ORIGINAL ARTICLE

DISEASE PROGRESSION VELOCITY AS PREDICTOR OF SEVERITY IN GUILLAIN-BARRE SYNDROME

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ABSTRACT

Objective: To identify the velocity of disease progression as a predictor of severity in patients with Guillain-Barre syndrome (GBS). **Materials and methods**: Prospective observational study of patients with confirmed diagnosis of GBS between May and August 2019 in four hospitals in Peru. The disease progression velocity (DPV) was defined as the time since the onset of neurological symptoms and the maximum peak of neurological severity. **Results**: Of 94 cases with GBS, the average age was 42 years; 73 (77.8%) patients presented severe GBS, the average hospital stay was 19 days; 45 (47.8%) patients had diarrheal symptoms previously, in 63 (67.1%) patients the onset of motor weakness was located in the upper limbs and in 31 (32.9%) it was located in the lower limbs, 9 (10.0%) patients presented some type of dysautonomy; admission to mechanical ventilation was needed in 8 (8.5%) patients, and the deceased were 2 (2.0%). The DPV ≤ 1 day has a 79% probability of developing severe disease, the two and three day DPV have the probability of 61% and 38% respectively of progressing to severe forms. **Conclusion**: DPV is a predictor of poor prognosis when it is less than 2 days and with a possible requirement for mechanical ventilation. The speed of progression of neurological disease is a practical and accessible clinical evaluation method that should be evaluated in patients with GBS.

Keywords: Guillain-Barre Syndrome; Prognosis; Severity of Illness Index; Disease Progression (Source: MeSH NLM).

Cite as: Montalvo R, Castañeda A, López JA, Mathey C. Velocidad de progresión de la enfermedad como predictor de severidad en el síndrome de Guillain-Barré. Rev Peru Med Exp Salud Publica. 2021;38(1):17-23. doi: https://doi.org/10.17843/rpmesp.2021.381.5106.

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Received: 17/01/2020
Approved: 04/11/2020
Online: 28/12/2021

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuropathy of autoimmune etiology, of worldwide distribution, generally triggered by infectious agents [1] and characterized by a progressive decrease in muscle strength and osteotendinous reflexes [2]. The overall incidence varies between 0.8 and 3 cases per 100,000 persons [3,4], the reported mortality rate varies between 3% and 7% and case fatality ranges from 3% to 20% [5,6]. In Peru, an epidemiological study of GBS cases showed that the overall case fatality was 3.5% and this figure was higher in older men [7].

People who die from GBS previously develop severe disease characterized by the absence of motor response from the four limbs, respiratory failure requiring mechanical ventilation, dysautonomia phenomena manifested by tachycardia, bradycardia, insomnia, anxiety, palpitations, orthostatic hypotension and syncope [8]. The known factors that condition severi-

ty are: age over 60 years, inadequate diagnosis and delay in receiving medical treatment [9,10]. However, there are some little studied clinical factors such as the velocity of neurological deterioration that could be related to the severity of the disease.

The aim of this study was to identify the velocity of disease progression as a predictor of severity in patients with GBS. In addition, the clinical and laboratory characteristics of the patients were described in an exploratory manner, according to their epidemiological history.

KEY MESSAGES

Motivation for the study: Guillain-Barré syndrome can cause severe complications, so it is relevant to identify predictors of severity; the most important is the disease progression velocity (DPV), defined as the time from the onset of weakness to the maximum peak of neurological severity.

Main findings: Patients with an DPV ≤ 1 day had 80% chance of developing severe disease, those with an DPV ≤ 2 days had 61% chance of progressing to severe forms.

Implications: DPV is a predictor of poor prognosis and of possible requirement of mechanical ventilation by patients, which should be included in the anamnesis.

