) |
| Distribution of lesions | |
| Single | 33.33% (2/6) |
| Multiple | 66.67% (4/6) |
| Treatment | |
| Acyclovir treatment | 100% (5/5) |
| Steroid treatment | 40% (2/5) |
| Outcome | |
| Good outcome (mRS 0–2) | 40% (2/5) |
| Unfavorable outcome (mRS 3–5) | 0% (0/5) |
| Death | 60% (3/5) |

Table 4
The characteristics of six intracerebral hemorrhage cases

| Case | Reference | Sex, age(years) | Immuno-suppression | Clinical features | Diagnosis test | Affected brain region | Treatment | Outcome (mRS) |
|---|---|---|---|---|---|---|---|---|
| 1 | Inés et al.2014 | Female,45 | Yes | Headache, hemianopia, nausea, vomi, right brachiocrural hemiparesis, rash | CSF and serum, anti-VZV IgG(+) | Hemorrhage in the occipital and right parietal lobes associated with a left frontal subarachnoid hemorrhage | Acyclovir | NIHSS 2(2) |
| 2 | Wonki et al.2012 | Female,66 | Yes | Headache, fever, papules, confusional mental state | CSF ,anti-VZV IgM(+) | Hemorrhage in the left midbrain region, left ventral pons and midbrain extending to the contralateral medial temporal lobe | Acyclovir Antibiotics | Death |
| 3 | Kazuya et al.2015 | Male,75 | No | Stupor | CSF ,anti-VZV IgM(+) and VZV DNA (+) | Hemorrhage in right intracerebellar | Acyclovir Methylprednisolone | Death |
| 4 | Jun et al.2018 | Male,75 | No | Herpes zoster, headache, fever, confusion, hemiplegia | CSF ,VZV DNA (+) | Hemorrhage in the left parietal lobe | Acyclovir | Death |
| 5 | Ganesh et al.2018 | Female,79 | No | Confusion, fever, rash, paraplegia, leg numbness | CSF ,VZV DNA (+) | Hemorrhage in the right parietal lobe, occipital horns of the lateral ventricles | Not reported | Not reported |
| 6 | Maria et al.2008 | Male,66 | No | Headache, nausea, vomit, disorientation, fever, neck stiffness and coma | CSF, VZV DNA and IgG (+) Serum, VZV IgG (+) | Hemorrhage in the temporal regions, intraventricular and subarachnoid hemorrhage | Acyclovir Dexamethasone Antibiotics | Complete recovery(0) |

## Venous Sinus Thrombosis

Three young men (20–30 years old) developed headache, fever, vomiting, papillary edema, and weakness in the left upper limb and left lower limb for two weeks after chickenpox infection. CSF was positive for anti-VZV IgG. MRV and MRI confirmed venous sinus thrombosis with diffuse cerebral edema. All patients had venous sinus thrombosis in the transverse sinus (TS). One of them had thrombosis in superior sagittal, bilateral transverse and right sigmoid sinuses. All patients improved completely with low-molecular-weight heparin and oral anticoagulants. Only one patient also received antiviral therapy and Another patient also had oral steroid.

The characteristics of the included cases were presented in Table 5.

Table 5
The characteristics of three venous sinus thrombosis cases

| Case | Reference | Sex, age(years) | Clinical features | Diagnosis test | Time from Herpes zoster infection | Affected brain region | Treatment | Outcome(mRS) |
|---|---|---|---|---|---|---|---|---|
| 1 | Anuradha et al.2018 | Male,20 | Chicken-pox, headache, fever, aphasic, left lateral rectus palsy, papilledema | CSF and serum ,anti-VZV IgM(+) | 2 weeks | Dural sinus thrombosis(left transverse, sigmoid sinuses, and internal jugular vein) | Mannitol, Anticoagulant Steroids | Complete recovery(0) |
| 2 | Gayathri et al.2016 | Male ,23 | Rash, headache, vomit, fever, weakness of left upper limb and left lower limb | CSF, anti-VZV IgG(+) and VZV DNA(+) | 2 weeks | Diffuse cerebral edema Thrombosis in superior sagittal, bilateral transverse and right sigmoid sinuses | Acyclovir Asprin Anticoagulants | Complete recovery(0) |
| 3 | Sujay et al.2012 | Male,30 | Chicken-pox, headache, vomit | CSF, anti-VZV IgG(+) | 15 days | Diffuse cerebral edema Thrombosis in superior sagittal and right transverse sinuses | Heparin Anticoagulants | Complete recovery(0) |

