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Editors' Note: In response to "Acute Zika infection with concurrent onset of Guillain-Barré syndrome," Dr. Gérardin et al. suggest that Zika-related Guillain-Barré syndrome (GBS) may have a different mechanism than postviral GBS. They discuss potential hyperacute immune response in patients who are dengue seropositive or direct neurotropic effect as possible mechanisms of action. Timmings et al., authors of the article, explain that in their patient and based on clinical data, they favor a direct pathogenic Zika virus effect on peripheral nerves. Dr. Avasarala asks several questions about the methods of the study and interpretation of the results in "Gray matter MRI differentiates neuromyelitis optica from multiple sclerosis using random forest." Authors Eshaghi and Ciccarelli answer the questions and make clarifications. They add that the random forest technique is nonparametric and is more robust to the effect of outliers in comparison with other methods.

—Chafic Karam, MD, and Robert C. Griggs, MD

LETTER RE: ACUTE ZIKA INFECTION WITH CONCURRENT ONSET OF GUILLAIN-BARRÉ SYNDROME

Patrick Gérardin, Saint-Pierre, Réunion; Van-Mai Cao-Lormeau, Papeete, French Polynesia; Patrice Tournebize, Saint-Pierre, Réunion; Thomas Cerny, Zurich, Switzerland: Siu et al.[1] reported the concurrent onset of polyradiculoneuritis and acute Zika virus (ZIKV) infection, while the virus was not cleared from the serum. Guillain-Barré syndrome (GBS) is usually described as a postinfectious disease during which progressive flaccid paralysis develops after a phase of latency following infection. In the most common pathogenetic framework, this free interval permits the generation of sufficient levels of antibodies that cross-react by molecular mimicry with specific components of peripheral nerves, causing myelin or axonal injury, as previously documented with ZIKV infection.[2] However, this case report suggested other mechanisms. Given ZIKV cross-reactivity with dengue virus and increasing reports of ZIKV-associated GBS in dengue-seropositive patients,[1,3] a hyperacute immune response is possible.[4] Given prolonged ZIKV shedding in bodily fluids, and the overlap between GBS onset and persistent shedding in fomites, a direct viral neuropathic effect may also contribute to ZIKV-associated GBS.[4] Indeed, ZIKV is able to infect cranial neural crest cells that stem Schwann cell formation.[5] ZIKV-associated GBS could reflect a direct viral neuropathic effect on the blood–nerve barrier, allowing cross-reactive antibodies formed during previous infections to have a deleterious effect on nerve function.

1. Siu R, Bukhari W, Todd A, et al. Acute Zika infection with concurrent onset of Guillain-Barré syndrome. Neurology 2016;87:1623–1624.
2. 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;387:1531–1539.
3. Parra B, Lizarazo J, Jimenez-Arango JA, et al. Guillain-Barré syndrome associated with Zika virus in Colombia. N Engl J Med 2016;375:1513–1523.
4. 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.
5. Bayless NL, Greenberg RS, Swigut T, Wysocka J, Blish CA. Zika virus infection induces cranial neural crest cells to produce cytokines at levels detrimental for neurogenesis. Cell Host Microbe 2016;20:423–428.

AUTHOR RESPONSE: ACUTE ZIKA INFECTION WITH CONCURRENT ONSET OF GUILLAIN-BARRÉ SYNDROME

Paul L. Timmings, Ronald Siu, Wajih Bukhari, Hamilton; New Zealand; Angela Todd, Wendy Gunn, Upper Hutt, New Zealand: We thank Gérardin et al. for the comments on our Clinical/Scientific Note on Zika virus (ZIKV).[1] Our patient was of particular interest because he had an illness clinically and electrophysiologically indistinguishable from Guillain-Barré syndrome (GBS) that developed within a few days of acute ZIKV infection, in the context of contemporaneous Zika viremia.[1] Concurrently obtained CSF was negative for ZIKV. Brain and spine MRI were also normal. Importantly, there was no serologic evidence of priming by previous dengue or other flaviviruses.

These clinical data suggested a direct ZIKV neural injury mechanism, without a requirement for priming. We postulated that although molecular mimicry

between ZIKV and peripheral nerve components might be relevant to antibody-induced GBS, such a rapidly developing polyradiculoneuritis mimicking GBS might also have been mediated by a direct pathogenic ZIKV effect on peripheral nerves.[2,3] This observation and ZIKV neurotropism may also account for delayed CNS ZIKV effects in some patients. The fact that our patient was ZIKV-negative in CSF suggests efficacy of the blood–brain barrier to ZIKV at that time point and strengthens the suggestion that ZIKV CNS invasion may be via neuronal transmission rather than directly across the blood–brain barrier.

