Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9334-22
Intern Med 62: 119-122, 2023
http://internmed.jp

【 CASE REPORT 】

Orofacial Dyskinesia and Intractable Hiccups in a Patient with Varicella-zoster Virus Encephalomyelitis

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Abstract:
A 73-year-old Japanese man with diabetic complications presented with involuntary lip movements and long-lasting hiccups after developing zoster rash. Magnetic resonance imaging revealed lesions involving the medial temporal lobe and C1 level of the spinal cord. Varicella-zoster virus (VZV) encephalomyelitis was diagnosed. We considered attributing the orofacial dyskinesia, a very rare symptom of VZV central nervous system (CNS) complications, to the temporal lobe lesion. Although the culprit lesion for the hiccups was unclear, further examinations may have clarified this issue. As immunocompromised patients with herpes zoster may develop CNS complications with a wide variety of symptoms, special care is needed.

Key words: dyskinesia, encephalomyelitis, encephalitis, hiccups, myelitis, VZV

(Intern Med 62: 119-122, 2023)
(DOI: 10.2169/internalmedicine.9334-22)

Introduction

Varicella-zoster virus (VZV) is a human herpesvirus that contributes to chickenpox (varicella) as its primary infection. The virus then establishes lifelong latent infection in the cranial nerve or dorsal root ganglia. Reactivation of the virus produces herpes zoster. The neurological complications of VZV include myelitis, encephalitis, aseptic meningitis, acute radiculitis, and multiple cranial neuropathies (1).

The total prevalence of these neurological diseases among immunocompetent people is 0.1-0.3% but reaches up to 35% among immunocompromised individuals (2, 3). Immunocompromised patients with herpes zoster, including those with diabetes mellitus (DM), have an increased risk for central nervous system (CNS) disease (4).

We herein report a Japanese patient with DM who developed VZV encephalomyelitis followed by a combination of orofacial dyskinesia and intractable hiccups. While cases of VZV-related intractable hiccups have been reported (5-12), orofacial dyskinesia in a patient with VZV-CNS complications is very rare. However, immunocompromised individuals with herpes zoster may manifest a wide variety of symptoms as CNS complications.

Case Report

A 73-year-old Japanese man with a 17-year history of type 2 DM presented to a neurology clinic with involuntary lip movements and long-lasting hiccups; both of these symptoms developed on the day of his visit. He was receiving medication for hypertension, type 2 DM, and previous cerebral infarction. His history included pontine infarction. He also had a six-day history of left parietal pain without any head computed tomography (CT) findings and a two-day history of rubefaction along with exanthema, for which he was receiving amenamevir.

On the day of his initial visit, involuntary lip movements were observed. Erythematous papules with crusting were scattered across the left eyelid and scalp in the parietal region. He was somnolent but able to follow simple instructions. A neurological examination revealed negative results for cranial nerve symptoms, nuchal rigidity, sensorimotor disturbance, depression of tendon reflexes, pathologic reflexes, and cerebellar and autonomic nervous system symptoms. An ophthalmologic examination revealed no evidence of diabetic retinopathy.

Laboratory tests revealed that serum levels of vitamin B_1,

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Received: January 4, 2022; Accepted: April 26, 2022; Advance Publication by J-STAGE: June 7, 2022
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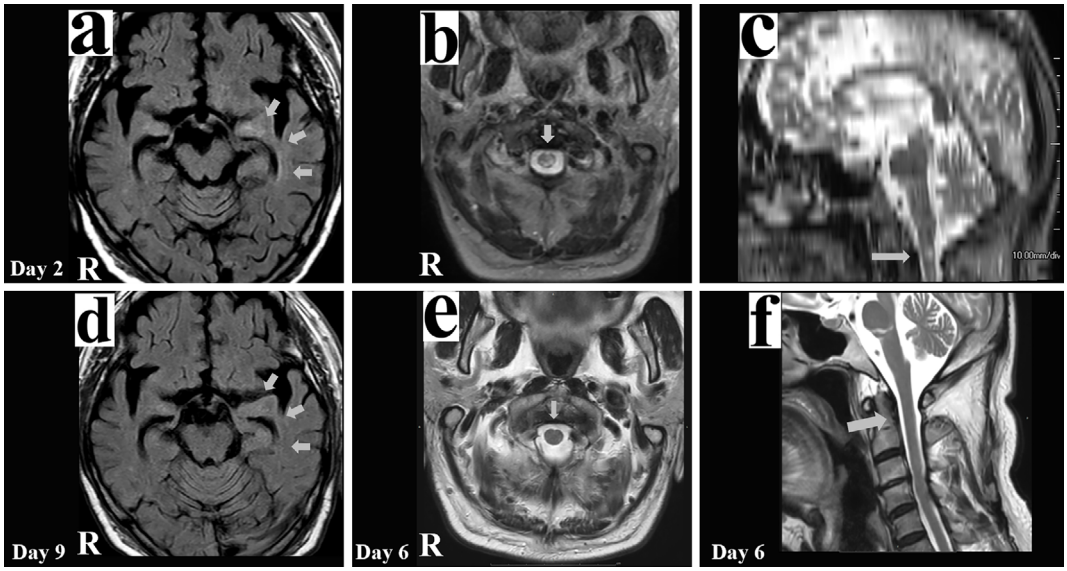

