Diagnostic accuracy and mechanical ventilation risk in Guillain-Barré syndrome

Acurácia diagnóstica e risco de ventilação mecânica na síndrome de Guillain-Barré

Precisión diagnóstica y riesgo de ventilación mecánica en el Síndrome de Guillain-Barré

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Resumo

Introdução. A síndrome de Guillain-Barré (SGB) pode assumir variações regionais tanto em relação a antecedentes de exposição a doenças, manifestações clínicas e prognóstico. No entanto, ainda carecem evidências da heterogeneidade da SGB no Brasil. **Objetivo.** Determinar as características da SGB, incluindo fatores predisponentes, acurácia diagnóstica, risco de ventilação mecânica e comparar os resultados com outros estudos epidemiológicos regionais e internacionais. **Método.** Neste estudo transversal retrospectivo, realizamos uma busca documental de pacientes tratados com SGB. Após a avaliação da confiabilidade diagnóstica pelos Critérios de Brighton, os dados foram coletados através de revisão de prontuário por neurologistas. Comparamos o risco estimado para ventilação mecânica usando o Escore Erasmus de Insuficiência Respiratória (EGRIS) e o desfecho do paciente dentro da primeira semana. **Resultados.** Ao todo, 33 pacientes foram incluídos, com razoável acurácia diagnóstica na maioria dos pacientes (75%). 15,2% dos pacientes necessitaram de ventilação mecânica. Houve associação positiva (p=0,013) entre baixo risco e ausência de necessidade de ventilação mecânica. O gatilho imunológico mais comum foi a gastroenterite (30,3%), seguido por infecção de vias aéreas superiores (15,2%). **Conclusões.** Este estudo fornece a primeira evidência de que o EGRIS pode ser usado para identificar pacientes com baixo risco para ventilação mecânica uma amostra brasileira. Estudos prospectivos de coorte são necessários para confirmar esse achado. As características clínicas e epidemiológicas dos pacientes são consistentes com de outros estudos observacionais na América Latina, exceto pela predominância da gastroenterite como principal desencadeante imunológico, a qual também foi observada no Distrito Federal, em Lima e Bangladesh.

Unitermos. Síndrome de Guillain-Barré; Ventilação Mecânica; Causalidade

Abstract

Introduction. Guillain-Barré syndrome (GBS) can assume regional variations based on antecedent illness exposure, clinical manifestations, and prognosis. Nonetheless, evidence of GBS heterogeneity in Brazil is still lacking. **Objective.** To determine GBS characteristics including predisposing factors, diagnostic accuracy, risk of mechanical ventilation and compare the results with other regional and international epidemiological studies. **Method.** In this retrospective cross-sectional study, we conducted a documental search for patients treated for GBS. After the assessment of diagnostic reliability using Brighton Criteria, data were collected using medical record review by expert neurologists. We compared predicted risk for mechanical ventilation using the Erasmus GBS Respiratory Insufficiency Score (EGRIS) and patient observed outcome within the first week. **Results.** In all, 33 patients were included, with reasonable diagnostic accuracy in most patients (75%). 15.2% of patients required mechanical ventilation. There was a positive association (p=0.013) between non-high risk and the absence of need for mechanical ventilation. The most common immune trigger was gastroenteritis (30.3%), followed by upper airway infection (15.2%). **Conclusions.** This study provides the first evidence that EGRIS may be used to identify patients with low risk for mechanical ventilation in a Brazilian sample. Prospective cohort studies are needed to confirm this finding. Clinical and epidemiological characteristics of patients are consistent with other Latin America observational studies, except on the predominance of gastroenteritis as a major immune trigger, as also observed in Brazilian Federal District, in Lima and Bangladesh.
Keywords. Guillain-Barré Syndrome; Mechanical Ventilation; Causality

