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症　　例

# Aciclovir-resistant Herpes Zoster Encephalitis Successfully Treated with Vidarabine : A Case Report

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**Abstract** A 78-year-old man developed herpes zoster virus (HZV) encephalitis. Initially, treatment with aciclovir (750 mg per day) improved CSF cell count and protein level. During the treatment, however, encephalitis in the patient deteriorated in spite of the treatment with aciclovir, suggesting that HZV in the patient had become resistant to aciclovir. Subsequent treatment with vidarabine (600 mg per day, for 15 days) resulted in dramatic improvement in CSF pleocytosis. About two months after the discontinuation of vidarabine, the CSF cell count was normal. The patient became alert gradually, but his amnestic syndrome remained unchanged. Vidarabine may be recommended in the treatment of HZV encephalitis when aciclovir is not effective.

## Introduction

Encephalitis is a rare complication of herpes zoster virus (HZV) infection. Early diagnosis is extremely important because HZV encephalitis is the only viral encephalitis, other than herpes simplex encephalitis, for which specific therapy is available[5].

We report a case of a 78-year-old man with aciclovir-resistant HZV encephalitis which was effectively treated with vidarabine.

To our knowledge, this is the first report of a previously healthy man with aciclovir-resistant HZV encephalitis effectively treated with vidarabine.

## Case report

A 78-year-old man was admitted to the Imazu Red Cross Hospital on June 28, 1992, because of fever, malaise and headache. On admission, he was drowsy and his body temperature was 38.9 °C. Neurological examination showed nuchal stiffness, weak tendon reflexes without pathological reflexes, and left facial palsy. On the next day, convulsion developed and shingles was seen on the lower extremities and buttocks.

Urine analysis and blood analysis were normal. Erythrocyte sedimentation rate was 30 mm/hr. Blood chemistry was normal except for creatine kinase; 230 units/L (normal range, <85 units/L). C-reactive protein was 2+. Serum antibody to HZV (IgG-EIA) was 3200 (negative<200). The CSF showed 80 cells/mm$^3$ (mostly lymphocytes), 660 mg/dl protein, and 103 mg/dl glucose (with 177 mg/dl in the blood). Neither bacteria nor fungus was found

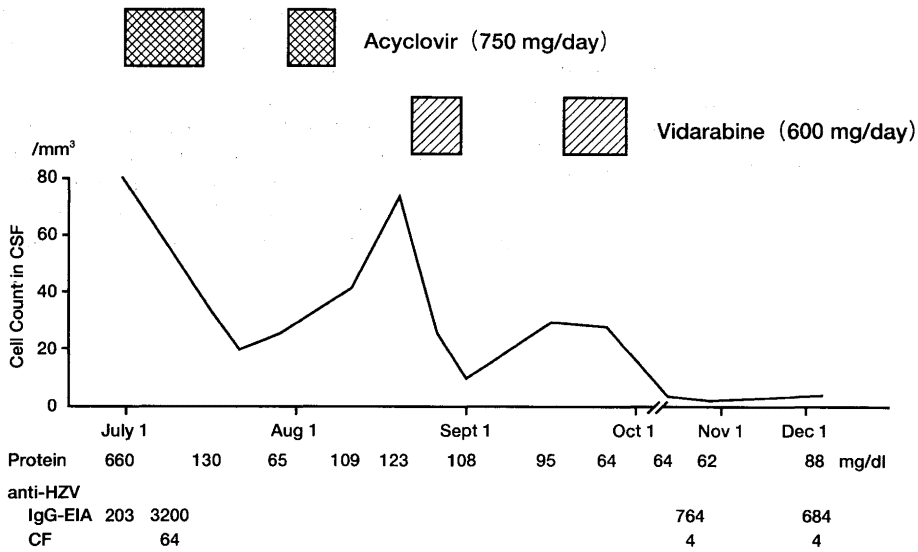
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in the CSF. Antibody to herpes zoster (IgG-EIA) in the CSF was 203 (negative<200). Electroencephalogram showed diffuse slowing of the background activity. Brain computed tomography was normal.

