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

Aline de Moura Brasil Matos, MD, Fernanda Martins Maia Carvalho, MD, PhD, Danielle Lima Malta, PhD, Cleonísio Leite Rodrigues, MD, PhD, Alívia Clara Félix, MSc, Claudio Sergio Pannuti, PhD, Amanda Dias da Rocha Lima, MSc, Danilo Lucuas Alves Espósito, PhD, Leonílida Maria Barbosa dos Santos, PhD, Felipe von Glehn, MD, PhD, FAA, Jeová Keny Baima Colares, MD, PhD, Benedito Antônio Lopes da Fonseca, MD, PhD, Augusto César Penalva de Oliveira, MD, PhD, and Camila Malta Romano, PhD

Neurol Neuroimmunol Neuroinflamm 2020;7:e833. doi:10.1212/NXI.0000000000000833

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 were 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 GBS4 (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 chain5 (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 to 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 τ 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: 00274418.7.0000.0068) and conducted according to appropriate Brazilian regulations. All subjects provided written informed consent.
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. 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 confined 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, a protein present in the juxtaparanode.

In one of the larger GBS cohort available, 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, 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.

**Acknowledgment**

The authors would like to thank Professor Steven S. Witkin from Weill Cornell Medicine for constructive comments and kindness in editing the manuscript; Vânia Maria Alves de Araujo from the Hospital Geral de Fortaleza for the laboratory assistance, and Rosa Maria Nascimento Marcusso from Instituto de Infectologia Emílio Ribas for the organizational support and revision of statistical analysis.

**Study funding**

CNPq/Brazil under the grant number 2016/407429 and Fundação de Amparo à Pesquisa do Estado de São Paulo-FAPESP/Brazil under the grants numbers 2014/26431-0 and 2019/03859-9.

**Disclosure**

A.d.M.B. Matos reports no disclosures. F.M. Maia Carvalho received financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico CNPq/Brazil under the grant number 2016/407429. D.L. Malta, C.L. Rodrigues, A.C. Félix, C.S. Pannuti, A.d.R. Lima, and D.L.A. Espósito report no disclosures. L.M.B. dos Santos received research financial support from Fundação de Amparo à Pesquisa do Estado de São Paulo-FAPESP/Brazil under the grant number 2014/26431-0. F. von Glehn, J.K.B. Colares, B.A.L. da Fonseca, and A.C.P. de Oliveira report no disclosures. C.M. Romano received financial support from Programa de fomento as atividades de lideranças científicas dos LIMs do Hospital das Clínicas (PROFAF-LIM/HCFMUSP) #10/2020. Go to Neurology.org/NN for full disclosures.

**Publication history**

Received by *Neurology: Neuroimmunology & Neuroinflammation* January 21, 2020. Accepted in final form May 26, 2020.

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**Appendix (continued)**

| Name                           | Location                        | Contribution                                                                 |
|--------------------------------|---------------------------------|------------------------------------------------------------------------------|
| Danielle Lima Malta, PhD       | Universidade de Fortaleza       | Study concept and design, data acquisition, and critical revision of the manuscript from important intellectual content. |
| Cleonísio Leite Rodrigues, MD, PhD | Hospital Geral de Fortaleza   | Study concept and design, data acquisition, and critical revision of the manuscript from important intellectual content. |
| Alvina Clara Félix, MSc        | Universidade de São Paulo      | Data acquisition and critical revision of the manuscript from important intellectual content. |
| Claudio Sergio Pannuti, PhD    | Universidade de São Paulo      | Critical revision of the manuscript from important intellectual content.     |
| Amanda Dias da Rocha Lima, MSc | Universidade de Campinas       | Data acquisition and critical revision of the manuscript from important intellectual content. |
| Danilo Lucas Alves Espósito, PhD | Universidade de São Paulo, Ribeirão Preto | Data acquisition and critical revision of the manuscript from important intellectual content. |
| Leonilda Maria Barbosa dos Santos, PhD | Universidade de Campinas     | Data acquisition and critical revision of the manuscript from important intellectual content. |
| Felipe von Glehn, MD, PhD, FAAN | Universidade de Campinas       | Data acquisition and critical revision of the manuscript from important intellectual content. |
| Jeová Keny Baima Colares, MD, PhD | Universidade de Fortaleza     | Critical revision of the manuscript from important intellectual content.     |
| Benedito Antônio Lopes da Fonseca, MD, PhD | Universidade de São Paulo, Ribeirão Preto | Data acquisition and critical revision of the manuscript from important intellectual content. |
| Augusto César Penalva de Oliveira, MD, PhD | Instituto de Infectologia Dr. Emílio Ribas, São Paulo | Study concept and design, analysis and interpretation of the data, and critical revision of the manuscript from important intellectual content. |
| Camila Malta Romano, PhD       | Universidade de São Paulo and hospital das Clínicas, São Paulo | Study concept and design, data acquisition, analysis and interpretation of the data, and critical revision of the manuscript from important intellectual content. |
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