Resumen

Introducción. El síndrome de Guillain-Barré (SGB) puede asumir variaciones regionales tanto en relación a antecedentes de exposión a enfermedades, manifestaciones clínicas y prognóstico. Sin embargo, aún falta evidencia de la heterogeneidad del SGB en Brasil. **Objetivo.** Determinar las características del SGB, incluyendo factores predisponentes, precisión diagnóstica, riesgo de ventilación mecánica y comparer los resultados con otros estudios epidemiológicos regionales e internacionales. **Método.** En este studio transversal restrospectivo, realizamos una búsqueda documental de pacientes tratados con SGB. Después de la evaluación de la confiabilidad diagnóstica por los Criterios de Brighton, los datos fueron recopilados através de la revisión de registros médicos por neurólogos. Comparamos el riesgo estimado para la ventilación mecánica utilizando el puntaje de insuficiencia respiratoria de Erasmus (EGRIS) y el resultado del paciente dentro de la primera semana. **Resultados.** Se incluyeron un total de 33 pacientes, con razonable precisión diagnóstica en la mayoría de los pacientes (75%). El 15,2% de los pacientes necesitaron ventilación mecánica. Hubo asociación positive (p=0,013) entre bajo riesgo y no necesidad de ventilación mecánica. El desencadenante inmunitario más frecuente fue la gastroenteritis (30,3%), seguida de la infección de las vias respiratorias superiores (15,2%). **Conclusiones.** Este estudio proporciona la primera evidencia de que el EGRIS puede usarse para identificar pacientes com bajo riesgo de ventilación mecánica en una muestra brasileña. Se necesitan estudios de cohortes prospectivos para confirmar este hallazgo. Las características clínicas y epidemiológicas de los pacientes son consistentes con otros estudios observacionales en América Latina, except por el predominio de la gastroenteritis como principal desencadeante inmunológico, que tambíen se observe en el Distrito Federal, en Lima y Bangladesh.
Palabras clave. síndrome de Guillain-Barré; ventilación mecánica; causalidad

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INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute immune-mediated inflammatory polyradiculoneuropathy, which classically causes progressive weakness and decreased reflexes in the affected limbs[1,2]. Sensory changes, manifested as pain, numbness, and tingling, usually precede or accompany motor symptoms. The natural history of GBS occurs with progression of neurologic deficits until nadir (plateau period) which occurs in up to four weeks. After a variable period of stability, there is usually a gradual recovery of neurological functions over a few years, which can be partial or complete[3]. Mortality can reach as high as 7% even with the best medical support, and is often attributable to respiratory insufficiency and dysautonomia[4].

There are features associated with worse prognosis: diarrhea or *Campylobacter jejuni* as antecedent immune trigger, severe weakness or age of at least 40 years old on admission and mechanical ventilation within the first week of symptoms[1,4-6]. On those who survive, some degree of residual weakness and fatigue are common and may cause functional distress in daily activities, affecting quality of life[2].

The average annual incidence of GBS in a meta-analysis was 1-2 cases per 100,000 people. The male gender is an independent risk factor for GBS and the incidence increases with age. In up to three quarters of GBS cases are preceded by an immune trigger, occurring in general one to four weeks before the onset of symptoms[5]. Infectious agents that cause

upper airway infection and gastroenteritis, especially *Campylobacter jejuni* and *Mycoplasma pneumoniae* are the most established in literature, but viruses Zika, cytomegalovirus, Epstein-Barr, influenza A, rabies, enterovirus D6811, hepatitis E virus and more recently the novel coronavirus SARS-CoV-2 are also responsible for immune activation in GBS[7-9].

Despite the existence of a well-established case definition of GBS, the last decades have been showing that the syndrome might present more diversity than that previously thought, with additional findings such as localized or incomplete patterns of weakness, cranial nerve palsies, ataxia and even decreased consciousness, leading to a complementary classification that could better fit to clinical practice. This classification includes Miller-Fisher syndrome (MFS), its overlap with GBS (MFS-GBS) and MFS incomplete subforms, as well as pharyngeal-cervical-brachial weakness, paraparetic GBS, bifacial weakness with paresthesias and Bickerstaff brainstem encephalitis (BBE)[10].

A 2009 systematic review of epidemiologic studies of GBS worldwide focused on European and North American populations because few studies from other parts of the world were published at time[11]. In 2018, a large multicenter comparative study published by IGOS Consortium documented that GBS can assume significant geographical variations, e.g. antecedent illness exposure, severity of clinical manifestations and prognosis, but no Brazilian center participated in the cohort[12]. From a clinical point of view, it

is difficult to extrapolate all international data to Brazil. Even among countries on the same continent there might be significant variation, including in mortality[13].

