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Research Article

Comparative Analyses of the Epidemiology and Clinical Findings of Herpes Simplex Virus and Varicella-Zoster Virus Encephalitis In 2012–2021

Hiroshi Shoji[1*], Yuta Noguchi[1], Yuka Kawahara[2], Yuichiro Ide[3], Noriyuki Koga[4], Shinji Kitsuki[4], Tadataka Mizoguchi[4], Mikiaki Matsuoka[4], Kenji Fukuda[2,4], Yasushi Okada[4], Tomonaga Matsushita[4]

[1]Division of Neurology, St. Mary's Hospital, Kurume, Fukuoka-830-8543, Japan
[2]St. Mary's Research Center, Kurume, Fukuoka-830-8543, Japan
[3]St. Mary's College, Faculty of Nursing, Kurume, Fukuoka-830-8543, Japan
[4]Cerebrovascular Medicine, St. Mary's Hospital, Kurume, Fukuoka-830-8543, Japan

***Corresponding Author:** Hiroshi Shoji, MD, Division of Neurology, St. Mary's Hospital, 422 Tsubukuhonmachi, Kurume 830-8543, Japan.

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Abstract

We conducted comparative analyses of (i) the epidemiology of herpes simplex encephalitis (HSE) and herpes zoster encephalitis (HZE) in elderly patients at our hospital in Kurume, Japan in 2012–2021 and (ii) the patients' clinical findings. Compared to the 2002–2011 values, the 2012–2021 incidence of HSE decreased from 14 to nine cases and that of HZE increased from four to eight cases; the HZE patients' average age was 79.6 years, indicating the population's aging (p=0.02). The comparison of clinical findings revealed that all of the HSE patients experienced acute limbic encephalitis, whereas only half of the HZE patients did (p=0.03). There was no significant between-group difference in the cerebrospinal fluid PCR positivity rate. MRI findings demonstrated between-group differences: unilateral predominance in HSE and bilateral prevalence in HZE. The main invasion routes from reactivation in HSE were via the olfactory nerve, brainstem, and meninges. HZE also showed hematogenous spread, with one case each of disseminated rash and chickenpox. Antibody titer tests of several patients at the onset of both types of encephalitis showed enzyme-immunoassay IgG-positive values for both viruses, which suggests that both viruses were repeatedly reactivated in the brain ganglia and parenchyma and other organs.

Keywords: Herpes simplex virus, Varicella zoster virus, Herpes simplex encephalitis, Herpes zoster encephalitis, Antibody test, Cranial nerve ganglia, Epidemiology

Introduction

Herpes simplex virus-1 (HSV) and varicella-zoster virus (VZV) commonly develop latent infections in the cerebrospinal ganglia and may later reactivate with immunosuppression, stress, and/or other factors, causing herpes simplex encephalitis (HSE), herpes zoster encephalitis (HZE), retinitis, and/or peripheral neuropathy, each of which severely impairs an individual's quality of life [1,2]. Both HSV and VSV remain in a latent state in the brain parenchyma and are involved in cerebral amyloid angiopathy and neurodegenerative disorders [3–5].

Our research group's prior review of 105 cases of acute encephalitis/encephalopathy treated at our hospital in Kurume, Fukuoka, Japan during the years 2002–2011 identified 14 cases of HSE and four cases of HZE [6]. We conducted the present comparative study of the epidemiology of HSE and HZE and evaluated the clinical findings of the patients with HSE and those with HZE treated at our hospital during two periods: 2002–2011 and 2012–2021. Similar comparative studies of HSE and HZE have been reported, but the differences in clinical findings, MRI findings, and invasion routes

between HSE and HZE have not been clarified [7,8].
The onset of HSE/HZE is thought to be caused mainly by reactivation in the cerebrospinal ganglia, followed by spread to the brainstem and meninges; the presence of latent HSV in the limbic system has been reported in HSV polymerase chain reaction (PCR) studies of healthy autopsy brains [9]. Old glial cell clusters were observed in the anterior nucleus of the spinal cord in two autopsy cases of HZ, suggesting VZV reactivation without clinical findings [10]. Considering these latency and reactivation events, in the present study we examined the mutual viral PCR/antibody titers during encephalitis caused by each of these viruses.

Patients and Methods

Research design and data collection

We asked our hospital records staff to extract the cases of hospitalized adults and elderly patients with HSE or HZE who were treated at our hospital's departments of cerebrovascular medicine and division of neurology during the period from January 2012 through December 2021, and they identified nine HSE cases and eight HZE cases. We retrospectively analyzed these patients' cases including their hospitalization history, underlying disease(s), presence/absence of skin rash, neurological form, length of hospitalization, cerebrospinal fluid (CSF) test results, CSF HSV/VZV PCR results, antibody findings, MRI results including contrast-enhanced fluid attenuated inversion recovery (FLAIR) images, and the treatment(s), outcomes, and sequelae, in a comparison with the same variables of the patients treated at our hospital during the preceding period, i.e., 2001–2011 (14 HSE cases and four HZE cases).

