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【 CASE REPORT 】

Right-sided Herpes Zoster Ophthalmicus Complicated by Bilateral Third, Fourth, and Sixth Cranial Nerve Palsies and Syndrome of Inappropriate Antidiuretic Hormone Secretion

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Abstract:

Cases of herpes zoster ophthalmicus (HZO) complicated by bilateral ophthalmoplegia are rare, and no cases of bilateral third, fourth, or sixth cranial nerve palsies have been reported. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a rare complication of HZO. We herein report an 80-year-old Japanese woman with right-sided HZO complicated by meningoencephalitis and discuss the pathogenesis of this condition. She developed bilateral third, fourth, and sixth cranial nerve palsies and SIADH almost simultaneously during treatment for HZO. The bilateral cranial palsy spontaneously resolved within a few months.

Key words: herpes zoster ophthalmicus, ophthalmoplegia, cranial nerve palsy, syndrome of inappropriate antidiuretic hormone secretion

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Introduction

Approximately 10-30% of patients with herpes zoster ophthalmicus (HZO) develop ophthalmoplegia (1). Although several cases of HZO with ipsilateral ophthalmoplegia have been reported, cases of bilateral ophthalmoplegia are rare (1). In particular, no cases of unilateral HZO with bilateral third, fourth, or sixth cranial nerve palsies have been reported. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a rare complication of herpes zoster.

We herein report a case of right-sided HZO with meningoencephalitis presenting almost simultaneously with bilateral third, fourth, and sixth cranial nerve palsies and SIADH.

Case Report

An 80-year-old Japanese woman with a history of surgery for right breast cancer developed blisters and pain on the right side of her forehead 5 days prior to admission to our hospital. She visited her family physician, who diagnosed her with right-sided HZO and prescribed amenamevir. Her food intake decreased because of pain, and she fell unconscious and was transferred to our hospital.

On admission, her vital signs were as follows: blood pressure, 171/101 mmHg; heart rate, 121 bpm; and body temperature, 38.6°C. The right side of her face was erythematous, swollen, and blistered in the distribution of the V1 dermatome. She had disturbance of consciousness, a Glasgow Coma Scale (GCS) score of E1V2M5, and no meningeal signs. She did not have quadriplegia; her tendon reflexes were within the normal range, and she had a negative Babinski reflex.

Her blood tests showed no abnormalities in blood counts, and biochemical tests showed a C-reactive protein level of 1.63 mg/dL and sodium concentration of 126 mmol/L; however, her liver and renal function were within normal limits.

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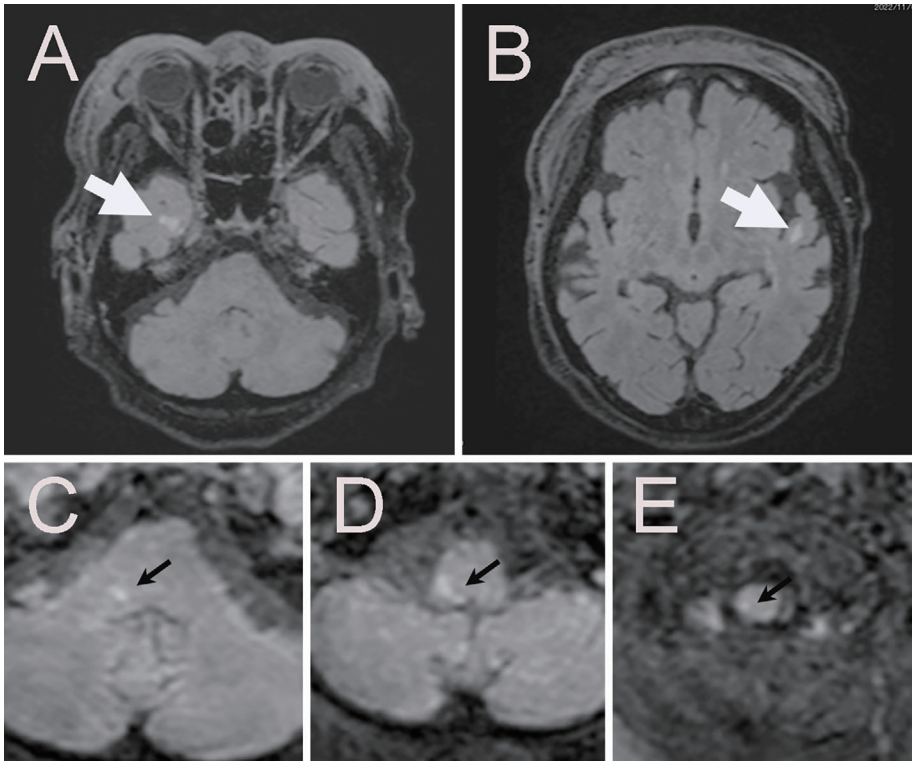

