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【 ORIGINAL ARTICLE 】

The Diversity of Neurological Complications Associated with Herpes Zoster: A Retrospective Case Series of 26 Patients

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Abstract:

Objective This study clarified a variety of neurological phenotypes associated with varicella-zoster virus (VZV) reactivation.

Methods This retrospective single-center study included consecutive patients with herpes zoster accompanied by neurological disturbances from April 2016 to September 2022. A comparative analysis was performed to examine whether or not the neurological phenotype and severity were associated with the distribution of herpes zoster, clinical and laboratory findings, and treatments.

Results Twenty-six patients with a median age of 74 years old were enrolled. None of the patients had been vaccinated against herpes zoster. Of the 26 patients, 14 (54%) developed monoparesis, 5 (19%) developed meningitis, 5 (19%) developed encephalitis, 1 (4%) developed paraplegia, and 1 (4%) developed bladder and rectal problems. Monoparesis of the upper limb is associated with herpes zoster involving the cervical and thoracic dermatomes, whereas meningitis and encephalitis often occur in patients with herpes zoster in the trigeminal and thoracic dermatomes. Neurological disability was generally severe [modified Rankin Scale (mRS) score ≥3] on admission [17 of 26 (65%) patients]. Good recovery after admission was associated with a lower mRS value before the onset of neurological disability, clinical meningitis, and elevated cell counts and protein levels in the cerebrospinal fluid. Good recoveries were observed in patients with herpes zoster in the trigeminal or thoracic dermatomes more frequently than in other dermatomes.

Conclusion This study revealed that VZV-related neurological complications are heterogeneous, commonly leading to severe disability and poor outcomes, and that neurological phenotypes and outcomes are related to the distribution of herpes zoster.

Key words: herpes zoster, neurological complications, monoparesis, meningitis, encephalitis

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Introduction

Varicella zoster virus (VZV) is a common pathogen that causes herpes zoster. Most Japanese people are thought to be in a state of latent VZV infection, and one-third of the Japanese population develops herpes zoster associated with reactivation of the virus by 80 years old (1). In addition to herpes zoster, reactivation of VZV is associated with various neurological disorders, including radiculitis, meningitis, and encephalitis (2). The extent of neurological disability varies from person to person; however, neurological recovery is generally incomplete in patients with neurological complications (3). Why neurological phenotypes and extent of neurological disability vary in relation to a single condition remains unclear.

We conducted a single-center retrospective study of patients with neurological complications associated with herpes zoster to clarify the variety of neurological deficits and the outcomes of these deficits.

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Materials and Methods

Study design

This was a single-center observational retrospective study conducted at Tokuyama Central Hospital.

Ethics

The study was approved by the institutional review board of Tokuyama Central Hospital (number: K446-20220706).

Data collection

Twenty-six consecutive patients with herpes zoster associated with neurological complications were enrolled. All patients were admitted to the Department of Neurology, Tokuyama Central Hospital between April 2016 and September 2022. Clinical data, including patient age, sex, herpes zoster, neurological findings, results of cerebrospinal fluid (CSF) assessments at admission, treatments, and modified Rankin Scale (mRS) values before the onset of neurological manifestations, at the nadir of manifestations, and at discharge, were collected from medical records.

The diagnosis of herpes zoster

The diagnosis of herpes zoster was performed by primary care physicians, dermatologists, or neurologists and was based on visual inspection of the skin rash with or without polymerase chain reaction (PCR) confirmation from swab specimens, although the reactivation of VZV was confirmed by PCR of CSF specimens in previous studies (3, 4). Herpes zoster has been observed in the trigeminal, cervical, thoracic, lumbar, and sacral dermatomes. Patients taking immunosuppressant medications and those with a history of diabetes were considered immunocompromised. The following neurological complications were observed: monoparesis, meningitis, encephalitis, paraplegia, and bladder/rectal disturbance. Monoparesis was defined as monoparesis without meningeal irritation, ongoing disturbance of consciousness, or seizures (3). Meningitis was defined as meningeal irritation without ongoing disturbance of consciousness, seizures, or limb paresis (3). Encephalitis was defined as an ongoing disturbance of consciousness or seizures irrespective of meningeal irritation (3). Paraplegia was defined as paraplegia without upper limb paresis, meningeal irritation, ongoing disturbance of consciousness, or seizures. Bladder/rectal disturbances were defined as new-onset subjective bladder or defecation symptoms without paresis, meningeal irritation, ongoing disturbance of consciousness, and seizures. Severe neurological disability was defined as an mRS score ≥3. The nadir period was defined as the period of the most severe neurological symptoms assessed by a neurologist. Good neurological recovery was defined as a decrease in the mRS score of ≥2 from the nadir period to discharge.

