BRIEF REPORT

CLINICAL CHARACTERISTICS AND PLASMA EXCHANGE RESPONSE IN GUILLAIN-BARRÉ PATIENTS

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ABSTRACT

The objective of the study was to describe the clinical characteristics, treatment response and possible associated factors of patients with Guillain-Barré syndrome at the National Institute of Neurological Sciences. A descriptive study on hospital discharges was conducted during the period 2017-2019. Treatment response was evaluated based on Hughes' disability scale. From 31 patients 61.3% were males and the mean age was 50 years. At admission, 87.1% of patients were on grade 3 or 4 of Hughes scale, most of them with axonal compromise which was associated to disability. Only 22 patients received plasma exchange; 6 months thereafter, 90.9% of patients decreased by at least one degree in Hughes scale and 42.8% were left without disability. In conclusion, a male and axonal subtype predominance was found, been the latter associated to disability.

Keywords: Cerebrospinal Fluid; Axonal Neuropathy; Demyelinating Neuropathy; Poliradiculoneuropathy; Plasmapheresis; Peru; Plasmatic Therapeutic Exchange; Guillain-Barré Syndrome (source: MeSH NLM).

INTRODUCTION

Guillain Barré syndrome (GBS) is an acute autoimmune polyradiculoneuropathy, characterized by progressive muscle weakness, sometimes with bulbar and respiratory impairment, and reaches maximum severity at between 2 to 4 weeks [1]. The incidence in Peru per 100,000 inhabitants/year varies between 0.62 and 0.92 [2] and at international level, it varies between 0.4 and 2.12 [3]. The most affected age group in Peru is 20-59 years, mostly men and with an overall case fatality rate of 8.4% [2]. In the first half of 2018, 53 patients with GBS were reported in Lima [4] and in May of the same year the Ministerio de Salud declared a regional epidemiological alert for the presence of 15 cases in La Libertad region [5].

Treatment consists of plasmapheresis or therapeutic plasma exchange (TPE) and intravenous immunoglobulin (IVIG) [6]. TPE is effective within the first 4 weeks, mainly in the first 7 days [7], hence the importance of early recognition of GBS. However, these treatments are not always available in all hospitals. The Instituto Nacional de Ciencias Neurológicas (INCN) currently has TPE and IVIG; but the clinical response is variable due to the influence of other factors such as age, time to treatment [8], type of neurophysiological involvement (axonal or demyelinating) [9] and preceding diarrhea [10]; on the other hand, the severity of motor involvement or degree of disability, in-hospital infections and the need for ventilation lead to a worse prognosis [11].

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The INCN receives patients with GBS from all over the country; Peru has a multicultural population; this allows us to describe our own clinical profile and to compare it with foreign publications; in addition, it is important to know if our response rate to treatment is comparable with other investigations. The objectives of our study are: 1) to describe the clinical and paraclinical characteristics of patients with GBS at INCN; 2) to determine the percentage of response to RPE; and 3) to identify the factors that influenced treatment.

KEY MESSAGES

Motivation for the study: At the Instituto Nacional de Ciencias Neurológicas (INCN) therapeutic plasma exchange (TPE) has been used since 2017, and immunoglobulin since 2019. This has increased patient referral from all over the country. In Peru, there are few studies that allow us to know the clinical profile and evolution after TPE.

Main findings: Guillain Barré syndrome was more frequent in men and the average age was 50 years. Axonal involvement was present in more than half of the patients. After six months of treatment 42.8% were free of disability.

Implications: The clinical profile of patients seen at INCN is similar to other studies, long-term follow-up allows better evaluation of therapeutic response.

THE STUDY

Design and population

A descriptive observational study was conducted at INCN, which is a specialized level IV health care institute that, being a national referral center, serves patients from all regions, languages, and cultures of Peru. We included all patients over 18 years of age hospitalized with the diagnosis of GBS, according to Brighton criteria [1], between January 2017 and April 2019; medical records with incomplete data were excluded.

Procedures

A list of patients hospitalized during the study period with ICD-10 codes G61, G62, G63, G64 and G65 was requested from the Statistics Unit. After reviewing the medical records, those that met the study criteria were selected. The information was recorded on an anonymous card and then transferred to an electronic database, maintaining confidentiality at all times.

Variables

Age, muscle strength (quantified from 0 to 5 points according to the Medical Research Council for each extremity), time of illness on admission, time of hospitalization, time of illness at the time of TPE and at the time of lumbar puncture and cytochemical characteristics were analyzed as quantitative variables. Sex, degree of functionality, in-hospital infection, presence of albumin-cytological dissociation and type of neurophysiological involvement were analyzed qualitatively. The response to treatment was evaluated according to the modified Hughes functionality scale [6]; according to the grade reached after six months of evolution, the patients were divided into two groups: a) without disability (grade 0 or 1) and b) with disability (grades 2, 3, 4 and 5).

