West Nile virus-associated vasculitis and intracranial hemorrhage

Adil Harroud, MD, Ahmad Almutlaq, MBBS, David Pellerin, MD, MSc, Dan Paz, MD, Grant J. Linnell, DO, and Daniel Gendron, MD

Correspondence

Dr. Harroud
adil.harroud@mail.mcgill.ca

Neurol Neuroimmunol Neuroinflamm 2020;7:e641. doi:10.1212/NXI.0000000000000641

West Nile virus (WNV) is a neurotropic flavivirus and the leading cause of mosquito-borne diseases in North America. In approximately 20% of cases, infection leads to a self-limited febrile illness and, in less than 1%, to a neuroinvasive disease often manifesting as meningoencephalitis with or without acute flaccid paralysis.¹ Herein, we report the first case of WNV-associated CNS vasculitis and intracranial hemorrhage, thus expanding the spectrum of WNV infection.

Case report

A 73-year-old woman was admitted in late summer to the Montreal Neurological Institute and Hospital in Montreal, Canada, with a 2-day history of acute confusion and high fever. She had a remote history of renal cell and breast carcinomas, both in complete remission and off treatment. Initial neurologic examination was remarkable for encephalopathy and right extensor plantar response. Antimicrobials for suspected meningoencephalitis were empirically started. Initial head CT scan was unremarkable. CSF examination revealed a lymphocytic pleocytosis (28 white cells/ μ L with 59% lymphocytes), no red cells, protein of 0.84 mg/dL, and glucose of 53.6 mg/dL. Antimicrobials were stopped the next day after negative CSF cultures and herpes simplex virus PCR. On day 6, the patient developed a markedly decreased level of consciousness and aspiration pneumonia requiring intubation. Brain MRI showed extensive and confluent leukoencephalopathy and interval appearance of bilateral convexity subarachnoid hemorrhage (SAH).

On day 8, the patient was found to have generalized myoclonus. Continuous EEG monitoring showed severe slowing but no epileptic activity. The patient was extubated a few days later and had persistent attention deficit, fluctuating dysphasia, and right extensor plantar response. Repeat brain MRI with angiography demonstrated interval enlargement of convexity SAHs (figure, A) and tapered stenosis of the left anterior cerebral artery A2 segments. A digital subtraction angiography (DSA) confirmed the findings on MRA (figure, B). Follow-up brain MRI with vessel wall imaging a month later showed a new small left frontal parasagittal intracerebral hemorrhage (ICH) in the absence of cortical or deep-seated microbleeds and intramural concentric enhancement of the wall of arteries in the circle of Willis (figure, C and D).

During hospitalization, WNV serology resulted positive for immunoglobulin (Ig) M and IgG in serum and CSF (performed on day 9 and repeated on day 41). A positive plaque reduction neutralization test (PRNT, titers 1:80 and 1:40 on days 9 and 41, respectively) confirmed the diagnosis of WNV neuroinvasive disease. An extensive additional workup ruled out coexisting autoimmune, paraneoplastic, and systemic vasculitis. Of note, varicella zoster virus CSF PCR

From the Department of Neurology and Neurosurgery (A.H., A.A., D. Pellerin, D.G.), Montreal Neurological Hospital and Institute, McGill University, Montreal, Quebec, Canada; Centre for Clinical Epidemiology (A.H.), Department of Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada; National Neuroscience Institute (A.A.), King Fahad Medical City, Riyadh, Saudi Arabia; and Department of Radiology (D. Paz, G.J.L.), Montreal Neurological Hospital and Institute, McGill University, Montreal, Quebec, Canada.

Go to [Neurology.org/NN](https://www.neurology.org/NN) for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

(A) Axial susceptibility-weighted image showing prominent blooming (arrows) in the sulci of the bilateral posterior parietal regions at the vertex, frontal lobes, and sylvian fissures, indicating subarachnoid hemorrhage. (B) DSA showing mild tapered stenosis in the proximal extent of the A2 segment of the left anterior cerebral artery (oval circle) and mild focal ectasia of left angular artery (rectangle). (C) Follow-up MRI demonstrating a new small left frontal intracerebral hemorrhage (arrow) on an axial susceptibility-weighted image. (D) Concentric gadolinium enhancement of the supraclinoid segment of the internal carotid arteries and proximal middle cerebral arteries bilaterally (arrows), seen on magnetic resonance vessel wall imaging. (E) Follow-up DSA showing interval resolution of the vascular changes previously noted in the A2 segment of the left anterior cerebral artery (oval circle) and left angular artery (rectangle). DSA = digital subtraction angiography.

and serologies for syphilis and HIV were negative. Whole-body PET/CT showed no evidence of recurrent cancer. The patient improved with supportive treatment including neurointensive care monitoring and IV hydration. Corticosteroids and other previously tried therapeutic agents for WNV (e.g., IV immunoglobulin, ribavirin, and interferon-alpha)¹ were considered but not administered, given the lack of evidence for efficacy and the patient's continuing clinical improvement. Repeat CSF examination on day 41 revealed improved pleocytosis (7 white cells/ μ L), and repeat DSA 3 days later showed resolution of the previously noted left A2 tapering (figure, E). Radiologic monitoring showed resolution of the intracranial hemorrhages and vascular stenosis over the ensuing months. She did not complain of overt headache during the course of the illness, although this was limited by the initial encephalopathy. On discharge, the patient was able to walk without support but suffered from residual cognitive deficits.