Diagnostic criteria and CSF PCR/serological tests

The diagnostic criteria for HSE and those for HZE were the presence of fever, headache, altered consciousness, abnormal behavior, and/or seizures. Cases with CSF HSV or VZV PCR positivity and MRI medial temporal lobe lesions were defined as including acute limbic encephalitis. Cases with fever and impaired consciousness as the main symptoms and lacking cerebral symptoms were judged to be acute encephalitis.
The patients' CSF PCR tests were performed as a single or real-time PCR. Their enzyme immunoassay (EIA) and complement fixation (CF) antibodies were each measured. Although false negatives can occur in a CSF PCR, the positive rate is high within 1–2 weeks of infection, and thereafter, increased values in CSF and serum antibody titers can be good indicators of reactivation and infection [11]. Enzyme immunoassay (EIA) IgG antibody persists for several years, and CF antibody has shown changes that are similar to those of EIA IgM antibody [12,13].

Ethical approval

This study was submitted to and approved by our Hospital's Ethics Committee (approval. no. 25-0601). The requirement for patients' informed consent was waived based on the study's retrospective design and the anonymization of the patients' information.

Statistical analyses

Differences in normally distributed data between the HSE and HZE groups were examined with Student's t-test, and categorical variables were analyzed using Fisher's exact test. The results are presented as the mean ± standard deviation, standard error, or number (percentage). Non-normally distributed data were analyzed using the Mann-Whitney U-test and are presented as the median and interquartile range (IQR). Probability (p)-values <0.05 were considered significant. All statistical analyses were performed using JMP ver. 18.1.1 software (SAS, Cary, NC, USA).

Results and Discussion

Our hospital is located in the city of Kurume, southwestern Japan and provides emergency medical care for ~300,000 local residents. The incidences of HSE and HZE are shown in Table 1. At our hospital, there were 14 cases of HSE in 2002–2011 and nine cases in the subsequent period 2012–2021, and the average age of all of these HSE patients was 65.5 years. Compared to the incidence of HSE in the previous 10 years, the incidence decreased from 14 to nine cases during the second ten-year period, while the incidence of HZE increased from four to eight cases. The average age of the HZE patients was 79.6 years, which was significantly older than the age at the onset of HSE (p=0.02).

	2002	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
HSE	2	1	1	2	2	1	0	0	3	2	14
HZE	0	0	0	3	1	0	0	0	0	0	4
	2012	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**Total**
HSE	1	0	0	2	1	3	1	0	1	0	9
HZE	0	1	1	0	0	1	0	1	3	1	8

Table1: Herpes simplex virus-1 encephalitis (HSE) and herpes zoster encephalitis (HZE) cases at our hospital in Kurume, Japan during the periods 2002–2011 and 2012–2021

The nationwide annual incidence of HSE in Japan is 3.5 cases per 1 million, whereas in Japan's Fukuoka prefecture (where our hospital is located) the incidence is 0.9 cases per 300,000; in the U.S., the incidence is 1 case per 250,000–500,000 individuals [12,14]. The population of the city of Kurume increased from 235,361 in 2002 to 304,666 in 2021. During the same period, the average annual cumulative incidence per 500,000 population over each of this study' 10-year periods decreased for HSE from 2.5 (2002–2011) to 1.5 (2012–2021), whereas for HZE the corresponding value increased from 0.7 to 1.3.

Table 2 summarizes the clinical characteristics of the HSE and HZE groups of patients seen during the latter decade (2012–2021). Concerning the patients' main symptoms at their presentation to our hospital, in addition to the presence of fever, headache, and impaired consciousness, six of the nine patients with HSE exhibited abnormal behavior due to limbic and/or temporal lobe disorder: talkativeness, disinhibition, aphasia, seizure attacks, and aphasia. Two of the eight patients with HZE during the latter period presented similar symptoms. Classified by their clinical disease form, all nine patients with HSE had acute limbic encephalitis, and among the eight patients with HZE, four had acute limbic encephalitis (p=0.03) [15].