Figure. **MRI findings on days 2, 6, and 9 after admission. (a) FLAIR imaging, (b) T2-weighted imaging, and (c) reconstructed T2-weighted imaging on the second hospital day. (d) FLAIR imaging on the ninth hospital day. (e, f) T2-weighted imaging on the sixth hospital day. Given that (c) is reconstructed, (c) and (f) cannot simply be compared. Each arrow indicates the location of the lesion.**

vitamin B_9, vitamin B_{12}, thyroid-stimulating hormone, free triiodothyronine, and free thyroxine were all within normal ranges. Glycemic control was relatively good, with a hemoglobin A1c of 6.9%. The renal function was preserved (estimated glomerular filtration rate 120.9 mL/min/1.73 m^2). Serum antinuclear antibodies, anti-Sjögren's syndrome-related antigen A or B antibodies, anti-neutrophil cytoplasmic antibodies specific for myeloperoxidase or proteinase 3, anti-human immunodeficiency virus antibodies, and anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies were all negative. An enzyme-linked immunosorbent assay for anti-aquaporin-4 antibodies in the serum likewise yielded negative results. An examination of the cerebrospinal fluid (CSF) revealed elevated cell counts (178 cells/μL; mononuclear cells, 55%; polymorphonuclear cells, 45%), protein (158 mg/dL), glucose (101 mg/dL), and an opening pressure at the upper limit of normal (180 mmH_2O). Real-time polymerase chain reaction (PCR) of the CSF detected VZV DNA (2×10^4 copies/mL) under the limit of detection for herpes simplex virus DNA (200 copies/mL). Whole-body CT revealed no pathological changes.

Based on the clinical findings, VZV meningoencephalitis was suspected. He was admitted and started on acyclovir 10 mg/kg every 8 hours. Thereafter, his lucidity gradually returned. We considered the involuntary lip movements to be orofacial dyskinesia. Magnetic resonance imaging (MRI) performed on the second hospital day revealed signal-hyperintense lesions on fluid-attenuated inversion recovery (FLAIR) imaging involving the left medial temporal lobe (Figure a) and on T2-weighted imaging involving the upper cervical cord (C1 level) (Figure b). Although not clear, a C 1-level lesion was observed on reconstructed sagittal T2-weighted imaging (Figure c). Lesions in the temporal lobe and cervical cord were distinctly separated. No signal change was found in these lesions on diffusion-weighted imaging. Hyperintensity in the pontine region was also seen, suggesting an old infarction based on his history.

The patient was diagnosed with VZV encephalomyelitis. The dyskinesia gradually improved and disappeared on the second hospital day. As the long-lasting hiccups disrupted his sleep, clonazepam was started at 0.5 mg/day on the second hospital day. The hiccups subsequently disappeared on the fifth hospital day. The patient did not report any nausea or vomiting throughout the clinical course. MRI performed on the sixth hospital day revealed no signal increase at the location of the C1-level lesion on T2-weighted imaging (Figure e, f). A CSF examination on the eighth hospital day revealed decreases in cell counts (29 cells/μL; mononuclear cells, 100%), protein (50.1 mg/dL), and glucose (83 mg/dL) compared to the CSF findings on the first day. Real-time PCR of the CSF-VZV DNA showed negative results. MRI performed on the ninth hospital day revealed a decrease in signal changes of the lesion involving the left medial temporal lobe on FLAIR imaging (Figure d).

As his neurological symptoms had improved, the patient was discharged 14 days after admission. Following discharge, no orofacial dyskinesia or long-lasting hiccups reoccurred.

Discussion

In patients with an immunocompromised status, herpes zoster in a cranial nerve dermatome or cutaneous dissemination increases the risk of CNS involvement by VZV (13). Due to its low transferability in CSF (14), patients with facial herpes zoster treated with amenamevir can have incom-

Table. Clinical Features of Cases of VZV-related Intractable Hiccups.