Discussion

This case illustrates some of the typical manifestations of WNV neuroinvasive disease, including encephalitis with lymphocytic pleocytosis and myoclonus. The diagnosis was confirmed based on positive IgM serologies and PRNT in serum and CSF. In addition, this case showcases the unique complication of SAH and ICH associated with WNV infection. Although rare cases of ischemic stroke in the setting of WNV have been described,²⁻⁴ intracranial hemorrhage had not been previously reported to our knowledge.

We also describe the rare occurrence of WNV-associated CNS vasculitis. A single report previously documented

vascular irregularities suggestive of a vasculopathy in a patient with positive WNV serology.³ In our case, intracranial vessel wall MRI was consistent with arterial inflammation, further supporting that the vasculopathy was secondary to WNV neuroinvasive disease. There is in vitro evidence that WNV may gain entry to the CNS and infect neurons partly through invasion of endothelial cells,^{1,5} providing a potential explanatory mechanism for the development of vasculitis in this setting. We hypothesize that the intracranial hemorrhages observed in this case were caused by rupture of small vasculitic vessels. This is analogous to the observations of retinal hemorrhages with WNV retinal vasculitis.⁶ Similarly, vasculitis accompanied by cerebral hemorrhage has been documented with other viral encephalitides, such as herpesviruses.⁷

In conclusion, this case highlights the need for clinicians to be vigilant for vasculitic complications, including intracranial hemorrhage, in cases of WNV infection. Similarly, WNV neuroinvasive disease should be considered in the differential diagnosis of infectious cerebral vasculitis and atypical hemorrhagic stroke.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures. Go to Neurology.org/NN for full disclosures.

Publication history

Received by *Neurology: Neuroimmunology & Neuroinflammation* July 18, 2019. Accepted in final form October 4, 2019.

Appendix Authors

Name	Location	Role	Contribution
Adil Harroud, MD	McGill University, Montreal, Canada	Author	Conception and design, drafting the manuscript, and review of the literature
Ahmad Almutlaq, MBBS	McGill University, Montreal, Canada	Author	Conception and design, drafting the manuscript, and review of the literature
David Pellerin, MD, MSc	McGill University, Montreal, Canada	Author	Revised the manuscript for intellectual content
Dan Paz, MD	McGill University, Montreal, Canada	Author	Revised the manuscript for intellectual content
Grant J. Linnell, DO	McGill University, Montreal, Canada	Author	Revised the manuscript for intellectual content and approved the final version for publication
Daniel Gendron, MD	McGill University, Montreal, Canada	Author	Revised the manuscript for intellectual content and approved the final version for publication

References

1. Suthar MS, Diamond MS, Gale M Jr. West Nile virus infection and immunity. *Nat Rev Microbiol* 2013;11:115–128.
2. Alexander JJ, Lasky AS, Graf WD. Stroke associated with central nervous system vasculitis after West Nile virus infection. *J Child Neurol* 2006;21:623–625.
3. Lowe LH, Morello FP, Jackson MA, Lasky A. Application of transcranial Doppler sonography in children with acute neurologic events due to primary cerebral and West Nile vasculitis. *AJNR Am J Neuroradiol* 2005;26:1698–1701.
4. Zafar S, Dash D, Chachere M, Cowart J, Kass J. West Nile virus infection associated with central nervous system vasculitis and strokes. *Neurology* 2012;78 (suppl 3): P03.264.
5. Maximova OA, Pletnev AG. Flaviviruses and the central nervous system: revisiting neuropathological concepts. *Annu Rev Virol* 2018;5:255–272.
6. Garg S, Jampol LM, Wilson JF, Batlle IR, Buettner H. Ischemic and hemorrhagic retinal vasculitis associated with West Nile virus infection. *Retina* 2006;26:365–367.
7. Zepper P, Wunderlich S, Forscher A, Nadas K, Hemmer B, Sellner J. Pearls & Oysters: cerebral HSV-2 vasculitis presenting as hemorrhagic stroke followed by multifocal ischemia. *Neurology* 2012;78:e12–e15.

Neurology® Neuroimmunology & Neuroinflammation

West Nile virus-associated vasculitis and intracranial hemorrhage

Adil Harroud, Ahmad Almutlaq, David Pellerin, et al.

Neurol Neuroimmunol Neuroinflamm 2020;7;

DOI 10.1212/NXI.0000000000000641

This information is current as of November 22, 2019

Updated Information & Services	including high resolution figures, can be found at: http://nn.neurology.org/content/7/1/e641.full.html
References	This article cites 6 articles, 0 of which you can access for free at: http://nn.neurology.org/content/7/1/e641.full.html##ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Encephalitis http://nn.neurology.org/cgi/collection/encephalitis Intracerebral hemorrhage http://nn.neurology.org/cgi/collection/intracerebral_hemorrhage Subarachnoid hemorrhage http://nn.neurology.org/cgi/collection/subarachnoid_hemorrhage Vasculitis http://nn.neurology.org/cgi/collection/vasculitis Viral infections http://nn.neurology.org/cgi/collection/viral_infections
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://nn.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://nn.neurology.org/misc/addir.xhtml#reprintsus

Neurol Neuroimmunol Neuroinflamm is an official journal of the American Academy of Neurology. Published since April 2014, it is an open-access, online-only, continuous publication journal. Copyright Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.. All rights reserved. Online ISSN: 2332-7812.