We report a case of a 62-year-old female with seizures and encephalitis. Molecular testing of the patient’s cerebrospinal fluid was positive for both herpes simplex virus 1 and 2 (HSV-1 and HSV-2). To our knowledge, this is the first report of simultaneous detection of HSV-1 and HSV-2 in cerebrospinal fluid.
HSV-1 and HSV-2 are neurotropic, double-stranded DNA viruses. Following infection, these viruses establish latency in sensory neural ganglia and are capable of causing recurrent bouts of disease ranging from cutaneous eruptions to neurologic disease. Central nervous system (CNS) infections secondary to HSV-1 and HSV-2 are well-recognized clinical entities and have been extensively studied. These infections can range in severity from mild and self-limiting to severe and fatal. While there is some overlap in the neurologic manifestations (fever, headache, and confusion) of HSV-1 and HSV-2, significant differences between the two have been described (4–7).

HSV-1 is considered to be the most common cause of sporadic encephalitis, affecting both immunocompetent and immunocompromised patients (7). Since the location of dormancy is usually within the trigeminal ganglia, encephalitis typically arises within the temporal or frontal lobes of the brain first. Brain lesions typically are necrotic and progress rapidly. Symptoms often include altered consciousness, fever, headache, seizure, and personality changes (8). The manifestations of HSV-1 CNS disease can be quite severe with a reported mortality rate as high as 16% and residual neurologic sequelae in up to 62% of patients, despite adequate treatment (5, 6).

In adult populations, HSV-2 usually causes milder disease in the CNS and typically presents as an aseptic meningitis (9). Patients may present with headache, fever, and symptoms of meningeval inflammation (e.g., stiff neck) (5). Cases are usually self-limiting, though treatment with acyclovir is recommended (7). Patients may develop a recurrent lymphocytic meningitis syndrome known as “Mollaret’s meningitis,” characterized by recurrent bouts of meningitis with an increase in atypical lymphocytes within the CSF known as “Mollaret cells.” While encephalitis caused by HSV-2 is rare in the adult population, it is a common cause of neonatal encephalitis. Infection in this population is usually due to acquisition of the organism through the birth canal of an infected and actively shedding mother. In these patients, the disease progression is rapid and severe, similar to adults with HSV-1 encephalitis.

Since HSV-1 and HSV-2 have different levels of severity in adult populations, several studies have emphasized the need for type-specific testing of CSF samples from symptomatic patients. Several PCR assays that are capable of differentiating between HSV-1 and HSV-2 have been reported (10–12). Subsequent publications have examined the clinical utility of such assays. A 2008 study by Meylan et al. demonstrated significant differences in outcomes between patients that were positive for HSV-1 versus HSV-2 in the CSF (13). A 2003 study by O’Sullivan et al. demonstrated that 89% of patients positive for HSV-1 in CSF had encephalitis, whereas most patients with HSV-2 had meningitis (5).

While many real-time PCR assays have the capability to detect and differentiate HSV-1 and HSV-2, dual infections are rarely described. A 2007 publication by Perkins et al. described a case of genital infection in a pregnant woman caused by both HSV-1 and HSV-2 (14). A large-scale (n = 8,249 specimens) retrospective study by Dhiman et al. examined the frequency of dual positivity for varicella-zoster virus and either HSV-1 or HSV-2 (15). They found only a 1.3% dual positivity rate, with dual positive results occurring exclusively for samples from dermal, genital, and oral mucosal surfaces. Pertaining to CNS infections, a study by Ibrahim et al. tested 106 serum samples from patients with encephalitis for a variety of members of the family Herpesviridae and found only 2 dual infections (one case of HSV-1 and cytomegalovirus [CMV] coinfection and one case of HSV-1 and human herpesvirus 6 [HHV-6] coinfection) (11). Several prior studies have assessed the prevalence of dual infections in the CSF and did not detect coinfections in these patients (4, 16).

In this report, we describe a patient with seizures and encephalitis who was positive for both HSV-1 and HSV-2 from a single CSF sample. Interestingly, the patient reported no known history of HSV-1 or HSV-2 infection, though studies have demonstrated that up to 82% of patients with HSV-2 CNS infection report no history of genital herpes (5). Due to the rarity of detecting both HSV-1 and HSV-2 in the same sample, we questioned whether amplicon contamination may have caused the dual positivity. However, the CSF sample was tested by two separate molecular methods targeting different regions of the HSV genome, and both assays were positive for HSV-1 and HSV-2. Several publications have described HSV isolates with variant melting curves arising from mutations specific to the probe binding site (3, 17). It is possible that mutations in the probe binding site may yield a melting curve that falls between the expected range for HSV-1 and HSV-2. However, this is rare (<1% prevalence; unpublished data) and does not appear as two unique peaks, as was observed in this case. Further evidence arguing against the possibility that this patient was infected with a single mutant virus is that the specimen was also positive for both HSV-1 and HSV-2 by a second PCR assay, and type-specific IgG serology was performed on a serum sample from this patient and was positive for IgG class antibodies to both HSV-1 and HSV-2, suggestive of past exposure to both viruses.
tient had MRI findings consistent with encephalitis, which is more commonly caused by HSV-1. However, the distribution of her brain lesions (parietal and occipital lobe involvement rather than temporal lobe involvement) was atypical for HSV encephalitis. Also, at presentation, the patient’s cerebrospinal fluid exhibited lymphocytic pleocytosis, more commonly caused by HSV-2. Her primary reason for medical treatment was seizure, a known complication of both viruses. It is also possible that one of the viral subtypes (e.g., HSV-2) was present but not associated with clinical disease. Subclinical reactivation and detection of herpesviruses (e.g., VZV) by real-time PCR has been previously described (18). Regardless, the patient responded to a second course of acyclovir and was ultimately discharged.

This case illustrates that, while rare, dual infections of the CNS with HSV-1 and HSV-2 are possible. Therefore, molecular assays (e.g., real-time PCR) should be capable of detecting both HSV-1 and HSV-2 viruses simultaneously. As multiplex molecular methodologies become more common in clinical laboratories, it is possible that more coinfections may be recognized, allowing further study of this interesting phenomenon.

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REFERENCES