Guillain-Barré syndrome in Mexico: clinical features and validation of Brighton Collaboration Group criteria

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Introduction. As SARS-CoV-2 vaccination is ongoing in Mexico and Guillain-Barré syndrome (GBS) cases have been reported, validation of Brighton criteria in Mexico is necessary. Moreover, epidemiology of GBS in Mexico differs from European and North American countries.

Objective. To describe the clinical, cerebrospinal and electrodiagnostic features in Mexican patients diagnosed with GBS and classify them according to the Brighton Collaboration Group diagnostic criteria.

Patrients and methods. An ambispective cohort study was conducted. We included patients that fulfilled the National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria for Guillain-Barré syndrome. Patients in this study were classified according to Brighton collaboration group levels of certainty for Guillain-Barré syndrome.

Results. Sixty eight percent of patients were male. Of the 248 patients included, 58.4% had history of a precedent infection, mean time from symptom onset to admission was 5 (1-30) days. Mean Medical Research Council sum score 30.3 ± 15.5. Almost 98% of patients had a monophasic course. Level 1 of certainty according to Brighton collaboration group criteria was fulfilled by 54.6% of patients, level 2 by 45% and level 4 by 0.6%. Patients meeting level 2 of certainty were mostly because normal cerebrospinal fluid findings or findings in nerve conduction studies not consistent with any GBS variants.

Conclusion. GBS is a frequent autoimmune neuropathy that has been associated with preceding infections and with vaccination campaigns. For SARS-CoV-2 vaccination campaign in Mexico, validation of Brighton Criteria is necessary. Although Mexico's GBS epidemiology has been changing throughout recent years, this study provides similar data compared to other countries.

Key words. Autoimmune. Brighton criteria. Guillain-Barré syndrome. Mexico. Polyneuropathy. Validation.

Introduction

Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis worldwide [1]. Currently, there is a misconception that GBS is a purely benign disease, as 20% of patients are unable to walk independently at 6 months and 5% die [2].

The first GBS diagnostic criteria were proposed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) in 1978 as a response to increasing frequency of GBS in persons vaccinated against a swine origin Influenza virus [3]. These criteria were reevaluated by Asbury and colleagues in 1990, until the Brighton Collaboration group proposed diagnostic criteria based on clinical features, cerebrospinal fluid (CSF) analysis, and electrophysiologic and further classified findings into certainty levels [4]. These new criteria were proposed in response to increased frequency of GBS during H1N1 swine flu vaccination campaign. These new Brighton case definitions have already been validated in Netherlands [5], Bangladesh [6], Malaysia [7], Denmark [8], Iran [9], Japan [10], and India [11].

As SARS-CoV-2 vaccination is ongoing in Mexico and GBS cases have been reported, validation of Brighton criteria in Mexico is necessary. Moreover, epidemiology of GBS in Mexico differs from European and North American countries. The objective of the current study is to describe the clinical, CSF and electrodiagnostic characteristics in Mexican population diagnosed with GBS and classify them according to the Brighton Collaboration Group diagnostic criteria.

Patients and methods

Patients

This study was based on an ambispective cohort of 248 patients admitted to the National Institute of Neurology and Neurosurgery in Mexico City between January 2016 and August 2021. We included patients that fulfilled the National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria for Guillain-Barré syndrome and were evaluated by a neurologist. We included patients who were unable to walk independently, who had a rapid progression of weakness, respiratory insufficiency, or those with severe autonomic or swallowing dysfunction. We also included patients with mild weakness who were still progressing and were admitted for observation. We excluded patients < 18 years of age, Miller-Fisher diagnosis, Bickerstaff brainstem encephalitis diagnosis, chronic inflammatory demyelinating polyneuropathy or patients with a previous Guillain-Barré syndrome episode.

