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# High proportion of Guillain-Barré syndrome associated with chikungunya in Northeast Brazil

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From 2013 to 2015, sanitary authorities reported an increased incidence of Guillain-Barré syndrome (GBS) associated with Zika virus (ZIKV) in French Polynesia, Caribbean, and Brazil.[1–3] After the end of ZIKV epidemics, GBS cases where still above the usual limits in countries where the arrival of chikungunya virus (CHIKV) was also a concern.[3]

Here, we report the findings from Hospital Geral de Fortaleza (HGF), a neuroinvasive arboviral disease vigilance center in Ceará State, Northeast Brazil.

## Methods

We performed a prospective observational study that enrolled patients aged 15 year or older with the diagnosis of GBS[4] (Brighton criteria I or II). All consecutive patients fulfilling the inclusion criteria from May 2015 to December 2017 were invited to participate.

Patients were evaluated for demographics, clinics (at admission and 6 months later), serum, and CSF complementary tests, and EMG. Owing to the local epidemics, besides investigating for classic GBS triggers, virologic tests for dengue virus, ZIKV, and CHIKV (i.e., ELISA IgM, IgG, and specific real-time PCR) were performed by a researcher blinded to clinical results. Neurofilament light chain[5] (NfL) was measured in CSF and related to death, need for mechanical ventilation (MV), and incomplete recovery. CSF from 10 healthy subjects served as the control for NfL.

For comparison, official reports of arboviral systemic infections and total GBS cases/year from 2013 to 2017 were requested to the local state government according the Law #12.527 November 18, 2011.

Continuous data were summarized as median and interquartile range (IQR). Categorical data were presented as counts and percentages. Kendall $\tau$ was used for correlations and Mann-Whitney test for comparisons. $p$ values <0.05 were deemed statistically significant. Data were analyzed using SPSS version 25.0. Graphs were constructed using Sigma Plot version 11.0. The study was approved by the HGF ethics committee (CAAE: 56572316.9.0000.5040) and the USP ethics committee (CAAE: 00274418.7.0000.0068) and conducted according to appropriate Brazilian regulations. All subjects provided written informed consent.

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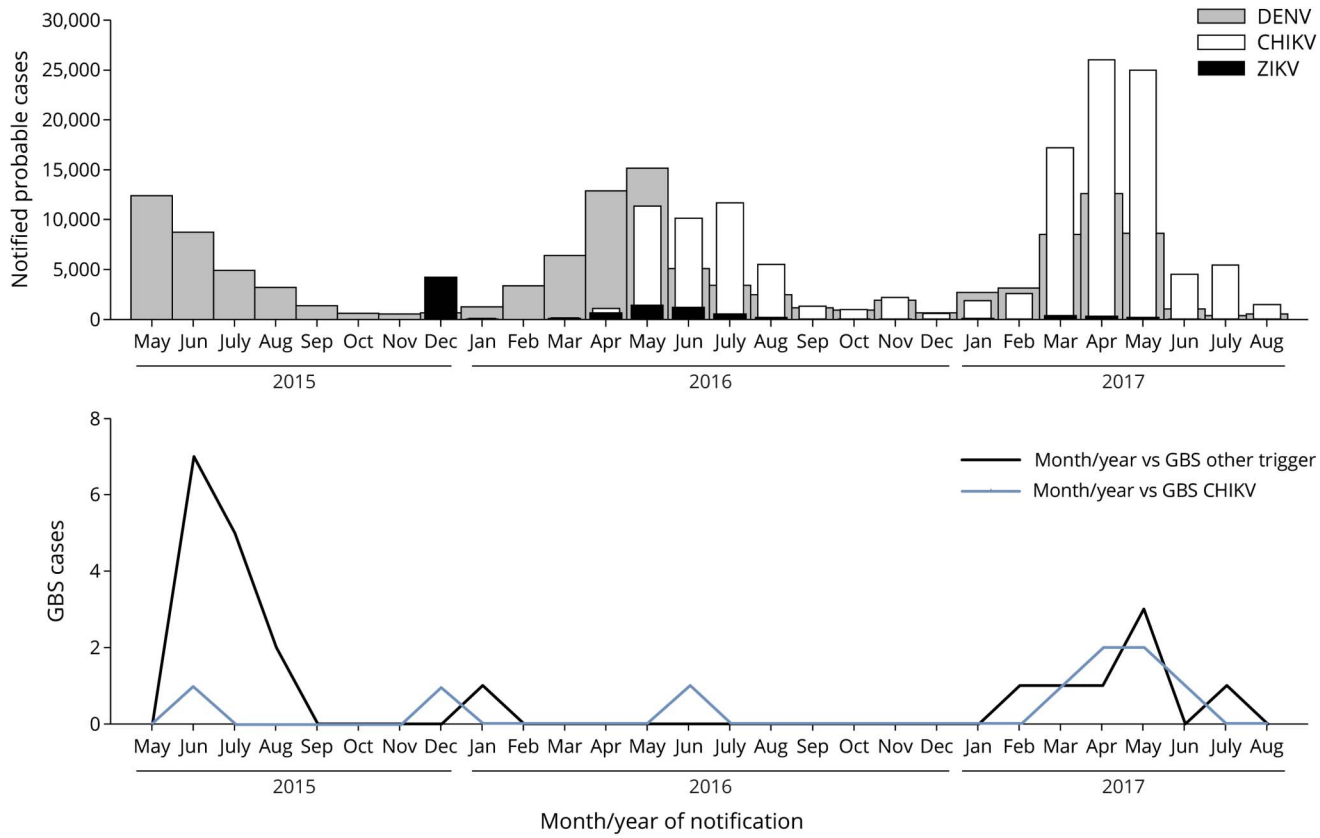
**Figure 1** Notified cases of dengue, Zika, and chikungunya in Ceará state and GBS cases in the study site




CHIKV = Chikungunya virus; DENV = Dengue virus; GBS = Guillain-Barré syndrome; ZIKV = Zika virus.

