Parainfectious Encephalomyeloradiculitis Associated with Herpes Simplex Virus 1 DNA in Cerebrospinal Fluid

T. Kusuhara, M. Nakajima, H. Inoue, M. Takahashi, and T. Yamada
Department of Neurology, School of Medicine, Fukuoka University, Fukuoka, Japan

We describe a patient with acute encephalomyeloradiculitis associated with herpes simplex virus 1 (HSV-1) DNA in the cerebrospinal fluid (CSF), and we also review 4 similar cases previously reported from Japan. A 59-year-old man presented with acute encephalitis and urinary retention. Initially, coma and CSF pleocytosis improved with acyclovir treatment, but brain stem encephalitis, transverse myelitis, and lumbosacral polyradiculitis subsequently occurred. These conditions responded to corticosteroid therapy and immunoadsorption plasmapheresis. Polymerase chain reaction detected HSV-1 DNA in the CSF during acute encephalitis but not thereafter. Serial magnetic resonance imaging revealed transient lesions in the thalamus and basal ganglia on both sides of the brain and in the pons, spinal cord, and cauda equina. Acute encephalomyeloradiculitis is a unique neurological syndrome that may be caused by HSV-1 infection of the central nervous system.

In addition to acute viral encephalitis, herpes simplex virus type 1 (HSV-1) may cause a variety of neurological illnesses. The results of PCR, which is used to identify HSV DNA in the CSF, have indicated that HSV is an etiologic agent associated with benign recurrent lymphocytic (Mollaret’s) meningitis [1], recurrent brain stem encephalitis [2], and recurrent ascending myelitis [3]. There have also been reports of postinfectious encephalopathy or encephalomyelitis following biopsy-proven HSV-1 encephalitis [4, 5]. Guillain-Barré syndrome may be included among the postinfectious neurological illnesses associated with HSV [6]. Marrie et al. [7] described 6 patients who presented with fever and headache and who then developed neurogenic bladder, transverse myelitis, and encephalopathy associated with CSF pleocytosis; for all 6 patients, nerve-conduction analysis revealed polyradiculopathy. Serologic investigations failed to detect the etiologic agent, and no PCR studies were performed. Merelli et al. [8] described a patient who had a similar neurological manifestation of encephalomyeloradiculitis (EMR); on the basis of PCR results, Epstein-Barr virus (EBV) DNA was identified in the patient’s CSF.

In the present article, we describe a patient who had EMR and whose CSF tested positive for HSV-1 DNA. In addition, we review reports of 4 patients in the Japanese-language literature who showed clinical features and lesion distributions on MRI that were similar to those of our patient [9–11]. Three of the patients who we describe had increased antibody titers for HSV-1 in the CSF, and one had HSV DNA detected in the CSF by PCR.

PATIENT, MATERIALS, AND METHODS

Case report. A previously healthy 59-year-old man experienced a low-grade fever for 10 days, followed by a temperature of 39.0°C, headache, and lethargy. Uri-
nary retention then occurred within a few days. Physical examination revealed neck stiffness, and CSF analysis revealed a WBC count of 127 cells/mm³ (100% mononuclear cells), a protein level of 360 mg/dL, and a glucose level of 39 mg/dL. After a presumptive diagnosis of herpes simplex encephalitis was made, acyclovir, 30 mg/kg per day, was administered for 3 days.

Because the patient’s consciousness deteriorated to a semicomatose state, he was referred to our hospital. At admission, his body temperature was 37.0°C. Although he was mute, he grimaced and moaned when he received painful stimuli or when each hip was flexed passively. His pupils were equal in size and were fully reactive to light. Oculocephalic responses were normal. On occasion, the patient’s arms and right leg moved voluntarily, but his left leg was flaccid. Tendon reflexes were hyperactive in the left arm and absent in the lower limbs. Babinski’s sign was positive on the left. Decreased bowel sounds and urinary retention were noted. Routine hematologic and blood chemistry studies revealed normal findings, except for a protein level of 120 mm of H₂O, a WBC count of 106 cells/mm³ (100% mononuclear cells), a protein level of 347 mg/dL, and a glucose level of 39 mg/dL. Results of bacterial and fungal cultures, as well as findings from antigen testing of CSF samples, were negative. Brain CT scans showed swelling of both hemispheres; swelling was worse on the right, but no focal abnormalities were evident. An electroencephalogram showed generalized, moderately slow activity.

