Herpes Simplex Virus Type 2 Encephalitis as a Cause of Ischemic Stroke: Case Report and Systematic Review of the Literature

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Background and aim: Our objective is to describe a patient who developed an ischemic stroke as a complication of herpes simplex virus type 2 (HSV-2) encephalitis and to review the literature. *Patients and methods:* A 45-year-old immune-competent Caucasian man presented with a 24-hour history of confusion and fever, and following clinical and laboratory examination was diagnosed with HSV-2 encephalitis. However, the brain magnetic resonance imaging also showed an acute ischemic infarct in the left frontal lobe corresponding to vascular territories of middle cerebral artery branches. Further screening failed to identify any other cause of the stroke. A systematic literature search was conducted in February 2015 using the PubMed database. *Results:* Six more cases of herpes simplex virus (HSV) central nervous system (CNS) infection that developed a definite ischemic stroke as a complication of the infection were identified. *Conclusions:* Ischemic stroke, although infrequent, can complicate the evolution of herpes simplex meningitis or encephalitis. Clinicians should include HSV CNS infection as a possible cause of ischemic stroke, especially in young patients with ischemic stroke of unknown etiology. **Key Words:** HSV-2—HSV-1—encephalitis—meningitis—stroke.

Introduction

Herpes simplex encephalitis (HSE) is the most frequent sporadic encephalitis worldwide and accounts for 10%-20% of all cases.[1] Herpes simplex virus type 1 (HSV-1) infection is more common in adults, and herpes simplex virus type 2 (HSV-2) infection predominates in neonates.[2]

Over the last 2 decades, clinicians have recognized a greater diversity of neurological complications because of HSE, due to the application of immunohistochemistry, in situ hybridization, and polymerase chain reaction (PCR) to cerebrospinal fluid (CSF) and tissues.[3] Until now, hemorrhagic stroke in adults has been reported in many cases of HSV-1 encephalitis[4] and in 2 cases of HSV-2 encephalitis.[5,6]

The aims of our paper were 2-fold: to report a rare case of a young patient with HSV-2 encephalitis who developed an ischemic stroke and to review the literature of herpes simplex virus (HSV) central nervous system (CNS) infections related to ischemic strokes.

Case

A 45-year-old immune-competent Caucasian man presented to the emergency department of our hospital with a 24-hour history of confusion and fever. He had a medical history of dyslipidemia and he was a nonsmoker without a history of drug or alcohol abuse. General physical examination, apart from mildly elevated temperature (T = 37.9°C), was unremarkable. Neurological examination revealed disorientation in time, place, and person, but no focal neurological signs. Routine blood and urine

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tests were unremarkable, apart from a slightly elevated C-reactive protein (1.2 mg/dL; normal values = 0-.5 mg/dL).

Cranial computerized tomography of the brain was normal. Because of the presenting clinical picture of confusion and fever, encephalitis was suspected and a lumbar puncture was performed. The opening pressure of the CSF was 12 cm. Further CSF analysis showed 64 lymphocytes/mm^3, a glucose level of 52 mg/dL, and a total protein level of 45 mg/dL. The CSF PCR was negative for cytomegalovirus, Epstein–Barr virus, HSV-1, and varicella zoster virus (VZV); however, it was positive for HSV type 2 (178 copies/mL). Treatment with intravenous acyclovir was commenced.

On day 2, the patient was still disorientated in time, place, and person, and the neurological examination showed mild right-sided facial palsy. The facial palsy had the characteristics of upper motor neuron damage, since the weakness involved only the lower facial muscles, whereas the frontalis and the upper orbicularis oculi muscles were spared.

The electroencephalogram showed slow wave activity over both temporoparietal areas, more so on the left.

