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REVIEW

Cerebrovascular Complications After Adult-Onset Varicella-Zoster Virus Encephalitis in the Central Nervous System: A Literature Review

Hangfei Wu*, Ruoru Wang*, Yuanyuan Li, Xu Sun, Jiasi Li, Xiaoying Bi

Department of Neurology, Shanghai Changhai Hospital, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiaoying Bi; Jiasi Li, Department of Neurology, Shanghai Changhai Hospital, No. 168, Changhai Road, Yangpu District, Shanghai, 200433, People's Republic of China, Email bixiaoying2013@163.com; lijiasisissi@163.com

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

Methods: Literature review from January 2000 to December 2019. We searched for studies published in PubMed, Embase and Chinese Biomedical Literature Database. Clinical symptoms, neuroimaging findings, treatment and outcome were evaluated.

Results: We analyzed 31 articles with a total of adult-onset 34 cases, including 25 cases of ischemic stroke, 6 of intracerebral hemorrhage and 3 with venous sinus thrombosis. Ischemic stroke was the major complication after VZV encephalitis accounting of 73.35%. There were more males than females in ischemia or venous sinus thrombosis groups. The middle-aged was prone to cerebral infarction, the elderly was for cerebral hemorrhage, and the young was for venous sinus thrombosis. Cognitive impairment was the most common symptom either in the ischemic group or hemorrhagic group. The lesions of VZV-associated cerebral infarction or hemorrhage were multifocal and mostly involved in the parietal lobe, followed by frontal or temporal lobes. Venous sinus thrombosis was common in the transverse sinus. Multiple stenosis of the anterior and posterior circulation vessels was found. A 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; however, 60% of the patients with intracerebral hemorrhage had a poor prognosis or died.

Conclusion: Ischemic stroke was the majority of cerebrovascular complications after VZV encephalitis, which mainly occurred in middle-aged men. The lesions of VZV-associated cerebral infarction or hemorrhage were multifocal and did not accord with the characteristics of cerebrovascular diseases induced by atherosclerosis. The patients with venous sinus thrombosis had a relatively good prognosis. When the patient represents with some neurological symptoms about one month after VZV encephalitis, and multiple lesions probably induced by vasculitis are showed in neuroimaging, cerebrovascular complications related to VZV infection should be considered.

Keywords: varicella-zoster virus encephalitis, ischemic stroke, cerebral infarction, intracerebral hemorrhage, venous sinus thrombosis, vasculitis

Introduction

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 that 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]

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VZV can also 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 as discribed in Nagel and Gilden.[4] A study consisting of pediatric patients showed the mortality rate of cerebrovascular diseases associated with VZV infection was as high as 35% in the 1970s.[5] In a population-based study, the stroke risk of older adults with herpes zoster infection within 3 months was reportedly increased 1.53-fold.[6]

In recent years, it has been gradually recognized that the complications following VZV encephalitis may manifest as subsequent cerebral hemorrhage or infarction. However, most of the researches were case reports with only several cases or involved with children. Here, we reviewed 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.

Materials and Methods

Literature Search and Selection

We performed a literature search to identify all published cases of cerebral vascular complications of patients with VZV proven central nervous system infection. We included patients aged 18 and more. 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 independent investigators to determine inclusion in the final review.

All the patients met the diagnostic criteria reported as follows:[7,8] (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,[9] and (3) exclusion of other causes for cerebral vascular disease.

Data Extraction

Two investigators collected data from the selected articles. The following information was extracted: last name of the first author, demographics, clinical symptoms, etiology, CSF examination, time from onset of varicella 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 mRS score of 0–2 points.[10]

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

Results

Literature Review

From January 2000 to December 2019, through 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,[11–33] 6 cases (6/34, 17.65%) with intracerebral hemorrhage,[34–39] and 3 patients (3/34, 8.82%) with venous sinus thrombosis.[40–42]

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. Sixty percent (15/25) of the patients had previous history of herpes zoster infection, and 8% (2/25) had varicella. Sixteen percent (4/25) had no history of herpes zoster experienced. Sixteen percent (4/25) were not reported whether it was varicella or herpes infection. About 66.67% (10/15) of the patients developed ischemic manifestations within one month after VZV infection. The longest interval of onset was seven months after the existence of VZV with a mean 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 outcomes were presented separately for patients with ischemic stroke in Table 1. The characteristics of the included cases are presented in Table 2.

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. About 83.33% (5/6) had previous history of herpes zoster infection, while the remaining 1 patient denied the history of herpes zoster experienced. The average time between the infection and the complications was 8 days. 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.