Clinical characteristic	**HSE, n=9**	**HZE, n=8**	**p-value**
Age, yrs, mean ± SD	65.7 ± 13.2	79.6 ± 7.8	0.02*
Males, females	2, 7	4, 4	0.33
Underlying disease:			
Brain disorder	3 (33.3%)	3 (37.5%)	1.00
Hypertension	4 (44.4%)	5 (62.5%)	0.64
Diabetes	1 (11.1%)	1 (12.5%)	1.00
Skin rash:			
Herpes simplex	0	8 (100%)	<0.01†
Herpes zoster	(1)**		
Neurologic form:			
Acute limbic encephalitis	9 (100%)	4 (50.0%)	0.03†
Acute encephalitis	0	3 (17.5%)	
Acute cerebellitis	0	1 (12.5%)	
Cerebrospinal fluid:			
Cell count, /μL (IQR)‡	46 (23–62)	121 (9–321)	0.41
PCR-positive	7 (77.8%)	8 (100%)	0.47
MRI findings:			
Unilateral lesions	8 (88.9%)	1 (12.5%)	<0.01†
Bilateral lesions	0	3 (37.5%)	
Treatment:			
Acyclovir, intravenous	9, 2–3 wks	8, 2–3 wks	
Prednisolone pulse	6 (66.7%)	2 (25.0%)	0.15
Hospitalization days, mean±SD	49.8±12.1	34.1±11.2	0.01*
Transfer to hospital or facility	6 (66.7%)	5 (62.5%)	1.00
Discharged to home	3 (33.3%)	3 (37.5%)	
Sequelae on discharge:			
Post-herpetic neuralgia	0	1 (12.5%)	1.00
Limbic system/temporal lobe	6 (66.7%)	2 (25.0%)	0.15
Cognitive disorder	1 (22.2%)	2 (25.0%)	0.58

Data are mean ± standard deviation or number (percentage).
‡Non-normally distributed data are median (interquartile range), by Mann-Whitney U-test.
*p<0.05 by t-test, †p<0.05 by Fisher's exact test
**HZ on before 1 year in one HSE case. PCR: polymerase chain reaction.

Table2: Clinical characteristics of each patient with herpes simplex virus-1 encephalitis (HSE) or herpes zoster encephalitis (HZE) (n=17, 2012–2021)

One patient with HSE had severe diabetes and another had experienced long-term epileptic seizures since childhood, and these underlying diseases were considered the triggers for the patients' HSE onsets. Brain surgery was added as a potential onset trigger relatively recently [16]. Regarding skin rashes, only 10% of the cases of patients with HSE were accompanied by herpes labialis [17], whereas none patients with HSE in this series was observed, and all of the patients with HZE had a zoster rash (p<0.01).

Animal models have shown that the HSV protein kinase UL13 or Us3 is involved in controlling the pathogenesis of this disease (18), but clinical application of this information is currently difficult. In contrast, CSF PCR and serum EIA IgG/IgM and CF antibody measurements can be used in clinical practice as objective indicators of reactivation/infection. These antibodies could be used to assess the risk of reactivation and determine the need for booster zoster vaccination, especially in elderly patients.

The median CSF cell counts were 46/μL in the HSE group and 121/μL in the HZE group. There was no significant between-group difference in the results of the single or real-time PCRs. Regarding MRI findings, eight of the patients with HSE showed unilateral predominance in the hippocampus, insula, and temporal lobe, and the remaining patient showed

no abnormality. In two HSE cases, MRI findings indicated that the initial site was the temporal lobe and insular lobe, suggesting the possibility of latent HSV infection. In the HZE group, one patient showed unilateral predominance, three showed bilateral predominance, and the remaining four patients revealed no change ($p<0.01$, Fig. 1).

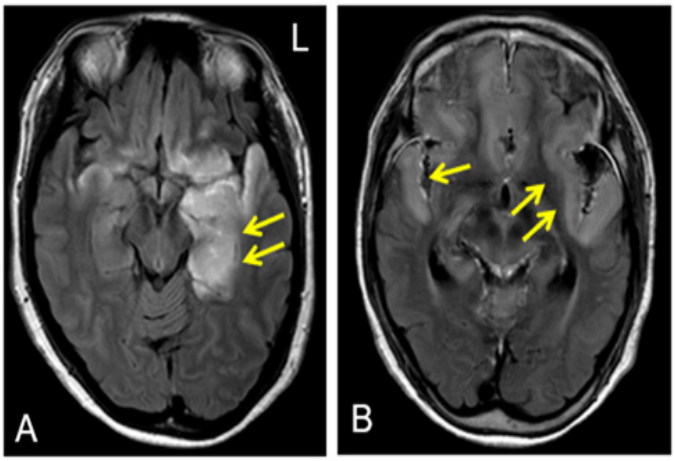

Figure1: MRI findings of a patient with herpes simplex virus-1 encephalitis (HSE) and a patient with herpes zoster encephalitis (HZE).

Patient 1. A: A 51-year-old woman with HSE and acute limbic encephalitis on the 16th day of illness. This Gd-enhanced MRI fluid attenuated inversion recovery (FLAIR) image shows typical high-intensity signals in the left medial temporal lobe and insular gyrus (arrows). ***Patient 2. B:*** An 86-year-old female with HZE and acute limbic encephalitis. MRI on the 16th day of illness: the Gd-enhanced FLAIR image shows high-intensity signals mainly in the cortex of the bilateral frontal lobes and insular gyrus with meningeal enhancement (arrows).