We collected clinical and demographical data using a standardized protocol that includes age, gender, time of onset of symptoms at diagnosis, history of precedent infection, cranial nerve involvement, autonomic dysfunction, and type of treatment. Weakness was assessed by the Medical Research Council (MRC) scoring system at diagnosis and nadir, ranging from 0 to 60 [12]. Nadir was defined as the time with the greatest GBS disability score or lowest MRC sum score. Clinical severity was evaluated by the GBS disability scale (GDS), ranging from 0 (normal) to 6 (death) [13]. Weakness was also classified as symmetrical and asymmetrical. Symmetrical weakness was defined as a difference of five or less in MRC sum scores between left and right limbs.

Duration of the plateau phase was defined as the number of days between nadir and improvement of five or more points in MRC sum score or one or more points in Guillain-Barre syndrome disability score. Treatment-related fluctuations were defined as a GDS score change of 1 or more occurring within 8 weeks after start of treatment after improvement or stabilization [14].

The presence of autonomic dysfunction was recorded at any point during the patient's evolution and was defined as variability in heart rate or blood pressure not explained by other causes. The type of treatment that each patient received was defined by a neurologist depending on treatment availability and patients' comorbidities. Patients received whether intravenous immunoglobulin (IVIG) 2 g/kg on 5 consecutive days or plasma exchange (PE) 200 mL/kg for 5 sessions on alternate days.

Cerebrospinal fluid was collected at admission and a protein level ≤ 45 mg/dL, cell count ≤ 5 cells/μL, and glucose ≥ two-thirds of serum glucose or within normal ranges was categorized as normal. Protein-cytological dissociation was defined as the presence of protein elevation > 45mg/dL with a CSF cell count ≤ 50 cells/μL. Also, CSF cell count ≥ 5 cells/μL was considered as pleocytosis. Nerve conduction studies were performed by an experienced neurophysiologist and defined as axonal, demyelinating, equivocal, inexcitable and normal according to Hadden's electrophysiologic criteria [15].

Patients in this study were classified according to Brighton collaboration group criteria for Guillain-Barré syndrome (Table I). The study was approved by our local ethics committee, and all patients provided an informed written consent.

Statistical analysis

For the descriptive analysis, the distribution of continuous variables was determined with the Kolmogorov-Smirnov test. Variables were described as means and standard deviation (SD) if normally distributed or medians and interquartile ranges if not normally distributed. Categorical variables were described as frequencies and percentages. To look for differences between groups, Student's *t* test was used to compare means, and the Mann-Whitney U test to compare medians. A value of $p < 0.05$ was considered statistically significant. SPSS Statistics 22.0 was used for statistical analyses.

Results

Clinical features

The clinical and demographical data of the 248 patients with Guillain-Barré syndrome included in this study are presented in table II. Sixty eight percent of patients were male and median age at admission was 46 years. Of the 248 patients included, 58.4% had history of a precedent infection, including gastrointestinal or respiratory. Mean time from symptom onset to admission was 5 (1-30) days.

Figure 1 shows the day of maximum weakness during the patient's evolution; 94.7% presented weakness in both upper and lower extremities and 94% presented decreased muscle stretch reflexes, and mean MRS sum score 30.3 ± 15.5. Patients with decreased muscle stretch reflexes had greater weak-

Table I. Brighton Collaboration Group Classification Criteria for Guillain-Barré syndrome.

	1	2	3	4
Bilateral and flaccid weakness of limbs	+	+	+	+/–
Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+/–
Monophasic course and time between onset-nadir 12 hr to 28 days	+	+	+	+/–
CSF cell count < 50 /μL	+	+[a]	–	+/–
CSF protein concentration > normal value	+	+/–[a]	–	+/–
NCS findings consistent with one of the subtypes of GBS	+	+/–[a]	–	+/–
Absence of alternative diagnosis for weakness	+	+	+	+

+ present; – absent; CSF: cerebrospinal fluid; GBS: Guillain-Barré syndrome, NCS: nerve conduction studies. [a] If CSF is not collected or results not available, nerve electrophysiology results must be consistent with the diagnosis Guillain-Barré syndrome.