A 14-day course of acyclovir was followed by improvement in the patient’s consciousness during his first week of hospitalization. On day 8 of hospitalization, he had fever (temperature, 39.0°C), coma, and pinpoint pupils. He then developed myoclonic jerks and rigidity of the upper limbs and flaccid paralysis of the lower limbs. Over a few days, his consciousness gradually improved, but the aforementioned symptoms continued, as did sensory loss below the ninth thoracic cord level and urinary retention.

Repeated analysis of CSF samples showed decreased WBC counts of 102 cells/mm³ on day 11 and 49 cells/mm³ on day 15 of hospitalization; the protein level remained elevated at 170 mg/dL on both of these days. Results of testing for oligoclonal IgG bands were negative. On day 20, the patient began to receive a 3-day course of intravenously administered methylprednisolone (20 mg/kg per day), which was followed by a return to clear consciousness and resolution of the pinpoint pupils and myoclonus of the arms. The patient had experienced retrograde amnesia over a span of several months preceding the onset of high fever, headache, and lethargy. His higher cortical function was otherwise normal.

On day 23 of hospitalization, electromyography showed acute extensive denervation from L1 to S2 in both lower limbs. Findings of analysis of sensory and motor nerve conduction were within the normal range for both the upper and lower limbs, except for the absence of F waves in the tibial and peroneal nerves. On day 25, CSF analysis revealed a WBC count of 34 cells/mm³ and a protein level of 80 mg/dL. Flaccid paraplegia and urinary retention persisted. From day 34 to day 44, the patient underwent immunoadsorption plasmapheresis, which was performed 5 times with a tryptophan column (TR 350; Asashi Medical) that filtered 12.5 L of plasma. While the patient underwent this treatment, muscle contraction in the hip adductors and touch sensation over the thigh on both sides returned.

Flaccid paraplegia lessened over the next months. On day 61 of hospitalization, CSF analysis revealed a WBC count of 9 cells/mm³ and a protein level of 103 mg/dL. During the patient’s 10th week of hospitalization, sensation in the lower limbs became normal, and his strength was scored as 3 (of 5) on the Medical Research Council scale. The increased muscular tone of the leg flexors, however, prevented walking. Muscular wasting was present in the distal leg muscles. Cystometric examination of the bladder showed uninhibited contractions. After 4 months of rehabilitation, the patient could walk with the assistance of crutches, and he returned home. However, he was unable to empty his bladder completely and had to perform self-catheterization.

**Serologic and virologic studies.** Acute-phase serum and CSF samples were obtained on the day of admission (day 1), which was 14 days after the onset of prodromal febrile illness. Both acute- and convalescent-phase serum samples obtained at 4 weeks after hospitalization were tested for antibodies to viruses. Antibodies to measles, rubella, mumps, herpes zoster viruses, HSV-1, herpes simplex virus 2 (HSV-2), and cytomegalovirus were assayed by CF, and antibodies to Japanese encephalitis were assayed by hemagglutinin inhibition. For EBV, serum IgM and IgG antibodies against viral capsid antigen, IgG antibody to EBV nuclear antigens, and early antigens were tested. Solid-phase ELISA was used to search for IgM and IgG antibodies to HSV-1 in the serial serum and CSF samples.

