Brief Report

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Herpes zoster peripheral nerve complications: Their pathophysiology in spinal ganglia and nerve roots

Hiroshi Shoji[1,*], Kouki Matsuo[1], Tomonaga Matsushita[2], Yoshihisa Fukushima[2], Kenji Fukuda[2], Toshifumi Abe[3], Shuichi Oguri[4], Masayuki Baba[5]

[1] Division of Neurology, St. Mary's Hospital, Kurume, Fukuoka, Japan;
[2] Cerebrovascular Medicine, St. Mary's Hospital, Kurume, Fukuoka, Japan;
[3] Dermatology, St. Mary's Hospital, Kurume, Fukuoka, Japan;
[4] Radiology, St. Mary's Hospital, Kurume, Fukuoka, Japan;
[5] Department of Neurology, Aomori Prefectural Central Hospital, Aomori, Japan.

SUMMARY Varicella zoster virus (VZV) causes chickenpox at the primary infection and then becomes latent in the spinal dorsal root ganglia; VZV can reactivate with aging, immunosuppression, stress, and other factors, occurring as herpes zoster (HZ) at 1–2 skin segments. HZ peripheral nerve complications caused by VZV reactivation include Hunt syndrome, segmental HZ paresis, post-herpetic neuralgia, and Guillain-Barré syndrome (GBS). We have encountered the rare HZ complications of upper-limb paresis, myeloradiculitis, and polyradiculoneuritis: an adult woman with upper-limb paresis consistent with the nerve root on segments above the thoracic HZ dermatome; another woman exhibiting ascending myeloradiculitis originating at the Th11–12 roots; an elderly woman with ascending VZV polyradiculoneuritis resembling GBS; an adult with VZV quadriplegia with disseminated HZ; and an elderly patient with VZV-associated polyradiculoneuritis. The three polyradiculoneuritis cases may be a new subtype of HZ peripheral neuropathy, but the pathophysiology for these HZ peripheral nerve complications unrelated to HZ dermatomes is unclear. We analyzed host factors, skin lesions, neurological and virological findings, and MRI results including 3D NerveVIEW in 15 Japanese patients treated at our facility for HZ peripheral neuropathy, including six differing from the HZ dermatome. Based on the clinical findings including MRI results of spinal ganglia and roots, we identified four possible routes for the patterns of VZV spread: (*i*) ascending spinal roots, (*ii*) ascending spinal cord, (*iii*) polyradiculopathy, and (*iv*) intrathecal spread. The incidence of HZ is increasing with the aging of many populations, and clinicians should be aware of these HZ neuropathies.

Keywords herpes zoster, varicella-zoster virus, spinal ganglia, neuropathy, segmental paresis, polyradiculoneuritis

1. Introduction

Varicella-zoster virus (VZV) causes varicella as a primary infection, then becomes latent in trigeminal and spinal ganglia. Decades later, herpes zoster (HZ) occurs when the latent VZV spreads to one or two dermatomes in adult and elderly individuals with a suppressed immune system (*1*). There are few pathological findings in the spinal ganglia, but the VZV extends beyond 2–3 spinal ganglia or the anterior horn of the spinal cord and the opposite side (*2,3*). HZ peripheral nerve complications include Hunt syndrome, segmental zoster paresis, Guillain-Barré syndrome (GBS), and post-herpetic neuralgia (PHN) (*4,5*). These HZ complications with radicular pain are intractable and severely impair an individual's activities of daily living and quality of life (*6*).

Since 2018, we have reported the rare HZ peripheral nerve complications of upper-limb zoster paresis, myeloradiculitis, and polyradiculoneuritis. For example, we treated a 53-year-old woman who presented upper-limb paresis corresponding to the nerve root on segments above the thoracic HZ dermatome, and a 32-year-old woman showed ascending myeloradiculitis that originated on HZ Th11–12 roots (*7,8*); in addition, an elderly woman who had an HZ duplex in the right auricle and left shoulder developed right Hunt syndrome, followed by left upper-limb paresis (*9*). We also treated an elderly woman with VZV-associated ascending quadriplegia with HZ rash on the cervical 7–8 regions, with an increase in cerebrospinal fluid (CSF) cells (*10*). An adult patient with VZV polyradiculoneuritis with disseminated HZ and an elderly patient with VZV-

associated polyradiculoneuritis were also treated at our hospital (*11,12*).

