Acute Cerebellitis Caused by Herpes Simplex Virus Type 1

Maria Ciardi, Giovanna Giacchetti, Cesare Giovanni Fedele, Antonio Tenerio, Antonella Brandi, Raffaella Libertone, Camilla Ajassa, Leonardo Borgese, and Salvatore Delia

Department of Infectious and Tropical Diseases, University "La Sapienza," Rome, Italy; and Diagnostic Microbiology Service, Centro Nacional de Microbiologia, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain

Cerebellar disorders due to herpes simplex virus (HSV) infection are rare and always associated with herpes simplex encephalitis. We report 2 cases of severe primary acute cerebellitis caused by HSV type 1 that were identified by nested polymerase chain reaction performed on cerebrospinal fluid samples.

Herpes simplex virus type 1 (HSV-1) is one of the most common causes of sporadic viral encephalitis in adults. Herpes simplex encephalitis (HSE) may be a consequence of both primary and recurrent HSV infections, and it is characterized by focal necrosis of the medial temporal and inferior frontal lobes and, occasionally, of the insular cortex and cingulate gyrus [1, 2]. Such lesions are unusual in other brain areas, and, to our knowledge, isolated cerebellar involvement has never been reported. Herein we describe 2 cases of HSV-1 acute cerebellitis in which HSV-1 DNA was detected in the CSF samples by nested PCR.

Case reports. Patient 1, a stammering 24-year-old woman who had experienced headache, dysarthria, ataxia, vomiting, and moderate fever for 7 days, was referred to our hospital because of a gradual worsening of her symptoms. At admission, neurologic examination revealed normal cognition, ataxia, dysarthria with exacerbation of her dysphasia, dysmetria on the entire left side of the body, and nystagmus. Reflexes were brisk, and there was no evidence of meningeal signs. Blood examination was notable for a mild increase in WBC count (11,790 cells/mm³ [78% neutrophils and 16% lymphocytes]) and an erythrocyte sedimentation rate of 56 mm/h. Results of liver and renal function tests were within normal ranges. Neurological evaluation included a head CT scan and electroencephalography, both of which revealed normal findings. An MRI of the brain revealed a bilateral cerebellar enhancement on T1-weighted images after gadolinium administration (figure 1A) and diffuse, increased signal intensity in the cerebellar cortex on fluid-attenuated inversion recovery images, suggesting an inflammatory process confined to the cerebellum (figure 1B). Furthermore, the cerebellar cortex appeared swollen, a finding consistent with diffuse cerebellitis.

Examination of CSF revealed a protein concentration of 56 mg/dL, a glucose concentration of 50 mg/dL, and a WBC count of 20 cells/mm³ (78% lymphocytes). Bacterial culture of CSF samples showed no growth, and the results of Gram staining of CSF were negative. PCR analysis of CSF for herpesviruses (HSV-1 and -2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, and human herpesvirus types 6–8), enteroviruses, and Chlamydia only revealed the presence of HSV-1 DNA. PCR for HSV-1 DNA detection was done using the primer sequences and methods described in Aurelius et al. [3] with some modifications. Reaction conditions for first- and second-round PCR analyses were as described elsewhere [4]. To avoid false-positive results, all reactions were performed under stringent conditions, DNA-free control was included, and all samples were tested at least twice in separate PCR analyses [5, 6].

Treatment with acyclovir (30 mg/kg/day iv) was immediately started, and dexamethasone (0.15 mg/kg/day iv) was also provided during the first 4 days. A few days after the initiation of treatment, neurological symptoms gradually improved, and they disappeared entirely within 2 weeks. PCR analysis of a second CSF sample obtained 14 days after the initiation of treatment was negative for HSV-1 DNA; an MRI performed 1 month after the onset of acute cerebellitis revealed complete disappearance of the bihemispheral enhancement of the cerebellar cortex (figure 1C and 1D).

Patient 2, a 16-year-old girl, received a diagnosis of HIV-1 infection in 1989. HAART was started in 1997 and the virological and immunological response was excellent. The latest assessment revealed an undetectable plasma viral load and a CD4 cell count of 600 cells/mm³. In February 2002, the patient presented with a moderate fever, dysarthria, severe headache associated with photophobia, and nausea. At admission to the hospital, cognition was intact, but there was mild dysarthria. Reflexes were brisk, findings of cranial nerve examination were normal, and no evidence of meningeal signs was found. Analysis...
of the patient’s blood was notable for an erythrocyte sedimentation rate of 60 mm/h and a mild increase in WBC count (10,500 cells/mm³ [neutrophils 74% and lymphocytes 25%]).