Statistical analysis

Frequencies and percentages were calculated for qualitative variables. For quantitative variables that did not show normal distribution according to the Shapiro-Wilk test, the median and interquartile range (IQR) were used. The Chi-square test (or Fisher's exact test, as appropriate) and the Mann Whitney U test were applied for the analysis of quantitative variables in relation to the presence of disability. A p value <0.05 was considered statistically significant. Data were analyzed with the Statistical Package for the Social Sciences (SPSS) version 20 program.

Ethical aspects

The study was reviewed and approved by the Institutional Research Ethics Committee of the INCN by certificate No 584-2019-CIEI-INCN. Only the investigators had access to patient information.

FINDINGS

Thirty-one medical records of patients with GBS were reviewed (28 patients belonged to level 1, and 3 patients belonged to level 2 of diagnostic certainty in the Brighton scale), most of them were male and had an average age of 50 years. At admission, the most frequent clinical findings were: quadriparesis in 28 patients, 13 of them also showed sensory symptoms in lower limbs, one patient also had cranial neuropathy, two patients presented Miller Fisher syndrome and one patient had the pharyngo-cervico-brachial variant.

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In addition, 16 (51.6%) presented dysautonomia (13 patients had altered heart rate and/or constipation, four had altered blood pressure and four had urinary retention). Seventeen patients were from the department of Lima. Only 22 patients (71%) received TPE; IVIG was not yet available (Table 1).

Cerebrospinal fluid (CSF) analysis was conducted in 27 (87.1%) patients (Table 2). In patients with normal CSF the analysis was carried out between 1 and 24 days of illness.

The neurophysiological test was carried out in 30 patients; nine cases (29%) were identified with the demyelinating variant or AIDP (acute inflammatory demyelinating neuropathy), 13 (41.9%) with the pure motor axonal form or AMAN (acute motor axonal neuropathy) and 5 (16%) with the acute motor-sensitive axonal form or AMSAN (acute motor-sensitive axonal neuropathy). Two patients had normal results from the test, and one patient had incomplete recruitment information; however, the presence of albumin-cytological dissociation supported the diagnosis according to Brighton criteria.

The TPE was conducted in 22 patients, all of whom received five sessions per day, 14 of whom were male (63.6%). One patient, who also had HIV infection, died of pneumonia two weeks after receiving TPE. After six months, 20 patients (90.9%) decreased at least one grade on the Hughes scale and nine patients (42.8%) had no disability (Table 3). No clinical complications associated with TPE were reported.

Of the total number of patients, 7 (22.6%) had in-hospital infections (three had urinary tract infection and four had pneumonia), of which 2 (6.4%) died of complicated pneumonia. Of these seven patients, five received TPE.

After analyzing age, sex, time of illness, time to initiation of TPE and the type of neurophysiological impairment, we found statistical significance in the latter, since the presence of axonal injury was significantly associated with disability after six months of evolution (p=0.02) (Table 4).

DISCUSSION

Our findings show male predominance, with an average age of 50 years; axonal involvement was associated with persistent disability, although most responded to treatment.

GBS predominantly affects males [3]. However, in an Indian study of 1,166 patients, Sudulagunta *et al.* found no sex differences and reported a mean age of 42.8 years [12]. On the other hand, in a multicenter study of 925 patients, Doets *et al.* found a slight male predominance (59.6%) and an average age

Table 1. Clinical and epidemiological characteristics of patients with Guillain Barré syndrome.

Characteristics	Total (n= 31)	TPE (n= 22)	No TPE (n= 9)
Age, years [a]	54 (29)	52 (33)	61 (30)
Male, n (%)	19 (61.3)	14 (63.6)	5 (55.6)
TI at admission [a]	5 (7)	4 (3)	16 (22)
Time of hospitalization [a]	21 (11)	21.5 (14)	19 (18)
Muscle strength at admission [a]	36 (18)	36 (14)	29 (21)
Muscle strength post TPE [a]	--	43.5 (15)	--
TI at the beginning of the TPE [a]	--	8 (5)	--
Mechanical ventilation, n (%)	2 (6.5)	1 (4.5)	--
Hughes Scale [b] at admission, n (%)			
1	1 (3.2)	1 (4.5)	1 (11.1)
2	3 (9.7)	1 (4.5)	2 (22.2)
3	11 (35.5)	10 (45.5)	1 (11.1)
4	16 (51.6)	10 (45.5)	6 (66.7)

[a] Median and interquartile range

[b] Hughes disability scale for GBS: 0 = healthy, 1 = minor symptoms, able to run, 2 = able to walk 10 meters without assistance, but unable to run, 3 = able to walk 10 meters with assistance, 4 = bedridden or wheelchair-bound, 5 = requires mechanical ventilation at least part of the day.
TI: time of illness on admission in days; TPE: therapeutic plasma exchange.

Table 2. Biochemical characteristics of cerebrospinal fluid and time of illness at the time of lumbar puncture.

Characteristics	Patients with CSF study (n = 27)	With dissociation (n = 16)
Protein, mg/dl [a]	80.30 (52.35)	
Glucose, mg/dl [a]	60.89 (9.31)	
Cells/mm^3 [a]	1.48 (1.18)	
TI, days [b]	11 (11)	12 (10)
Range of days of illness, n(%)		
1-7		3 (11.1)
8-14		6 (22.2)
15-21		5 (18.5)
> 21		2 (7.4)

[a] Mean and standard deviation
[b] Median and interquartile range.
CSF: cerebrospinal fluid; TI: time of illness at lumbar puncture; TPE: therapeutic plasma exchange.

