Neuromyelitis optica spectrum disorder associated with Zika virus infection

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In September 2017, a healthy 35-year-old Brazilian man with a medical history of dengue fever 18 months prior (confirmed by serology at the time) developed fever, a sore throat, myalgia, and arthralgia. Four days later, he was hospitalized with urinary retention, proximal paraparesis (Medical Research Council [MRC] grade 4), and paresthesias in lower limbs and face. On the first day of hospitalization, sagittal short T1 inversion recovery (STIR) spine MRI showed hyperintense, nonenhancing lesions between T1–T4 and T6–T9 compatible with an acute myelitis (figure, A). Brain MRI was normal. Lumbar puncture revealed $1/\text{mm}^3$ cells, 56 mg/dL protein, 60 mg/dL glucose, and presence of oligoclonal bands. Immunoglobulin G (IgG) index was 0.55. Zika virus (ZIKV) PCR was positive in CSF, blood, urine, and saliva. PCR in the CSF for other viruses, including herpes, dengue (DENV), chikungunya, yellow fever, West Nile, and Saint Louis encephalitis, were all negative. Blood aquaporin-4 IgG (AQP4-IgG) was negative. Rheumatologic disease and other infections, including syphilis, hepatitis, HIV, cytomegalovirus, Epstein-Barr virus, and tuberculosis, were all negative in serologic testing. Methylprednisolone (1 g/d IV for 5 days) was started on the second day of hospitalization. One day later, the patient deteriorated, with increased weakness of the legs (MRC 1), bilateral Babinski sign and ankle clonus, a T2 sensory level, oscillatory vertigo with central pattern nystagmus, constipation, vomiting, somnolence, and discrete hearing loss. Brain MRI 7 days after admission revealed hyperintensity in the pons, superior and middle left cerebellar peduncle, and periependymal lesions on T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences (figure, B). At this time, the patient met the criteria¹ for NMOSD with negative AQP4-IgG based on the presence of acute brainstem syndrome with periependymal lesion and acute myelitis with a compatible MRI (intramedullary lesion extending over 3 segments). After corticosteroid therapy, he received IV immunoglobulin for 5 days (2 g/kg total dose) and was discharged with minor sensory impairment and partial recovery of bladder and bowel control, and was able to walk using a walker. The day after discharge, however, the patient returned with visual impairment, dyschromatopsia, afferent pupillary defect, and pain in the right eye (day 27). Another brain MRI showed hyperintense T2 signs of the right optic nerve and an extensive T1 gadolinium-enhancing lesion compromising at least 50% of the nerve length, compatible with optic neuritis (figure, C). Another methylprednisolone course was administered, and his visual acuity improved. Maintenance treatment with oral prednisone (60 mg/d) was started. After remaining stable for 1 month, the patient developed tactile and temperature allodynia of both arms (day 63). Sagittal STIR spinal MRI showed hyperintensities at C3 to C6 segments (figure, D). AQP4-IgG and ZIKV PCR in blood were negative. Anti-MOG was not available for testing. He received a third course of methylprednisolone followed by 5 plasmapheresis sessions, which improved his symptoms. Currently, he has been stable for 6 months using maintenance treatment with azathioprine 2 mg/kg/d and prednisone 20 mg/d.

PRACTICAL IMPLICATIONS

Consider Zika infection in the diagnostic workup of neuromyelitis optica spectrum disorder (NMOSD) in epidemic areas.

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(A) Sagittal short T1 inversion recovery (STIR) spine MRI shows hyperintense, non-enhancing lesions in the T1–T4 and T6–T9 segments. (B) Fluid-attenuated inversion recovery axial brain MRI demonstrates hyperintensity in the pons, superior and middle left cerebellar peduncle, as well as periependymal lesion. (C) Axial orbit MRI T1 postcontrast shows extensive gadolinium-enhancing lesion compromising at least 50% of the right nerve length compatible with optic neuritis. (D) Hyperintensities at level C3 to C6 are depicted on sagittal STIR spine MRI.

Discussion

The ZIKV epidemic in 2015 in Latin America was followed by an increase in microcephaly and Guillain-Barré syndrome cases, and ZIKV has subsequently been linked to other neurologic complications including myelitis, encephalitis, and acute disseminated encephalomyelitis.^{2,3} Nevertheless, this is a rare case reported of NMOSD linked to ZIKV infection. How ZIKV can cause or trigger neurologic disease is not yet fully understood and could be due to direct virus neurotropism⁴ or immune-mediated processes.^{3–6} Other viral infections, including DENV, varicella-zoster virus, and cytomegalovirus, have previously been associated with NMOSD. The suggested pathologic mechanisms include molecular mimicry and increased self-antigen presentation due to tissue destruction.⁵ In this NMOSD case report, the positive PCR in the CSF and other biological materials at onset suggest a direct viral pathogenicity. However, new severe neurologic symptoms occurred when PCR for ZIKV was already negative, suggesting a postinfectious or parainfectious mechanism. Furthermore, the preceding DENV infection, as some studies indicate, could intensify ZIKV neurologic manifestations due to cross-reactive antibodies.⁶

The precise pathophysiology of NMOSD and viral infections is yet to be established and further research is required to specifically investigate the relation between ZIKV and NMOSD. Following this case, we recommend neurologists working in areas with ongoing transmission of ZIKV to consider the possibility of ZIKV infection in NMOSD cases, including patients who have not had arboviral symptoms before the onset of neurologic symptoms.⁷

Author contributions

Maíra Cardoso Aspahan, Sonja Emily Leonhard, Rodrigo Santiago Gomez, and Fidel Meira: analysis/interpretation of the data and drafting and reviewing the manuscript for intellectual content. Eder da Silva Rocha, Michelle Ramos da Silva Vilela, Pedro Paulo Martins Alvarenga, Paula Eillanny Silva Marinho, Erna Geessien Kroon: acquisition of data and revising the manuscript for intellectual content.

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References

1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015;85:177–189.
2. da Silva IRF, Frontera JA, Bispo de Filippis AM, Nascimento O; RIO-GBS-ZIKV Research Group. Neurologic complications associated with the Zika virus in Brazilian adults. *JAMA Neurol* 2017;74:1190–1198.
3. Bharucha T, Breuer J. Review: a neglected flavivirus: an update on Zika virus in 2016 and the future direction of research. *Neuropathol Appl Neurobiol* 2016;42:317–325.
4. Tang H, Hammack C, Ogden SC, et al. Zika virus infects human cortical neural progenitors and attenuates their growth. *Cell Stem Cell* 2016;18:587–590.
5. Sellner J, Hemmer B, Muhlau M. The clinical spectrum and immunobiology of parainfectious neuromyelitis optica (Devic) syndromes. *J Autoimmun* 2010;34:371–379.
6. Dejnirattisai W, Supasa P, Wongwiwat W, et al. Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with Zika virus. *Nat Immunol* 2016;17:1102–1108.
7. Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009;360:2536–2543.