MATERIALS AND METHODS

Type of study and population

This prospective observational study was conducted to consecutively enroll patients diagnosed with GBS. Participants were recruited from four Peruvian hospitals: Hospital Daniel Alcides Carrión de Huancayo (regional hospital specialized in the care of adults in clinical and surgical diseases), Hospital Regional Materno Infantil El Carmen (specialized in the care of pathologies in pediatric and maternal population), Hospital Nacional Ramiro Prialé Prialé (general care) and Hospital Víctor Lazarte Echegaray - EsSalud de La Libertad (general care) from May to August 2019.

Patients diagnosed with GBS were included, as defined by the Brighton criteria [11], which includes data on clinical presentation, cerebrospinal fluid (CSF) laboratory results and electrophysiological findings; cases that did not meet these criteria were not included in the study; patients were of any age and sex. Reviews of patients and laboratory results were performed periodically until hospital discharge. Data collected were obtained using a previously established data extraction form that included demographic data, disease history, neurological physical examination, laboratory results, electromyography study, and hospital discharge status. The Hughes disability score was calculated at admission and discharge to define disease severity [12]. Patients were followed up until hospital discharge or death.

Variables

The variable of interest was the disease progression velocity (DPV), estimated by the difference in days between the onset of symptoms and the maximum peak of neurological severity, for which the milestones were considered to be the day on which the patient was admitted to mechanical ventilation, the day on which the progression of the disease was halted, or the day on which the patient died before being admitted to mechanical ventilation.

Other variables of interest were age, sex, comorbidity, gestation, hematology laboratory results, CSF results, and clinical characteristics at admission. Data were obtained from the interview, from the physical examination performed by the investigators on patients with progressive motor weakness and decreased osteotendinous reflexes, and from the laboratory results obtained from the medical records of patients with GBS.

Statistical analysis

Microsoft Excel for Windows was used for the double data entry process, and the statistical program Stata version 12 (STATA Corp, College Station, TX, USA) was used for the analysis. The statistical analysis was performed with a description of the demographic and clinical characteristics, which were tabulated according to the Hughes scale. Categorical variables were compared using the Chi-square test or Fisher's exact test, while numerical variables were compared using Student's t-test. Likewise, mean DPV, the mean of hemogram results, mean CSF and blood gas results were calculated for each group according to GBS severity.

For the multivariate analysis, the following were considered as independent variables: age in years, sex, clinical and demographic characteristics, history of previous disease, hematological, biochemical, arterial gas and CSF results. The variables that showed significant association in the bivariate analysis and included in the model were CO_2 pressure, bicipital arreflexia, velocity of disease progression, monocytosis in the hemogram, age and sex, which were categorized ac-

https://doi.org/10.17843/rpmesp.2021.381.5106

cording to previous studies and referenced values [9-10]. During the multiple multivariate analysis, the Hughes scale (> 3 as the cut-off point for the determination of the severity of GBS) was considered as a dependent variable. Relative risks (RR) were calculated with 95% confidence intervals (95% CI) and a value of $p < 0.05$ was considered to indicate statistical significance.

To evaluate the probability of developing severe GBS according to DPV, we estimated DPV cut-off points by using ROC curves, determined the probability of developing severe disease according to each DPV cut-off point measured in days, and obtained the best DPV cut-off point. We used the *roctab* command of Stata 12 (StataCorp, College Station, Texas, USA) to evaluate the ability to predict SGB severity.

Ethical Aspects

The research ethics committees of the Hospital Daniel Alcides Carrión (Exp. N°: 379-19) and the Hospital Nacional Ramiro Prialé (Exp. N°: 143-19) approved the study. Likewise, all hospitals authorized the use of patient information. Finally, the research was conducted in compliance with internationally required ethical standards, respecting patient confidentiality.

RESULTS

Of 121 patients who entered the study, 27 (22%) were lost during follow-up due to the following: voluntary discharge in 9 (0.7%) patients; 11 (0.9%) were referred to another public or private hospital center; and 7 (0.6%) were diagnosed with another disease during hospital follow-up, such as encephalitis, infectious polyneuropathy or cerebrovascular disease. Finally, 94 cases with GBS were evaluated; mean age of the patients was 42 years (range 8-73); 77.8% presented severe GBS (Hughes scale >3); 64 (68%) were male; mean hospital stay was 19 days (range 1-129). The average time of illness at admission was 4 days; 12 (12.8%) patients had some comorbidity; 3% received some type of vaccination in the last month before admission; the average body mass index (BMI) was 26.4 (Table 1).