Further investigations, including carotid and vertebral artery Doppler ultrasound, heart ultrasound, and 24-hour cardiac tape, were negative. The following autoantibodies were also negative: antinuclear, anti-ds-DNA, perinuclear antineutrophil cytoplasmic antibodies, cytoplasmic antineutrophil cytoplasmic antibodies, antithyroglobulin, and antithyroid peroxidase. Thrombophilic states were sought, but antithrombin III, factor V Leiden, Activated protein C resistance, and protein C and S levels were within normal limits. The molecular genetic screening for thrombophilia was also negative.

The patient continued to improve cognitively and the facial palsy subsided. Magnetic resonance imaging (MRI) of the brain was performed on day 10 and showed a 4×6 cm left frontal lobe lesion, affecting the middle frontal gyrus, the inferior frontal gyrus, the precentral gyrus, and the head of the caudate nucleus, and which was hyperintense in the T2 and fluid-attenuated inversion recovery sequences. The lesion showed diffuse postcontrast enhancement, and as it corresponded characteristically to vascular territories of middle cerebral artery branches, it was consistent with an ischemic stroke (Figs 1, 2).

The patient received a 3-week course of intravenous acyclovir and improved significantly. Follow-up examination showed minimal cognitive deficits.

Discussion

Hemorrhagic stroke as a complication of HSE has mainly been reported in patients with HSV-1 encephalitis.[4] Although the cause of the bleeding remains unclear, based on the finding of fibrinoid necrosis in the pathological sample of the evacuated hematoma, Politei et al[7] suggested a virally induced small-vessel vasculitis of the brain resulting in endothelial damage with secondary bleeding, a hypothesis that has also been suggested by other authors.[8] Other hypotheses include an immune-mediated inflammatory reaction that would make the brain tissue more prone and vulnerable to bleeding, an increase in intracranial pressure, the existence of a particularly virulent, hemorrhagic-prone strain of the virus, and the comorbid presence of arterial hypertension.[4] On the other hand, ischemic stroke related to HSE has rarely been reported until now.

A systematic literature search was carried out in February 2015 using the PubMed database, covering all articles published until then. For each individual search we used 2 Medical Subject Headings terms in either the title or the abstract. Term A was "herpes simplex," "herpes encephalitis," "herpes meningoencepahlitis," "HSV," "HSV-1," or "HSV-2." Term B was "ischemic stroke," "ischemic

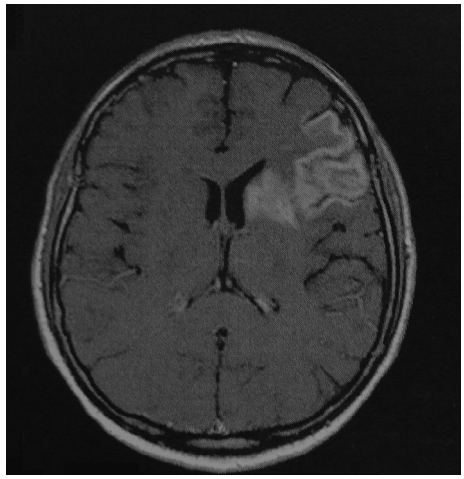

Figure 1. *Brain MRI (T1 post-IV contrast) showing enhancement in the area of the ischemic stroke. Abbreviations: IV, intravenous; MRI, magnetic resonance imaging.*

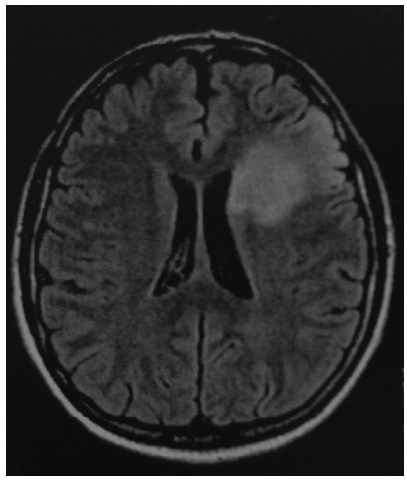

Figure 2. *Brain MRI (T2 FLAIR), showing a hyperintense lesion corresponding to the ischemic stroke. Abbreviations: FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.*