Table 6
Comparison of demographics, Clinical features between ischemic stroke and intracerebal hemorrhage

| | | Ischemic stroke | Intracerebral hemorrhage | *P* |
|---|---|---|---|---|
| *n* | | 25 | 6 | |
| Age(years) | | 52 | 70.5 | 0.158 |
| Sex, *n* (%) | male | 18(72) | 3(50) | 0.358 |
| | female | 7(28) | 3(50) | |
| History of varicella zoster infection, *n* (%) | | 15(60) | 5(83.33) | 0.383 |
| Headache, *n* (%) | | 9(36) | 4(66.67) | 0.208 |
| Fever, *n* (%) | | 6(24) | 4(66.67) | 0.067 |
| Cognitive impairment, *n* (%) | | 14(56) | 5(83.33) | 0.363 |
| Hemiplegia, *n* (%) | | 8(32) | 4(66.67) | 0.174 |
| Antiviral drug combined steroid, *n* (%) | | 15(n = 24, 62.50) | 2(n = 5, 40) | 0.370 |
| *For statistical test analysis, $\chi^2$test or Fisher exact test was used to compare categorical variables. Date of age use mean and SD. | | | | |

## Discussion

In this study, we found that the incidence of ischemic stroke associated with VZV infection was high, accounting for about 73.53%, while intracerebral hemorrhage or venous sinus thrombosis was relatively rare. The incidence in men was higher than in women in ischemia or venous sinus thrombosis groups. In terms of onset age, the middle-aged was common in the ischemic stroke group, the elderly in the hemorrhagic group, and the young in the venous sinus thrombosis group. Compared with other clinical symptoms, cognitive impairment was the most common either in the ischemic group or hemorrhagic group. The lesions after VZV-associated cerebral infarction or hemorrhage were mutifocal and was most common in the parietal lobe. If venous sinuses were involved, thrombosis was common in TS. Multiple stenosis of the anterior and posterior circulation vessels was found by DSA or MRA. Antiviral treatment may be useful in the ischemic group and anticoagulant therapy was essential in the venous sinus thrombosis group, while the role of glucocorticoids remained unclear in the treatment of VZV-associated stroke. Among the three groups, the patients with venous sinus thrombosis improved completely, however, the patients with intracerebral hemorrhage had poor prognosis.

There was no statistical significance in onset age or sex in our study despite the trend observed, which may need many large samples to get a credible conclusion. There was median time with 42.8 days from herpes zoster infection to the occurrence of neurologic symptoms in patients with ischemic stroke. Previous study has shown that there was usually a long delay (mean 4.1 months) [42]. The discrepancy was caused by different included samples, that is to say, children were included in other studies. Larissa et al. [43] reported that the time from symptom onset to admission was 3.5 days after HSV infection. It meant there were some biological differences although both VZV and HSV were alpha-viruses. Clinical reactivation of HSV can occur repeatedly and mostly in the young, whereas clinical VZV reactivation typically occurs once per individual and predominantly in 25 % of the elderly [44]. DNA replication occurs within 24 h for HSV, while VZV DNA replication can be seen as late as 5 days in human trigeminal ganglionic explants [45]. There may partly contribute to the different latency between HSV and VZV infection.

The main clinical manifestations of patients were cognitive impairment, followed by headache, hemiplegia whether in the ischemic group or in the hemorrhagic group, which may be related with cerebral damaged locations caused by vasculopathy associated with VZV infection. In the two groups, the lesions were multiple and involved in the parietal, frontal or temporal lobes. It didn't accord with the characteristics of cerebrovascular diseases induced by atherosclerosis, and was more prone to angioinflammatory lesions. In this study, we found all the three men had have thrombosis in TS. As we know the superior sagittal sinus was the major anatomical site of sinus thrombosis, followed by TS. However, hypoplasia or aplasia of TS is a common anatomic variation [46, 47].This made some people with the variation more prone to sinus thrombosis in the presence of certain risk factors, such as inflammation, infection or hypercoagulability.

Ischemic lesions associated with VZV encephalitis were common while herpes simplex encephalitis (HSE) is a hemorrhagic necrotizing inflammatory process, indicating different mechanisms of vasculopathy after infection of the two viruses. It has been found that direct cytolytic virus replication and indirect immune-mediated processes are responsible for neurons, glial and axonal damage in the pathologic course of HSE [48]. But after VZV reactivation, the virus spreads axially along the trigeminal nerve and other cerebral ganglion where it is long dormant, to infect the arterial adventitia and then extend transmurally through the whole artery well. The pathological manifestations were disruption of the internal elastic lamina,hyperplastic intima, decreased medial smooth muscle cells and inflammatory cell infiltration. It was further confirmed by Gilden et al., and they found the existence of VZV particles in the cerebral vessels through anatomical and pathological examination of the whole brain in the patients who died after VZV infection[49]. To some extent, it explained the mechanism of vasculitis response after VZV infection. In this research, multiple stenosis of the anterior and posterior circulation vessels was examined by DSA or MRA. Lesions in large vessels were common, followed by small vessels in ischemic group and multiple beaded stenosis were showed in hemorrhagic group. All three patients with venous sinus thrombosis had thrombus in two or more vessels. This angiopathic characteristics were more consistent with vasoinflammatory lesions.