Statistical analyses

The EZR software program (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used to perform statistical analyses. Values of $p<0.05$ by the Mann-Whitney *U*-test or Fisher's exact test were considered significant. All tests were two-sided.

Results

Characteristics of neurological disturbances in patients with herpes zoster

The study included 14 men and 12 women. The median age of the onset was 74 (range, 23-84) years old. None of the patients had been vaccinated against herpes zoster. Of the 26 patients, 14 (54%) developed monoparesis, 5 (19%) developed meningitis, 5 (19%) developed encephalitis, 1 (4%) developed paraplegia, and 1 (4%) developed bladder and rectal disturbances. None of the patients had any neuroophthalmic manifestations. The median age of patients with meningitis was 31 years old, which was significantly lower than that of other types of patients ($p=0.0018$). The median number of days from the onset of herpes zoster to the onset of neurological manifestations was 4 (range, -16-64) days. The median number of days from the onset of neurological manifestations to the first visit to our Department of Neurology was 7 (range, 0-54) days. Ten patients (38%) were immunocompromised. A PCR analysis for VZV using CSF samples was positive in 6 of the 20 (30%) patients tested. The median number of days from the onset of herpes zoster to the first visit to our department was significantly shorter in the PCR-positive patients than in the PCR-negative one (2 days vs. 34 days; $p=0.0019$), but other clinical characteristics did not significantly differ between the groups.

Seventeen (65%) patients received oral antiviral agents before their first visit to the Department of Neurology. Of these patients, eight received amenamevir, an oral antiviral agent that was thought to be unable to cross the blood-brain barrier (5). Every patient received intravenous acyclovir after admission, and intravenous methylprednisolone pulse therapy (1,000 mg/day for 3 days) or oral prednisolone (1 mg/kg body weight/day for 5 days) was administered to 18 (69%) patients. There were no significant differences in the age, sex, CSF findings, or mRS score at each point between the steroid-treated and non-steroid-treated groups.

Relationship between neurological manifestations and herpes zoster

The associations between neurological phenotypes and herpes zoster distribution are shown in Table 1. Of note, herpes zoster was detected in the cervical and thoracic dermatomes of all 12 patients with upper limb monoparesis, whereas it was detected in the lumbar and sacral dermatomes of all patients with lower limb monoparesis, paraple-

Table 1. Association of Location of Herpes Zoster with Neurological Phenotypes.

Neurological phenotype		Herpes zoster				
		Trigeminal (n=3)	Cervical (n=10)	Thoracic (n=13)	Lumbar (n=6)	Sacral (n=2)
Monoparesis	U/E (n=12)	0	9	6	1	0
	L/E (n=2)	0	0	0	2	1
Meningitis	(n=5)	1	0	4	0	0
Encephalitis	(n=5)	2	1	3	1	0
Paraplegia	(n=1)	0	0	0	1	1
Bladder/rectal disturbance	(n=1)	0	0	0	1	0

U/E: upper extremities, L/E: lower extremities

Table 2. Clinical Characteristics of Patients with Severe Neurological Disability Subsequent to Herpes Zoster.