This is the first Brazilian epidemiological study on GBS to use EGRIS score and to address the level of diagnostic accuracy using Brighton criteria[14,15]. We also aimed to describe the clinical and epidemiological characteristics of GBS including incidence, mortality, data from antecedent illness exposure and cerebrospinal fluid (CSF) profile in Barbacena´s health care region and compare with the results from other epidemiologic studies from Brazil and IGOS Consortium Latin American cohort profile.

METHOD
Sample

This is a population-based observational retrospective cross-sectional study, with a quantitative approach and general descriptive objective. We conducted a documental search using ICD tenth edition G61.0 code for patients treated for GBS and reported to Unified Health System (Sistema Único de Saúde [SUS], in Portuguese) in the fifteen cities from Barbacena´s health care region (251630 total population) between November 2014 and April 2020 (5 years and 5 months period). Eligible patients were selected for the study by expert neurologists if they met the Asbury and Cornblath diagnostic criteria for GBS or its variants[1,7,10,16] and had no alternative neurological diagnosis during the hospitalization period. Diagnostic accuracy was assessed for

epidemiological reasons using Brighton Criteria[14,15] and then classified as excellent (level 1), reasonable (level 2) or regular (level 3) according to the characteristics of the physical examination, natural evolution of the disease, alterations in cerebrospinal fluid and electrodiagnostic study (if available).

This research was approved by the Research Ethics Committee of Federal Fluminense University (approval n. 93547218.8.0000.5243) and follows the ethical standards of National Health Council of Brazil. Consent Form was obtained from all patients.

Procedure

Data were collected using medical record review through Integrated Hospital Management System (IHMS) software, regarding antecedent illness or vaccine exposure, demography, neurological symptoms and signs, time to disease nadir, prevalence, and nature of clinical complications during hospitalization, need of Intensive Care Unit (ICU) and mechanical ventilation.

To evaluate the probability of the need for mechanical ventilation within the first week of symptoms of GBS, the Erasmus GBS Respiratory Insufficiency Score (EGRIS) was assessed at patient´s admission. Patients who obtained up to two points had a low predicted risk of mechanical ventilation; with three or four points had an intermediate risk and patients with at least five points had a high risk of need for a ventilatory prosthesis[17].

The modified Rankin scale (mRS) was used to assess patient´s functional status at discharge[15]. Patients were classified with a slight disability with up to two points; three points moderate deficiency; four points moderately severe deficiency; five or six points with severe functional sequelae (including death). Clinical classification and autonomic dysfunction were left to neurologist´s decision who reviewed the medical record. Results of routine cerebrospinal fluid (CSF) examination were registered. Hyperproteinorraquia was defined by protein level as >45mg/dl and cytoalbuminological dissociation was defined as a CSF count <50 cells/µl combined with hyperproteinorraquia.