One hundred percent (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 patients had a poor prognosis or died (not mention of therapy and prognosis in one patient).

Demographics, clinical features, imaging abnormalities, and outcomes were presented separately for patients with intracerebral hemorrhage in Table 3. The characteristics of the included cases are presented in Table 4. Comparison of demographics, clinical features between ischemic stroke and intracerebral hemorrhage in Table 5.

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. One patient had previous history of herpes zoster infection, and the other two had varicella. These three patients developed neurological manifestations about two weeks after

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 (mean), 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)

VZV 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 are presented in Table 6.

Table 2 The Characteristics of Twenty-Five Ischemic Stroke Cases

Case	Reference	Gender, Age (Years)	Clinical Features	Diagnosis Test	Time from VZV Infection	Affected Brain Region	Treatment	Outcome (mRS)
1	David et al. 2015[11]	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[12]	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[13]	Male,72	Headache, anorexia, nausea, herpes zoster, memory deficit, incoherent speech	CSF, PCR VZV (+)	11 days	Posterior ischemic optic neuropathy	Prednisolone Acyclovir	Not reported
4	Francisco et al. 2014[14]	Male,26	Herpes zoster, VZV meningitis	CSF, PCR VZV (+)	4 months	Right occipital lobe	Not reported	Not reported
5	Francesca et al. 2014[15]	Female,67	Herpes zoster, 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[16]	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, no history of zoster	CSF, anti-VZV IgG (+)	No history of zoster experienced	Left corona radiata, basal ganglia, right basal ganglia, both thalamus, periventricular white matter, right superior cerebellum	Cyclophosphamide Prednisone; Acyclovir	Complete recovery (0)
7	Yu-Miyazaki et al. 2008[17]	Male,66	Headache, fever, and altered mental status, herpes zoster, 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. 2005[18]	Male,57	Fever, headache, abnormal behavior, mental retardation, no history of zoster	CSF, PCR VZV (+)	Not reported	Amygdala, cerebellum, brainstem, deep white matter	Acyclovir	Death
9	Manuel et al. 2003[19]	Female,68	Mental retardation, difficulty walking, right hemiplegia, aphasia, herpes zoster	CSF, PCR VZV (+)	Not reported	Left internal capsule	Acyclovir	Death
10	Nasir et al. 2003[20]	Male,52	Chicken pox, headache, nausea, vomit, photophobia, confusion	CSF, viral culture VZV (+)	5 weeks	Left frontal, left parietal, right medial temporal, and right occipital lobes	Ceftriaxone Methylprednisolon Acyclovir	Right-side hemiparesis persisted (2)

(*Continued*)

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Table 2 (Continued).

Case	Reference	Gender, Age (Years)	Clinical Features	Diagnosis Test	Time from VZV Infection	Affected Brain Region	Treatment	Outcome (mRS)
11	John et al. 2013[21]	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[22]	Female,67	Herpes zoster, 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[23]	Male,36	Locked-in syndrome	CSF, PCR VZV (+)	Not reported	Bilateral pons and midbrain	Acyclovir Methylprednisolone	Severe (5)
14	Katchanov et al. 2010[23]	Male,32	Global aphasia, right hemiplegia	CSF, VZV-IgG antibody (+)	Not reported	Left MCA territory, left PCA territory	Acyclovir, Methylprednisolone	Severe (5)
15	Gilden et al. 2002[24]	Male,71	Herpes 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[24]	Male,76	Herpes zoster, headache, lost vision in the left eye	CSF, VZV-IgG antibody (+)	7 months	Posterior ischemic optic neuropathy	Acyclovir	Complete recovery (0)
17	Richard et al. 2011[25]	Male,80	Herpes 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[26]	Male,28	HIV+, HCV+, progressive dizziness, left-side weakness	CSF, VZV DNA and IgG antibody (+)	No history of zoster experienced	Right occipitotemporal, parieto-occipital cortices	Acyclovir	Complete recovery (0)
19	Andrew et al. 2003[27]	Female,51	Confusion, disorientation, vertigo, decreased right hearing, right-sided clumsiness left leg weakness, seizure,	CSF, VZV IgG antibody (+)	No history of zoster experienced	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[28]	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)
21	Deepti et al. 2012[29]	Female,48	HIV+, herpes zoster, headache, vomit, numbness of the left half of the face and right arm	CSF, IgG antibody (+)	7 days	Left lateral medullary	Aspirin Acyclovir Prednisone	Complete recovery (0)
22	Gustavo et al. 2008[30]	Female,24	HIV+, herpes zoster, left peripheral facial palsy, headache and mild left sided weakness, dysarthria, and dysphagia	CSF, VZV DNA (+)	2 weeks	Acute ischemic pontine infarction MRA: multiple areas of narrowing and beading in posterior and anterior circulation 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 Methylprednisolone	Complete recovery (0)
23	Kalita et al. 2004[31]	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[32]	Male,35	HIV+, left-sided body weakness and slurred speech	CSF, VZV DNA (+)	Not reported	An acute right basal ganglia infarct Bilateral carotid arteries revealed occlusion	Acyclovir	Minimal residual weakness (1)
25	Eleonora et al. 2008[33]	Female,85	Headache, confusion and seizures	CSF, VZV DNA and IgG antibody (+)	Not reported	Right superior temporal gyrus, left paramedian parieto-occipital cortex	Acyclovir Methylprednisolone	Death