Searches for the genomic sequence of HSV-1 were done with DNA extracted from the CSF by nested PCR [12]. CSF samples were stored at −80°C without centrifugation. For each PCR assay, 2.0 μL of DNA from each sample was resuspended in a PCR mixture that contained 50 mM of KCl, 10 mM of Tris-HCl (pH 8.3), 1.5 mM of MgCl₂, 200 μM of each dNTP, and 0.5 U of Taq DNA polymerase (Takara Shuzo), for a final volume of 25 μL. The outer and inner primers used for HSV-1 DNA amplification were BHHSV1, 1; BHHSV1, 2; BHHSV1, 3; and BHHSV1, 4. After DNA denaturation was done for 5 min at 92°C, the initial 25 cycles of PCR were performed at 95°C for 5 min, 55°C for 30 s, and 72°C for 60 s. The second PCR
Parainfectious Encephalomyeloradiculitis

assay used the same steps for 35 cycles. Final extension was performed for 7 min at 72°C. The amplified DNA was applied to a 3% agarose gel. After electrophoresis, DNA was visualized by ethidium bromide staining. Strict precautions were taken to avoid contamination [13].

MRI studies. Conventional qualitative T1- and T2-weighted images, as well as postgadolinium T1-weighted images, were obtained with a 1.5-T Visart imager (Toshiba).

RESULTS

Serologic and virologic findings. None of the convalescent-phase serum samples obtained were found to be positive for antibodies to the viruses mentioned in the Patient, Materials, and Methods section. The serum samples were positive for EBV viral capsid antigen and EBV nuclear antigen IgG antibodies, whereas the acute-phase sample was negative for the viral capsid antigen IgM and early antigen IgG antibodies. HSV-1 antibodies were detected by the CF test and had the same titers in the acute- and convalescent-phase serum samples. HSV-1 IgG, as measured by ELISA, was detected in the acute-phase serum and CSF specimens. Titers were found to have decreased in the convalescent-phase specimens. The antibody index [14] for the acute-phase specimens was 0.69, which indicated that there was no intrathecal antibody synthesis. HSV-1 IgM antibodies were not detected in the acute-phase serum and CSF samples. HSV-1 DNA sequences were present in the PCR products of CSF samples obtained on day 1 of hospitalization (figure 1), but they were not present in CSF samples obtained on day 25.

MRI findings. T2-weighted images of the brain obtained on day 4 of hospitalization showed multiple high-intensity spots bilaterally in the thalamus and corpus striatum (figure 2A) and a few spots in the cerebral deep white matter. There were no lobar abnormalities. T1-weighted images showed contrast enhancement of these lesions. The pons also showed meningeal and parenchymal enhancement (figure 2B). Analysis of MRIs obtained on day 34 showed multiple high-intensity spots in the brain stem on the T2-weighted images. The high intensity in the pons was oriented horizontally, which is consistent with the orientation of the pontine transverse fibers (figure 2C). The number of high-intensity spots in the hemispheres had decreased. MRI of the spine performed on days 18 and 20 revealed an intramedullary lesion from the 9th to 11th thoracic vertebrae (figure 3A), and the conus medullaris and cauda equina showed meningeal enhancement (figure 3B and 3C). A second spinal MRI performed on day 50 revealed that these lesions had resolved.

DISCUSSION

Acute EMR is a unique neurological syndrome that was first reported in 6 adults, aged 18–38 years, from Nova Scotia [7]. EMR was defined by febrile illness followed, within days, by neurological illness that consisted of neurogenic bladder, paraparesis, altered consciousness, and CSF pleocytosis. The other clinical features were brain stem or cranial nerve involvement. Although microbial and serologic investigations failed to identify the etiologic agent, immune-mediated injury was suspected because of the excellent recoveries of seriously ill patients, possibly after administration of corticosteroids. Another study described a 42-year-old man from Italy with acute EMR [8]. Virologic and serologic studies showed that his acute febrile illness preceding neurological symptoms was associated with primary cytomegalovirus infection. Intercurrent reactivation of EBV was suspected from analysis of the serum panel of EBV antibodies, and EBV DNA was detected in early samples of his peripheral blood mononuclear cells and in CSF obtained 30 days after disease onset.

