

EDITORIAL



Zika Getting on Your Nerves? The Association with the Guillain–Barré Syndrome

Jennifer A. Frontera, M.D., and Ivan R.F. da Silva, M.D., Ph.D.

Parra and colleagues¹ report in the *Journal* the results of a prospective study of 68 Colombian patients who had a syndrome consistent with the Guillain–Barré syndrome, 66 of whom had previously had symptoms of Zika virus (ZIKV) infection. Major strengths of this study include the documentation of a temporal relationship between the Guillain–Barré syndrome and ZIKV infection (marked by a substantial increase in the incidence of the Guillain–Barré syndrome after the introduction of ZIKV, from 20 to 90 cases per month throughout Colombia), the criteria applied for the diagnosis of the Guillain–Barré syndrome, and the molecular and serologic flavivirus data from analyses of serum, cerebrospinal fluid (CSF), and urine.

However, the difficulties related to diagnosing ZIKV infection are multifold. First, the symptoms associated with ZIKV infection are similar to those caused by dengue virus (DENV) and chikungunya virus, both of which are endemic in Colombia. Second, the serologic cross-reactivity among flaviviruses (including yellow fever virus, West Nile virus, DENV, and Japanese encephalitis virus) have been well described.² Although the Centers for Disease Control and Prevention (CDC) recommends neutralizing antibody testing with a plaque-reduction neutralization test to distinguish among flaviviruses,³ this testing is expensive, requires cell culture, and is also susceptible to cross-reactivity.⁴ Polymerase-chain-reaction (PCR) testing can definitively identify ZIKV, but molecular studies of serum are usually sensitive only during the first week after infection. Because the Guillain–Barré syndrome has been linked to mi-

crobial pathogens through a molecular mimicry mechanism, it is typically diagnosed 1 week or longer after an infection. Indeed, Parra et al. observed that the median time to onset of the Guillain–Barré syndrome was 7 days after ZIKV infection.

The authors deal with these diagnostic dilemmas by showing that ZIKV PCR testing of other body fluids (particularly urine) may remain sensitive for a longer duration than does testing of serum. Indeed, in 13 patients, ZIKV PCR results were positive only in urine, whereas serum, CSF, or both were PCR-negative when tested in a similar time frame. IgM antibody testing of CSF for both ZIKV and DENV may be another diagnostic strategy, since the IgM pentamer is too large to cross the blood–brain barrier.⁵ Therefore, CSF that is positive for ZIKV IgM and negative for DENV IgM would be suggestive of a primary central nervous system ZIKV infection. Of the patients who tested positive for ZIKV by PCR and underwent CSF IgM testing, 8 were PCR-positive but ZIKV IgM–negative in CSF, which suggested that ZIKV PCR testing of urine may be more sensitive than serologic testing of CSF.

The difficulties in diagnosing ZIKV infection are borne out in this study, as only 17 patients had definitive laboratory evidence of recent ZIKV infection. On the basis of Table S5 in the Parra et al. Supplementary Appendix, of these 17 patients, only 14 had electrophysiological data consistent with the Guillain–Barré syndrome and therefore could have met Brighton level 1 diagnostic criteria for the syndrome, although the actual number of patients meeting level 1 criteria may have been

smaller because we do not know the corresponding results of CSF testing for these patients.⁶ Because of these limitations in diagnostic certainty for both ZIKV infection and the Guillain–Barré syndrome, a strong association was identified in approximately 20% of patients in this cohort (14 of 68). Among the 25 ZIKV PCR–negative patients, DENV IgG antibodies were present in the CSF of 12 patients and in the serum of 10 patients, and serum DENV IgM test results were positive in 1. These data raise the possibility of primary DENV infection and false positive ZIKV serologic test results due to cross-reactivity. In addition, data on yellow fever vaccination or infection were not provided; yellow fever is also endemic in much of Colombia and may complicate the interpretation of the ZIKV serologic results.