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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)
Days from Herpes zoster infection to the occurrence of neurologic symptoms (mean), n=5	8(1–16)
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)

Discussion

In this study, we found that ischemic stroke was the major complication after VZV encephalitis accounting of 73.35% followed with intracerebral hemorrhage and venous sinus thrombosis. There were more males than females 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 multifocal and were 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 VZV 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).[43] The discrepancy was caused by different included samples, that is to say, children

were included in other studies. Hauer et al[44] 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.[45] 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.[46] 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 to 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 did not 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.[47,48] 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.[49] 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.[50] 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 was showed in hemorrhagic group. All three patients with venous sinus thrombosis had thrombus in two or more vessels. These 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.[23] 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.[51] High-resolution MRI (HRMR)[52] revealed vessel wall thickening and enhancement in patients with VZV vascular disease, and after treatment showed improvement in 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.[53]

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.[54] The diagnosis of vascular diseases related to 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 that 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%.[55] But the efficacy of anti-platelet drugs in acute ischemic events of infection-associated stroke was unknown. Prospective, multicenter and randomized controlled trials

Table 4 The Characteristics of Six Intracerebral Hemorrhage Cases

Case	Reference	Gender, Age (Years)	Time from VZV Infection	Clinical Features	Diagnosis Test	Affected Brain Region	Treatment	Outcome (mRS)
1	Inés et al.2014[34]	Female,45	16 days	Headache, hemianopia, nausea, vomit, hemiparesis, herpes zoster	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[35]	Female,66	7 days	Headache, fever, herpes zoster, confusion	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[36]	Male,75	2 days	Herpes zoster, coma	CSF, anti-VZV IgM (+) and VZV DNA (+)	Hemorrhage in right intracerebellar	Acyclovir Methylprednisolone	Death
4	Jun et al.2018[37]	Male,75	1 days	Herpes zoster, headache, fever, confusion, hemiplegia	CSF, VZV DNA (+)	Hemorrhage in the left parietal lobe	Acyclovir	Death
5	Ganesh et al.2018[38]	Female,79	2 weeks	Confusion, fever, herpes zoster, 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[39]	Male,66	Not reported	Headache, nausea, vomit, disorientation, fever, neck stiffness and coma, no herpes zoster	CSF, VZV DNA and IgG (+) Serum, VZV IgG (+)	Hemorrhage in the temporal regions, intraventricular and subarachnoid hemorrhage	Acyclovir Dexamethasone Antibiotics	Complete recovery (0)

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.

Table 5 Comparison of Demographics, Clinical Features Between Ischemic Stroke and Intracerebral 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

Table 6 The Characteristics of Three Venous Sinus Thrombosis Cases

Case	Reference	Gender, Age (Years)	Clinical Features	Diagnosis Test	Time from VZV Infection	Affected Brain Region	Treatment	Outcome (mRS)
1	Anuradha et al. 2018[40]	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[41]	Male,23	Herpes zoster, 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 Aspirin Anticoagulants	Complete recovery (0)
3	Sujay et al. 2012[42]	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)

Conclusion

Cerebral vascular diseases associated with VZV encephalitis is not uncommon. When the patient represents with some neurological symptoms about one month after VZV encephalitis, and multiple lesions probably induced by vasculitis are showed in neuroimaging, cerebrovascular complications related to 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.

We acknowledge several limitations of our study. A publishing bias for severe cerebral vascular diseases after VZV encephalitis 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.

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.

Data Sharing Statement

All data are fully available without restriction.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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