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## ENCEPHALOMYELITIS FOLLOWING DEFINITIVE ZIKA VIRUS INFECTION

**OPEN**

An 18-year-old woman without previous medical issues was examined at an academic medical center for a complaint of ascending numbness in the legs following viral illness. She had taken a trip in early spring 2016 to the Dominican Republic, during which time she was bitten several times by mosquitoes. Approximately 2 weeks following return, she developed malaise, nausea, and a nonpruritic macular rash of the trunk, legs, palms, and soles of the feet. Initial workup was notable for a positive serum Zika virus PCR (Wadsworth Center, NYC Health Department). Her symptoms gradually resolved. Six weeks

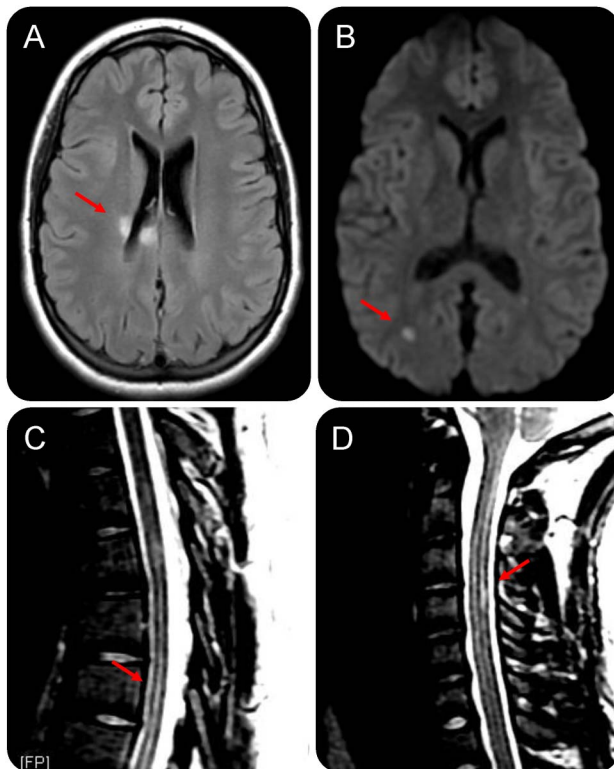
after the onset of her viral syndrome, she awoke with numbness in both legs extending circumferentially from both knees to both feet; the numbness gradually extended proximally to the trunk above the umbilicus, at which time she presented to the emergency department. On initial evaluation, she was afebrile and with stable vital signs. Her examination was remarkable for impairment of fine touch, temperature, and pinprick from the T6 dermatome extending distally, and a symmetric gradient fine touch, temperature, and pinprick deficit was also noted in both hands. Right-sided deep tendon reflexes were 3+ throughout, and Babinski sign was positive on the left foot.

MRI of the cervical, thoracic, and lumbar spine with and without contrast demonstrated multiple T2 hyperintense, nonenhancing lesions in the cervical and thoracic cords. Brain MRI with and without contrast was significant for multifocal subcortical and callosal T2/fluid-attenuated inversion recovery hyperintense lesions, some of which with faint enhancement and restricted diffusion (figure). Lumbar puncture was performed; opening pressure was 17 cm H<sub>2</sub>O; red blood cell count was 74; white blood cell count was 10 with 99% lymphocytes; protein was 26 mg/dL; and glucose was 56 mg/dL. CSF Zika PCR was negative, and immunoglobulin M (IgM) levels were indeterminate. Three unique oligoclonal bands were present in the CSF, and myelin basic protein was elevated at 180 mg/dL. Extensive evaluation of alternative etiologies was unremarkable (table). Repeat serum testing performed for Zika virus real-time PCR was negative, and the Zika IgM value was equivocal. She was treated with 3 days of IV methylprednisolone for inflammatory encephalomyelitis with symptomatic improvement.

**Discussion.** Few reports of Zika virus exist involving the CNS in adolescence and adulthood. Here, we describe a teenage patient with no neurologic history presenting with inflammatory lesions of both the brain and spinal cord, consistent with an acute demyelinating process, 47 days following proven Zika virus infection by serum PCR.

The long latency period between acute systemic Zika virus infection and her neurologic presentation

**Figure** Multifocal CNS lesions following Zika virus infection



(A) MRI brain axial FLAIR sequence. Two characteristic lesions, periventricular and splenium of corpus callosum. (B) MRI brain axial DWI sequence. Characteristic lesion with diffusion restriction (ADC not shown). (C) MRI thoracic spine sagittal MRI T2 sequence with characteristic lesions. (D) MRI cervical spine sagittal MRI T2 sequence with C3-4 lesion. FLAIR = fluid-attenuated inversion recovery.

