Correspondence

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Herpes zoster central nervous system complication: An increasing trend of acute limbic encephalitis

Hiroshi Shoji[1,*], Shino Umeda[1], Makoto Kanazawa[2], Noriyuki Koga[3], Hayato Takaki[3], Shinji Kitsuki[3], Mikiaki Matsuoka[3], Tomonaga Matsushita[3], Yoshihisa Fukushima[3], Kenji Fukuda[3]

[1] Division of Neurology, St. Mary's Hospital, Kurume-City, Fukuoka, Japan;
[2] Department of Neurology, Fukuoka Red Cross Hospital, Fukuoka-City, Japan;
[3] Cerebrovascular Medicine, St. Mary's Hospital, Kurume-City, Fukuoka, Japan.

SUMMARY: Varicella zoster virus (VZV) causes chickenpox as the primary infection and then becomes latent in the cranial and spinal ganglia. VZV can reactivate with aging, immunosuppression, stress, and other factors. In our series of 15 patients with herpes zoster (HZ) central nervous system complications (8 males and 7 females, ages 41-86 years), we identified several types of complications: acute encephalitis, vasculitis, meningitis, and cranial nerve palsies, with acute limbic encephalitis (ALE) (n = 5) being particularly noteworthy. The elderly patient treated initially showed skin rash around the eye, altered consciousness, and medial temporal lesions on MRI; four similar patients were then observed. Aside from a few case reports, there are no comprehensive reports of HZ ALE. The HZ rashes of our five HZ ALE patients were mostly in the trigeminal nerve area, with two cases of disseminated rashes. Five patients had positive cerebrospinal fluid VZV polymerase chain reaction results, and MRI revealed medial temporal lobe lesions. Compared to HZ peripheral nerve complications, more variable invasive routes were presumed, *via* the brain-stem, vasculopathy root, meningeal spread, and viremia. The incidence of HZ is increasing worldwide, and clinicians should be aware of HZ ALE that shows fever, HZ skin rash, and altered consciousness.

Keywords: herpes zoster, varicella-zoster virus, cranial nerve ganglia, acute limbic encephalitis, limbic system

1. Introduction

Varicella zoster virus (VZV) causes varicella as the primary infection and then becomes latent in trigeminal and spinal ganglia (*1,2*). Herpes zoster (HZ) central nervous system (CNS) complications caused by VZV reactivation include acute encephalitis, cerebral infarction due to vasculitis, meningitis, and cranial nerve palsies, and cases of patients with HZ CNS complications have been accumulating from medical departments such as internal medicine, dermatology, ophthalmology, and otolaryngology (*3-5*). In an aging society, HZ is more prevalent in adults and elderly persons with immunosuppression (*6*), and these individuals' complications can severely impair one's quality of life (QOL) and make long-term hospitalization necessary.

In our present retrospective analyses of the cases of 15 patients with HZ CNS complications who were treated at our hospital in 2012-2023, it was particularly noteworthy that five of the patients had acute limbic encephalitis (ALE). We first observed an 86-year-old woman with Alzheimer's disease who presented with an HZ skin rash on the trigeminal nerve area, impaired consciousness, and seizures. Her cerebrospinal fluid (CSF) was positive in a VZV polymerase chain reaction (PCR), and magnetic resonance imaging (MRI) revealed medial temporal lobe lesions (*7*). Four similar patients with ALE were encountered after this patient. The invasive routes of CNS complications from VZV reactivation in the trigeminal ganglia are presumed to be *via* the brainstem or carotid artery or meningeal spread.

Our search of the relevant literature identified no comprehensive reports of HZ ALE, and the pathophysiology is not clear. We report results of our retrospective analysis of mainly five patients with ALE among 15 patients with HZ/VZV, focusing on the patients' underlying diseases, vaccination history, skin rash distribution, virological test results such as CSF VZV PCR, MRI findings, treatments, and related disorders.

