면역이 정상인 소아에서 발생한 대상포진과 무균성 수막염에 대한 증례기록

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Herpes Zoster with Aseptic Meningitis in Immuno-competent Children: A Case Series

Primary clinical features of rash and neurological complications due to varicella zoster virus (VZV) reactivation are rare in a healthy population, especially in immuno-competent children. Early diagnosis and prompt treatment are delayed often due to their rarity. We present four immunocompetent children with VZV reactivation resulting in aseptic meningitis and herpes zoster affecting multiple cranial and spinal nerves. We reviewed the clinical manifestations, laboratory findings, treatment options and outcome of aseptic meningitis associated VZV reactivation. All patients presented with the typical skin lesion of VZV reactivation and definitive laboratory findings of central nervous system infection, without systemic inflammation. Initial manifestations of VZV reactivation included Ramsay Hunt syndrome, herpes zoster ophthalmicus, and herpes zoster affecting the left thoracic dermatomes 4-5. Intravenous acyclovir was administered and all patients recovered fully without any significant sequelae. VZV reactivation can lead to various neurological complications in immunocompetent children. Early recognition and treatment with acyclovir are important for improving the outcome of neurologic complications of VZV reactivation.

Key Words: Herpes zoster, Varicella zoster virus, Chickenpox, Aseptic meningitis

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Introduction

Infection with neurotropic herpes viruses, including herpes simplex virus (HSV) type 1 and 2, and varicella zoster virus (VZV), is common in humans. After primary infection with VZV or VZV vaccination, these viruses persist within the cranial nerves, dorsal roots, and autonomic ganglia causing latent infections following reactivation¹⁻³. With advancing age and various conditions leading to immunosuppression, the decreased immunity to VZV and virus reactivation causes herpes zoster (shingles). VZV reactivation can be complicated by central and peripheral nervous system involvement⁴. Although VZV infection of the central nervous system (CNS), such as encephalitis, meningitis, myelitis, or angitis, occurs less frequently, it is closely associated with numerous unfavorable outcomes^{1,2,5}. Usually CNS complications of VZV reactivation appear along with the typical skin lesions of herpes zoster, but it can rarely develop without a skin lesion^{1,2,6,7}.

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Acute infection or VZV reactivation affects predominantly older individuals and/or immunocompromised patients^{1,2)}. The development of the neurological complications of VZV reactivation is relatively uncommon in immunocompetent patients and mainly reported in adults⁸⁻¹¹⁾. Only a few case reports of VZV reactivation and neurologic complications in children have been reported.

Here, we describe four cases of an immunocompetent children and adolescents with herpes zoster and aseptic meningitis due to VZV reactivation and their clinical characteristics, laboratory findings, and their outcomes.

Case reports

Case 1

A previously healthy 14-year-old boy presented to the emergency room with a 2-day history of fever, nausea, vomiting, left earache, and left peripheral facial palsy. His body temperature was 37.8°C. Physical and neurological examination revealed prominent left peripheral facial palsy, and a few vesicles were noticed on the left external auditory meatus. Magnetic resonance imaging (MRI) showed focal meningitis of the left internal auditory canal with neuritis of the left facial nerve with contrast enhancement (Fig. 1). Analysis of the cerebrospinal fluid (CSF) showed a lymphocytosis with 264 cells/ μ L with 97% lymphocytes and 3% other cells, and slightly elevated protein content (53.9 mg/dL). The results of polymerase chain reaction (PCR) of CSF were positive for VZV deoxyribonucleic acid (DNA) and negative for enterovirus and HSV type 1 and 2. He was diagnosed with Ramsay Hunt syndrome. Treatment with intravenous acyclovir (10 mg/kg/dose, three times per day for 10 days) was commenced. The patient was discharged on the eleventh hospital day, when he was afebrile and only minimal left facial palsy remained. One month after the onset of symptoms, he had no neurological sequelae and made an uneventful recovery.

Case 2

A 9-year-old previously healthy boy, who had just returned from a 5-day vacation, presented to the emergency room with multiple vesicles on the right forehead and right eyelid, pruritus, and vomiting. Lumbar puncture revealed lymphocytosis with 74 mononuclear cells/ μ L with 76% lymphocytes and 24% other cells, and normal protein content (26.1 mg/dL). As viral meningitis was suspected, the patient was immediately given acyclovir at 10 mg/kg/dose interval every 8 hours. Serological test results for HSV and VZV DNA showed no evidence of present or recent infection. In CSF, anti-VZV IgG and anti-VZV IgM antibody titers

were positive, compatible with reactivation of the previous VZV infection. He was diagnosed with herpes zoster ophthalmicus and aseptic meningitis. Intravenous acyclovir (10 mg/kg/dose, three times per day for 10 days) was administered. He recovered fully without any sequelae.