1. Siu R, Bukhari W, Todd A, et al. Acute Zika infection with concurrent onset of Guillain-Barré syndrome. Neurology 2016;87:1623–1624.
2. Neal JW. Flaviviruses are neurotropic, but how do they invade the CNS? J Infect 2014;69:203–215.
3. Velandia ML, Castellanos JE. Flavivirus neurotropism, neuroinvasion, neurovirulence and neurosusceptibility: clues to understanding flavivirus- and dengue-induced encephalitis. In: Garcia ML, Romanowski V, editors. Viral Genomes: Molecular Structure, Diversity, Gene Expression Mechanisms and Host-virus Interactions. Rijeka: InTech; 2012: 219–240.

LETTER RE: GRAY MATTER MRI DIFFERENTIATES NEUROMYELITIS OPTICA FROM MULTIPLE SCLEROSIS USING RANDOM FOREST

Jagannadha Avasarala, Greenville, NC: The article by Eshaghi et al.[1] gave a glimpse of where neuroradiology is headed. Pertinent questions include the following:

Did the algorithm miss aquaporin-4 autoantibody-positive cases? If so, what were the false-negative numbers?

Did this model pick up disease at the earliest stage of evolution, since treatment options could be instituted earlier? Also, as opposed to autoantibody (Ab) testing for neuromyelitis optica spectrum disorder (NMOSD), algorithms probably suffered from poor specificity at the earliest stages of disease evolution unless it was shown across patient cohorts that cortical atrophy and deep gray matter changes occur very early.

Since clinical evaluation is the only option to diagnose Ab-negative NMOSD, how was the gold standard set up? Was the Ab-negative NMOSD cohort set up after evaluation by experts in neuroimmunology?

Would specificity of the algorithm suffer as disability worsens? For example, is it possible that cases in the secondary progressive multiple sclerosis stage would overlap with NMOSD as far as deep gray matter atrophy is concerned?

It is possible that algorithms are not sensitive at the outliers or extremes of a bell curve and, therefore, limited in clinical setting utility? The more pressing question: How early can these changes be correctly identified?

1. Eshaghi A, Wottschel V, Cortese R, et al. Gray matter MRI differentiates neuromyelitis optica from multiple sclerosis using random forest. Neurology 2016;87:2463–2470.

AUTHOR RESPONSE: GRAY MATTER MRI DIFFERENTIATES NEUROMYELITIS OPTICA FROM MULTIPLE SCLEROSIS USING RANDOM FOREST

Arman Eshaghi, Olga Ciccarelli, London: We thank Dr. Avasarala for the comment on our article.[1] Since the majority of patients with neuromyelitis optica (NMO) were positive for anti-aquaporin-4 autoantibody, the classification results (table 2)[1] are expected to remain similar after excluding seronegative patients (negative predictive value 76%). This is expected as patients with multiple sclerosis (MS) and NMO are heterogeneous in clinical and MRI assessments, and volumes in different brain regions may overlap (figure 1).[1] Including other features, such as spinal cord atrophy, may increase the accuracy.[2]

We included patients with a secure diagnosis, meaning the disease duration on average was 7.5 years (table 1).[1] Therefore, we cannot comment on the earliest stages of NMO spectrum disorder. We previously applied a similar method to patients with clinically isolated syndrome to predict future evolution to relapsing-remitting multiple sclerosis (RRMS).[3] The gold standard was clinical diagnosis by an expert neurologist in each center according to the Wingerchuk et al.[4] 2006 criteria. We cannot exclude false-negative anti-aquaporin-4 autoantibody patients, but similar results were obtained when only seropositive NMO patients and when all seropositive and seronegative NMO patients were included.

Although this study only included patients with RRMS,[1] we expect to see increased accuracy if the algorithm distinguished between patients with secondary progressive MS (SPMS) and NMO. Patients with SPMS have a longer disease duration, which increases atrophy in gray matter.[5] This will make it easier to distinguish SPMS and NMO. Outliers can have an effect on the performance of the machine learning techniques. However, random forest technique is nonparametric, and is more robust to the effect of outliers in comparison with other methods.[6]

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2. Liu Y, Wang J, Daams M, et al. Differential patterns of spinal cord and brain atrophy in NMO and MS. Neurology 2015;84:1465–1472.
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Author disclosures are available upon request (journal@neurology.org).

Author response: Gray matter MRI differentiates neuromyelitis optica from multiple sclerosis using random forest

Arman Eshaghi and Olga Ciccarelli

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