Table II. Demographical and clinical characteristics of Guillain-Barré syndrome patients.

	n (%)
Male gender	168 (67.7)
Age, median (min-max)	46 (18-86)
Precedent infection	
Diarrhea	92 (37.1)
Respiratory infection	53 (21.4)
GDS score at admission	
2	26 (10.4)
3	37 (14.9)
4	110 (44.3)
5	75 (30.2)
Sensory symptoms	154 (62)
Cranial nerve involvement	135 (54.4)
Autonomic dysfunction	67 (27)
Treatment	
Plasma exchange	65 (26.2)
Intravenous immunoglobulin	141 (56.9)
Only supportive treatment	42 (16.9)

GDS: *Global Deterioration Scale.*

ness through the MRC score scale versus patients with normal muscle stretch reflexes (29.7 ± 15.5 versus 41.7 ± 12.5 points, p = 0.009). In 80% of the patients, the time from the onset of symptoms to the nadir of weakness was 4 (1-24) days. At the nadir of symptoms, only 3.2% presented normal muscle stretching reflexes and the score on the MRC score scale was 28.5 ± 15.5. Almost 98% of patients had a monophasic course. Of the 141 patients who were treated with IVIG, 6 (4.2%) presented treatment related fluctuations (Table III).

Cerebrospinal fluid analysis

A lumbar puncture was performed in 182 (73.3%) of the 248 patients included. The median time interval between symptom onset and CSF analysis was 6 (IQR 6-9) days. A lumbar puncture within 7 days from symptom onset was performed in 119 patients (65.3%). The median protein concentration was 49.5 (IQR 32-87.5) mg/dL, 54.9% had elevated protein concentration and 86.8% had < 5 cells/μL (Figure 2). No patient presented with > 50 cells/μL on CSF analysis. Lumbar punctures performed > 7 days after symptom onset had higher protein concentration versus those performed on ≤ 7 days –48 (40.3%) versus 53 (84.1%) p = < 0.001–.

Nerve conduction studies

Nerve conduction studies were performed in 229 (92.3%) of the 248 patients included. The median time since symptom onset and nerve conduction study examination was 5 (IQR 5-11) days. Of the 229 patients with NCS, 45.8% fulfilled Hadden criteria for acute inflammatory demyelinating polyneuropathy, 44.5% for axonal variant, 4.4% for inexcitable and 3.9% for equivocal. Only 1.3% had normal nerve conduction studies. We did not perform a second study in our patients.

Validation of Brighton criteria

Complete clinical data was available for 248 patients, but only 173 (70%) of them had complete data, including clinical course, nerve conduction studies and cerebrospinal fluid analysis. For these 173 patients, level 1 of certainty according to Brighton collaboration group criteria was fulfilled by 54.6% of patients, level 2 by 45%, and level 4 by 0.6%. Patients meeting level 2 of certainty were mostly because normal CSF findings or findings in NCS not consistent with any GBS variants (Table IV).

For patients who met level 1 certainty, both the time to perform the lumbar puncture –8 (IQR 5-12) versus 4 (IQR 3-6) days, $p = < 0.001$– and nerve conduction studies –9 (IQR 6.75- 14) versus 6 (IQR 4-8) days, $p = < 0.001$– was longer than time in patients who fulfilled criterial for other level of certainty.

If all 248 patients were considered (including those without NCS and CSF analysis), 38% are considered to fulfill level 1 certainty and 57% level 2.

Discussion

In this moment, this is the biggest GBS cohort in our country. One hundred and seventy-three (70%) patients fulfilled inclusion criteria, including clinical course data, CSF analysis and nerve conduction studies. Like other populations, there is a slight male predominance [16]. Studies have shown that GBS incidence increases with age. We found in our population a median age of 46, compared to other populations were median age ranges between 50 to 60 years [17]. This may be due to a higher number of young population in our country and a greater incidence of infections. GBS is preceded by an infection in 2/3 of cases, which may be gastrointestinal (GI) or respiratory [18]. Fifty eight percent of our patients had an infection 2 to 5 weeks before symptom onset, with a GI majority (37.1%). Local studies have demonstrated a greater incidence in summer due to high rates of GI infections, which are mostly related to acute motor axonal neuropathy (AMAN) [19]. We hypothesize this is the reason why AMAN was in the previous years the most frequent electrophysiologic variant in our country. Our epidemiology is currently changing, as AIDP is becoming the most frequent variant in Mexico as observed in our patients. Mexican healthcare policies have changed, and GI infections are decreasing in our country while respiratory infections are increasing [20].