Although the mechanism or mechanisms of CNS injury are unknown, one of the herpesviruses must be involved in the development of acute EMR. The clinical features of the patient we describe in the present report were similar to those of the patients described in the literature. Our patient had experienced prodromal febrile illness for 10 days, followed by symptoms of
mengoencephalitis and urinary retention. Clinical signs of brain stem encephalitis and transverse myelitis developed within 2 weeks of disease onset. MRI detected lesions in the brain stem and basal ganglia early in the course of illness. The occurrence of acute denervation in the flaccid leg muscles within 4 weeks of disease onset also indicates early involvement of the spinal roots. In contrast, the patient's retrograde amnesia after recovery of consciousness suggests that the limbic system was affected, although brain CT, MRI, and electroencephalography provided no confirmatory findings.

Serologic investigations indicated probable reactivation of HSV-1 with no evidence of intrathecal HSV-1 antibody synthesis. PCR, however, showed HSV-1 DNA in CSF samples obtained on day 1 of hospitalization, but not in the sample obtained on day 25. Absence of HSV-1 and HSV-2 antibodies in the CSF, in spite of a positive PCR result, has been reported.

Figure 2. Brain MRI performed on days 4 (A and B) and 34 (C) of the patient's hospitalization. A, Bilateral high-signal lesions in the basal ganglia and thalamus appear on the T2-weighted image. B, Preenhancement (top) and postenhancement (bottom) images of the pons. Arrows denote meningeal enhancement. C, Arrows denote lesions along the transverse fibers of the pontine base (top) and in the middle cerebellar peduncles (bottom).

Figure 3. MRI of the spine. An intramedullary high-signal lesion is present from the 9th to the 11th thoracic vertebrae on the T2-weighted image (A). Meningeal enhancement of the conus medullaris (B) and cauda equina (C) are denoted by arrows.
Table 1. Descriptions of 4 cases of parainfectious encephalomyeloradiculitis in the Japanese-language literature.

<table>
<thead>
<tr>
<th>Reference, authors and year of publication</th>
<th>Patient age in years, sex</th>
<th>Prodomal Meningo-encephalitis</th>
<th>Brain stem encephalitis</th>
<th>Myelitis</th>
<th>Polyradiculitis</th>
<th>MRI site(s)</th>
<th>Findings of CSF analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>[9] Nakamura et al., 1993</td>
<td>48, M</td>
<td>Fever, headache, vomiting</td>
<td>Stiff neck, delirium to coma</td>
<td>Pinpoint pupils, opsoclonus, limb ataxia, myoclonus, ataxic breathing</td>
<td>Paraparesis, bladder disturbances, sensory loss below T4</td>
<td>Prolonged areflexia</td>
<td>Basal ganglia, pons, cerebellum, thoracic cord</td>
</tr>
<tr>
<td>[10] Ohtsubo et al., 1995</td>
<td>24, M</td>
<td>Fever, headache, nuchal pain</td>
<td>Stiff neck, delirium, convulsion</td>
<td>Pinpoint pupils, nystagmus, myoclonus, hypopnea</td>
<td>Paraplegia, bladder disturbances</td>
<td>Prolonged hyporeflexia</td>
<td>Basal ganglia, pons, conus medullaris</td>
</tr>
<tr>
<td>[11] Nomura et al., 1997</td>
<td>25, M</td>
<td>Headache, fever</td>
<td>Stiff neck, delirium to coma</td>
<td>Gaze-evoked nystagmus, opsdonous</td>
<td>Urinary incontinence, tetraplegia, sensory loss below T5</td>
<td>Distal muscular atrophy, prolonged areflexia</td>
<td>Spinal cord(*)</td>
</tr>
<tr>
<td></td>
<td>52, M</td>
<td>Fever, headache, lethargy</td>
<td>Stiff neck, delirium</td>
<td>Gaze-evoked nystagmus, conjugate gaze palsy</td>
<td>Urinary incontinence, tetraparesis, sensory loss below T7</td>
<td>Distal muscular atrophy, prolonged hyporeflexia</td>
<td>Thoracic cord</td>
</tr>
</tbody>
</table>