2. Research design and data collection

From April 2012 to March 2023, 15 patients with

HZ CNS complications such as acute encephalitis, meningitis, vasculitis, and others were treated at the departments of cerebrovascular medicine and neurology at our hospital in Fukuoka, Japan. We retrospectively analyzed the patients' cases based on their hospitalization histories concerning underlying disease, HZ skin rash, neurological form, length of hospitalization, CSF test results, CSF VZV PCR results, VZV antibody findings, MRI results including contrast-enhanced fluid attenuated inversion recovery (FLAIR) images, and the time course of these findings, as well as treatment(s) and outcomes.

The diagnostic criteria for HZ ALE are the presence of: fever, rash, impaired consciousness, abnormal behavior, seizures, CSF VZV PCR-positivity, and MRI results exhibiting medial temporal lobe lesions. Cases in which ALE was clinically suspected but MRI findings were unclear were classified as possible ALE. In several cases, electroencephalography (EEG) findings were examined. We considered patient cases lacking localized brain symptoms and showing fever, headache, meningeal irritation symptoms, and an increased CSF cell count as having meningitis. This study was conducted in accord with the Declaration of Helsinki and was submitted to and approved by our Hospital's Ethics Committee (Research 24-0505).

3. Key research findings

Our hospital is located in southwestern Japan and provides emergency medical care for ~300,000 local residents. Table 1 summarizes the patients' clinical characteristics. The mean age of the eight males and seven females was 74.1±10.3 years (range 41-86 years). The neurologic forms were classified according to the above diagnostic criteria: ALE (n = 5, including one patient with possible ALE), acute encephalitis (n = 3), cerebellitis (n = 1), meningitis (n = 5), and multiple cranial nerve palsies (n = 1). The patients' underlying diseases were hypertension (n = 9), dyslipidemia (n = 3), Alzheimer disease (n = 2), lumbar deformity (n = 2), colon cancer (n = 1), prostatic hypertrophy (n = 1), and others. Regarding the HZ dermatome, we identified the trigeminal region (first branch n = 6, second n = 2), VIII region (n = 1), VIII + generalized (n = 2), cervical region + generalized (n = 1), varicella rash (n = 1), thoracic region (n = 1), and sacral region (n = 1).

The hospitalization period was 32.5±10.3 days, and ten patients required a 1-month hospitalization at the acute stage for antiviral therapy. Average length of hospital stay for the five patients with ALE was 36.0±3.7 days, which is longer compared to the other types. An increase in the CSF cell number > 5 cells was observed in all 15 patients (mean 73.5 cells, range 7-381/μL). The VZV PCR result for the CSF was positive in 13 patients. All patients were intravenously administered acyclovir 500 mg 3×/day for 2-3 weeks, and 3 days of prednisolone pulse was added for three patients.

Table 1. Clinical characteristics of the 15 patients with herpes zoster central nervous system complications treated in 2012-2023

Clinical characteristics	Patients, *n* (%).
Age, years, mean ± SD, gender	74.1 ± 10.3 years 8 males, 7 females
Underlying disease	
Hypertension	9 (60%)
Alzheimer type dementia	2 (13%)
Malignancy	2 (13%)
Diabetes	2 (13%)
Other	5 (33%)
Herpes zoster	
V-1, V-2	6, 2 (40, 13%)
VIII, VIII + generalized	1, 2 (7, 13%)
C + generalized	1 (7%)
Varicella rash	1 (7%)
Th, S	1, 1 (7, 7%)
Neurologic form	
Acute limbic encephalitis	5 (33%)
Acute encephalitis	3 (20%)
Cerebellitis	1 (7%)
Meningitis	5 (33%)
Cranial nerve palsies	1 (7%)
Cerebrospinal fluid	
Cell count, /μL mean (range)	73.5 ± 79.5 (7-381)
VZV PCR positive	13/15 cases positive
Blood VZV PCR positive	1/15
Treatment:	
ACV IV	2-3 weeks
VCV IO	
PLS pulse, 3 days	3 (20%)
Hospitalization, mean (range)	32.5 ± 10.3 days (16-52)
Acute limbic encephalitis, mean (range)	36.0 ± 3.7 days (31-45)
Sequelae	
Post-herpetic neuralgia	5 (33%)
Cognitive disability	4 (27%)
Bed-patient with full assistance	2 (13%)
Non	4 (27%)

ACV IV: acyclovir intravenous, C: cervical, PLS pulse: prednisolone pulse, PCR: polymerase chain reaction, S:sacral, Th: thoracic, VCV: valacyclovir intraoral, V: trigeminal, VII/VIII: facial/acoustic.