The treatment for all of the patients (both those with HSE and those with HZE) was 2–3 weeks of intravenous acyclovir. The mean duration of hospitalization was 49.8 days for the HSE group and significantly shorter at 34.1 days for the HZE group ($p=0.01$).

In elderly and other adult patients, HSV/VZV is thought to cause a central nervous system (CNS) infection mainly via the brainstem and intrathecal spread after reactivation in the trigeminal ganglia [1,9]. Spinal ganglion lesions have been clearly revealed by contrast MRI FLAIR in cases of VZV polyneuropathy ascending up the spinal roots or multiple roots [15], but no intracranial ganglionic lesions were detected in the present patients with HSE or HZE.

The PCR and antibody titer findings summarized in Table 3 suggest mutual viral reactivation at the onset of HSE and that of HZE. The results of the patients' CSF PCR and serum EIA IG, IgM and CF antibody tests indicated that the two viruses did not develop simultaneously; rather, they reactivated at different times.

Patient	HSE	Patient	HZE
82, F	CSF: HSV VZV PCR-negative serum/CSF HSV EIA IgG antibody ratio 11.6 (<20) CSF: HSV EIA IgM 8.71→12.72+ Prior 1 yr of HSE, presence of HZ means reactivation, VZV EIA IgG 87.8+	86, F	CSF: VZV PCR >5.0×105 copies HSV PCR<1.0×102 Serum: HSV EIA IgG >128
82, F	CSF: HSV PCR 3×103 → <2×102 HSV EIA IgG 12.7→110.2+ Serum: VZV EIA IgG 45.2	86, F	CSF: VZV PCR + Serum: VZV EIA IgG 128 VZV CF 128× Serum: HSV CF 16×→16×
45, M	Resemble findings		

CF: complement fixation, CSF: cerebrospinal fluid, EIA: enzyme immunoassay, PCR: polymerase chain reaction, VZV: varicella-zoster virus.

Table3: PCR and antibody findings in herpes simplex virus-1 encephalitis (HSE) and herpes zoster encephalitis (HZE) suggestive of mutual viral reactivation during the onset of both types of encephalitis

In particular, among the cases of HSV encephalitis, an 82-year-old woman had a negative CSF HSV PCR result, but her serum/CSF EIA IgG antibody ratio was 11.6 with a high CSF HSV EIA IgM level, which together supported the diagnosis of HSE. She had a history of cervical herpes zoster (HZ) observed 1 year prior to her HSE diagnosis, which confirmed VZV reactivation in the cervical ganglia. Another 82 year-old woman had a positive CSF HSV PCR result and a high serum HSV EIA IgG titer; in addition, an increased VZV EIA IgG value was observed, suggesting VZV reactivation over the past several years without her past history.

Conversely, the serum of an 86-year-old woman with HZ encephalitis, VZV PCR >5.0×105 copies, and HSV PCR-negative status showed HSV EIA IgG >128. These findings supported the possibility of asymptomatic reactivation in the nervous system or other organs, and they suggest that PCR and antibody measurements will be important diagnostic indicators in the future.

HSE and HZE are treated with intravenous acyclovir combined with a prednisolone pulse, but severe sequelae such as talkativeness, disinhibition, memory impairment, and seizures remain for a long time in HSE. In patients with dementia who have either herpes simplex or herpes zoster en-

cephalitis, there is a tendency for dementia to worsen. It is expected that the expanded use of a live varicella vaccine or subunit vaccine for elderly individuals and other adults will lead to a decrease in the risk of HZ infection in these populations [19,20]. It is important to note too that with the widespread use of HZ vaccines, atypical skin rash and neurological complications are possible. We thus propose that measuring both EIA and CF antibodies is useful for evaluating the possibility of reactivation/infection.

Our findings are limited by the study's design as a retrospective clinical analysis, the source of data as a single hospital in a single region of Japan, and the small number of patients. Nevertheless, the results revealed by our analyses help clarify the trends in HSE and HZE in an aging population.

Conclusion

In conclusion, our investigation of nine elderly patients with HSE and eight with HZE at our hospital revealed a mild decline in the incidence rate of HSE in 2012–2021 compared to 2002–2011, while the incidence of HZE increased and may reflect the population's aging. All of the patients with HSE and three of the patients with HZE had acute limbic encephalitis. The changes in mutual antibody titers at the onset of both types of viral encephalitis suggest that both viruses are sometimes repeatedly reactivated. The use of both EIA and CF antibodies to evaluate the trends of HSV/VZV reactivation and neurological complications will contribute to further research in this field.

Declarations

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Conflicts of Interest: The authors have no conflicts to disclose.

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