During extensive vaccination campaigns, specially from viral vectors, there is an increased concern as GBS cases have increased. This has been taken seriously into account as GBS cases have been reported with different SARS-CoV-2 vaccines, as BNT162b2, although infrequent (0.43 per 100,000) [21]. Validation of Brighton Criteria in Mexico is necessary as more than 50% of our population has received a vaccine and GBS cases are increasing in our country.

All our patients reached the disease nadir within 4 weeks. Seventy five percent of our patients had a GDS score ≥ 4 at admission, which correlates with

Figure 1. Progression of weakness (days) at patients' arrival to the emergency department.

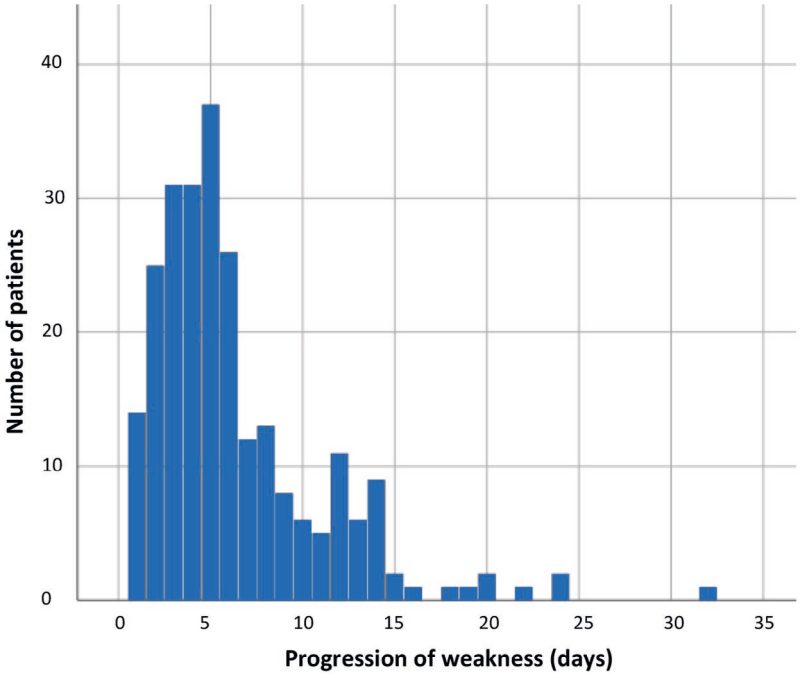

Figure 2. Time between onset of weakness and lumbar puncture realization.

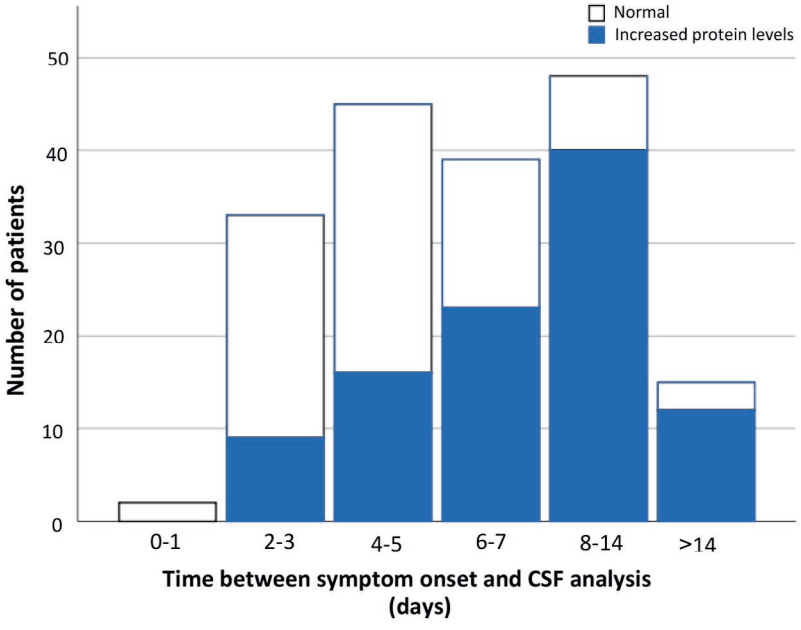

Table III. Diagnostic characteristics for Guillain-Barré syndrome patients.