Infectious symptoms prior to muscle weakness were present in 71 (81%) patients with GBS, of whom 45 (47.8%) had diarrhea and 22 (23.4%) had a flu-like syndrome (Table 1). The duration of these symptoms averaged 3 days. The average time between the onset of these symptoms and the onset of motor weakness was 5 days (range 1-21).

The site of the onset of motor weakness in the upper limbs was evident in 63 (67.1%) patients and 31 (32.9%) patients started with weakness in the lower limbs (Table 1). The distribution by site of onset of weakness was not significantly different when compared with GBS severity ($p = 0.121$).

The pharmacological treatment administered was immunoglobulin in 86 (91.0%) patients and plasmapheresis in 6 (7.0%) patients (Table 1). The mean Hughes scale at hospital discharge was 2 (range 0-5). Regarding complications, 9 (10.0%) patients presented some type of dysautonomia. Admission to mechanical ventilation was necessary for 8 (8.5%) patients.

CSF analysis did not show results associated with GBS severity (Table 2); the values of carbon dioxide pressure (PCO_2) evidenced in arterial gas analysis and monocyte count in hemogram were higher in severe GBS ($p = 0.001$ and $p = 0.023$, respectively).

In the multivariate analysis, DPV for more than 3 days behaved as a protective factor for not developing severe disease (RR = 0.27; 95%CI: 0.07 - 0.95; p value = 0.041) (Table 3). Likewise, it is evident that the lower the DPV value, the greater the probability that the disease will become more severe (Table 4).

DISCUSION

This study identified that the most important factor that conditions the course of severe disease in GBS is DPV. The scale used to determine the degree of severity was the Hughes scale [12]. This study showed that 78% of patients with GBS were admitted in wheelchair or bedridden (Hughes >3), this percentage of severity was similar to the data obtained by Yosria *et al.* [13] and Parmar *et al.* [14] who reported that the majority of patients seen with GBS had grade ≥ IV, with 75% and 83.7% respectively. These authors explain that the reason for the high frequency of disease severity was the delay in treatment administration. This study confirmed that the velocity of weakness progression is associated with severity, showing that patients with DPV less than or equal to one day have about 80% probability of developing severe disease.

The average DPV was three days in patients with severe GBS, similar to a study [15], that also found elevated concentrations of antibodies against gangliosides GM1, GD1a, GalNac-GD1a and Gd1b in peripheral nerve axons, these antibodies can be induced by infectious agents such as Campylobacter jejuni [16], which produce damage in the myelin sheath segment and to the proximal nerve root [6].

Table 1. General characteristics of patients with Guillain-Barré syndrome.