Statistical analysis

Data were analyzed by an statistician and treated using the Statistical Package for Social Sciences software (IBM SPSS) version 22.0. Categorical variables were organized and represented in graphics and tables with their respective absolute and relative frequencies. Data from CSF biochemical parameters included mean cellularity and mean protein concentration.
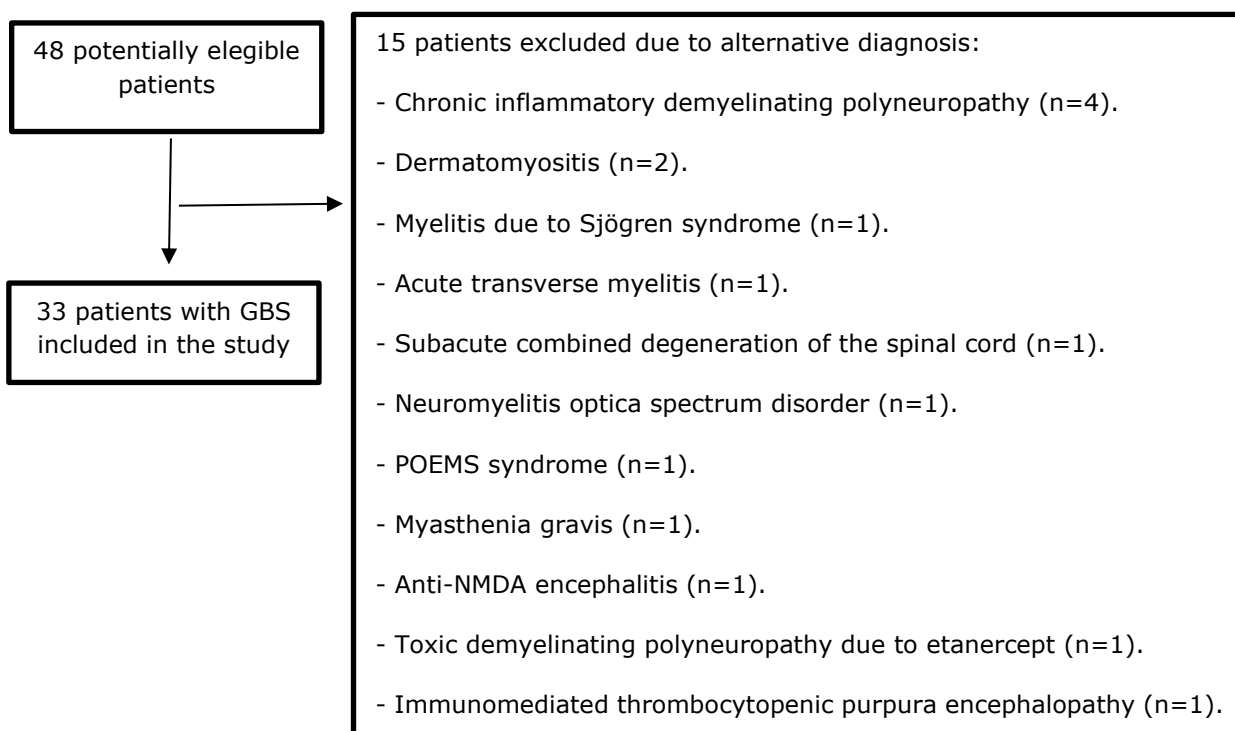
For cross-tabulation comparisons between scores evaluated at hospital admission and outcomes during hospital stay, we performed chi-squared test or Fisher test. P-values below 0.05 were considered significant. The basic comparisons conducted were among: incidence of cases in 2015-2016 biennium (the time of the outbreak of GBS in Brazil) in relation to the 2017-2018 biennium; incidence of

cases between different seasons; comparison between predicted risk at hospital admission and the need for mechanical ventilation within the first week of hospital stay.

RESULTS

A total of 48 patients were initially eligible for the research, however 15 of them were excluded due to alternative diagnosis during the hospital stay. Therefore, our study analyzed 33 patients with GBS, which were effectively included (Figure 1). All patients met the criteria for the definition of GBS case using the Brighton criteria, being 12.12% (n=4) excellent, 66.7% (n=22) reasonable and 21.18% (n=7) regular. All patients were submitted to lumbar puncture for cerebrospinal fluid analysis, and the presence of cytoalbuminological dissociation was present in 78.8% (n=26) of cases at some point during hospital stay.

Figure 1. Flow chart of the search results.

48 potentially elegible patients	15 patients excluded due to alternative diagnosis:
	- Chronic inflammatory demyelinating polyneuropathy (n=4).
	- Dermatomyositis (n=2).
	- Myelitis due to Sjögren syndrome (n=1).
	- Acute transverse myelitis (n=1).
33 patients with GBS included in the study	- Subacute combined degeneration of the spinal cord (n=1).
	- Neuromyelitis optica spectrum disorder (n=1).
	- POEMS syndrome (n=1).
	- Myasthenia gravis (n=1).
	- Anti-NMDA encephalitis (n=1).
	- Toxic demyelinating polyneuropathy due to etanercept (n=1).
	- Immunomediated thrombocytopenic purpura encephalopathy (n=1).