These patients' cases shared the characteristic of main lesions in the spinal nerve root, but the pathophysiology for the HZ neurological complications that are unrelated to the HZ dermatomes has not been clarified. In the past 7 years at our hospital, there have been 15 patients with HZ peripheral nerve complications, including the above-mentioned cases with ascending upper-limb paresis, myeloradiculitis, and polyradiculoneuritis. We conducted the present study to retrospectively analyze these 15 patients' cases regarding host factors, HZ skin rash, neurological findings, virological testing, CSF, and magnetic resonance imaging (MRI) findings.

2. Patients and Methods

From June 2014 to March 2021, 15 patients with HZ/VZV peripheral nerve complications and HZ segmental paresis were seen at our hospital's departments of neurology and cerebrovascular medicine: segmental upper-limb paresis (n = 5), ascending upper-limb paresis (n = 2), ascending myeloradiculitis (n = 1), PHN (n = 1), polyradiculoneuritis (n = 3), and Elsberg syndrome (n = 3). Eleven of the patients required hospitalization due to limb paresis or four-limb paresis with radicular pain, as well as urinary retention and fecal incontinence for 1–3 months. We used the patients' hospitalization histories and outpatient records for the present analyses.

We focused on the HZ peripheral nerve complications unrelated to the dermatome concerning host risk factors, HZ skin rash, immunologic test results, neurological findings, anti-ganglioside (GM)1 antibody, VZV antibody, the VZV polymerase chain reaction (PCR) result for the CSF, a nerve conduction velocity including the F-wave, and MRI findings. The MRI examinations provided contrast-enhanced T1-weighted fat-suppressed images in 11 cases, and 3D NerveVIEW (Philips, Best, the Netherlands) MRI was performed in four patients at the acute stage for the cervical spine, thoracic spine, and lumbar spine.

This study was conducted in accord with the principles of the Declaration of Helsinki and was approved by our Hospital's Ethics Committee (Ron 21–203). Each of the patients provided informed and written consent to have their anonymized data and images published.

3. Results and Discussion

The results of the 15 Japanese patients with HZ peripheral nerve complications are summarized in Table 1, and the

Table 1. Fifteen patients with herpes zoster peripheral nerve complications (June 2014 to March 2021)