Case 3

A 11-year-old girl, who was previously otherwise healthy and had a history of chickenpox 3 years ago, presented with grouped, painful vesicular lesions on the left eyebrow, left forehead, and scalp. One week prior to presentation, she had felt left earache and was treated with an antiviral agent. However, she presented with 2-day history of fever, severe headache, nausea, and vomiting. Lumbar puncture revealed lymphocytosis with 79 lymphocyte cells/ μ g with 3% neutrophils, 72% lymphocytes, 5% monocytes and 20% other cells, and slightly elevated protein content (95.2 mg/dL). Bacterial culture of CSF yielded no growth. VZV DNA was detected in CSF using PCR. Treatment with intravenous acyclovir (10 mg/kg/dose, three times per day for 10 days) was initiated. Given the favorable course of the illness, the child was discharged without further therapy after the 10-day treatment period.

Case 4

A previously healthy 14-year-old boy, who had a history of

Fig. 1. Enhancement observed within the left internal auditory (arrow) led to the diagnosis of the inflammation of the cistern segment and meatal segment of left facial nerve. (axial T1 weighted spin-echo acquisition/fat suppression cranial magnetic resonance image with gadolinium enhancement).

chickenpox when he was an infant, presented with grouped, painful vesicular lesions of the left thoracic dermatomes 4 and 5. A clinical diagnosis of herpes zoster was made and symptomatic local treatment was initiated. On the day after onset, the child had an acute onset of intense headache. On physical examination, the boy was in a moderately well condition and febrile with an axillary body temperature of 38.3°C; all other vital signs were normal. Neurological examination revealed the stiffness of the neck with positive Brudzinski's and Kernig's signs. Lumbar puncture revealed 476 leukocytes/ μ L with 70% lymphocytes and 30% other cells. CSF glucose and protein levels were within the normal range. The VZV-IgG antibody titer was positive and VZV DNA was not detected in the blood using PCR. Intravenous acyclovir (10 mg/kg/dose, three times per day, for 10 days) was started empirically. Bacterial culture of CSF yielded no growth. Four days later, we repeated the lumbar puncture. Analysis of the CSF found lymphocytosis with 168 cells/ μ L, slightly elevated glucose (58 mg/dL), and normal protein content (45.3 mg/dL). The boy's general condition normalized gradually over the next few days.

Discussion

There are few case reports of Herpes zoster infection and VZV reactivation complicated by meningitis in immunocompetent children after reactivation of wild-type VZV. With the advent of novel diagnostic methods for detection of VZV DNA, VZV has increasingly been implicated in central nervous system (CNS) infections in immunocompetent individuals. We report four cases of an immunocompetent children and adolescents with herpes zoster and aseptic meningitis due to VZV reactivation.

In generally, herpes zoster mainly affects elderly individuals, with 8-10 times higher incidence in people over 60 years old and immunocompromised patients (due to acquired immunodeficiency or medications) than that in younger subjects¹²⁾. In specially, bone marrow transplant recipients and human immunodeficiency virus (HIV)-seropositive patients have an increased risk of VZV reactivation¹³⁾. Abnormal cell-mediated immunity is closely associated with the increased incidence of herpes zoster and its complications.

Varicella-zoster virus meningitis has recently been reported in children. Our four cases have mostly been related to history of chickenpox or breakthrough cases of chickenpox in previously vaccinated children. There are three routes of primary exposure of VZV, such as intrauterine exposure to VZV, postnatal exposure to wild-type VZV, and exposure due to vaccination with the live-

attenuated strain of the virus. Either strain may cause a latent infection and subsequent eruption of Herpes zoster. After VZV infection or vaccination, VZV remains latent in the sensory dorsal root ganglia. Antibody titers against VZV remain unchanged or may even increase with age^{4,13)}, which explains why VZV reactivation is rare in immunocompetent children^{4,14)}. When VZV is reactivated, viruses replicate along the course of the nerve and appear as a vesicular skin rash^{4,14,15)}. Although most cases follow wild-type virus infection, herpes zoster has been rarely associated with the vaccine strain^{16,17)}. Aseptic meningitis is one of possible complications of VZV reactivation. It is not one of the most severe neurological complications and usually does not lead to the major brain damage characterizing VZV myelopathy, vasculopathy, or eye disease⁴⁾. The clinical manifestations and CSF profile in VZV CNS complications are variable and indistinguishable from other types of viral meningitis. Screening for VZV using PCR, and determining the status of antibodies against VZV in the serum and CSF is recommended for patients suspected to have VZV CNS complications.

Table 1 summarizes the clinical characteristics and laboratory findings of the four patients. All patients were vaccinated and two patients had a history of varicella. Three patients had a skin lesion in the head and neck region, one with Ramsay Hunt syndrome and two with herpes zoster ophthalmicus. Tests for the immune screening and the systemic inflammatory syndrome were normal in all patients. We confirmed VZV reactivation through CSF VZV PCR or serum anti VZV IgM positivity. Although the laboratory tests did not reveal VZV reactivation in case 4, we diagnosed herpes zoster with aseptic meningitis through typical skin lesions and CSF pleocytosis. Because of, herpes zoster is caused by reactivation of latent VZV infection and other virus DNA, such as HSV and enterovirus, were not detected in CSF using PCR.