All patients had hyporeflexia in the affected limbs. Nearly all patients presented weakness (n=32, 97%), most of them clearly symmetrical (n=30). Weakness evolved with stabilization of progression within two weeks in 81.8% of patients, up to three weeks in 90.9% of patients and within four weeks in all patients. Neuropathic pain and facial palsy were other common signs. The list of neurological signs and symptoms in decreasing order of prevalence is presented in Table 1.

Table 1. Neurological signs and symptoms of GBS.

Sign/symptom	N (%)
Hyporeflexia	33 (100)
Weakness	32 (97.0)
Sensory sign/symptoms	24 (72.7)
Facial palsy	11 (33.3)
Dysphagia	8 (24.2)
Dysautonomia	8 (24.2)
Ataxia	6 (18.2)
Ophtalmoparesis	3 (9.1)

The age of patients with GBS ranged from 17 to 91 years old, the mean age was 51.5 years. The absolute frequency of GBS was twice as high in males (n=22, 66.7%) as compared with females (n=11, 33.3%), and there was a clear increase of cases with increasing age. The average GBS incidence coefficient calculated in the region was 1.9 per 100.000 persons-year. There was no significant difference in the incidence of GBS due to seasonality (p=0.616).

Six patients (18.2%) were admitted to the ICU, five of them needed mechanical ventilation support (15.2%). There was an association between an estimate of non-high risk (mild or intermediate) and the absence of the need for mechanical ventilation in the study population (p=0.013). All patients were treated with immunoglobulin. The mortality rate due to GBS was 6%. The rate of clinical complications during hospitalization was 48.5% (n=16), mainly infections and consequences of clinical dysautonomia.

There was a disproportionate increase in the number of cases in the 2015-2016 biennium compared to 2017-2018 biennium (p=0.041). Immune triggers were observed in 21 patients (63.6%; Table 2). Among patients with post-vaccination GBS, two were vaccinated against influenza A/H1N1, one against Yellow Fever (the oldest in the case series) and one against measles. The patient with GBS and autoimmune disease had rheumatoid arthritis. No patient presented malignancy or surgery as triggers for GBS. Only one patient had a confirmed clinical and serological diagnosis of dengue infection preceding GBS by up to four weeks. No patient had a confirmed Zika virus infection, although one of them had a suggestive clinical picture (skin rash and conjunctival hyperemia) but did not ask for medical attention at the time.

Fifteen patients (45.46%) with GBS were discharged from hospital with moderate neurological disability and thus needed external support to basic daily activities. The remaining were equally distributed between the two

extremes (27.27% for each one): nine had mild neurological deficits and nine had severe neurological disability, including two deaths.

Table 2. Profile of immune triggers.

Immune trigger	N (%)
Gastroenteritis	10 (30.3)
Infection of the upper airways	5 (15.1)
Vaccination	4 (12.1)
Pregnancy	1 (3.0)
Auto-immune disease	1 (3.0)

DISCUSSION

The average GBS incidence coefficient (1.9 per 100.000 persons-year) in Barbacena´s health care region was within the range found in well-designed international epidemiological studies (between 1-2 per 100.000 persons-year)[17], even though our study was retrospective and cross-sectional. Two epidemiologic Brazilian studies obtained lower incidence coefficients (0.3-0.54 per 100.000 persons-year). Probably this might be due to the inclusion of pediatric patients, a population in which GBS is less common[18-21]. The classic sensorimotor form of GBS was the most common (57.6%). The degree of diagnostic accuracy of GBS was excellent or reasonable in most cases (75.8%). However, about a quarter (24.2%) showed regular accuracy, which means that the diagnosis was only clinical. This may be a limitation of the study and reflects the lack of access to nerve conduction studies in the region, as only 24% of the patients

performed the exam. Despite that, all patients performed lumbar puncture to liquor analysis and the prevalence of albumin-cytological dissociation was slightly higher (78.8%) when compared to other studies (68-70%)[4,7].