It is noteworthy that five patients with ALE were identified among 15 patients with VZV reactivation and CNS lesions. ALE as a complication requires long-term hospitalization and severely impairs an individual's activities of daily living (ADLs) and quality of life (QOL). As a representative case (Figure 1A), an 86-year-old woman with Alzheimer's disease presented at our hospital in 2013 with HZ skin rashes on the trigeminal nerve area, altered consciousness, and seizures in the left half-body. Her CSF was positive in a VZV PCR, and MRI diffusion-weighted imaging revealed high-intensity on the medial temporal lobe. EEG showed left-predominant slowing. The patient's cognitive ability was worsening, requiring transfer to a facility (*7*).

An 84-year-old woman presented with HZ skin rashes on the left thoracic spinal Th11–12 site, fever, and impaired consciousness. Her CSF showed increased cells at 106/μL, VZV PCR-positivity was observed,

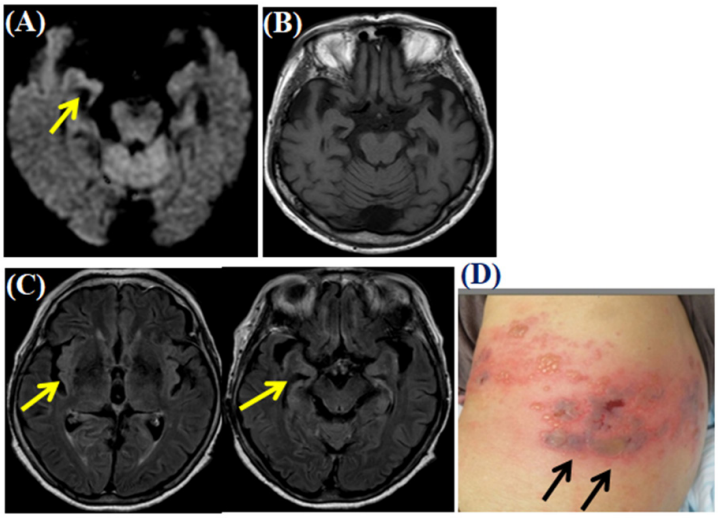

Figure 1. MRI findings of two patients with herpes zoster (HZ) acute limbic encephalitis and HZ skin rash. (A) An 86-year-old female with Alzheimer disease, had acute limbic encephalitis (ALE) with HZ in the first branch of the right trigeminal nerve, and impaired consciousness. This MRI diffusion-weighted image at acute stage showed high-intensity at medial temporal lobe (*arrow only on right side*). **(B)** MRI T1 image at recovery stage exhibited atrophy of the bilateral hippocampal regions. The MRI images are reprinted with permission from reference reported by Matsuoka *et al.* (*7*). **(C, D)** This 84-year-old female with left thoracic spinal Th11–12 HZ showed fever, and impaired consciousness. Contrast-enhanced fluid attenuated inversion recovery (FLAIR) MRI images showed bilateral medial temporal lobe and insular lobe lesions (*arrow only on the right side*).

and MRI exhibited bilateral medial temporal lobe and insula lesions (Figure 1B, C). She received 3 weeks of treatment with acyclovir and prednisolone 3-day pulse and was eventually transferred to a rehabilitation hospital with cognitive disability.

4. Discussion

A typical example of ALE is herpes simplex virus (HSV) encephalitis caused by HSV-1. Acute encephalitis in adults and the elderly caused by HSV-1 appears with fever, impaired consciousness, convulsions, abnormal behavior, hallucinations, and meningeal irritation symptoms; CSF tests show increased cell counts, HSV PCR is positive, and MRI shows limbic system lesions in the hippocampus, amygdala, insula, and/or temporal lobes with a unilateral predominance. An early administration of acyclovir allows approx. half of the treated patients to return to society (*8*). Additional forms of ALE are non-herpetic ALE, N-methyl-D-aspartate (NMDAR) ALE, autoimmune limbic encephalitis, and several paraneoplastic ALE (*9*).

