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Mitchell S.V. Elkind, MD, MS

Pearls & Oy-sters: Cerebral HSV-2 vasculitis presenting as hemorrhagic stroke followed by multifocal ischemia

P. Zepper, MD
S. Wunderlich, MD
A. Förschler, MD
K. Nadas, MD
B. Hemmer, MD
J. Sellner, MD

Correspondence & reprint requests to Dr. Sellner: sellner@lrz.tum.de

PEARLS

- The main clinical challenge in the management of acute stroke is the identification of rare but treatable causes
- Ischemic and hemorrhagic stroke are well-known complications of CNS infection; cerebral vasculopathy related to herpes simplex virus 2 (HSV-2) presenting as brain hemorrhage has so far not been described in the literature

OYSTERS

- Infectious vasculopathy needs to be considered in the workup of hemorrhagic or ischemic stroke, particularly in individuals with the combination of fever, focal neurologic symptoms, or clinical deterioration
- Prompt initiation of antiviral and antimicrobial treatment are mandated in case of suspected CNS infection

HSV causes a wide range of pathologies in the human CNS including meningitis, myelitis, and encephalitis (HSE). Even with early initiation of antiviral treatment and advances in neurocritical care, HSE remains a life-threatening condition associated with high mortality and morbidity. Cerebrovascular complications contribute to the devastating prognosis and include brain edema, ischemic stroke, and intracerebral hemorrhage.[1]

Primary or secondary vasculitis related to an underlying disease may be restricted to the nervous system or involve multiple organs in the context of systemic disease. The list of pathogens that may cause vascular inflammation within the CNS is comprehensive.[2] Among herpesviruses, a high frequency of vasculitic complications is reported for varicella zoster virus (VZV).[3]

Here, we report a case of cerebral HSV-2 vasculitis, which was masked by the initial presentation as thalamic hemorrhage and followed by an encephalitic syndrome and multifocal ischemic stroke.

CASE REPORT A 72-year-old immunocompetent man was referred with acute onset of nonfluent aphasia and right-sided weakness. CT scan revealed a 4 × 1.8 cm left thalamic hemorrhage. He was taking ramipril and a combination of pioglitazone/metformin due to hypertension and diabetes, respectively. Since he had been living alone, details on prior signs and symptoms were scarce and complicated by aphasia. Laboratory examinations including coagulation parameters were normal.

Two days later, his clinical condition started to deteriorate with development of somnolence. CT scan did not show an expansion of the thalamic hemorrhage (figure, A) but revealed a new left parietal hypodensity, consistent with ischemic stroke. Transcranial Doppler sonography (TCD) on day 3 detected slightly elevated velocities in both middle cerebral arteries (MCA, right 170 cm/s, left 150 cm/s). The following day, velocities increased to 220 cm/s (right) and 170 cm/s (left), respectively. Calcium channel blockers were instituted considering vasospasm. MRI at 3 T (Achieva, Philips Healthcare, Best, the Netherlands) with diffusion-weighted imaging (DWI) corroborated the left parietal ischemia and demonstrated additional ischemic lesions within territories supplied by the left MCA and the right posterior inferior cerebellar artery (PICA) (figure, C). Time-of-flight (TOF) angiography determined irregular narrowing over short segments in various large to medium-sized cerebral arteries, e.g., right MCA, right PICA, and both posterior cerebral arteries (PCA) (figure, D). The right-sided weakness increased in intensity after 3 days of admission. Fever up to 39.6°C (103.3°F) developed and a chest x-ray showed pneumonic infiltrates within the right basal lobe. We started empirical antibiotic treatment with piperacillin and tazobactam, and *Citrobacter koseri* was isolated in the tracheal swab. Transesophageal echocardiogram, urine analysis, and blood cultures could not identify a further infectious focus. Serum C-reactive protein peaked at 6.1 mg/dL, whereas leu-

From the Department of Neurology (P.Z., S.W., B.H., J.S.), Institute of Neuroradiology (A.F.), and Institute of Virology (K.N.), Klinikum rechts der Isar, Technische Universität München, München, Germany; Department of Neurology & Neurosurgery (P.Z.), McGill University, Montreal, Canada; and Department of Neurology (J.S.), Christian-Doppler-Klinik, Paracelsus Medical University, Salzburg, Austria.