Figure 1. **Brain magnetic resonance imaging. (A, B) On admission, hyperintense FLAIR areas were observed in both temporal lobes (white arrows). (C-E) At 32 days after admission, a hyperintense FLAIR area appeared along the right trigeminal spinal tract nucleus (black arrows). FLAIR: fluid-attenuated inversion recovery**

A cerebrospinal fluid (CSF) examination revealed the following: leukocyte count, 64/μL (92% mononuclear cells); glucose, 56 mg/dL; and protein, 246 mg/dL. The varicella-zoster virus (VZV) polymerase chain reaction (PCR) test was positive. Brain magnetic resonance imaging (MRI) revealed fluid-attenuated inversion recovery (FLAIR) hyperintense areas in both the temporal lobes (Fig. 1A, B).

The patient was diagnosed with right-sided HZO with concomitant meningoencephalitis, and treatment with intravenous acyclovir and dexamethasone was initiated. On an ophthalmological examination the day after admission, she was diagnosed with conjunctivitis and keratitis of the right eye and prescribed acyclovir ointment.

A few days after admission, her level of consciousness improved, and she was able to eat and walk independently. Dexamethasone tapering was completed, and intravenous acyclovir was replaced with oral valaciclovir hydrochloride. Brain MRI showed reduced FLAIR hyperintense areas in the bilateral temporal lobes, and a CSF examination performed 12 days after admission was negative for VZV.

However, approximately 13 days after admission, redness and swelling on the right side of the forehead worsened, suggesting recurrence of right-sided HZO, and intravenous vidarabine was administered. Approximately 18 days after admission, she complained of difficulty opening her left eyelid, but no abnormalities in ocular movements or pupils of the left eye were observed. The cutaneous symptoms improved after initiation of intravenous vidarabine; however, 24 days after admission, the patient's unconsciousness rapidly progressed to a GCS of E1V2M2.

Blood tests showed no abnormalities that could lead to a disturbance of consciousness, and the serum sodium concentration was 134 mmol/L. Brain MRI revealed no new abnormalities. Electroencephalography revealed no epileptic waves; however, frequent high-amplitude slow waves were observed bilaterally in the frontal and parietal regions. She was diagnosed with antiviral drug-induced encephalopathy, and oral valaciclovir hydrochloride and intravenous vidarabine were discontinued.

Twenty-five days after admission, the serum sodium concentration was 129 mmol/L, and she was infused with normal saline (1,500 mL/day). Twenty-eight days after admission, her disturbance of consciousness improved slightly to a GCS of E1V3M4. However, 29 days after admission, her disturbance of consciousness worsened again, and her serum sodium concentration was 120 mmol/L. Although saline infusion was limited to 1,000 mL/day, and sodium chloride was started at 3 g/day through a feeding tube, her serum sodium concentration decreased to 116 mmol/L 30 days after admission. With continued water restriction and an increase in sodium chloride dosage to 9 g/day, the patient's serum sodium concentration gradually increased. Thirty-two days after admission, when her serum sodium concentration was 126 mmol/L, laboratory tests revealed a urinary sodium concentration of 141 mmol/L, a urine osmolality of 436 mOsm/kg, and a serum osmolality of 262 mOsm/kg. Her serum

