Myelitis Due to Varicella-Zoster Virus in Two Patients with AIDS: Successful Treatment with Acyclovir

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Only a few cases of varicella-zoster virus (VZV) myelitis have been described, and nearly all have been diagnosed post-mortem. There have been no reports in the literature of successful treatment of VZV myelitis with antiviral medications. We report on two patients with AIDS who had acute severe myelitis accompanied by herpes zoster. The presence of VZV DNA in cerebrospinal fluid (CSF) was documented by the polymerase chain reaction (PCR) technique. Early treatment with acyclovir was followed by a slow but complete recovery after a phase of initial aggravation. After a follow-up of >1 year, the two patients remained asymptomatic. We conclude that (1) VZV should be considered a curable cause of myelitis in patients with AIDS, (2) PCR assay of CSF will assist in early diagnosis, and (3) early treatment with acyclovir should aid in recovery.

Spinal cord disease is observed frequently in the setting of HIV-1 infection. The disorder is often ascribed solely to HIV, but a variety of infectious agents have been incriminated. Although varicella-zoster virus (VZV) infection of the CNS is more common in patients with AIDS than in immunocompetent individuals and accounts for up to 2% of cases of CNS involvement [1], VZV-associated myelitis has been described only rarely and usually is recognized post mortem. We report herein on the features of VZV-associated myelitis in two patients with AIDS, who completely recovered following treatment with acyclovir.

Case Reports

Case 1. A 35-year-old woman was found to be seropositive for HIV-1 during an episode of Pneumocystis carinii pneumonia in February 1992. Current medications included zidovudine and trimethoprim-sulfamethoxazole. In January 1993 she was admitted to the hospital because of headache and fever of 2 days’ duration. Initial examination showed an elevated temperature (39°C), meningism, and a right sensory loss to the T-4 vertebral level. The CD4 cell count was 5/mm³. Cranial CT scanning revealed no abnormalities. The CSF contained four lymphocytes and 65 mg of protein per dL but was negative for lPN-a, and no VZV DNA was detected by PCR. The neurological deficit was static, and the patient was able to return to work. She was still asymptomatic 2 years after the onset of the disease.

On day 2 after admission, CSF values were as follows: WBCs, 830/µL; protein, 700 mg/dL; and IFN-β, 100 IU/mL. On day 3, two cutaneous cervical lesions of herpes zoster appeared, and PCR revealed VZV DNA in the two CSF specimens but not in the serum; PCR for cytomegalovirus (CMV), herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), and Epstein-Barr virus (EBV) was negative. The patient was treated with iv acyclovir (30 mg/[kg · d] for 35 days), and zidovudine was withdrawn. Defervescence occurred promptly (within 4 days), but the neurological condition worsened until day 20, when the maximal deficit included Brown-Séguard syndrome, encephalopathy, and bilateral palsies involving cranial nerves VII and VIII, which resulted in complete deafness.

At that time the CSF contained four lymphocytes and 65 mg of protein per dL but was negative for IFN-β, and no VZV DNA was detected by PCR. The neurological deficit was static, and slow clinical improvement was noticed from day 30. The patient was discharged for rehabilitation while receiving oral acyclovir (1 g/d). Improvement was remarkable during the following weeks and continued during the next 10 months. Neurological findings on follow-up examination in November 1993 were normal except for persistence of the right sensory loss, and the patient was able to return to work. She was still asymptomatic 2 years after the onset of the disease.

Case 2. A 29-year-old man who was seropositive for HIV-1 was seen in January 1993 with trigeminal herpes zoster. Treatment with acyclovir was successful. The patient then received maintenance therapy with didanosine. In April 1993 he was admitted to the hospital because of urinary retention. His temperature was 38.6°C, and physical examination showed a right-sided thoracic zoster with a T-10 dermatomal distribution. Neurological examination revealed weakness in the iliopsoas, quadriceps, and gluteal muscles bilaterally, as well as a bilateral extensor planter response. The CD4 cell count was 16/mm³. Lumbar puncture revealed clear CSF with a WBC count of 380/µL (76% lymphocytes), a protein concentration of 91 mg/dL, a glucose level of 3.7 mmol/L, and an INF-β level of 100 IU/mL. Findings on MRI of the spinal cord were normal.
Didanosine was withdrawn; therapy with iv acyclovir (30 mg[kg·d]) was immediately started and was given for 21 days. Diagnosis was confirmed by PCR, which revealed VZV DNA in the CSF but not HSV, EBV, or CMV. Eight days later, the CSF was negative for IFN-α, while the VZV PCR signal was still positive but with a marked decrease in intensity. The neurological status worsened until day 15, leading to complete paraplegia with perianal sensory loss. Neurological improvement was noticed from day 20 and continued during the following weeks. The patient was discharged for rehabilitation and was then given oral acyclovir (1 g/d). His condition continued to improve, and he has since returned to work. On the last follow-up, 15 months after onset of the myelopathy, recovery was complete.