		Neurological disability at nadir		p value
		Severe (n=17)[a]	Not severe (n=9)	
Median age (range)		79 (23-84)	68 (31-83)	NS
Herpes zoster	Trigeminal, n (%)	3 (100%)	0 (0%)	NS
	Cervical, n (%)	7 (70%)	3 (30%)	NS
	Thoracic, n (%)	7 (54%)	6 (46%)	NS
	Lumbar, n (%)	5 (83%)	1 (17%)	NS
	Sacral, n (%)	2 (100%)	0 (0%)	NS
Immunocompromised condition, n (%)		6 (60%)	4 (40%)	NS
Median mRS before onset (range)		0 (0-4)	0 (0-0)	NS
Median days from onset of neurological symptom to first visit (range)		9 (0-38)	6 (1-54)	NS
Neurological phenotype	Monoparesis, n (%)	8 (57%)	6 (43%)	NS
	Meningitis, n (%)	3 (60%)	2 (40%)	NS
	Encephalitis, n (%)	5 (100%)	0 (0%)	NS
CSF	Cell count (/μL), median (range)	22 (0-371)	10 (0-202)	NS
	Protein (mg/dL), median (range)	75 (42-217)	56 (38-173)	NS
Therapy	Acyclovir, n (%)	17 (100%)	9 (100%)	NS
	Steroid, n (%)	13 (76%)	5 (56%)	NS
Median hospitalization days (range)		27 (6-77)	18 (14-70)	0.023

NS: not significant (p≥0.05), mRS: modified Rankin Scale. CSF: cerebrospinal fluid

[a]Defined by mRS of 3 or more at nadir.

gia, or bladder/rectal disturbances. Furthermore, herpes zoster was confirmed in the trigeminal or thoracic dermatomes of all patients with meningitis and encephalitis.

Neurological disability at nadir

Seventeen (65%) patients had severe disability (mRS score ≥3) at the nadir. Patients with severe disabilities had longer hospitalization durations than those without severe disabilities (p=0.023). Other clinical characteristics, including the age, immunocompromised condition, mRS value before onset, CSF findings, and type of therapy, were not significantly associated with severe disability at nadir (Table 2). Extensive distribution of herpes zoster (≥2 areas among 5) was identified in 6 (35%) severely disabled patients but was not significantly related to neurological severity (p=0.36).

Recovery from severe neurological disability

Of the 17 severely disabled patients, 8 (47%) showed a good neurological recovery by discharge (defined as a decrease in the mRS score of ≥2 from nadir to discharge) (Table 3). Elevated CSF cell counts and protein levels were significantly associated with a good recovery (p=0.038 and p=0.027, respectively). Furthermore, all 3 severely disabled patients with meningitis were determined to have obtained a good recovery, but the p value was not significant (p=0.082). More patients with herpes zoster located in the trigeminal or thoracic dermatomes showed a better recovery than those with herpes zoster in other dermatomes (70% vs. 14%; p=0.0498). None of the patients who had been treated with steroids showed a good recovery. The frequency of a good recovery was significantly lower in the steroid-treated

Table 3. Comparison between the Clinical Characteristics of Patients with and without Good Recovery from Severely Disabled Condition at Nadir.

		Neurological recovery		p value
		Good (n=8)[a]	Poor (n=9)	
Median age (range)		77 (23-84)	79 (69-83)	NS
Herpes zoster	Trigeminal, n (%)	2 (67%)	1 (33%)	NS
	Cervical, n (%)	2 (29%)	5 (71%)	NS
	Thoracic, n (%)	5 (71%)	2 (29%)	NS
	Lumbar, n (%)	1 (20%)	4 (80%)	NS
	Sacral, n (%)	0 (0%)	2 (100%)	NS
Immunocompromised condition, n (%)		2 (33%)	4 (67%)	NS
Median mRS before onset (range)		0 (0-1)	0 (0-4)	NS
Median days from onset of neurological symptom to first visit (range)		4 (0-33)	11 (0-38)	NS
Neurological phenotype	Monoparesis, n (%)	2 (25%)	6 (75%)	NS
	Meningitis, n (%)	3 (100%)	0 (0%)	NS
	Encephalitis, n (%)	3 (60%)	2 (40%)	NS
CSF	Cell count (/μL), median (range)	51 (8-371)	9 (0-328)	0.038
	Protein (mg/dL), median (range)	116 (69-217)	62 (42-205)	0.027
Therapy	Acyclovir, n (%)	8 (100%)	9 (100%)	NS
	Steroid, n (%)	4 (50%)	9 (100%)	0.029
Median hospitalization days (range)		24 (15-49)	39 (6-77)	NS

NS: not significant (p≥0.05), mRS: modified Rankin Scale. CSF: cerebrospinal fluid

[a]Defined by decreased of mRS of 2 or more from nadir to discharge.

group than in the non-steroid-treated group (p=0.029). Other clinical characteristics, including the age, immunocompromised status, and mRS before the onset, were not associated with a good recovery.