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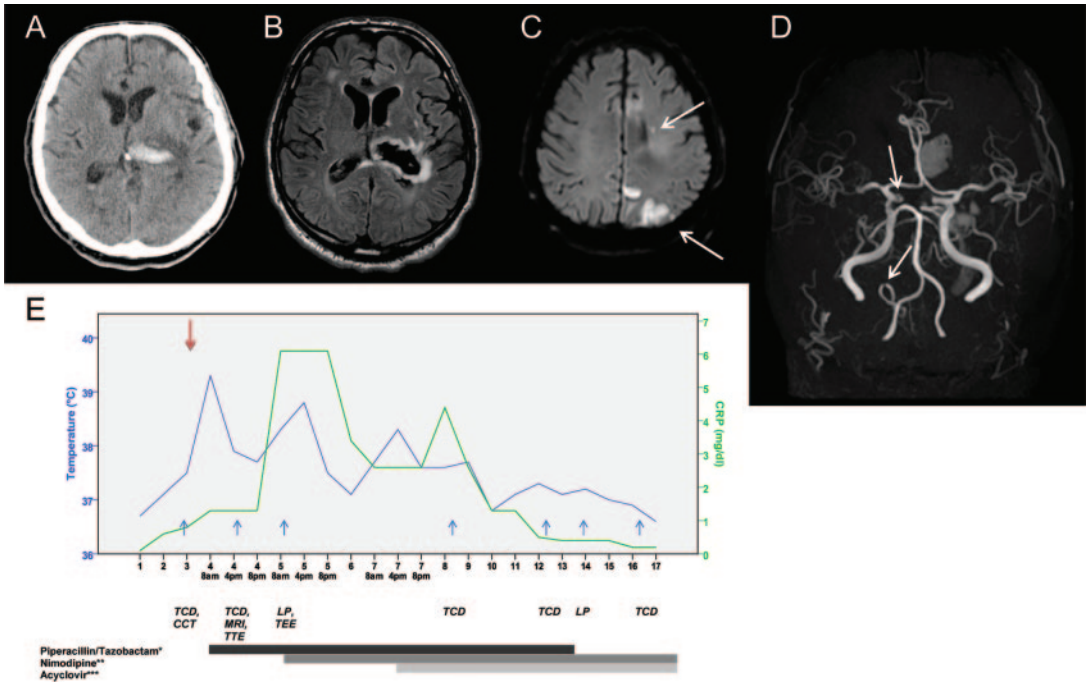
Figure **Observation in the course of HSV-2–related cerebral vasculitis initially presenting as thalamic hemorrhage**



(A) The follow-up CT scan 3 days after admission continued to show a 4 × 1.8 cm left thalamic hemorrhage with perifocal edema, and extension of blood to the ventricles (not shown). (B) No evidence for a causative pathology was found on MRI using fluid-attenuated inversion recovery sequences, which was performed 4 days after admission. (C) Diffusion-weighted imaging revealed areas with increased signal intensity in multiple vascular territories; this image depicts acute ischemic lesions in the territory supplied by the left middle cerebral artery (MCA) (arrows). (D) Time-of-flight angiography, however, determined multiple short-segment stenoses in large to medium-sized intracranial vessels in terms of vasculitis. The most prominent stenoses were detected in the right MCA, the right posterior inferior cerebellar artery, and both posterior cerebral arteries (not shown). (E) Time course of clinical events, diagnostic procedures, and treatment. The x-axis indicates days post admission. The blue curve illustrates temperature changes, whereas the green line (dashed) shows the course of C-reactive protein (CRP, threshold <0.5 mg/dL). The downward arrow (red) indicates the start of clinical deterioration; the smaller upward arrows point at the time points of individual diagnostic procedures. HSV-2 = herpes simplex virus 2; LP = lumbar puncture; TCD = transcranial Doppler sonography; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography. *Piperacillin/tazobactam 5/0.5 g IV every 8 hours. **Nimodipine 60 mg per os every 4 hours. ***Acyclovir 750 mg IV every 8 hours.