Pt. no.	Age, Sex	HZ dermatome, Radicular pain -, +, ++ Underlying disease	Paresis [a]after or [b]before HZ Adm	CSF cells /μL CF	Spinal MRI including 3D NerveVIEW	NCV study F-wave
1	63, F	HZ duplex, R VIII, L-C, ++, None	R-Hunt, L-upper-limb paresis, [a]5 days, Adm	21 cells 256x	High-intensity lesions at C5-8 nerve root	Upper-limb NCV & F-wave NWL
2	62, M	L-C6-Th1, ++ CS	L-upper-limb paresis [a]5 days	ND 256x	High signals with enhancements at C5-8	Needle EMG; Fib+ F-wave WNL
3	78, M	Disseminated, ++ CS, Renal disease	R-upper-limb paresis [a]5 days, Adm	ND 128x	Not detected	Needle EMG Fib+ F-wave decreased
4	77, F	R-C8-Th1, ++ CS	R-upper-limb paresis [a]5 days, Adm	4 cells 256x	Not detected	Upper-limb NCV & F-wave WNL
5	79, F	R-6-7, + CS	R-upper-limb paresis [a]2–3 days	ND 128x	Cervical MRI not detected	Upper-limb NCV WNL
6	64, M	L-Th8, ++ None	PHN, [a]1–2 weeks	ND 32x	3D Nerve VIEW High-intensity at Th8	ND
7	53, F	L-Th4, + Breast cancer	L-upper-limb paresis [a]4–5 days, Adm	ND 32x	High-intensity lesions at C8-Th4 nerve roots	ND
8	72, F	R-Th7-8, + None	R-upper-limb paresis [a]1 month	ND	Thoracic MRI not detected	MCV SCV WNL
9	32, F	R-Th11-12, + None	Ascending myelo- radiculitis, [a]40 days, Adm	19 cells 64x	MRI T1WI high signals at Th2-Th8,	ND
10	76, F	R-C7-Th1, + Interstitial pneumonia	Polyradiculoneuritis,[b]2–3 days	21 cells IgM+	MRI T1WI high signals at C5-8, L4-S2	R-dominant demyelinating
11	34, M	Disseminated, ++ Stress	Polyradiculoneuritis Same time, Adm	32 cells 128x	3D NerveVIEW high signals at C4-T1, L2-5	Lower-limb F-wave decreased
12	82, F	L-Hunt, − None	Polyradiculoneuritis, [b]2–3 days, Adm	143 cells PCR+	3D NerveVIEW high signals at L2-5, S1-2	Lower-limb F-wave decreased
13	62, M	L-S2-3, − None	Elsberg syndrome Same time, Adm	156 cells PCR+,32x	Contrast MRI T1WI not detected	ND
14	67, F	R-S-2-3, −	Elsberg syndrome [b]4 days, Adm	ND 512x	Contrast MRI T1WI High signals at R-S 2-3	ND
15	74, F	R-S3-5, + Colon cancer	Elsberg syndrome [a]5–6 days, Adm	11 cells	Contrast MRI T1WI not detected	ND

Adm: admission, C: cervical, CF: complement fixation titer, CS: cervical spondylosis, CSF: cerebrospinal fluid, F: female, Fib: fibrillation potential, HZ: herpes zoster, L: left, M: male, NCV: nerve conduction study, ND: not down, PCR: polymerase chain reaction, Pt: patient, R: right, S: sacral, Th: thoracic, WNL: within the normal limit.

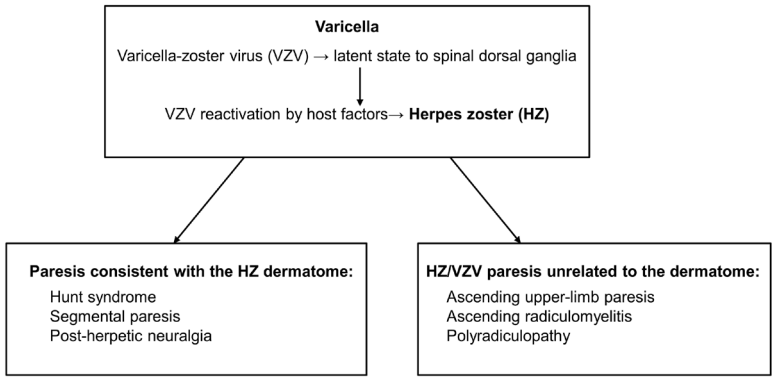

Figure 1. Herpes zoster (HZ) peripheral nerve complications. These usually appear at the segmental regions, consistent with the dermatome, but in our present patient series, there were six cases of rare upper-limb paresis, myeloradiculitis, or polyradiculoneuritis that differed from the patient's HZ dermatome.

Table 2. Clinical characteristics of patients with herpes zoster peripheral nerve complications (n = 15, 2014–2021)

Clinical characteristics	Patients
Underlying disease:	
Malignancy	3 (20.0%)
Cervical spondylosis	3 (20.0%)
Interstitial pneumonia	1 (6.7%)
Stress	1 (6.7%)
None	7 (46.7%)
Herpes zoster rash:	
Disseminated rash	2 (13.3%)
Cranial nerve VIII region	2 (13.3%)
Cervical region	4 (26.7%)
Thoracic region	4 (26.7%)
Sacral region	3 (20.0%)
HZ peripheral paresis:	
Segmental upper-limb paresis	5 (33.3%)
Ascending upper-limb paresis	2 (13.3%)
Post-herpetic neuralgia	1 (6.7%)
Ascending myeloradiculitis	1 (6.7%)
Polyradiculoneuritis	3 (20.0%)
Elsberg syndrome	3 (20.0%)
Radicular pain:	
–	3 (20.0%)
+	6 (40.0%)
++	6 (40.0%)
Paresis after or before HZ rash:	
After	10 (66.7%)
Same time	2 (13.3%)
Before	3 (20.0%)

The data are for five males and 10 females, age 65 ± 0 yrs (mean ± SD).