Cases	Age/ Sex	Immunodeficiency	MRI lesions in medulla/ cervical spine	Vomiting	Herpes skin lesion	Treatment (improvement of disease)
(5)	76 M	DM	-/-	+	-	Acy+Ste (+)
(6)	73 M	-	-/-	+	Larynx, pharynx, external ear	Acy+Val+Ste (+)
(7)	29 M	-	n/a	-	C3-5	Acy (+)
(8)	70 M	-	n/a	-	L2-3	- (+)
(9)	73 M	-	n/a	-	C2-3	Val (+)
(10)	54 M	n/a	-/-	n/a	n/a	Acy+Ste (-)
(11)	37 F	-	+/-	+	-	Asy+Val+Ste (+)
(12)	9 M	n/a	n/a	+	n/a	Corticotropin (+)
Present case	73 M	DM	-/ C1	-	C2	Acy (+)

M: male, F: female, DM: diabetes mellitus, Acy: acyclovir, Ste: steroids, Val: valacyclovir, n/a: not available
Note. Adapted from reference 5.

plete treatment of herpes zoster in the cerebral nerve region, possibly leading to VZV meningoencephalitis or CNS vasculitis (15).

VZV encephalitis is considered to be the result of vasculopathy affecting large/small vessels or other causes. Large-vessel encephalitis is characterized by stroke. For treatment, acyclovir and steroid are recommended. Small-vessel encephalitis is characterized by subacute neurologic symptoms and is mainly seen in immunocompromised patients. Several ischemic or demyelinating changes are often predominant in the deep white matter on MRI. Because these characteristics were found in our patient, with no signal change suggesting stroke apparent on MRI, small-vessel vasculitis was suggested as a cause of the encephalitis. Two distant signal changes found on MRI implied demyelination in this inflammation rather than ischemic changes. He was treated with acyclovir monotherapy as recommended (16, 17).

While orofacial dyskinesia, as a type of involuntary movement, is commonly seen as an extrapyramidal side effect of antipsychotics (18), patients with Huntington's disease, chronic hepatic encephalopathy, or infectious or paraneoplastic encephalitis can also show these abnormal movements (19). Oral involuntary movements are also observed in some forms of limbic encephalitis, although no definitive conclusions have been reached regarding the underlying mechanisms (20, 21). The present case had no clinical history involving drug use or diseases that could cause dyskinesia. Laboratory examinations showed negative results for anti-NMDAR antibodies. The mechanism underlying his involuntary movement was unclear. However, as seen in patients with limbic encephalitis, we noted MRI signal changes in the medial temporal lobe in our patient. Although we did not perform an electroencephalogram, temporal lobe epilepsy has been suggested to relate to oral automatism (22), so medial temporal lobe involvement of VZV-related inflammation might have contributed to the orofacial dyskinesia in our patient. The development of orofacial dyskinesia is rare among patients with CNS complications caused by VZV. We reviewed the literature using the search terms "VZV," "zoster," "oral dyskinesia," "orofacial dyskinesia," "oral movement," "orofacial movement," "oral involuntary movement," "orofacial involuntary movement" with AND/OR in the PubMed and Google Scholar databases but found no reports of patients with VZV-CNS complications who developed oral or orofacial dyskinesia.

VZV myelitis is a rare finding in patients with VZV and is reported to occur in 1 of 1,210 cases of herpes zoster (23). Myelitis is commonly seen one to two weeks after acute varicella or zoster skin rush in immunocompetent patients (24).

Various contributions, including structural or functional impairment of the vagus nerve and solitary bundle nuclei in the medulla oblongata, or the upper cervical cord at the C3-5 level, have been suggested as possible causes of intractable hiccups (25-27). The patient in this case showed no evidence of ear, nose, throat, intrathoracic, intraabdominal, or psychiatric disease or metabolic or toxic change, suggesting that the primary cause of the hiccups, based on the timing of onset, was CNS involvement. Along with the present case, a few cases of VZV-related intractable hiccups have been reported (Table) (5-12). Among these, one case besides ours showed an immunodeficient status due to DM. A cervical spine lesion on MRI was only reported in our case, and some cases reported patients with no MRI signal changes in either the medulla or cervical spine. While the combination of steroids and acyclovir is reportedly effective for treating intractable hiccups (29), some patients improved without steroids. The present patient had DM and was treated with acyclovir alone, considering the risk of using steroids.

On MRI, a signal change was observed at the C1 level of the upper cervical cord but did not extend to the medulla oblongata. However, including meningitis, inflammation may have extended to the medulla oblongata without noticeable signal changes. Furthermore, as VZV myelitis can manifest as multifocal lesions (28), inflammation may have occurred at the C3-5 level. Performance of contrast-enhanced MRI to check for meningitis and inclusion of the C3-5 level in imaging may have allowed us to better clarify the culprit lesion behind the intractable hiccups.

Conclusion

Patients with VZV-CNS complications who develop orofacial dyskinesia and intractable hiccups are rarely reported. The present findings indicate that special care is needed when treating immunocompromised patients with herpes zoster who may develop CNS complications that present as a wide variety of symptoms.

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

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