Regarding patients' gender, an overall male to female ratio of 2:1 was observed. This difference was 50% greater than that found by IGOS consortium in its multicenter study (1.5:1), but which in any case points to the male gender as a risk factor[12]. In other Brazilian studies this male predominance in the number of cases was considerably lower, around 55-57% of the cases were men[19,20], except for an observational cross-sectional study that showed similar ratio (1.7:1)[21]. In a Peruvian longitudinal report with 92 patients the male/female ratio was even higher (2.4:1)[22]. The cause of this convergence of cases for males is unknown and atypical for other autoimmune conditions. Interestingly, with regard to the patient´s age, the overall mean age of the cohort was 51.5 years, very close to that of IGOS consortium (51 years)[12] .

Concerning the immune triggers events preceding GBS, the most recent literature has recognized that they are slightly more common (up to 3/4, approximately 75%) than previously thought (2/3, approximately 66%)[1,3,12,17]. In our study, the prevalence of these events was 63.6%, very close to that found in other Brazilian studies (58-63.7%)[19,20]. However, it is noteworthy an important difference in the immune trigger profile. The IGOS consortium found a higher prevalence of upper airway infections (35%) followed by

gastroenteritis (27%) in European, American and Asian countries, except in Bangladesh[12]. However, the multicentric study included only one Latin American country (Argentina). Although some Brazilian epidemiological studies until then had similar patterns of predisposing factors for GBS[19,20], there is some evidence of regional variations within Brazilian national territory. In a recent hospital-based epidemiological study in Federal District, the most common immune trigger was gastroenteritis (26%)[21]. Our study observed that the most prevalent immune trigger was, also, gastroenteritis (30.3%) followed by upper airways infection (15.2%) and vaccination (12.1%). Furthermore, these results bring us closer to what happens in Peru, where gastroenteritis is also the most common immune trigger for GBS (30.4%)[22].

Notably, in Bangladesh gastroenteritis is the most common predisposing factor for GBS, which is associated with severe motor deficit, including bulbar, less sensory symptoms, greater involvement of cranial nerves and higher mortality when compared to other countries around the world[12]. In our retrospective sample the majority (54.4%) were admitted with moderately severe weakness (four points in Hughes Severity Scale), that is, they were bedridden or wheelchair users. However, this did not result in higher bulbar weakness prevalence or higher mortality.

A statistically significant increase in the number of GBS cases in 2015-2016 was observed when compared to the expected in 2017-2018 period. Particularly, there was an epidemic of GBS associated with the Zika virus in Brazil in

this period[23-25] which caused an increase in the incidence of GBS[26]. This finding, however, should be interpreted with caution, since only one patient was suspected of having Zika infection preceding GBS. In addition, in Brazil, the cocirculation of other arboviruses, e.g. dengue and chikungunya that might be related to GBS is frequent, and this is probably a bias factor to determine a causal relationship between GBS and Zika infection[27]. As in other countries, data regarding differences in the incidence of GBS due to seasons in Brazil presents conflicting evidence[11]. However, except in two hospital-based studies which showed slight increase in GBS incidence in rainy seasons[19,21], some other Brazilian studies did not reveal significant changes, including our research[18,20].

The mortality rate due to GBS was 6%, which is also within the range of 3-10% (world average of 7%)[3,12,28]. Despite that, the prevalence of clinical complications was considered high (48,5%) and the impact of them was not evaluated prospectively after discharge. There is some evidence that patients in mechanical ventilation are in increased risk for these complications[21,29]. Some of them, as decubitus ulcers and aspiration pneumonia may be avoided with measures as decubitus repositioning and monitoring of swallowing functions[7].

This research revealed that 15.2% of the patients required mechanical ventilation and 18.2% needed intensive care, which is in line with the overall prevalence estimated in a recent consensus statement[7]. This was the first study

conducted with a Brazilian sample of patients that found that the EGRIS score may help to predict the absence of need for mechanical ventilation, as those with up to four points (low or intermediate predicted risk) statistically did not need ventilatory mechanical support within the first week of symptoms. Thus, it is reasonable, if there are no other risk factors, to consider hospitalization in the ward.

The study used well-established diagnostic criteria (Asbury and Cornblath) for GBS and validated auxiliary tools to assess diagnostic accuracy (Brighton criteria), risk of mechanical ventilation (EGRIS score) and functional status (modified Rankin Scale). To prevent bias, we used a standardized data collection form and expert neurologists excluded alternative diagnoses.