General characteristics	n = 94	%	Distribution of patients according to Hughes scale		p Value
			Hughes ≤3 n (%)	Hughes >3 n (%)	
Age: average in years (range)	42	(8-73)	41 (10-81)	42 (8-73)	0.972
<40	36	38.0	11 (52.4)	25 (34.3)	0.033
40-59	45	48.0	5 (23.8)	40 (54.8)	
>59	13	14.0	5 (23.8)	8 (10.9)	
Sex: male	64	68.0	9 (42.9)	55 (75.4)	0.008
Hospital stay: average (range)	18.4	(1-129)	10.3 (1-24)	22.5 (1-129)	0.110
Time of illness: average (range) [a]	4	(1-8)	4 (1-8)	3 (0.5-7)	0.077
Comorbidities	12	12.8	3 (10.4)	9 (12.5)	0.527
Previous vaccination	3	3.3	1 (4.7)	2 (2.7)	0.091
BMI: mean (range)	26.4	(18-45)	25 (18-31)	26 (19-45)	0.242
<18.5	3	3.2	3 (14.3)	0 (0.0)	0.276
18.5 – 24.9	28	29.8	6 (28.6)	22 (30.1)	
25 – 29.9	47	50.0	10 (50.0)	37 (50.7)	
≥30	16	17.0	2 (7.1)	14(19.2)	
Previous symptoms [b]					
Diarrhea	45	47.8	12 (57)	33(47)	0.303
Flu syndrome	22	23.4	3 (14)	19 (26)	
Fever	4	4.3	2 (10)	2 (3)	
None	18	19.2	4 (19)	14 (19)	
Duration of symptoms: mean (range)	3.3	(1-10)	4.6 (1-10)	3 (1-7)	0.062
Days between symptom onset and weakness: mean (range)	5	(1-21)	5.7 (1-15)	4.2 (0-21)	0.237
Type of areflexia					
Patellar areflexia	16	17.1	8 (38.1)	8 (10.9)	0.003
Bicipital areflexia	14	14.9	4 (19.1)	10 (13.7)	
Patellar and bicipital areflexia	37	39.4	4 (19.1)	33 (45.3)	
Other types of areflexia	27	28.6	5 (23.7)	22 (30.1)	
Type of polyneuropathy					
Motor	59	62.7	17 (94.4)	42 (87.5)	0.660
Motor and sensitive	7	7.5	1 (5.6)	6 (12.5)	
Disease progression velocity (DPV): mean (range) [c]	3.6	(1-9)	5 (1-9)	3 (0.5-7)	0.006
Place of origin					
Lower limbs	31	32.9	10 (47.6)	21 (28.8)	0.121
Upper limbs	63	67.1	11 (52.4)	52 (71.2)	
Hughes scale at admission: mean (range)	3	(1-5)	1.7 (1-2)	3.4 (2-5)	<0.01
Treatment					
Immunoglobulin	86	91.0	19 (90.5)	67 (91.8)	0.024
Plasmapheresis	6	7.0	0	6 (8.2)	
None	2	2.0	2 (9.5)	0	
Hospital discharge					
Deceased	2	2.0	0	2 (2.7)	0.58
Hughes scale at discharge: mean (range)	2	(0-5)	1.4 (1-2)	2.5 (1-5)	0.003
Complications					
Dysautonomia	9	10.0	0	9 (12.3)	0.034
Mechanical ventilation [d]	8	8.5	0	8 (10.9)	0.192

[a] Days between the onset of weakness and hospital admission. [b] Five patients presented nonspecific symptoms such as general malaise, hyporexia, headache, abdominal pain. [c] Time in days from the onset of weakness and the maximum peak of neurological severity (DPV). [d] Two patients continued on ventilator until the end of the study period.
BMI: body mass index.

https://doi.org/10.17843/rpmesp.2021.381.5106

Table 2. Comparison of laboratory parameters at hospital admission of patients with Guillain-Barré syndrome.

