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Human Herpesvirus 6 Encephalomyelitis

To the Editor: Denes et al. (1) reports successful treatment of human herpesvirus 6 (HHV-6) encephalomyelitis. The patient was an immunocompetent young woman whose symptoms were fever, urinary retention, blurred vision, quadriparesis, bilateral papillitis, and optic neuritis. Magnetic resonance imaging (MRI) showed multiple lesions on the spinal cord white matter and the left thalamus, and the cerebral spinal fluid (CSF) showed inflammation. The patient was treated with acyclovir for 3 days, high-dose methylprednisolone

for 5 days, cidofovir for 1 day, and ganciclovir for 15 days, starting on day 23 of hospitalization. By establishing a relationship between antiviral drug doses, serial determinations of HHV-6 DNA by polymerase chain reaction (PCR) in CSF, and neurologic improvement, Denes et al. concluded that antiherpesvirus drugs led to her recovery.

This case fits well in the spectrum of acute disseminated encephalomyelitis (ADEM), an inflammatory demyelinating disease of the central nervous systems of children and young adults, which occur in close temporal relationship with several infectious illnesses and immunizations (2–6). The disease has particular predilection to the optic nerves, spinal cord, brainstem, basal ganglia, and cerebral and cerebellar hemispheres. Maximal neurologic deficits are reached within several days, and resolution takes weeks or months. The condition is typically monophasic, but relapses have been reported (7). Histologic multifocal areas of inflammation and demyelination are found. In the pathogenesis of ADEM, an initial injury caused by an infectious agent, followed by a secondary autoimmune response, has been postulated, and animal models have provided experimental support; both CD4 and CD8 T cells have been implicated in a secondary autoimmune response (6). Despite the lack of controlled studies, corticosteroids are widely used to treat ADEM and high-dose methylprednisolone is the drug of choice (3,4). The largest series of ADEM in adults included 40 patients with a mean follow-up period of 38 months. The patients were given a standardized treatment regimen of methylprednisolone, 500 mg daily intravenously for 5 days, with no additional therapy if they recovered completely. In patients with persistent neurologic deficits, the initial intravenous therapy was followed by a regimen of oral methylprednisolone, which was

slowly tapered over 4 to 6 weeks. In patients with no response to this therapy, or whose condition had deteriorated during therapy, cyclophosphamide was given to seven patients, and immunoglobulin was given to one patient. Thirty-eight of 40 patients improved during the acute phase of the illness; in 7, symptoms completely resolved. One patient's condition remained unchanged and one patient died; no antiviral drugs were given (5).

The neurotropism of HHV-6 and that the CNS may be a site of viral persistence or latency are well recognized (8,9). On autopsy, evidence of fulminant encephalitis with HHV-6 DNA demonstrated by PCR, immunohistochemical staining, or nucleic acid hybridization, confirms that HHV-6 causes acute CNS disease (8). Nevertheless, whether evidence of HHV-6 DNA in CSF demonstrated by PCR can be solely relied on is debatable. HHV-6 DNA was detected in the CSF of 41 (28.9%) of 142 children with a history of HHV-6 infection (9). HHV-6-DNA was detected in the CSF of 47 (61%) of 77 children examined after primary HHV-6 infection. In the remaining 30 children (39%), HHV-6 DNA was detected in both peripheral blood mononuclear cells and CSF samples. HHV-6 variant A was detected more frequently in CSF than in specimens of other sites, which suggests that HHV-6A has greater neurotropism (10).

The role of HHV-6 in acute multifocal neurologic disease in immunocompetent adults requires additional observation, and its role in multiple sclerosis is in question. Much can be learned from careful study of patients (1).

I caution the casual reader who may conclude that using antiviral drugs against herpes viruses is recommended when acute multifocal neurologic disease clinically compatible with ADEM is indicated. High-dose IV methylprednisolone is the most utilized treatment, and the patient in

the Denes et al. report was given it early in her hospital stay. The available evidence supports methylprednisolone as an essential drug in the management of ADEM.

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In Reply: The disease that we reported (1) was encephalomyelitis induced by a human herpesvirus 6 (HHV-6) reactivation. Our aim was to emphasize that HHV-6 can cause such a disease, even when the patient is immunocompetent, and to urge physicians to search for it.

Implicating HHV-6 in the pathogenesis of neurologic manifestations in the reported case can be challenged, as suggested by Dr. Soto-Hernandez (2). Polymerase chain reaction (PCR) results must be interpreted cautiously, especially in cases that lack corroborating clinical evidence of infection. In our case, the diagnosis was made initially when HHV-6 was found in the patient's cerebral spinal fluid (CSF) by using PCR, by the absence of other cause, and by our experience; adult CSF is usually negative for HHV-6 by using PCR. Moreover, in our case, clinical symptoms and HHV-6 in the patient's CSF evolved in the same way. The neurologic tropism of HHV-6 is well known, and the main manifestation in adults is encephalitis, especially in an immunosuppressed context. Diagnosis is usually based on finding HHV-6 genetic material in the CSF (3,4), which has now replaced brain biopsy. Positive tissue results do not distinguish latent from productive infections when PCR-positive CSF indicates viral particle production in the central nervous system (CNS). In our case, the absence of brain tissue did not allow immunohistochemical staining or in situ hybridization. In the study by Caserta et al. (5), cited by Dr. Soto-Hernandez, HHV-6 PCR was positive in CSF and negative in peripheral blood mononuclear cells in 28.9% of children ≤ 3 years old with prior HHV-6 infection. These results provide evidence of HHV-6 persistence in the CNS; this phenomenon is now well recognized. Nevertheless, HHV-6 persistence after primary infection is quite different from reactivation in an immunocompetent adult. High-avidity anti-HHV-6 immuno-

globulin G detected in the patient's serum when the symptoms started proved that our patient had been infected with HHV-6 previously.