Some limitations of this study were the retrospective design and the modest sample size. Potential sources of bias in our study methodology were the possibility of existence of patients with mild GBS who were not hospitalized, and patients treated in the private health network that may not have been included in the survey.

Due to the limitations of the generalization of the findings of this research, prospective case-control or cohort studies are needed to confirm the preliminary evidence of the current investigation that gastroenteritis was the most common immune trigger for GBS in Barbacena´s health care region. Routine nerve conduction studies may evaluate whether this might be associated with axonal variants, as in Asian countries[12].

A significant disproportionate increase in the number of GBS cases in 2015-2016 was observed during Zika epidemic, but there was no clear causal relationship between GBS and Zika infection, due to the lack of ancillary investigations and the probable cocirculation of other arboviruses.

CONCLUSIONS

In this retrospective analysis of medical record review, it was observed that the cardinal clinical and epidemiological characteristics of GBS in Barbacena´s health care system (Minas Gerais, Brazil) are in line with the Americas/Europe pattern described by IGOS consortium: men are more vulnerable than women, age is a risk factor, most patients develop the classic sensorimotor GBS in addition to albumin-cytological dissociation. However, unlike other studies, gastroenteritis was a more prevalent immune trigger, followed by upper airways infection and vaccination.

This is the first preliminary evidence in Brazilian patients that EGRIS may be used as an auxiliary tool to predict which patients will not need mechanical ventilation within the first week of admission (up to four points in the score). Further prospective studies are needed to confirm these associations.

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REFERENCES

1.Willison HJ, Jacobs BC, Doorn PA Van. Guillain-Barré syndrome. Lancet 2016;388:717-27. https://doi.org/10.1016/S0140-6736(16)00339-1

2.Wijdicks EFM, Klein CJ. Guillain-Barré Syndrome. Mayo Clin Proc 2017;92:467-79. https://doi.org/10.1016/j.mayocp.2016.12.002

3.Donofrio PD. Guillain-Barré Syndrome. Contin (Minneap Minn) 2017;23:1295-309. https://doi.org/10.1212/CON.0000000000000513

4.Van Den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, Van Doorn PA. Guillain-Barré syndrome: Pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol 2014;10:469-82. https://doi.org/10.1038/nrneurol.2014.121

5.Esposito S, Longo MR. Autoimmunity Reviews Guillain – Barré syndrome. Autoimmun Rev 2017;16:96-101. http://doi.org/10.1016/j.autrev.2016.09.022

6.Walgaard C, Lingsma HF, Ruts L, Van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barré syndrome. Neurology 2011;76:968-75. https://doi.org/10.1212/WNL.0b013e3182104407

7.Leonhard SE, Mandarakas MR, Gondim FAA, Bateman K, Ferreira MLB, Cornblath DR, et al. Diagnosis and management of Guillain–Barré syndrome in ten steps. Nat Rev Neurol 2019;15:671-83. https://doi.org/10.1038/s41582-019-0250-9

8.Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, *et al*. Guillain-Barré Syndrome Associated with SARS-CoV-2. N Engl J Med 2020;382:2574-6. https://doi.org/10.1056/NEJMc2009191

9.Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020;19:383-4. https://doi.org/10.1016/S1474-4422(20)30109-5

10.Wakerley BR, Uncini A, Yuki N. Guillain-Barré and miller fisher syndromes - New diagnostic classification. Nat Rev Neurol 2014;10:537-44. https://doi.org10.1038/nrneurol.2014.138

11.McGrogan A, Madle GC, Seaman HE, De Vries CS. The epidemiology of Guillain-Barré syndrome worldwide: A systematic literature review. Neuroepidemiology 2009;32:150-63. https://doi.org/10.1159/000184748

12.Doets AY, Verboon C, van den Berg B, Harbo T, Cornblath DR, Willison HJ, *et al*. Regional variation of Guillain-Barré syndrome. Brain 2018;141:2866-77. https://doi.org/10.1093/brain/awy232

13.Wong AHY, Umapathi T, Shahrizaila N, Chan YC, Kokubun N, Fong MK, *et al*. The value of comparing mortality of Guillain-Barré syndrome across different regions. J Neurol Sci 2014;344:60-2.