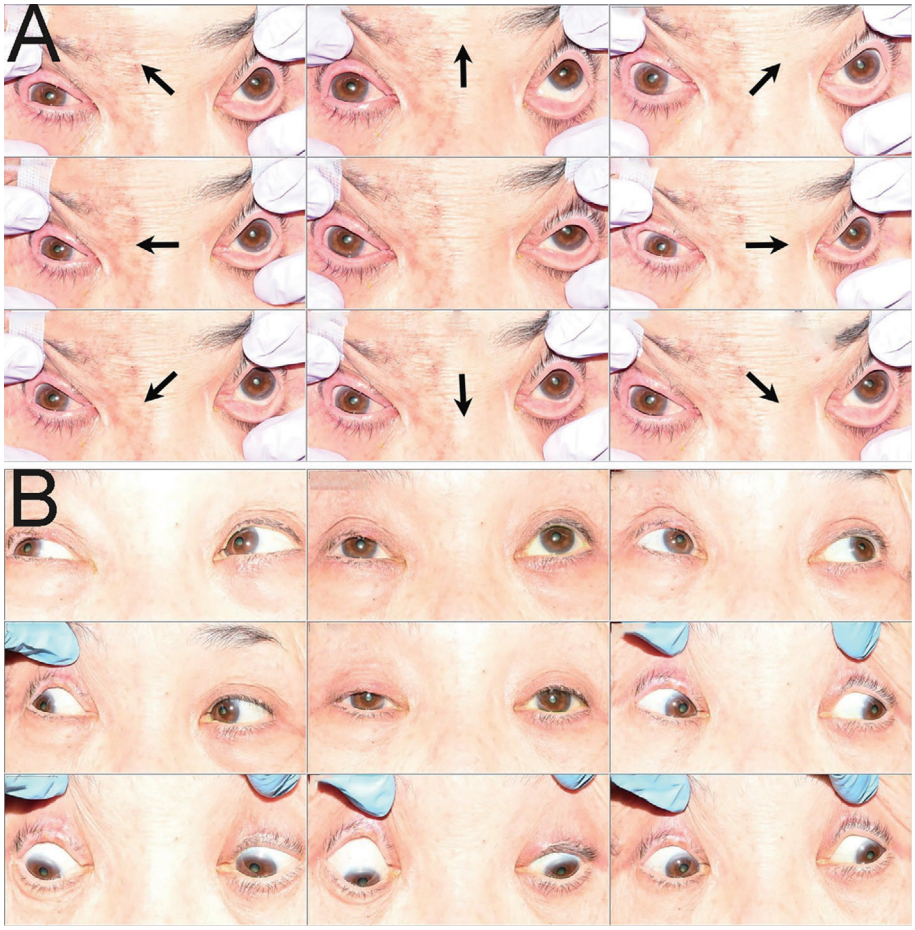

Figure 2. Nine cardinal directions of ocular movement. (A) At 33 days after admission, the right eye had omnidirectionally impaired ocular movement, and the left eye was capable of slight supination and abduction. (B) Three months after discharge, only slight ptosis of the right eyelid remained, and no ophthalmoplegia was observed in either eye.

uric acid concentration was 2.5 mg/dL, and the thyroid and adrenocortical function test results were normal, consistent with SIADH.

Thirty-three days after admission, her serum sodium concentration was 134 mmol/L, and she was able to communicate. Despite a reduction in swelling on the right side of her forehead, she could not independently open her bilateral eyelids. An evaluation of both the eyes revealed bilateral ophthalmoplegia. Although her pupils were normal bilaterally, her right eye had impaired omnidirectional ocular movement, and her left eye was only slightly capable of supination and abduction (Fig. 2A). These findings, along with the bilateral ptosis, were consistent with palsy of the bilateral third and sixth cranial nerves. There was no inward torsion of the eyeballs during downward gaze in either eye, which therefore suggested palsy of the bilateral fourth cranial nerves.

A CSF examination revealed the following: leukocyte count, 5/μL (100% mononuclear cells); glucose, 53 mg/dL; protein, 86 mg/dL; and VZV PCR test, negative. Serum GQ1b and GM1 antibodies were negative. Brain MRI revealed a new FLAIR hyperintense area along the right trigeminal spinal tract nucleus (Fig. 1C-E). Based on these findings, she was diagnosed with bilateral third, fourth, and sixth cranial nerve palsies, secondary to right-sided HZO.

She was not administered steroids or antiviral drugs for the cranial nerve palsies because of her history of recurrent HZO and antiviral drug-induced encephalopathy. She resumed oral feeding, and the saline infusions and oral sodium chloride were tapered off; however, the serum sodium concentration did not decrease. At the time of transfer for rehabilitation, 46 days after admission, there was no improvement in the bilateral ptosis or ophthalmoplegia. However, when she visited our outpatient clinic three months later, only slight ptosis of the right eyelid persisted, and ophthalmoplegia was not observed in either eye (Fig. 2B).

Discussion

The mechanism underlying cranial nerve palsy associated with HZO has not yet been elucidated but is assumed to be VZV-induced vasculopathy, a reactive immunological response to VZV, or a direct cytotoxic effect of VZV. However, the localized and bilateral damage to the third, fourth, and sixth cranial nerves in our case was difficult to explain fully.

The clinical course of this case most likely suggests a reactive immunological response mechanism, such as Fisher syndrome, because acute ophthalmoplegia following the onset of infection resolved spontaneously within a few months. Rizzo et al. reported a case of Fisher syndrome in a patient who developed right third cranial nerve palsy 20 days after the onset of right-sided HZO and tested positive for serum GQ1b antibody (2). In Fisher syndrome, serum GQ1b antibodies are detected at a high frequency of 83-100% and are considered strong serological diagnostic markers. However, cases of GQ1b antibody-negative Fisher syndrome are known to occur, and some patients with GQ1b antibody-negative Fisher syndrome have been reported to have IgG antibodies to individual gangliosides, such as GM1b, GD1a, GalNAc-GD1a, and GT1a (3). Although anti-ganglioside antibodies other than GQ1b and GM1 were not detected in this case, it is possible that the patient had GQ1b-negative Fisher syndrome. Unfortunately, ataxia and areflexia, which are also characteristics of Fisher syndrome in addition to ophthalmoplegia, were not evaluated after the appearance of cranial nerve palsies.