As another herpesvirus group, human herpesvirus-6 (HHV-6-A) has caused ALE in hematopoietic stem cell transplants (*10*); it peaked 3 weeks after transplantation and occurred most frequently 2-6 weeks post-transplant. The hippocampus is the most common site, and recent memory impairment has been observed. The antiviral medication foscarnet was administered. Epstein-Bar virus and cytomegalovirus can also be problematic.

Regarding the HZ ALE literature, in 2001 Tattevin *et al.* reported the first case of subacute limbic encephalitis in an 82-year-old immunocompromised patient with microscopic polyangiitis who presented with a lack of skin rash, altered consciousness, medial temporal lobe lesions on MRI, positive VZV PCR, negative HSV PCR, and a protracted course leading to death on day 43 (*11*). Shindo *et al.* described the case of an 83-year-old woman with Parkinson's disease who presented with somnolence, fever, a painful rash in the left lumbar region, a CSF cell count at 344/μL, positive VZV PCR, negative NMDR antibodies, and symmetrical high-intensity lesions in the limbic system on MRI (*12*).

Among the 105 patients with acute encephalitis treated at our hospital during the years 2002-2012, we observed 20 cases of influenza encephalopathy, 14 of HSV-1 encephalitis, 10 of NMDR limbic encephalitis, and five with VZV acute encephalitis, but no cases of HZ ALE (*13*). Our comparison of these data with the study results from the same facility over the prior 10 years (2012-2023) revealed an increasing trend in HZ ALE cases.

In their study of 96 patients with HSV and VZV CNS infections, Kaewpoowat *et al.* observed 18 patients with VZV CNS infection including five encephalitis patients (*14*). Similarly, in a comparison of HSV1, HSV2, and HZ neurological complications by Lee *et al*., seven patients had HZ encephalitis, but their MRI findings revealed multiple lesions due to vasculitis (*15*). VZV limbic encephalitis was not described in these HZ complication studies.

In our group's paper on HZ neurological complications in the limbs and trunk, we noted that the spread of VZV from latency in the spinal ganglia could take four routes: *via* the spinal roots, ascending the spinal cord, multiple roots, or intrathecal spread (*16*). In patients with HZ ALE, the routes from the cranial ganglia to the limbic areas may be more variable and include pathways

via the brain-stem root, carotid artery, meningeal spread, or viremia. In HSV ALE, the olfactory nerve pathway is considered to be the predominant invasive route of infection (*17,18*), but in HZ ALE, the wide range of routes of VZV seems to be a distinctive characteristic.

The numbers of chickenpox cases have recently decreased due to the widespread use of chickenpox vaccination in children, and the antibody titers in adults and the elderly have decreased more quickly, increasing the risk of HZ in adults and the elderly. Of the present 15 patients with HZ CNS complications, most had no history of prior vaccination. It is expected that vaccination with live chickenpox vaccine or a subunit vaccine will reduce the risk of HZ infection in adults and the elderly (*19,20*).

Our study has limitations to consider; it was a retrospective analysis of patients in a single region. There were no autopsy cases, and thus no autopsy findings to support the pathology in HZ CNS complications were available.

In conclusion, our study of HZ CNS complications identified five patients with HZ ALE whose average age was 82.4 years and whose underlying diseases included hypertension, Alzheimer disease, and hyperlipidemia. The major skin rashes of these five patients were on the trigeminal nerve region, with two cases of generalized rashes. The five patients had a positive CSF VZV PCR result, and MRI showed medial temporal lobe lesions. With the widespread use of varicella vaccines, the risk of developing HZ is increasing in adults and elderly individuals, and attention should be paid to the HZ CNS complication HZ ALE.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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**Address correspondence to:*
Hiroshi Shoji, Division of Neurology, St. Mary's Hospital, 422 Tsubukuhonmachi, Kurume, Fukuoka 830-8543, Japan.
E-mail: hshoji@st-mary-med.or.jp

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