Katchanov et al. detected a direct enhancement of the arterial wall in their patients with VZV vasculopathy [22]. The detection of contrast material within the vessel wall on enhanced T1-weighted images was considered to be a direct radiological sign of vasculitis and visualizes the inflammatory process in the vessel wall [50]. High-resolution MRI (HRMR) [51] revealed vessel wall thickening and enhancement in patients with VZV vascular disease, and after treatment showed improvement of stenosis. Swartz et al. evaluated intracranial vascular lesions induced by atherosclerotic disease or CNS inflammatory disease. They found there was focal, eccentric vessel wall enhancement for the former, However, there was diffuse, concentric vessel wall enhancement for the CNS inflammatory diseases [52].

Specificity of VZV DNA is 97%, enabling rapid diagnosis and early treatment. But VZV DNA in the CSF cannot be detected 14–50 days after infection because of the incubation period. The value of anti-VZV IgG antibody is greater than that of VZV DNA in chronic cases [53]. The diagnosis of vascular diseases related with VZV can only be ruled out when both CSF VZV DNA and anti-VZV IgG antibodies are negative. In our study, the diagnosis was confirmed by detecting anti-VZV IgG antibody or VZV DNA in CSF. In particular, one patient was diagnosed by viral culture.

In ischemic stroke group, early intravenous acyclovir was given to all patients whose treatments were referred to, and most of them improved. It suggested antiviral treatment may be useful. There was no significant difference in either mortality or favorable prognosis between antiviral medication therapy alone and antiviral drug combined with steroid, suggesting the role of glucocorticoids in the treatment of VZV-associated ischemic stroke remains unclear. Only one patient received anti-platelet treatment besides the usage of antiviral and steroid and recovered well. In a randomized clinical trial of tuberculous meningitis, aspirin reduced mortality by 19% [54].But the efficacy of anti-platelet drugs in acute ischemic events of infection-associated stroke was unknown. Prospective, multicenter and randomized controlled trials are currently required to evaluate the efficacy of antiplatelet drugs and/or steroid therapy in ischemic stroke induced by VZV infection.

More than half of the patients with intracerebral hemorrhage had poor prognosis. The reasons may be related to advanced age of onset, brain stem compression, cerebellar involvement and severe tissue edema. The three young male patients with venous sinus thrombosis in our study had good prognosis after anticoagulant therapy, indicating the necessity of anticoagulation therapy.

## Conclusion

Cerebral diseases associated with VZV encephalitis is not uncommon. When the patient represents with some neurological symptoms within 2 months after VZV infection, and multiple lesions probably induced by vasculitis showed in neuroimaging, cerebral complications related with VZV infection should be considered even though the existence of some vascular risk factors for atherosclerosis. HRMR is an alternative method to distinguish the nature of vascular lesions. Ischemic stroke related with VZV encephalitis is common and mainly affects the middle-aged. In general, the young patients with venous sinus thrombosis improve completely, however, the old patients with intracerebral hemorrhage have poor prognosis.

We acknowledge several limitations to our study. A publishing bias for severe cerebral vascular diseases after VZV infection must be anticipated. There were only six cases of intracerebral hemorrhage and three cases of venous sinus thrombosis. More large samples and evidence-based medical studies are needed to clarify informative conclusions.

## List Of Abbreviations

VZV
varicella-zoster virus; HSV:herpes simplex virus; CNS:central nervous system; CT:computed tomography; MRI:magnetic resonance imaging; MRA:magnetic resonance angiography; MRV magnetic resonance venography; DSA:digital subtraction angiography; CSF:cerebrospinal fluid; mRS:modified Rankin scale; TS:transverse sinus; HSE:herpes simplex encephalitis; HRMR:high-resolution magnetic resonance imaging

## Declarations


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Not applicable.


### Authors' contributions

The final manuscript was read and approved by all authors. Hangfei Wu performed the experiments, analyzed the data, generated the figures, and drafted the manuscript. Ruoru Wang analyzed the data, generated the figures, and drafted the manuscript. Yuanyuan Li and Xu Sun analyzed the data. Jiasi Li and Xiaoying Bi designed and monitored this study and edited the manuscript.

### Availability of data and materials

All data are fully available without restriction.


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### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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