kocyte count and procalcitonin (0.1 ng/mL on day 4 and 5, reference level < 0.5 ng/mL) remained normal. Yet CSF pleocytosis of 588 cells/μL with elevated protein (1.75 g/L) and increased lactate levels (5.5 mmol/L) indicated intrathecal inflammation. Antiviral therapy with IV acyclovir was implemented and continued over 14 days while antibiotic treatment remained unaltered. CSF-PCR for HSV-2 was positive with high copy numbers (9,650 genomic equivalents/mL), whereas CSF-PCR for HSV-1, VZV, and cytomegalovirus (CMV) was negative. Serology for HIV and hepatitis viruses was negative. Clinical condition and TCD velocities improved under antiviral therapy. Vigilance returned to normal and the right-sided weakness improved to an even better state than on the day of admission. Serology indicated a primary (de novo) HSV-2 infection (serum immunoglobulin G antibodies negative on days 5 and 14 post admission). A CSF examination 8 days later revealed a decline of the pleocytosis (52 cells/μL) and serology pointed at a CNS-specific HSV-2 infection (antibody-specific index 2.1).

An MRI scan 6 months later visualized a nearly complete resolution of the hemorrhage, whereas TOF angiography documented a residual stenotic appearance of intracranial vessels. Neuropsychological testing revealed moderate cognitive impairment with deficits regarding psychomotor velocity, concentration, and calculating as well as short and medium term memory function. An almost complete recovery of the right-sided hemiparesis and aphasia were noted.

DISCUSSION The number of HSE cases admitted very early in the course and with atypical presentations is anticipated to increase during the next years. Atypical presentations such as hemorrhage, multifocal ischemic stroke, or mild encephalitic syndromes

may be easily missed. Suspicion for HSE is raised by a progressively deteriorating level of consciousness, fever, abnormal CSF indices, and focal neurologic findings. In our patient, no typical encephalitic syndrome preceded admission. However, such symptoms could be lacking since the potential encephalitic lesion was small or did not involve eloquent regions. Approximately 20% of patients with HSE have mild or atypical syndromes.[4] Whether these mild or atypical courses later develop classic HSE is unknown. Diagnostic criteria for atypical HSE are defined as acute encephalopathy with mild alteration in mental status or level of consciousness in the absence of focal findings on neurologic examination.[4] Indeed, our patient is likely to fulfill these criteria but signs and symptoms caused by hemorrhage and ischemia had overlapped.

Whether an encephalitic lesion was the initial trigger for hemorrhage development in our case cannot be ruled out since a potential lesion was masked by the extensive bleeding. A prospective study of hemorrhage occurrence in pediatric HSE found an unexpectedly high rate of 25% (4 children out of 16, age range 2 months to 14 years).[5] In the literature there are reports on early (1 day after initiation of acyclovir treatment) as well as delayed (9–16 days) occurrence of hemorrhage in HSE. Indeed, HSE is a necrotizing-hemorrhagic encephalitis and weakening of cerebral vessels is found early in the course of experimental HSE and linked to the transmigration of leukocytes and degradation of the neurovascular matrix by matrix-metalloproteinase 9.[6] However, encephalitic lesions in HSV-2 CNS infection in immunocompetent adults are rare and limited to a few case reports.[7]