Parameters	Mean (range)	Hughes ≤3 Mean (range)	Hughes >3 Mean (range)	p Value [b]
LCR[a]				
Leucocytes (mm^3)	7.9 (0-47)	6.1 (0-43)	8.7 (0-47)	0.572
Polymorphonuclears (%)	13.4 (0-30)	3.3 (0-30)	5.1 (15-30)	0.554
Mononuclears (%)	89.4 (0-100)	76.8 (0-100)	95.1 (70-100)	0.051
Adenosine deaminase (U/L)	8 (4-11,7)	7.4 (4-10)	7.8 (4-11.7)	0.744
Proteins (mg/dL)	52 (10-193)	43.7 (10-119)	56 (10-193)	0.383
Glucose (mg/dL)	54.5(41-74)	54.6 (46-74)	54.5 (41-72)	0.971
Hemogram at admission				
Leucocytes (mm^3)	8,124.9 (3,060-17,100)	7,089 (5,030-10,600)	8,320 (3,060-17,100)	0.143
Neutrophils (mm^3)	5,381.8 (440-13,950)	4,957(2,820-7,150)	5,311(440-13,950)	0.714
Eosinophils (mm^3)	128.6 (0-910)	106 (0-248)	134 (0-910)	0.551
Basophils (mm^3)	67.6 (0-910)	53.3 (0-560)	73.8 (0-910)	0.612
Monocytes (mm^3)	463.8 (0-1,539)	364 (82-636)	484 (40-850)	0.023
Lymphocytes (mm^3)	2,097.3 (154-3,920)	2049 (390-3,286)	2,135 (154-3,920)	0.753
Band neutrophils (mm^3)	53.2 (0-1368)	18 (14-150)	63.3 (0-1,368)	0.413
Platelets (mm^3)	336,682.5 (170,000-501,000)	299,500 (192,000-395,000)	289,425 (170,000-501,000)	0.662
Gasometry and biochemistry				
PO_2 (mmHg)	69.2 (51-85.9)	73.2 (72-74.4)	69.2 (51-85.9)	0.524
PCO_2 (mmHg)	30.3 (20-39.3)	38.9 (25.7-44)	30.8 (21.7-39.3)	0.001
FiO_2 (%)	22.9 (21-50)	21 (21-21)	23.1 (24-50)	0.663
Sodium (mmol/L)	139.3 (132-148)	135 (132-138)	139 (133-148	0.131
Calcium (mmol/L)	1.2 (0,9-1,85)	1.2 (1.1-1.19)	1.2 (0.9-1.85)	0.812
Lactate dehydrogenase (U/L)	370.4 (42,4-900)	115 (42.4-188)	370 (351-900)	0.213
Transaminase (GOT U/L)	45.2 (14-170)	26.7 (25.2-27.8)	50.3 (14-170)	0.390
Transaminase (GPT U/L)	65.1 (16-313)	27.3 (24-30.5)	72.2 (16-313)	0.511
Urea (mg/dL)	32.3	26,1 (19.3-31)	32.2 (20.6-84.6)	0.183
Creatinine (mg/dL)	0.9	0.8 (0.59- 0.96)	0.9 (0.14-1.29	0.324
Total proteins (g/dL)	7.4	7.2 (6.3-7.9)	7.6 (5.9-10.1)	0.532
Glucose (mg/dL)	94.8	96.4 (81-123)	94.2 (71-139)	0.764
CRP (mg/dL)	24.7 (0.23-96)	14.4 (0.23-62)	34.7 (3-96)	0.481

[a] Mean of CSF results taken on day 7 of illness. [b] Student's t-test was used to calculate the p value.
CSF: cerebrospinal fluid; CRP: C-reactive protein; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; FiO2: inhaled fraction of oxygen; PO2: partial pressure of oxygen measured in mmHg.

Several studies agree that severe cases of GBS can occur at any age and regardless of sex [15]. Although other studies indicate that GBS is more frequent in men and with an average age ranging from 32 to 44 years [17-18], similar findings have been evidenced in our study, where 68% of those affected were male and the average age was 42 years; however, these two characteristics were not associated with the severity of the disease.

According to the study by Mao *et al.* [19] the case fatality rate for GBS is 6%, according to the findings from our study the case fatality rate was 2%, much lower than that found in other studies, this low rate could be due to the typical form of presentation. The causes of death were related to delayed admission to mechanical ventilator or prolonged exposure to mechanical ventilator. In this study, 2 patients died, one of them was admitted in poor general condition and died on the first day of hospitalization due to delayed admission to mechanical ventilator and the second due to infectious complications caused by pan-resistant *Acinetobacter baumanni* due to prolonged use of mechanical ventilator on day 112 of hospitalization.

The most frequent complication was the presence of dysautonomia which was evident in 19% of patients with

Table 3. Predictors of severity in patients with Guillain-Barré syndrome.