We appreciate Dr. Soto-Hernandez's suggestion concerning acute demyelinating encephalomyelitis (ADEM) in our case. ADEM is an inflammatory demyelinating disease of the CNS, occurring mostly in children and rarely in young adults, soon after an infection or a vaccination. The disease is often associated with exanthema. A virus is often thought to be the cause, but viral symptoms are often not documented and rarely treated. ADEM may evolve into multiple sclerosis, and HHV-6 has been proposed as one of the causes of that condition (6). For example, multiple sclerosis developed in 14% of children and 35% of adults with ADEM in the study by Schwarz et al. (7).

Spontaneous improvement of ADEM is regularly reported; however, when treatment is needed, especially during the acute phase, steroid therapy is frequently used. In our case, corticosteroids did not affect the evolution of the patient's neurologic symptoms. Conversely, introducing the antiherpes drugs (cidofovir and ganciclovir) was followed by improved clinical signs and negative results for HHV-6 in the CSF by PCR. Corticosteroids likely influence inflammation associated with ADEM, but if ADEM is the result of a viral infection with persistent viral replication, steroids might be deleterious, allowing an increase in viral replication (8,9).

In conclusion, we think that viruses, particularly HHV-6, should be considered in ADEM, even in immunocompetent patients. In case of a positive result, antiviral treatment must be given, eventually in association with corticosteroids. We cannot recommend using corticosteroids alone because of the risk of spreading the infection.

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Vancomycin Heteroresistance in Methicillin-resistant *Staphylococcus aureus*, Taiwan

To the Editor: In 1997, Hiramatsu and colleagues reported the first clinical isolate of methicillin-resistant *Staphylococcus aureus* (MRSA) showing reduced susceptibility to vancomycin (1). Soon thereafter, vancomycin-intermediate *S. aureus* (VISA) or heteroresistant VISA was reported to have disseminated in Japanese hospitals (2). In Taiwan, a survey of >5,000 clinical isolates of *S. aureus* at one tertiary medical center from 1999 to 2001 showed negative results for VISA or vancomycin-resistant *S. aureus* (VRSA) (3,4). We report the first two isolations of heteroresistant VISA in Taiwan.

In June, 2000, an 89-year-old man (patient A) with a history of cerebrovascular accident underwent ileal resection for ischemic bowel disease, and primary MRSA bacteremia developed during the hospitalization. Vancomycin was given for 14 days, and his fever rapidly abated. In October 2000, a Port-A-Cath (Smiths Industries Medical Systems, Deltec, Inc., St. Paul, MN) was inserted in the left subclavian vein. On June 14, 2001, he had another blood isolate of MRSA during an episode of *Enterococcus faecalis* bacteremia. Fever resolved after 4 days of intravenous vancomycin treatment (1 g every 12 h), and vancomycin treatment was continued for 21 days. Subsequent culture of blood drawn from the Port-A-Cath and peripheral veins on June 29 and July 6, 2001, did not yield any organism. MRSA bacteremia relapsed in November 2001, and the patient received intravenous teicoplanin treatment (400 mg every 2 days) for 3 weeks, and fever resolved

rapidly. Transthoracic echocardiographic tests showed no vegetation on the cardiac valves. The patient was hospitalized again in March 2002 because of relapsing MRSA bacteremia. The Port-A-Cath was removed, and culture of fluid from the indwelling pocket yielded MRSA. Fever and MRSA bacteremia persisted, with 17 sets of positive blood culture from March to May 2002, even under an adequate dose of intravenous vancomycin (serum trough level of vancomycin = 9–24 µg/mL and serum peak level = 18–30 µg/mL) and rifampin (600 mg/day). An infected thrombus over the subclavian vein was detected by venous duplex and thought to be an unresolved focus. Linezolid (600 mg every 12 h) was given for 10 days (April 30–May 9, 2002) but discontinued because of progressive thrombocytopenia. Vancomycin and rifampin were resumed on May 10, and positive blood culture with MRSA was noted on May 14. Oliguric renal failure developed in the patient on May 21 followed by shock, and he died on May 23.

A 72-year-old man (patient B) with coronary artery disease and chronic renal insufficiency underwent coronary artery bypass grafting and aortic grafting for abdominal aortic aneurysm in December 1999. The postoperative course was complicated with second-degree atrioventricular block and progressive renal failure. He was implanted with a permanent pacemaker and started long-term hemodialysis in March 2000. In April 2000, catheter (double lumen for hemodialysis)-related MRSA bacteremia developed in the patient. Vancomycin (1 g/week) was administered and the catheter was changed, but 17 successive episodes of MRSA bacteremia recurred from May to July 2000, despite an adequate serum level of vancomycin (trough level = 13–21 µg/mL and peak level = 24–38 µg/mL). Transesophageal echocardiographic