**NOTE.** Ab, antibodies; HSV-1, herpes simplex virus 1; OB, oligoclonal IgG band; +, positive; -, negative.

* Diffuse atrophy.
in patients with acute herpetic encephalitis [15]. Early intervention with acyclovir therapy may have resulted in a forme fruste of herpetic encephalitis. The involvement of multiple levels of the neuraxis is more apt to be an immune-mediated process than a direct invasion by the virus. Excellent recovery from paraplegia, together with resolution of a lesion in the spinal cord as demonstrated by MRI, would be unlikely if there had been direct invasion of the spinal cord by HSV-1.

The presence of lumbosacral polyradiculitis and MRI findings that suggest demyelination in the pons support the idea of immune-mediated injury. In this respect, acute EMR resembles acute disseminated encephalomyelitis (ADEM). Herpes simplex encephalitis has been suggested as the cause of ADEM [4, 5]. However, in ADEM, involvement of the peripheral nerves and spinal roots rarely occurs [16, 17]. The stereotypical combination of encephalitis, brain stem encephalitis, transverse myelitis, and polyradiculitis suggests that this condition is a variant of ADEM. It is unknown whether invasion of the CNS by HSV-1 is a prerequisite or whether only reactivation of latent HSV-1 is sufficient to cause EMR.

Our search of the Japanese-language literature produced 4 similar cases of EMR associated with possible HSV-1 infection of the CNS [9–11]. The clinical features and results of virologic studies of EMR are presented in table 1. All 4 patients had experienced a prodromal illness with fever and headache. The initial neurological symptom, altered consciousness, was either accompanied by or immediately followed by signs of meningeal irritation and brain stem involvement. Analysis of CSF samples revealed mononuclear pleocytosis and elevated protein concentrations. The onset of transverse myelitis differed among the patients. The 2 patients described by Nomura et al. [11] experienced urinary incontinence early in the illness, and paralysis of the limbs and sensory loss below the thoracic cord level were present once the 2 patients recovered consciousness at 1 and 4 weeks. The other 2 patients described had transverse myelitis of apparently delayed onset [9, 10]. They had flaccid paraplegia, a thoracic sensory level, and bladder disturbances 3–4 weeks after the onset of encephalitis. No onset of polyradiculitis can be identified in these cases, because no electromyography findings were reported.

In the lower limbs, an absence of or decrease in reflexes appeared at the onset of paraplegia and persisted for months in association with muscular wasting. Slowing of nerve conduction in the lower limbs was present in 3 patients. MRI revealed that all 4 patients had spinal cord lesions. Findings of MRI of the brain and the brain stem were unremarkable for the 2 patients described by Nomura et al. [11]. The other 2 patients had lesions that involved the basal ganglia and pons, as did the lesions of our patient. For 3 of the patients, high titers of IgG antibody against HSV-1 were observed in acute-phase serum and CSF specimens. And an increase in titer was found in convalescent-phase CSF samples. The other patient had seroconversion of HSV-1 IgG and PCR results that were positive for HSV DNA in the CSF. Three of the patients made an excellent recovery; 2 had been treated with corticosteroids or intravenous immunoglobulins. One patient remained wheelchair-bound.

In conclusion, acute EMR should be regarded as a unique neurological syndrome, as previously reported [7, 8]. HSV-1 is one agent that could cause acute EMR. Although the mechanism of CNS injury is unknown, we propose that immune-mediated injury is most likely because of transient MRI findings, excellent prognosis following paraplegia, and possible beneficial effects of immunosuppressive or immunomodulatory treatment.

Acknowledgment

We thank Yuko Naito for her technical assistance.

References

12. Aurelius E, Johansson B, Sköldenberg B, Selandal Å, Forsgren M. Rapid...