Methods

PCR for VZV DNA was performed with use of previously described primers [2] on DNA recovered from 100 μL of CSF by means of boiling and ethanol precipitation. In each reaction, both positive (VZV-infected cell cultures) and negative controls (PCR mixture without DNA) were run. Moreover, in each assay, 10–15 CSF specimens from patients without known VZV CNS disease (including HIV-infected patients) were analyzed by VZV PCR; all of them were negative. In addition, strict precautions were taken to avoid contaminations, such as use of positive-displacement pipettes and strict separation of pre- and post-PCR work. PCR products were characterized by their size on agarose gels and then by hybridization with a digoxigenin-labeled specific oligonucleotide probe. PCR for HSV-1, HSV-2, EBV, and CMV was performed as previously described [3].

Discussion

VZV myelitis is a rare entity that develops mainly in the immunocompromised host. In the literature, most reports have described only a single case or a few cases. In 1991 Devinsky et al. [4] described 13 cases of VZV myelitis and analyzed the 33 previously reported cases. Only three patients with AIDS were involved. Usually, spinal cord dysfunction began within 3 weeks of the onset of rash, and maximal deficit occurred within 10 weeks. In two of the three AIDS patients described, there was a long interval (2 and 6 months) between the initial and maximal deficit [4]. In contrast, a case of fulminant VZV ascending myeloradiculopathy and ventriculitis in a patient with AIDS who died 4 days after onset of paraplegia was recently reported [5].

The diagnosis of VZV myelitis is usually presumptive and based on the association of spinal cord dysfunction with characteristic zoster eruption. However, myelitis may appear before herpes zoster (as in our patient 1) or without it [6, 7]. Until recently, no confirmation of the viral pathogen could be obtained, since isolation of VZV from CSF is usually noncontributive to the diagnosis. Intrathecal detection of specific antibodies to the virus is delayed and can be difficult in cases involving immunocompromised patients. The detection of herpesvirus genomes in CSF by PCR has been shown to be the most specific and rapid tool for early diagnosis of neurological infections due to HSV, EBV, CMV, and VZV [3, 8, 9]. In our two patients, PCR detected high amounts of VZV DNA in the CSF specimens, as visualized by simple ethidium-bromide staining of agarose gels, but it did not reveal HSV-1, HSV-2, EBV, or CMV DNA. However, interpretation of the presence of viral DNA in the CSF must be cautious if genomic material is present in the serum. Indeed, breakthrough of the blood-brain barrier, especially in immunocompromised patients, can result in a positive CSF PCR in the absence of CNS infection. This hypothesis can be ruled out at least in one patient (case 1), since no VZV DNA could be detected by PCR in the serum obtained the same day. Moreover, VZV DNA was not found in the CSF of the first patient 2 weeks after the initiation of acyclovir therapy, paralleling the decrease in lymphocytosis and in the level of IFN-α in the CSF.

The most striking feature of our observations is the complete clinical resolution of neurological abnormalities following treatment with acyclovir. This antiviral agent is used for treatment of herpes zoster in immunocompromised patients and has been quite successful in cases of encephalitis [10, 11]. There are few data for evaluating the efficacy of antiviral therapy for VZV myelitis. In the series of Devinsky et al. [4], only four of 46 patients were treated with acyclovir or vidarabine, and the outcomes for these patients were not specified. In the same series, the spontaneous outcome for untreated patients with immunosuppressive disorders appeared poor. Follow-up information was available for 14 immunocompromised patients: 11 died within 4 months of rash, and only 3 partially recovered [4]. No complete and lasting response of VZV-associated myelitis to treatment with antiviral agents has been previously reported. The case of an AIDS patient with myelopathy due to VZV whose treatment with acyclovir was not successful was recently reported; however, acyclovir probably was administered too late (2 months after the onset of paraparesis) [12].

The pathogenesis of VZV CNS involvement is still debated. The pathological finding of active viral infection as the basis of cord injury [4] is an indication for therapy with acyclovir, which can prevent multiplication and spread of the virus in the CNS. In our two patients, the level of IFN-α in the CSF specimens obtained within the first days after the onset of myelopathy was markedly elevated (suggesting viral replication) [13, 14] and decreased after treatment. An initial phase of neurological worsening was noticed despite the early institution of acyclovir therapy; we interpret this circumstance as the result of VZV-associated vasculitis. In cases of VZV myelitis diagnosed at autopsy, vasculitis with necrotic and hemorrhagic changes have been observed [5].

In conclusion, we think that VZV is a probably underdiagnosed cause of myelopathy in patients with AIDS and that PCR assay of CSF is a rapid diagnostic tool. Although the exact role of acyclovir therapy remains to be defined, these two cases
suggest that prompt institution of treatment is associated with recovery from VZV myelitis.

References