This study included three patients who had already been disabled (mRS score of ≥2) before the onset of neurological manifestations, and none of these three patients achieved a good recovery. Among the 6 severely disabled patients with extensive distribution of herpes zoster, 4 (67%) had a poor neurological recovery. The extensive distribution of herpes zoster was not related to the neurological recovery (p=0.62).

Discussion

We found that the neurological complications in 26 patients with herpes zoster included monoparesis, meningitis, and encephalitis, and that they were associated with the distribution of herpes zoster. Among the 17 severely disabled patients, 47% had achieved a good recovery by discharge. None of the patients who received steroids showed a good recovery. The frequency of a good recovery was significantly lower in the steroid-treated patients than in the non-steroid-treated patients.

The proportion of patients with specific neurological phenotypes associated with VZV infections has been investigated in French populations, and investigators found that 23% of patients exhibited monoparesis and cranial nerve palsy, 38% exhibited meningitis, and 39% exhibited encephalitis (3). In contrast, we found that a smaller proportion of VZV-infected patients in the Japanese population had meningitis (19%) or encephalitis (19%). Although this discrepancy might reflect racial or geographic differences between populations, we believe that the discrepancy between the results might be accounted for by the differences between the study inclusion criteria for patients. The French investigators only included patients in whom VZV reactivation had been confirmed by PCR of CSF specimens, whereas our study also included patients in whom CSF specimens were not tested by PCR. The difference between the criteria may have biased the results regarding the proportions of neurological phenotypes. Patients with monoparesis might have been excluded from the French study by not conducting a CSF analysis, leading to a larger proportion of patients with encephalitis or meningitis. It is also possible that the proportions of neurological phenotypes differ depending on the characteristics of the VZV infecting the hosts. Therefore, further investigation is warranted.

Our study found that limb paralysis was closely associated with the distribution of prior herpes zoster episodes in patients, which suggests that reactivation of VZV in the dorsal root ganglia affects the nearby motor neurons. In contrast, all patients with encephalitis and meningitis in our study had herpes zoster within the trigeminal, thoracic, or both dermatomes. This result is compatible with a previous report that herpes zoster is frequently located within the trigeminal or thoracic dermatomes in patients with VZV meningitis [6 of 9 (67%) patients] (6). Why inflammation can spread from the thoracic dorsal root ganglion to the distant cerebrum and meninges remains unclear. There may be a particular mechanism underlying distant spread across the nervous system.

This study showed that increased cell counts and CSF

protein levels, decreased mRS values before the onset, and no use of steroids were associated with a good neurological recovery in our study patients, which is partly consistent with previous findings (3, 4). We also discovered a novel relationship between the neurological recovery and herpes zoster location, possibly due in part to the fact that patients with a meningitis phenotype often have herpes zoster in the trigeminal or thoracic dermatomes and also often show a good recovery. Further research involving a larger study population is needed to clarify whether or not the distribution of herpes zoster is associated with the neurological outcome.

Whether or not steroids are effective in the treatment of neurological complications associated with VZV reactivation remains unclear. In our study, none of the steroid-treated patients showed a good recovery; however, steroids were often used in severe cases [13 of 18 patients (72%)], indicating that the effectiveness of steroids could not be adequately evaluated in our study. The Association of British Neurologists has recommended corticosteroids be used to treat VZV encephalitis in patients with concomitant vasculitis. However, the French Federation of Neurology does not recommend treatment with corticosteroids, irrespective of vasculitis (7, 8). Steroids may have an effect on the treatment of VZV-associated vasculopathy (9). Randomized controlled trials should be conducted to determine the efficacy of steroids for neurological complications associated with VZV.

In conclusion, we found that the diversity of neurological complications manifested by the reactivation of VZV was associated with the distribution of herpes zoster. The limitations of this study are the relatively small number of study patients (n=26) and the retrospective nature of the study. Our findings should be confirmed in larger-scale prospective studies.

The authors state that they have no Conflict of Interest (COI).

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