**Table** Laboratory evaluation

| Laboratory test                                                                                                                                                                                                               | Reference range, adults | Result                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|----------------------------------------------------------------------------------------------|
| <b>Infectious studies: serum</b>                                                                                                                                                                                              |                         |                                                                                              |
| Zika virus serum PCR                                                                                                                                                                                                          | Negative                | Negative                                                                                     |
| Zika virus serum IgM by MAC-ELISA                                                                                                                                                                                             | Negative                | Equivocal                                                                                    |
| Zika virus serum PRNT                                                                                                                                                                                                         | Negative                | Positive                                                                                     |
| Dengue virus serum PRNT                                                                                                                                                                                                       | Negative                | Negative                                                                                     |
| West Nile virus serum microsphere immunofluorescence assay                                                                                                                                                                    | Nonreactive             | Nonreactive                                                                                  |
| Arbovirus PRNT                                                                                                                                                                                                                | Nonreactive             | Results suggest evidence of a current or recent infection with Zika virus                    |
| <b>T-cell panel</b>                                                                                                                                                                                                           |                         |                                                                                              |
| CD4 T cells, cells/ $\mu$ L                                                                                                                                                                                                   | 393-1489                | 764                                                                                          |
| CD8 T cells, cells/ $\mu$ L                                                                                                                                                                                                   | 148-788                 | 381                                                                                          |
| B cells, cells/ $\mu$ L                                                                                                                                                                                                       | 61-530                  | 367                                                                                          |
| Natural killer cells, cells/ $\mu$ L                                                                                                                                                                                          | 25-488                  | 176                                                                                          |
| CD4/CD8 ratio                                                                                                                                                                                                                 | 0.7-3.6                 | Normal                                                                                       |
| Serum HSV1/2, CMV, VZV, and EBV PCR testing                                                                                                                                                                                   | Negative                | Negative                                                                                     |
| Serum EBV-VCA, IgG                                                                                                                                                                                                            | Negative                | Positive                                                                                     |
| <b>CSF studies</b>                                                                                                                                                                                                            |                         |                                                                                              |
| <b>Admission CSF profile</b>                                                                                                                                                                                                  |                         |                                                                                              |
| Erythrocytes (per microliter)                                                                                                                                                                                                 | 0-0                     | 136 (tube 1); 74 (tube 4)                                                                    |
| Leukocytes (per microliter)                                                                                                                                                                                                   | 0-5                     | 15 (tube 1: 98% lymphocytes and 2% monocytes); 10 (tube 4: 99% lymphocytes and 1% monocytes) |
| Protein, mg/dL                                                                                                                                                                                                                | 15-45                   | 26                                                                                           |
| Glucose, mg/dL                                                                                                                                                                                                                | 40-70                   | 56 (serum glucose 121)                                                                       |
| Zika virus CSF PCR                                                                                                                                                                                                            | Negative                | Negative                                                                                     |
| Zika virus CSF IgM                                                                                                                                                                                                            | Negative                | Equivocal                                                                                    |
| Adenovirus, West Nile, CMV, VZV, EBV, enterovirus, HHV-6, Eastern equine encephalitis virus, St. Louis encephalitis virus, human parechovirus, and CSF PCR testing                                                            | Negative                | Negative                                                                                     |
| <i>Escherichia coli</i> K1, <i>Haemophilus influenzae</i> , <i>Listeria monocytogenes</i> , <i>Neisseria meningitidis</i> , <i>Streptococcus agalactiae</i> , <i>S pneumoniae</i> , and <i>Cryptococcus neoformans/gattii</i> | Negative                | Negative                                                                                     |
| CSF myelin basic protein                                                                                                                                                                                                      | 0-5.5                   | 179.6                                                                                        |
| CSF IgG index                                                                                                                                                                                                                 | 0.09-0.25               | 0.36                                                                                         |
| CSF immunoglobulins                                                                                                                                                                                                           | 0-6                     | 4.6                                                                                          |
| <b>Urine studies</b>                                                                                                                                                                                                          |                         |                                                                                              |
| Zika virus urine PCR                                                                                                                                                                                                          | Negative                | Negative                                                                                     |

Abbreviations: CMV = cytomegalovirus; EBV = Epstein-Barr virus; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; MAC-ELISA = IgM antibody capture ELISA; PRNT = plaque-reduction neutralization test; VCA = viral capsid antigen; VZV = varicella zoster virus.

is unusual, as previous studies have identified similar manifestations including Guillain-Barré syndrome, transverse myelitis, and meningoencephalitis within

4 weeks of acute viral symptoms.<sup>1-5</sup> The prolonged latency between the onset of systemic viral symptoms and development of active inflammatory lesions, however, suggests the possibility of a postinfectious inflammatory response, although it is also possible that her neurologic presentation was not related to her previous Zika virus infection given the lack of antibody detection of Zika virus in the CSF.

Our patient's imaging met the 2010 McDonald criteria for MS; although a future polyphasic course would be consistent with MS, a monophasic presentation would be more typical of acute disseminated encephalomyelitis (ADEM). Encephalomyelitis in the absence of altered mental status also points to an MS-like phenotype, although this patient may prove to have no further signs of relapsing-remitting disease.

Infection with Epstein-Barr virus (EBV) has already been proposed as a possible predisposing factor for developing MS.<sup>6</sup> Epidemiologic data have shown MS risk as being 10 times greater among individuals who experienced an undiagnosed EBV infection in childhood and at least 20-fold greater among individuals who developed mononucleosis.<sup>6</sup> Exacerbations of both MS and ADEM are also known to be triggered by a variety of other systemic viral infections, which can stimulate production of proinflammatory cytokines, CD8<sup>+</sup> T-cell activation, and subsequent central demyelination.<sup>7</sup>

Although Zika virus is not yet among the viruses postulated to play a pathogenic role in the onset or exacerbation of central demyelinating syndromes, it is known to cause neurologic disease both directly and by secondary autoimmunity as evidenced by the growing number of cases of congenital birth defects and Guillain-Barré syndrome. Emerging evidence suggests that Zika virus causes a spectrum of neurologic manifestations, and further studies are required to fully define this spectrum. With the recent international spread of Zika virus, practitioners should be aware of the range of potential neurologic effects of immediate and delayed impact of Zika virus infection in both infants and adults.

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