VZV-induced vasculopathy is one of the most significant complications of herpes infection. After reactivation in the ganglion, the VZV migrates transaxially to the adventitia of the cerebral arteries, where the nerves terminate. VZV then spreads transmurally into the media and intima of cerebral arteries, causing pathological vascular remodeling and consequent vascular occlusion (4). Although no cases of cerebrovascular innervation of the trigeminal nerve have been reported in humans, studies in monkeys by Simons and Ruskell have shown that the anterior part of the arterial circle of Willis receives input only from the ipsilateral trigeminal ganglion (5). As the third, fourth, and sixth cranial nerves receive their blood supply from the branches of the ipsilateral internal carotid artery (6), we speculated that the mechanism involved in VZV-induced vasculopathy could not explain the contralateral ophthalmoplegia in the present case.

The direct cytotoxic effects of VZV are attributable to its retrograde spread from the trigeminal ganglion to the nucleus of cranial nerve V. In the present case, a hyperintense FLAIR area was observed along the nucleus of the right trigeminal spinal tract. A case with the same imaging findings has been reported previously (7), and a finding of VZV spreading along the trigeminal spinal tract was considered. As direct connections between the trigeminal spinal tract nucleus and the nuclei of the third, fourth, and sixth cranial nerves have not been identified, the VZV is speculated to diffuse randomly within the brainstem to reach each nerve nucleus, thus causing brainstem encephalitis. However, our findings do not support this hypothesis. The disturbance of consciousness observed in this case was associated with antiviral drug-induced encephalopathy and altered serum sodium concentrations. In addition, because our case of HZO was accompanied by meningoencephalitis, we considered the possibility of direct infiltration of VZV from the CSF into the cranial nerves. However, this cannot explain why the symptoms were limited to the eyes.

A possible mechanism by which HZO causes SIADH is that reactivation of VZV in the trigeminal nerve may cause osmoreceptor dysfunction, or severe pain may stimulate ADH secretion (8). In previous reports, the time from the onset of herpes zoster to confirmed SIADH was usually three to seven days (8, 9). The long latency in our case suggests that the pathogenesis of SIADH differs from that previously reported. Although extremely rare, cases of SIADH as a side effect of vidarabine have been reported (10, 11). Interestingly, in our case, the appearance of SIADH and manifestation of cranial nerve palsy occurred at approximately the same time, suggesting that they may have been triggered by the same pathology. Fisher syndrome, which may be the underlying mechanism of ophthalmoplegia in this case, may be accompanied by SIADH as a complication (12-14). Cerebral salt-wasting syndrome (CSWS) is a common cause of hyponatremia in patients with neurological disorders and is difficult to differentiate from SIADH, owing to overlapping symptoms and key laboratory data. One of the factors that helps differentiate these two syndromes is that, in SIADH, the intravascular volume status is normal or increasing, whereas in CSWS, it is hypovolemic due to increased urine output (15, 16). In our case, a urinary catheter was inserted, and urine output measurement was initiated after the disturbance of consciousness appeared 24 days after admission. However, there was no increase in urine output or negative fluid balance before her hyponatremia became severe. In addition, the treatments for both syndromes are diametrically opposite, with water restriction called for in cases of SIADH and volume replacement with isotonic saline for CSWS (15, 16). The improvement in hyponatremia with water restriction in our case supports the diagnosis of SIADH.

Antiviral drugs and steroids have been used empirically to treat ophthalmoplegia associated with HZO (17, 18); however, these are only case series studies based on published cases, and their efficacy has not been established. Our patient presented with severe bilateral third, fourth, and sixth cranial nerve palsies; however, neither antiviral drugs nor steroids were administered because of concerns regarding the recurrence of antiviral drug-induced encephalopathy and herpes zoster caused by steroids. Despite this, the only sequela she experienced three months after discharge from the hospital was mild ptosis of the right eyelid, which did not interfere with her daily life. Although the pathogenesis of ophthalmoplegia associated with HZO may not be uniform, further case studies are required to verify the efficacy of antivirals and steroids.

Conclusion

We herein report a unique case of right-sided HZO complicated by bilateral third, fourth, and sixth cranial nerve palsies and SIADH with spontaneous resolution of severe ocular symptoms. We believe that our case contributes to the

elucidation of the pathogenesis of ophthalmoplegia associated with HZO.

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

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