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. Urí-
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 semi-comatose 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 360 mg/dL, and a glucose level of 39 mg/dL. Results of testing for oligoclonal IgG bands were negative. 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 trypothan 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.

Sequences of 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 BJHSV1, 1; BJHSV1, 2; BJHSV1, 3; and BJHSV1, 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 30 s. The second PCR
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.

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>
<thead>
<tr>
<th>Reference, authors and year of publication</th>
<th>Patient age in years, sex</th>
<th>Prodomal signs or symptoms</th>
<th>Meningoencephalitis</th>
<th>Brain stem encephalitis</th>
<th>Myelitis</th>
<th>Polyradiculitis</th>
<th>MRI sites</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>
<td>HSV-1 IgG Ab (+), OB (+)</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>
<td>HSV DNA (+), OB (+)</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, opsoclonus</td>
<td>Urinary incontinence, tetraplegia, sensory loss below T5</td>
<td>Distal muscular atrophy, prolonged areflexia</td>
<td>Spinal cord&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HSV-1 IgG Ab (+), OB (-)</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>
<td>HSV-1 IgG Ab (+), OB (-)</td>
</tr>
</tbody>
</table>

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

<sup>a</sup> Diffuse atrophy.
in patients with acute herpetic encephalitis [15]. Early intervention with acyclovir therapy may have resulted in aforme
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 find-
ings that suggest demyelination in the pons support the idea
of immune-mediated injury. In this respect, acute EMR resem-
bles 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 con-
centrations. 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 pa-
ralysis 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 poly-
radiculitis can be identified in these cases, because no electro-
myography findings were reported.

In the lower limbs, an absence of or decreased in reflexes
appeared at the onset of paraplegia and persisted for months
in association with muscular wasting. Slowing of nerve con-
duction 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
titters 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 wheel-
chair-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 mecha-
nism of CNS injury is unknown, we propose that immune-
mediated injury is most likely because of transient MRI find-
ings, excellent prognosis following paraplegia, and possible
beneficial effects of immunosuppressive or immunomodulatory
treatment.

Acknowledgment

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References

1. Tedder DG, Ashley R, Tyler KL, Levin MJ. Herpes simplex virus in-
fection as a cause of benign recurrent lymphocytic meningitis. Ann

2. Tyler KL, Tedder DG, Yamamoto LJ, et al. Recurrent brainstem en-
cephalitis associated with herpes simplex virus type 1 DNA in cere-

current ascending myelitis: an unusual presentation of herpes simplex

4. Koenig H, Rabinowitz SG, Day E, Miller V. Post-infectious encepha-
lomyelitis after successful treatment of herpes simplex encephalitis with
300:1089–93.

5. Abramson JS, Roach ES, Levy HB. Postinfectious encephalopathy after
treatment of herpes simplex encephalitis with acyclovir. Pediatr Infect

6. Bernsen HJ, Van Loon AM, Poels RFJ, Verhagen WIM, Frenken
CWGM. Herpes simplex virus specific antibody determined by im-
munoblotting in cerebrospinal fluid of a patient with the Guillain-

7. Marrie TJ, Purdy RA, Johnston BL, et al. Encephalomyeloradiculopa-
thy of infectious or parainfectious etiology: a new entity? Clin Infect
Dis 1995; 20:945–53.

ciated with Epstein-Barr virus: primary infection or reactivation? Acta

simplex encephalitis followed by myelopathy [in Japanese]. No To
Shinkei 1993; 45:553–8.

disseminated encephalomyelitis, triggered by herpes simplex type-1 infec-

11. Nomura K, Tomioka R, Mitui T, Ohno R, Hamaguchi K. Two cases of
encephalo-myelo-radiculopathy, triggered by herpes simplex virus