Variable	Crude model	p Value	Multivariate model [a]	p Value
	RR (95% CI)		RR (95% CI)	
CO_2 pressure (mmHg)*				
<32	Reference		Reference	
≥32	0.61 (0.31 to 0.96)	0.011	0.58 (0.34 to 1.00)	0.050
Bicipital reflex				
Present	Reference		Reference	
Absent	4.93 (1.01 to 29.7)	0.037	4.69 (0.78 to 28.0)	0.091
Velocity of progression (days)				
≤3	Reference		Reference	
>3	0.39 (0.06 to 0.91)	0.002	0.27 (0.07 to 0.95)	0.041
Monocytes (/mL)				
≤500	Reference		Reference	
>500	1.17 (1.01 to 1.33)	0.023	1.01 (0.98 to 1.01)	0.082
Sex				
Male	Reference		Reference	
Female	0.08 (-16.91 to 5.01)	0.084	0.03 (-17.10 to 5.32)	0.303
Age (years)				
≥60	Reference		Reference	
<60	0.98 (-2.91 to 2.02)	0.972	0.97 (-3.28 to 1.33)	0.407

a Adjusted for comorbidity, treatment and place of onset of weakness.
RR, relative risk; 95% CI, 95% confidence interval.

severe GBS. There are other clinical and laboratory characteristics in patients with severe GBS such as bicipital areflexia, PCO_2 values > 30 and monocytes > 490, but which were not significantly higher in the group of patients with severe GBS when the multivariate analysis was performed.

The findings of the CSF evaluation found normal or slightly elevated lymphocytes < 50 cells/mm3 and that protein levels were elevated from the first week of illness, this shows in more than 90% of those affected by GBS [20]. This study shows the results of CSF analysis at the first week of admission; the average CSF protein values were 52 mg/dL and albumin-cytologic dissociation was seen in 90% of cases. The elevation of CSF protein is due to increased antibody deposits, complements and myelin products upon breakdown, while the level of IgG and anti-ganglioside antibodies are related to the prognosis of the disease [21].

Table 4. Probability of developing severe Guillain-Barré syndrome according to disease progression velocity.

Disease progression velocity (days)	Probability of developing severe disease	95% CI
≤1	0.79	0.64-0.89
2	0.61	0.45-0.74
3	0.38	0.25-0.53
4	0.20	0.10-0.33
5	0.06	0.02-0.17
6	0.04	0.01-0.14

95% CI: 95% confidence intervals

The velocity of neurological disease progression is a practical and accessible evaluation method that should be considered by physicians and included in GBS severity prediction scales. In this study, we observed that when the value is equal to or less than one day, the probability of the patient developing the severe form is approximately 80% and this probability is reduced to 60% if it is two days, behaving as a predictor of poor prognosis when the DPV is less than two days and with possible requirement of mechanical ventilation.

The strength of this study lies in the nature of longitudinal data collection to assess the velocity of disease progression as a predictor of GBS severity. However, this study has some limitations. First, the losses of patients during the months of follow-up that accounted for more than 20%; thus, it is necessary to find out what happened to those lost patients to assess the nature of the final outcome, deceased or recovered. Second, there are some data that were not explored in depth, such as the elec-

https://doi.org/10.17843/rpmesp.2021.381.5106

tromyography study, due to the lack of equipment to perform this evaluation in some hospitals or due to the high demand for this equipment during the period of the GBS outbreak. Finally, although we presented a strong correlation between DPV and severity of GBS, our findings should be verified with a prospective study with a larger number of patients including serological analysis of inflammatory markers.

The results of our study support the hypothesis that, in patients with GBS, neurological DPV should be assessed and that a duration of less than two days was found to be associated with a high probability of severe disease, thus reflecting the impact of DPV on severity and its possible usefulness as a prognostic marker.

Author contributions: RM, AC, JL, and CM participated in the conception of the article, data collection, data analysis and interpretation, drafting and critical revision of the manuscript, and approval of the final version. All authors are responsible for the content of the article.

Funding: Self-funded.

Conflicts of interest: There are no conflicts of interest for the publication of the article.

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