Hemorrhagic transformation of initial ischemic stroke needs to be considered in the differential diagnosis of thalamic hemorrhage. In addition, such a presentation might be seen in acute hemorrhagic leukencephalitis (AHLE). This rare disorder is characterized by diffuse hemorrhagic necrosis and extensive perivascular demyelination caused by vasculitis within the cerebral white matter.[8] AHLE has a very poor prognosis with rapid deterioration and death within days to 1 week after onset of symptoms. Of note, there is a case of AHLE manifesting as intracerebral hemorrhage and in association with HSV-1 CNS infection in the literature.[9]

HSV-2 is mostly responsible for meningoencephalitis in neonates and meningitis in adults. Cerebral vasculitis related to HSV-2 infection has so far not been described. Further evidence for a direct involvement of HSV-2 is derived from rapid improvement of both the patient's condition and the increased flow velocities of intracranial vessels after initiation of antiviral treatment. Knowledge of the natural course of infection-related cerebral vasculopathies is limited and mostly related to VZV.[3] A therapy escalation with steroids according to the bacterial meningitis scheme[10] would have been considered in the lack of improvement of clinical course and TCD velocities. The observation stands in contrast to the course of vasospasm induced by hemorrhage, which was initially considered following the detection of increased TCD velocities, short-segment narrowing of intracranial vessels in TOF angiography, and development of multifocal ischemic stroke. Notably, intraventricular hemorrhage due to ruptured arteriovenous malformations can cause delayed vasospasm, even in the absence of a subarachnoidal blood fraction.[11] Yet a vascular malformation or other causative pathology could not be confirmed in the follow-up MRI. In a recent study on infectious CNS vasculitis, magnetic resonance angiography was shown to detect vasculopathic signs in all 8 patients.[12] In our case, TOF angiography with a 3 T scanner was sufficient to visualize alterations in large to medium-sized arteries. Contrast-enhanced T1-weighted images may be even more sensitive by detection of vessel wall enhancement, particularly if medium to small vessels are affected.

Development of fever and deterioration of consciousness in hospitalized patients not only requires a search for nosocomial infections. The slightest scrap of suspicion of a CNS infection should entail a proactive approach for a spinal tap and further diagnostics and commencement of appropriate antiviral and antimicrobial therapies.

AUTHOR CONTRIBUTIONS

Dr. Zepper: design and conceptualization of the case report, analysis and interpretation of the data, drafting and revision of the manuscript. Dr. Wunderlich: design and conceptualization of the case report, analysis and interpretation of the data, revision of the manuscript. Dr. Förschler: design and conceptualization of the case report, analysis and interpretation of the data. Dr. Nadas: design and conceptualization of the case report, analysis and interpretation of the data. Dr. Hemmer: design and conceptualization of the case report, analysis and interpretation of the data, revision of the manuscript. Dr. Sellner: design and conceptualization of the case report, analysis and interpretation of the data, drafting and revision of the manuscript.

DISCLOSURE

Dr. Zepper, Dr. Wunderlich, Dr. Förschler, and Dr. Nadas report no disclosures. Dr. Hemmer has served on scientific advisory boards for Roche, Novartis, Biogen Idec, Merck Serono, Bayer Schering Pharma, and Genzyme Corporation; has received funding for travel from Bayer Schering Pharma, Novartis, Biogen Idex, Merck Serono, Teva Pharmaceutical Industries Ltd., Roche, and Genentech, Inc.; serves on the international advisory board of *Archives of Neurology*; has received speaker honoraria from Bayer Schering, Novartis, Biogen Idec, Merck Serono, and Teva Pharmaceutical Industries Ltd; serves as consultant to Genentech Inc., Gerson Lehrman Group, Micromet Inc., Roche, and Novartis; and receives research support from Roche, metanomics GmbH, Protagenic Therapeutics Inc., Biogen Idec, Bayer Schering Pharma, Merck Serono, Novartis, Deutsche Forschungsgemeinschaft, Bundesministerium

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