Treatment studies are insufficient, probably because neurological complications have been regarded as a small problem and the number of patients with VZV CNS disease has been underestimated¹⁸⁾. VZV is susceptible to several antiviral drugs but acyclovir, a synthetic acyclic purine nucleoside analogue, relatively safe antiherpes drug with activity against varicella-zoster virus, makes it especially important that all patients suspected of having viral CNS disease, especially those with skin lesions suspicious for varicella zoster or those with a recent history of such lesions, be actively tested for this virus. Since the bioavailability of oral acyclovir is poor, intravenously administered acyclovir is recommended for severe VZV CNS infections such as meningitis, encephalitis, myelitis, brain infarction and cerebellitis. The role of corticosteroids in VZV CNS infections has not been systematically investigated, but in vasculitis and cranial nerve palsies, such the-

Table 1. Summary of Clinical Characteristics and Laboratory Findings

	Case 1	Case 2	Case 3	Case 4
Clinical findings				
Age, years	14	9.8	11	14
Gender	M	M	F	M
History of varicella	No	No	Yes	Yes
VZV vaccination	Yes	Yes	Yes	Yes
Skin lesion	Left ear	Right forehead and eyelid	Left forehead, scalp, and eyelid	Left thoracic dermatomes 4-5
Initial diagnosis	Ramsay Hunt syndrome	Herpes ophthalmicus	Herpes ophthalmicus	Herpes zoster on left thoracic dermatomes 4-5
Presenting symptoms	Fever, vomiting, earache, left peripheral facial palsy	Pruritus, vomiting	Fever, headache, nausea, vomiting, left earache	Fever
Treatment	IV acyclovir	IV acyclovir	IV acyclovir	IV acyclovir
Outcome	CR	CR	CR	CR
Duration of hospital stay, days	11	10	10	11
Laboratory findings				
Blood				
WBC count (/μL)	8,490	5,770	5,030	11,360
CRP	0.01	0.01	0.07	0.08
ESR	8	4	4	27
Anti VZV IgM/G	-/+	+/+	Equivocal/+	-/+
Immunologic screening				
T cell subset	Normal	Normal	Normal	Normal
Immunoglobulin level	Normal	Normal	Normal	Normal
CSF				
Leukocyte count (cells/μL)	264	74	79	476
Protein (mg/dL)	53.9	26.1	95.2	131.2
Glucose (mg/dL)	65	54	60	59
VZV PCR	Positive	Negative	Positive	ND
HSV PCR	Negative	Negative	ND	Negative
Brain MRI	Focal meningeal enhancement of left internal auditory canal with neuritis of left facial nerve	ND	ND	Normal

VZV, varicella zoster virus; CR, complete recovery; WBC, white blood cells; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CSF, cerebrospinal fluid; PCR, Polymerase chain reaction; HSV, herpes simplex virus; ND, not done; MRI, magnetic resonance imaging.

rapy may be considered¹⁸⁾. If patients don't treated properly, the neurological sequelae, such as encephalitis, meningitis, cranial nerve palsies including Ramsay-Hunt syndrome, cerebellitis, myelitis and vasculopathies, are shown to be frequent and often serious. We administered intravenous acyclovir (10 mg/kg/dose, three times per day for 10 days) and all patients showed complete recovery without any sequelae.

Healthy immunocompetent children with a history of previous VZV infection or VZV vaccination can develop herpes zoster and aseptic meningitis due to VZV reactivation. Early recognition, appropriate diagnostic tests, and prompt treatments improve the outcome of this condition.

요약

수두바이러스의 재활성화에 의한 피부 발진과 신경학적 합병증은 건강한 인구, 특히 면역이 정상인 소아에서는 드물다. 드문 발생 빈도

로 인해 조기 진단과 즉각적인 치료가 지연되기도 한다. 저자들은 면역이 정상인 소아에서 발생한 수두바이러스 재활성화와 이로 인한 대상포진과 무균성 수막염 4예를 보고하고자 한다. 모든 환자는 수두바이러스 재활성화의 특징적인 피부 병변과 중추신경계 감염의 확실한 검사 소견을 보였으나, 전신적인 염증 반응은 관찰되지 않았다. 수두바이러스 재활성화의 초기 증상은 Ramsay Hunt 증후군, 눈대상포진 (herpes zoster ophthalmicus), 좌측 4번째와 5번째 피부분절의 대상포진이었다. 모든 환자가 정맥내 acyclovir를 투여 받았으며, 특별한 후유증 없이 완전히 회복되었다. 수두바이러스의 재활성화는 면역이 건강한 소아에서도 다양한 신경학적 합병증을 병발할 수 있다. 조기 진단과 정맥내 acyclovir 등 항바이러스제 투여는 수두바이러스 재활성화에 의한 신경학적 합병증의 예후를 향상시키는데 중요하다.

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