As is true with most clinical studies, proving a causal relationship between ZIKV infection and the Guillain–Barré syndrome is challenging. In keeping with Hill criteria for causality,⁷ the authors show a consistent, specific, temporal relationship, which is analogous to relationships between ZIKV infection and the Guillain–Barré syndrome observed in other countries.^{8,9} What is more difficult to demonstrate is pathophysiological plausibility. The authors point out that 20 patients had neurologic symptoms immediately after the viral syndrome (only 9 of 20 had definite laboratory-proven ZIKV) and speculate that other mechanisms, including a hyperacute immune response or direct viral neuropathic mechanisms, may be in effect, rather than postinfectious molecular mimicry. Although studies using human neural progenitor cells have shown that ZIKV infection increases cell death and dysregulates cell-cycle progression,¹⁰ evidence of direct neurotropism in adult neuronal cells is still lacking. A recent study showed that there is a high peptide overlap between the ZIKV polyprotein and human proteins related to myelin and axons, which suggests that an immune-mediated mechanism may be more likely.¹¹ Although protein epitopes and antibodies that are normally involved in the genesis of the Guillain–Barré syndrome seem not to be highly involved in one cohort with ZIKV-associated acute motor axonal neuropathy,⁸ it is possible that differences in subtypes of the Guillain–Barré syndrome and host genetic factors may

lead to varying immune-mediated mechanisms in different populations.

Overall, the study by Parra and colleagues supports the association between ZIKV and the Guillain–Barré syndrome, although confirmation in another cohort would strengthen this assertion. Although high rates of seropositivity may prove protective against further waves of ZIKV-related Guillain–Barré syndrome in Central and South America, the ZIKV pandemic is just beginning in North America and Africa, and an increase in the incidence of the Guillain–Barré syndrome may follow.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Cerebrovascular Center of the Neurological Institute, Cleveland Clinic, Cleveland (J.A.F.); and the Neurology Department, Universidade Federal Fluminense, Niteroi (I.R.F.S.), and the Neurocritical Care Department, Americas Medical City, Rio de Janeiro (I.R.F.S.) — both in Brazil.

This article was published on October 5, 2016, at NEJM.org.

1. Parra B, Lizarazo J, Jiménez-Arango JA, et al. Guillain–Barré syndrome associated with Zika virus infection in Colombia. *N Engl J Med*. DOI: 10.1056/NEJMoa1605564.
2. Mansfield KL, Horton DL, Johnson N, et al. Flavivirus-induced antibody cross-reactivity. *J Gen Virol* 2011;92:2821-9.
3. Update on interim Zika virus clinical guidance and recommendations: Clinician Outreach and Communication Activity (COCA) call. Atlanta: Centers for Disease Control and Prevention, February 25, 2016 (http://emergency.cdc.gov/coca/ppt/2016/03_3_16_zika_update.pdf).
4. Laboratory testing for Zika virus infection. Geneva: World Health Organization, March 23, 2016 (http://apps.who.int/iris/bitstream/10665/204671/1/WHO_ZIKV_LAB_16.1_eng.pdf?ua=1).
5. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008;47:303-27.
6. Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2011;29:599-612.
7. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300.
8. Cao-Lormeau VM, Blake A, Mons S, et al. Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet* 2016;387:1531-9.
9. da Silva IR, Frontera JA, Moreira do Nascimento OJ. News from the battlefield: Zika virus-associated Guillain-Barré syndrome in Brazil. *Neurology* 2016 July 15 (Epub ahead of print).
10. Tang H, Hammack C, Ogden SC, et al. Zika virus infects human cortical neural progenitors and attenuates their growth. *Cell Stem Cell* 2016;18:587-90.
11. Lucchese G, Kanduc D. Zika virus and autoimmunity: from microcephaly to Guillain-Barré syndrome, and beyond. *Autoimmun Rev* 2016;15:801-8.

DOI: 10.1056/NEJMe1611840

Copyright © 2016 Massachusetts Medical Society.