Analysis of CSF revealed a lymphocytic pleocytosis (180 lymphocytes/mm³) with normal protein and glucose levels. Results of bacterial cultures and Gram and India ink stains of CSF were negative. Electroencephalography revealed nothing abnormal, and a brain MRI revealed a partial bitemporal cerebellar enhancement after gadolinium administration on T1-weighted images and an increased signal intensity with a mild cerebellar swelling on fluid-attenuated inversion recovery images (figure 2A and 2B). CSF PCR analysis for herpesviruses (HSV-1 and -2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, and human herpesvirus types 6–8), enteroviruses, and Chla-
mydri only demonstrated the presence of HSV-1 DNA. Treatment with acyclovir (30 mg/kg/day iv) was started, and dexamethasone (0.15 mg/kg/day iv) was also provided during the first 6 days. After 2 weeks of treatment, HSV-1 DNA was undetectable by CSF PCR analysis, and an MRI performed 1 month after the initiation of treatment showed a marked reduction of the cerebellar neuroradiological alterations (figure 2C and figure 2D). Although total length of treatment lasted 21 days, the patient experienced a clinically complete recovery 2 weeks after the initiation of treatment.

Discussion. Acute cerebellitis is a neurological condition characterized by mild or high-grade fever, nystagmus, tremor, truncal ataxia, dysarthria, headache, and altered mental state [7]; on the other hand, acute cerebellar ataxia is defined as the acute onset of gait ataxia without fever, prominent meningismus, seizures, or a significant alteration of mental state [8, 9].
Acute cerebellitis is furthermore characterized by CSF pleocytosis and/or neuroradiological evidence of inflammation, such as cerebellar swelling [10, 11]. Acute cerebellar inflammation may occur during several illnesses, including measles, mumps, pertussis, scarlet fever, diphtheria, and typhoid fever, as well as during infections due to coxsackievirus, poliovirus, echovirus, rotavirus, varicella-zoster virus, and Epstein-Barr virus [12–15]. Coxiella burnetii and Borrelia burgdorferi have also been reported to cause acute cerebellitis [16–18], and a syndrome of unexplained cerebellar degeneration associated with HIV infection has also been described [19]. Although neuroradiological cerebellar involvement has been described in 2 patients with HSE [20, 21], and ataxia has been reported in a patient with HSV brainstem encephalitis [22] and in 40% of patients with HSE [23], a primary HSV-1 infection of the cerebellum has not yet been described, to our knowledge.

Acute cerebellitis was diagnosed in our patients on the basis of clinical symptoms and laboratory findings, including high-grade fever, severe headache, and mild CSF pleocytosis. MRI of the brains of the patients revealed increased signal intensity without focal lesions of the cerebellar cortex, which appeared to be swollen. Etiological diagnosis was made by PCR detection of HSV-1 DNA in CSF. The clinical courses and the MRI findings were similar for our patients but quite different from those described in cases of acute cerebellitis due to other causes, in which foci of edema or demyelination in cerebellar white matter were observed [7, 24, 25].

Our patients experienced rapid clinical improvement and complete recovery after 2 weeks of treatment; HSV-1 DNA was undetectable in CSF samples obtained after 14 days of treatment, which is not surprising considering that HSV-1 DNA can disappear from CSF as early as 1 week after the beginning of specific antiviral therapy [3, 6]. One month after the initiation of treatment, MRI findings demonstrated a marked decrease of the diffuse hyperintense signal in both patients. Although involvement of the cerebellum has been reported to occur during the course of HSE [20–23], we are not aware of any other patient who has manifested HSV-1 acute cerebellitis. Therefore, this is the first report of a definite diagnosis of acute cerebellitis due to HSV.

Our findings suggest that primary cerebellar involvement may occur during the course of HSV-1 infection. MRI findings associated with positive PCR results, obtained as early as 1 day after admission to the hospital, allowed us to establish a definite diagnosis and immediately to administer specific treatment. In contrast to virus isolation, which is less sensitive and more time-consuming, PCR assay proved to be a reliable and sensitive tool for the early diagnosis of HSV-caused neurological disease [1, 3, 12]. Although the clinical diagnosis of most cases of HSV-caused neurological disease is eased by the presence of clinical symptoms and brain lesions (such as focal necrosis), PCR for HSV DNA detection in CSF specimens is especially valuable in those cases in which atypical clinical and neuroradiological findings are observed. Moreover, the feasibility of an early definite diagnosis by PCR analysis could help investigators determine whether there is a trend toward the reduced severity of HSV-related neurological alterations, with less severe forms of the diseases and better outcomes [26]. It has been argued that isolated cerebellar abnormalities that occur in patients with HIV infection may be caused by other diseases for which the patients were not tested, rather than by HIV infection [27]. Alternative diagnoses must be excluded early for these patients, including etiologic association with other viral infections, such as HSV infection. In conclusion, we believe that HSV infection may be partly responsible for some of the undiagnosed cases of acute cerebellitis and therefore should be considered as a possible etiological agent of this condition.

References