Neurological characteristics at admission		*n* (%)
Normal strength		5 (2)
Unilateral limb weakness		0 (0)
Weakness in arms and legs		235 (94.7)
Weakness in legs only		5 (2)
Weakness in arms only		3 (1.2)
Severity of weakness (MRC sum score), mean ± SD		30.3 ± 15.5
Decreased deep tendon reflexes		233 (94)
Normal tendon reflexes in affected arms		9 (3.6)
Normal tendon reflexes in affected legs		6 (2.4)
Duration of progressive phase	Number of days between onset of weakness and admission	5 (1-30)
	Number of days between onset of weakness and nadir	4 (1-24)
Neurological symptom at nadir	Weakness in arms and legs	239 (96.3)
	Weakness in legs only	3 (1.2)
	Weakness in arms only	1 (0.4)
	Decreased deep tendon reflex	242 (97.6)
	Normal tendon reflex in weak limbs	6 (2.4)
	Severity of weakness (MRC sum score)	28.5 ± 16.5
Fluctuations in clinical course	Monophasic course	242 (97.5)
	Treatment related fluctuations within 8 weeks after onset of weakness	6/141 (4.1)
Cerebrospinal fluid examination (*n* = 182)	Cell count < 5μL	158 (86.8)
	Cell count between 5-10 μL	15 (8.2)
	Cell count between 10-30μL	4 (2.2)
	Cell count between 30-50 μL	2 (1)
	Cell count between > 50 μL	3 (1.6)
	Elevated protein concentration > 45 mg/dL	100 (54.9)
Nerve conduction study (*n* = 229)	Demyelinating subtype	105 (45.8)
	Axonal subtype	102 (44.5)
	Inexcitable	10 (4.4)
	Equivocal	9 (3.9)
	Normal	3 (1.3)

MRC: Medical Research Council; SD: standard deviation.

the presentation severity. Moreover, most of our patients were admitted within day 5 of symptom onset and maximum weakness was reached in the first week. On the other hand, patients with GDS 1 rarely seek medical attention in Mexico due to the mild severity of symptoms. Half of our patients had cranial nerve involvement, being bilateral facial paralysis the most common, which is consistent with other cohorts [22].

Based on treatment availability in Mexico, most patients were treated with IVIG. A recent metanalysis demonstrated no difference between PLEX and IVIG for GBS patients [23]. Approximately 96% of our patients had bilateral symmetric weakness including upper and lower limbs at presentation as well as decreased/absent deep tendon reflexes (94%). This is practically the same as the study by Asbury and Cornblath which reported 5% of patients with normal reflexes [24].

Patients that met criteria for level 1 certainty had a longer time since symptom onset to lumbar puncture or nerve conduction studies compared with other levels. This may be explained because 50% of those patients who undergo lumbar puncture within the first week since symptom onset present elevated CSF protein concentration (> 45 mg/dL), compared to 80% when it is performed within two weeks [25]. Probably if CSF analysis were performed later, our patients with level 2 would have met criteria for level 1 certainty. The same principle applies for nerve conduction studies. In the study by Hadden et al, for nerve conduction studies performed in patients within 15 days since symptom onset, a considerable number of patients fulfill criteria for equivocal findings. Moreover, a small number of patients that met criteria for axonal variant in a first study met criteria for demyelinating variant in a second study performed 4 weeks after the first [15]. As some of our patients met equivocal criteria based on Hadden criteria, they were classified into level 2 of certainty. Other criteria have been proposed to define axonal or demyelinating variants in early stages, especially in the first seven days since symptom onset. Rajabally and Uncini criteria may be further included to Brighton Collaboration group criteria as they have demonstrated better performance if performed in the first week since symptom onset [26,27]. We did not perform serial studies in any of our patients.