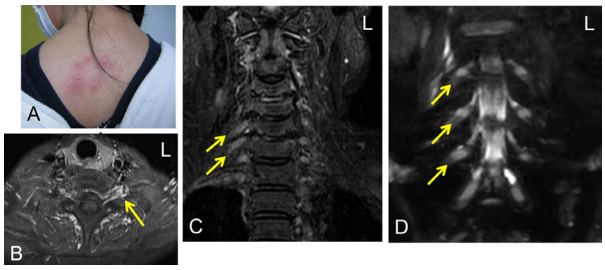

Figure 2. Herpes zoster (HZ) skin rash and MRI findings. (A) Patient 7 developed HZ in the left back of her trunk on the Th4 dermatome, and 5 days later she showed upper-limb paresis in the left C8 region. **(B)** Contrast MRI T1WI revealed high-intensity lesions with enhancements at the C8 nerve root region (*arrow*) (*7*). **(C)** Patient 10: Gd-enhanced cervical root coronary MRI T1WI showed high signals on both sides at the C6 and C7 nerve roots (*right side arrows*) (*10*). **(D)** Patient 12: Lumbar root coronary MRI using 3D NerveVIEW imaging showed high-intensity lesions on both sides at L2–4 spinal roots (*arrows*) (*12*). The HZ skin rash and CT/MRI images are reprinted with permission from references (*7*), (*10*), and (*12*).

patients' clinical characteristics are described in Table 2. The average age of the 15 patients (five males, 10 females) was 65 years. Eleven patients required 2–3 months' hospitalization at the acute stage for antiviral therapy, severe pain, and urinary impairment. We found no history of VZV vaccination among the patients.

Eight patients had underlying diseases: malignancy (n = 3), cervical spondylosis (n = 3), interstitial pneumonia (n = 1) and stress (n = 1), and the other seven patients had no disease. Regarding the HZ dermatome, we identified generalized HZ rash (n = 2), cranial nerve region (n = 2), cervical region (n = 4), thoracic region (n = 4), and sacral region (n = 3). Concerning radicular pain, the medical records revealed patients without pain (n = 2), mild-moderate + pain (n = 6), and severe ++ pain (n = 6). GM1 antibody was negative in Patients 10 and 12. The serum complement fixation (CF) antibody values for VZV were 32x–512x (positive < 8x in 11 patients), in which CF antibodies were parallel with the enzyme-immunosorbent assay IgM value (data not shown). In serum and CSF, the VZV PCR result was positive in Patients 12 and 13. An increase in the CSF cell number > 5 cells was observed in seven of the eight patients examined (mean 50.9 cells, range 4–518/μL).

HZ peripheral nerve complications are usually segmental paresis consistent with the dermatome (*13,14*). However, in the present patient series, there were six cases of rare upper-limb paresis (n = 2), myeloradiculitis (n = 1), and polyradiculoneuritis (n = 3) that differed from the HZ dermatome (Figure 1). Patient 7 presented segmental upper-limb paresis in the left C-8 region at 5 days after an HZ rash had developed on the Th4 dermatome, and contrast MRI T1WI showed high signals with enhancements at C8 nerve root regions; ascension along spinal roots was suspected to be the VZV propagation route (Figure 2, A and B) (*7*).