https://doi.org/10.1016/j.jns.2014.06.021

14. Fokke C, Van Den Berg B, Drenthen J, Walgaard C, Van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain 2014;137:33-43. https://doi.org/10.1093/brain/awt285

15. Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, *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. https://doi.org/10.1016/j.vaccine.2010.06.003

16. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27:S21-4. https://doi.org/10.1002/ana.410270707

17. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: A systematic review and meta-analysis. Neuroepidemiology 2011;36:123-33. https://doi.org/10.1159/000324710

18. Dias-Tosta E, Kückelhaus CS. Guillain barré syndrome in a population less than 15 years old in Brazil. Arq Neuropsiquiatr 2002;60:367-73. https://doi.org/10.1590/S0004-282X2002000300005

19. Guimarães Rocha MS, Dozzi Brucki SM, De Siqueira Carvalho AA, Poti Lima ÚW. Epidemiologic features of Guillain-Barré syndrome in São Paulo, Brazil. Arq Neuropsiquiatr 2004;62:33-7. https://doi.org/10.1590/s0004-282x2004000100006

20. Dourado ME, Félix RH, da Silva WKA, Queiroz JW, Jeronimo SMB. Clinical characteristics of Guillain-Barré syndrome in a tropical country: A Brazilian experience. Acta Neurol Scand 2012;125:47-53. https://doi.org/10.1111/j.1600-0404.2011.01503.x

21. Oliveira DRCAB, Fernandez RNM, Grippe TC, Baião FS, Duarte RL, Fernandez DJ. Epidemiological and clinical aspects of Guillain-Barré syndrome and its variants. Arq Neuropsiquiatr 2021;79:497-503. https://doi.org/10.1590/0004-282X-ANP-2020-0314

22. Velásquez-Rimachi V, López-Saavedra AV, Rodriguez-López E, Elguera-Huaman H, Meza K, Alva-Díaz C, *et al.* Clinical-epidemiological characteristics associated with discharge outcomes and seasonality among surviving patients with Guillain-Barré syndrome in a national third-level Hospital, Lima, Perú. Arq Neuropsiquiatr 2021;79:697-704. https://doi.org/10.1590/0004-282X-ANP-2020-0154

23. Styczynski AR, Malta JMAS, Krow-Lucal ER, Percio J, Nóbrega ME, Vargas A, *et al*. Increased rates of Guillain-Barré syndrome associated with Zika virus outbreak in the Salvador metropolitan area, Brazil. PLoS Negl Trop Dis 2017;11:1-13. https://doi.org/10.1371/journal.pntd.0005869

24. Araujo LM, Ferreira MLB, Nascimento OJM. Síndrome de Guillain-Barré associada ao surto de infecção por vírus Zika no Brasil. Arq Neuropsiquiatr 2016;74:253-5. https://doi.org/10.1590/0004-282X20160035

25. Angelo JR, Fuller TL, Leandro BBS, Praça HLF, Marques RD, Ferreira

JMC, *et al*. Neurological complications associated with emerging viruses in Brazil. Int J Gynecol Obstet 2020;148:70-5. https://doi.org/10.1002/ijgo.13050

26.Leonhard SE, Conde RM, Gondim FAA, Jacobs BC. Diagnosis and treatment of Guillain-Barré syndrome during the Zika virus epidemic in Brazil: A national survey study. J Peripher Nerv Syst 2019;24:340-7. https://doi.org/10.1111/jns.12358

27.Keesen TSL, Almeida RP, Gois BM, Peixoto RF, Pachá ASC, Vieira FCF, *et al*. Guillain-Barré syndrome and arboviral infection in Brazil. Lancet 2017;17:693-4. https://doi.org/10.1016/S1473-3099(17)30333-X

28.Vucic S, Kiernan MC, Cornblath DR. Guillain-Barré syndrome: An update. J Clin Neurosci 2009;16:733-41. https://doi.org/10.1016/j.jocn.2008.08.033

29.Walgaard C, Lingsma HF, Ruts L, Van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barré syndrome. Neurology 2011;76:968-75. https://doi.org/10.1212/WNL.0b013e3182104407