Most patients that fall in level 3 certainty occur in low-income countries in which clinical criteria are only considered and complementary studies are unavailable. From our entire cohort, only 4.8% fell into level 3 level of certainty, and in those cases the

reason for not having CSF analysis or NCS was associated to transitory unavailability of both. Only one patient felt into level 4 of certainty as results were not available. Our rate of level 3 and 4 is lower that other cohorts, as most of our patients have complete CSF and NCS [28].

Six of our patients (4.1%) presented treatment-related fluctuations.

In conclusion, this incidence is less than reported in other populations, ranging from 8 to 16% [14]. Those patients benefited from a second IgIV course with further improvement.

Table IV. Classification of Guillain-Barré syndrome patients according to Brighton Collaboration Group criteria.

	Complete data (*n* = 173)	All patients (*n* = 248)
Level 1	94 (54.4)	94 (38)
Level 2	78 (45)	141 (57)
Normal NCS	3 (1.7)	3 (1.2)
Normal CSF protein concentration	75 (43.3)	75 (30.2)
NCS missing	0 (0)	8 (3.2)
CSF missing and NCS consistent with GBS	0 (0)	55 (22.1)
Level 3	0 (0)	12 (4.8)
NCS and CSF missing	0 (0)	11 (4.4)
Normal NCS and missing CSF	0 (0)	1 (0.4)
Level 4	1 (0.6)	1 (0.4)
Progressive phase 28 days	1 (0.6)	1 (0.4)
No monophasic course	0 (0)	0 (0)

CSF: cerebrospinal fluid; NCS: nerve conduction studies.

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Síndrome de Guillain-Barré en México: características clínicas y validación de los criterios de Brighton

Introducción. Dado que la vacunación contra el SARS-CoV-2 está en curso en México y se han notificado casos de Guillain-Barré, es necesaria la validación de los criterios de Brighton en México. La epidemiología de Guillain-Barré en México difiere de la de los países europeos y norteamericanos.

Objetivo. Describir las características clínicas, cerebroespinales y electrodiagnósticas en pacientes mexicanos con diagnóstico de Guillain-Barré y clasificarlos según los criterios diagnósticos del Brighton Collaboration Group.

Pacientes y métodos. Se realizó un estudio de cohorte ambispectivo. Se incluyó a pacientes que cumplen con los criterios del National Institute of Neurological Disorders and Stroke para el síndrome de Guillain-Barré (SGB). Se clasificó a los pacientes según los niveles de certeza del Brighton Collaboration Group para el SGB.

Resultados. El 68% de los pacientes eran hombres. De los 248 pacientes incluidos, el 58,4% tenía antecedentes de infección previa. La media desde el inicio de los síntomas hasta el ingreso fue de 5 (1-30) días, y la puntuación media de la suma del Medical Research Council, de 30,3 ± 15,5. El nivel 1 de certeza según los criterios del Brighton Collaboration Group se cumplió en el 54,6% de los pacientes; el nivel 2, en el 45%; y el nivel 4, en el 0,6%. Los pacientes que alcanzaron el nivel 2 de certeza se debieron principalmente a hallazgos normales en el líquido cefalorraquídeo o a hallazgos en estudios de neuroconducción que no cumplen los criterios de ninguna variante de SGB.

Conclusión. El SGB es una neuropatía autoinmune frecuente que se ha asociado con infecciones previas y con campañas de vacunación. Para la campaña de vacunación contra el SARS-CoV-2 en México es necesaria la validación de los criterios de Brighton. Aunque la epidemiología del SGB en México ha ido cambiando a lo largo de los últimos años, este estudio proporciona datos similares en comparación con otros países.

Palabras clave. Autoinmune. Criterios de Brighton. México. Polineuropatía. Síndrome de Guillain-Barré. Validación.