Patient 9, a 32-year-old woman, developed ascending myeloradiculitis after exhibiting an HZ rash at the Th11–12 dermatomes, and the demyelinating process after HZ infection was suspected due to the patient's high myelin-

basic protein titer (*8*); the peak value was 942 pg/mL at the acute stage and then decreased. Patient 1, an elderly woman who had an HZ duplex in her right auricle and left shoulder, developed right Hunt syndrome, followed by left upper-limb paresis (*9*). Our search of the literature indicated that HZ segmental limb-paresis distant from the dermatome or HZ demyelinating myeloradiculitis is relatively rare (*15,16*).

Cortese *et al.* reported the case of a 79-year-old man with flaccid paralysis of the lower limbs without HZ rash; CSF pleocytosis and a VZV DNA PCR-positive result were detected in his CSF, and MRI findings showed cauda equina radiculopathy (*17*). We later reported the cases of the following three patients with VZV polyradiculoneuritis that differed from their HZ dermatomes (*10-12*). Patient 10, an elderly woman, presented VZV-associated polyradiculoneuritis, ascending motor paralysis in the limbs, and a CSF cell increase (21 cells/μL); VZV IgM antibody persisted, and cervical and lumbar spine MRI contrast T1WI revealed high-intensity lesions in the C7–Th1 (Figure 2C) (*10*) and L4–5 spinal root regions. Patient 11 exhibited quadriplegia in the proximal lower limbs with disseminated HZ (*11*). Patient 12 showed VZV polyradiculoneuritis that had initially developed in the lower spinal ganglia, in which 3D NerveVIEW and MRI T1WI showed high signal intensities at the L2–4 spinal ganglia and roots (Figure 2D) (*12*).

These patients' cases shared the characteristic of main lesions in the spinal nerve root, and their cervical and lumbar MRI examinations using 3D NerveVIEW imaging clearly revealed lumbar ganglia and nerve root lesions. These MRI findings may suggest VZV propagating routes. We speculate that our three above-described patients may have had a new subtype of HZ peripheral neuropathies that differs from that of GBS. Based on the clinical findings and MRI results of the patients' spinal ganglia and roots, it appears that the patterns of VZV spread follow three or four routes: *i*) ascending spinal roots, *ii*) ascending spinal cord, *iii*) polyradiculopathy, and *iv*) intrathecal spread. The patients' polyradiculopathy originating from spinal ganglia or ascending radiculomyelitis including neuropathies varied, but in our comparison of the group of five patients with paresis consistent with the dermatome, no differences were identified in terms of host factors, underlying disease, CF antibody titer, or CSF cells.

Regarding the incidence of Elsberg syndrome showing urinary dysfunction and meningitis, Patients 13–15 had Elsberg syndrome involving sacral-region HZ with urinary injury and meningitis (*18,19*). Patient 14 presented with urinary and fecal incontinence, and MRI on the cauda equina nerve showed high-intensity lesions.

HZ/VZV neurological infections are treated with specific antiviral drugs, steroid hormones, and/or high-dose intravenous immunoglobulin therapy (IVIg), but sequelae such as PHN persist for a long time, significantly impairing patients' activities of daily living and quality of life. It is expected that the generalization of live varicella vaccines or subunit vaccines for the elderly will lead to a reduction in the risk of HZ infection (*20*).

The limitations of this study are as follows. Its design was a retrospective clinical analysis. CSF testing and spinal MRI including 3D NerveVIEW had not been performed for all patients. There were also few cases of HZ peripheral nerve complications associated with an unrelated dermatome, and no autopsies to support the pathology of spinal ganglia and roots in HZ/VZV peripheral nerve complications were available.

In conclusion, we analyzed host factors, skin lesions, and the neurological, virological and MRI/3D NerveVIEW findings in 15 patients with HZ peripheral nerve complications. Six of the patients had the rare conditions of upper-limb paresis, myeloradiculitis, or polyradiculoneuritis that differed from the HZ dermatome. Based on the clinical findings and MRI results of the patients' spinal ganglia and roots, we speculate that the patterns of VZV spread involve ascending spinal roots or ascending spinal cord, polyradiculopathy, and intrathecal spread. The VZV propagation process from VZV reactivation varied among the present patients. The incidence of HZ is increasing with the aging of many populations, and clinicians should thus be aware of the potential HZ neuropathies described herein.

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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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