The changes in CSF cell count, protein level, and antibody to HZV are shown in the figure. Aciclovir (750 mg per day) was administered intravenously for 14 days from June 29th. The CSF on July 16th showed reductions in cell count (33 cells /mm$^3$) and protein level (130 mg/dl). Antibody to HZV in the CSF was 3200 by IgG-EIA and 64 by complement fixation (CF) test. However, the patient was still drowsy. Intravenous aciclovir with 750 mg per day was again administered during a period from July 29th to August 6th. In spite of the treatment with aciclovir, the CSF on August 11th showed an increase in cell count (43 cells/mm$^3$) and protein level (123 mg/dl). Since the cell count in the CSF on August 18th deteriorated to 75 cells/mm$^3$, intravenous vidarabine (600 mg per day) was administered for another 5 days for from August 20th. Six days later, the CSF showed 11 cells/mm$^3$ and 62 mg/dl protein. Disturbance of consciousness improved gradually and the patient became alert on September 3rd. However, he suffered from severe amnestic syndrome. Since the CSF on September 16th showed 31 cells /mm$^3$ and 64 mg/dl protein, additional vidarabine (600 mg per day) was administered intravenously for 10 days from September 17th. The CSF on October 12th showed 5 cells/mm$^3$ and 64 mg/dl protein. Antibody titer to HZV in the CSF was 764 by IgG-EIA and 4 by CF. After the discontinuation of vidarabine, the patient had no relapse until the time of this report.

## Discussion

Herpes zoster encephalitis is a very rare entity. Jemsek et al[2]. proposed the following diagnostic criteria for HZV encephalitis, (A) encephalopathic clinical state, (B) clinical evidence of herpes zoster, (C) diffusely abnormal electroencephalogic findings and (D) cerebrospinal fluid findings compatible with encephalitis. High risk groups for HZV encephalitis are the elderly, patients with disseminated herpes zoster, and immunocompromised




Changes in cell count, protein level, and antibody to herpes zoster virus in the cerebrospinal fluid.

patients[3]. The present case was a 78-year-old immunocompetent patient.

The patient suffered from headache, drowsiness, convulsion, stiff neck and facial palsy, and the laboratory findings diagnostic of HZV encephalitis were diffuse slowing of the electro-encephalogram, pleocytosis and elevated protein levels in the CSF, and elevated antibody titer to HZV in both serum and CSF.

Although both aciclovir[3)4)5)6)] and vidarabine[2)4)5)] and effective anti-viral agents in the treatment of HZV encephalitis, aciclovir is more commonly used than vidarabine because it inhibits virus-specific polymerase selectively[4]. In the present case, treatment with aciclovir improved encephalitis initially. During the treatment, however, encephalitis in the patient deteriorated in spite of the treatment with aciclovir, suggesting that HZV in the patient had become resistant to aciclovir; the abnormal laboratory findings of herpes zoster encephalitis improved dramatically after intravenous administration of vidarabine.

Jacobson et al[1]. reported four cases of aciclovir-resistant herpes zoster infection in patients with acquired immunodeficiency syndrome (AIDS) and demonstrated that viral isolates from these four patients were highly resistant in vitro to aciclovir, but susceptible to a plasma achievable level of vidarabine. Since aciclovir inhibition of HZV replication requires drug monophosphorylation by virus-encoded thymidine kinase unlike vidarabine inhibition[4], alteration or deficiency of viral thymidine kinase may cause resistance to aciclovir[1].

The mean duration of the central nervous system symptoms has been reported to be about two weeks[3]. However, the disturbance of consciousness lasted for about two months in the present case despite 21-day aciclovir treatment. Physicians should be aware of the existence of aciclovir-resistant herpes zoster virus. Vidarabine should be used when aciclovir treatment is not effective.

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(和文抄録)

# Vidarabineが有効であったaciclovir耐性帯状疱疹ウイルス脳炎の一例

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aciclovir治療経過中にaciclovirに対する耐性が出現したが，vidarabineが有効であった帯状疱疹ウイルス(HZV)脳炎の一例を経験した．症例は78歳男性．14日間のaciclovir(750 mg/日)の投与にて髄液の細胞数，蛋白量は減少したが，効果が不十分なため，さらに，7日間のaciclovirの投与を行った．しかし，治療に抵抗して，髄液の細胞数，蛋白量が増加し，ウイルスがaciclovirに耐性を得たことが疑われた．このため，vidarabine(600 mg/日)に変更したところ，髄液所見は著明に改善した．vidarabine中止後2カ月たっても髄液中の細胞数は正常であった．HZV脳炎でaciclovirによる治療が無効の場合にはvidarabineを使用すべきであると考えられた．