## Results

A total of 42 patients with GBS suspicion were admitted. Eight patients were excluded (figure e-1, links.lww.com/NXI/A278). From the 34 remaining, GBS trigger was attributed to CHIKV for 9 patients.[6] For those, median age was 47 (IQR 31–55), 56% were men and most without comorbidities (56%). The mean number of GBS cases in the previous 2 years of the study was 52 cases/year; from 2015 to 2017, it was 88 cases/year. Most CHIKV-GBS cases concentrated in the CHIKV epidemic peak (figure 1).

At admission, patients were confine to bed/wheelchair (56%), walking with support (33%), or unable to run (11%). During in hospital stay, 22% required MV and no patient died. Median days in hospital were 16 (IQR 12–25.5). Recovery after 6 months was complete for 33%, whereas 67% remained with minor signs or symptoms (table e-1, links.lww.com/NXI/A278).

Major laboratory results can be found in supplementary material (links.lww.com/NXI/A278). EMG was primary demyelinating (75%) or primary axonal (25%). Although NfL presented higher titles than control (figure e-2), there was no correlation with death, MV or, recovery.

## Discussion

We found that 26% of the cases enrolled were associated with CHIKV as an infectious trigger. The increase was coincident with the first local epidemics of CHIKV and followed a ZIKV epidemics. The association might be the result of a molecular mimicry autoimmune mechanism because CHIKV E1 glycoprotein shares homology with contactin-2,[7] a protein present in the juxtaparanode.[8]

In one of the larger GBS cohort available,[9] although no laboratory tests are mentioned, there are no reports of rash/arthralgia as prodromal symptoms. Despite that, reports of GBS-ZIKV associations are well known,[1,3] unlike GBS-CHIKV which are rarely reported. Regarding clinical outcomes, differences are also apparent from our GBS-CHIKV to this same cohort. For recovery, all of our patients achieved Hugues score of "0" or "1" in 6 months (vs 61%). No patient with GBS-CHIKV died (vs 7%). As for MV, we have similar numbers (22% vs 19%).

A limitation of our study is the small sample size. This was unavoidable because of the rare nature of GBS disease and the seasonality of arbovirus infections. In addition, we were not able to access antiganglioside tests. However, we performed a clinical follow-up of at least 6 months and adopted strict criteria for GBS, allowing proper exclusion of diagnostic mimics.

Our findings suggest CHIKV as an important trigger for GBS during epidemics, overcoming classic triggers as *Campylobacter jejuni*, Epstein-Barr virus, and influenza virus. Good outcomes were a commonplace in our study; however, sanitary authorities of areas affected by CHIKV should be aware of a possible increase in GBS incidence and as a consequence an increased necessity for intensive care unit beds and rehabilitation treatments.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## Disclosure

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## References


1. Cao-Lormeau VM, Blake A, Mons S, et al. Guillain-Barre syndrome outbreak associated with Zika virus infection in French polynesia: a case-control study. Lancet 2016; 387:1531–1539.
2. Arias A, Torres-Tobar L, Hernández G, et al. Guillain-Barré syndrome in patients with a recent history of Zika in Cucuta, Colombia: a descriptive case series of 19 patients from December 2015 to March 2016. J Crit Care 2017;37:19–23.
3. Mehta R, Soares CN, Medialdea-Carrera R, et al. The spectrum of neurological disease associated with Zika and chikungunya viruses in adults in Rio de Janeiro, Brazil: a case series. PLoS Negl Trop Dis 2018;12:e0006212.
4. Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barre syndrome and validation of Brighton criteria. Brain 2014; 137:33–43.
5. Rajabally YA, Uncini A. Outcome and its predictors in Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry 2012;83:711–718.
6. Center for Disease Control and Prevention. Arboviral diseases, neuroinvasive and non-neuroinvasise 2015 case definition. In: NNDSS, ed. Available at: wwwn.cdc.gov/nndss/conditions/arboviral-diseases-neuroinvasive-and-non-neuroinvasive/case-definition/2015/2015. Accessed January 2020.
7. Reddy V, Desai A, Krishna SS, Vasanthapuram R. Molecular mimicry between chikungunya virus and host components: a possible mechanism for the arthritic manifestations. PLoS Negl Trop Dis 2017;11:e0005238.
8. Masuda T. Contactin-2/TAG-1, active on the front line for three decades. Cell Adhes Migration 2017;11:524–531.
9. Doets AY, Verboon C, van den Berg B, et al. Regional variation of Guillain-Barre syndrome. Brain 2018;141:2866–2877.