Table 4. Factors associated with response to treatment.

Characteristics	6 months after TPE [a]		p Value
	No Disability	With disability	
Sex			0.697 [d]
Male	6	7	
Female	3	5	
Neurophysiological involvement			0.020 [d]
Axonal	5	2	
Not axonal	3	10	
Age [b]	52 (40)	53 (24)	0.602 [e]
TI [b]	4 (1)	3 (4)	0.702 [e]
Time TPE [b,c]	8 (3)	7 (7)	0.602 [e]

[a] 21 patients are considered at six months, due to one death.
[b] Median and interquartile range.
[c] Time in days from admission to initiation of therapeutic plasma exchange (TPE).
[d] Fisher's exact test
[e] Mann-Withney U test

of 51 years [13]. Finally, in the Peruvian epidemiological study of 955 patients by Munaico *et al*. the male sex represented 60.6% of the population and the average age was 40 years [2]. The average age and the predominance of the male sex found by our study is in concordance with what has been previously published, although there is currently a lack of studies that propose a biological explanation for the latter finding.

Most patients arrived at the INCN during the second week of illness, while in European and North American studies they arrived during the first week [13]; this reflects the difficulty in accessing hospitals and the delay in diagnosis in developing countries, such as Peru. Consequently, the time of illness at the time of treatment was longer than what was described in other publications [14]. Hospital stay was longer than in other reports [2,12], since after treatment patients should continue with in-hospital rehabilitation until they reach the highest degree of independence possible, which is often not achieved due to lack of access to healthcare.

Table 3. Evolution of functionality in patients who received therapeutic plasma exchange.

Hughes Scale [a]	At admission (%)	At 6 months after TPE (%) [b]
0	0 (0.0)	2 (9.5)
1	1 (4.5)	7 (33.3)
2	1 (4.5)	7 (33.3)
3	10 (45.5)	4 (19.0)
4	10 (45.5)	1 (4.9)

[a] Hughes disability scale for GBS: 0 = healthy, 1 = minor symptoms, able to run, 2 = able to walk 10 meters without assistance, but unable to run, 3 = able to walk 10 meters with assistance, 4 = bedridden or wheelchair-bound, 5 = requires mechanical ventilation at least part of the day.
[b] 21 patients are considered at six months due to one death.

The classic presentation (sensorimotor) of GBS can reach up to 85% and the rest corresponds to atypical presentations [15], as shown in our results. Dysautonomia is well described in the literature [15] and coincides with our results, the most frequent types are heart rate and rectal sphincter alteration.

Albuminocytological dissociation is defined as an increase in CSF proteins and cellularity lower than 50 [1]. However, normal protein levels do not rule out the diagnosis and the presence of marked pleocytosis forces the search for infectious causes [15]. The frequency of this dissociation coincides with the medical literature.

Neurophysiological tests are not essential for diagnosis, but are recommended for atypical presentations [15]. In the patients of this study, the axonal subtype predominated, similar to what was described in other national publications [16]; however, in an investigation conducted at Hospital Dos de Mayo, the demyelinating subtype predominated [17]. In Latin America, demyelinating predominance has also been described when GBS was associated with arboviruses [10]. Other studies in Bangladesh and India also report a predominance of the demyelinating subtype [12,13]. This variation could be explained by genetic determination, local exposure to infections (*Campylobacter jejuni* associated with the axonal subtype) and geographical origin [13].

Mechanical ventilation was required in 6.5% of the population, this proportion was lower than in other studies [12,13],

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even reaching 26% [18]. Our rate of in-hospital infections (19.3%) was also lower than other reports (37.5% to 49%) [12,14]. Finally, we found a mortality of 6.4%, which is within the 5% to 10% range reported in population-based studies [2,18].

TPE was introduced in 1980 as the first treatment and in 1992 IVIG started to be used, both with the same effectiveness [19]. INCN has had TPE since 2017 and IVIG since May 2019. Nine patients did not receive TPE mainly because they were outside the therapeutic window (4 weeks); of the remaining 22, 43.8% did not present disability after six months. In most patients, the Hughes scale decreased by at least one grade.

Improvement rates increase when the follow-up time is longer, as described in a systematic review where 57.1% reached at least one grade of improvement on the Hughes scale at four weeks after TPE, and complete recovery after 12 months in 67.8% of patients [18]; likewise, a multicenter study found that, after 12 months, 93.6% reached grade 0 and the remaining 6.4%, grade 1 [12].

Our study has limitations inherent to its design. The type of previous infection was not recorded in all cases. The lack of association of the factors influencing treatment can be explained by the size of the population. However, this is the first study in our setting in which the response to treatment after prolonged follow-up is analyzed. It is important to develop prospective studies in larger populations, including patients treated with IVIG.

In conclusion, GBS was more frequent in males, most with grade 3 or higher according to the Hughes scale, accompanied by dysautonomia in more than 50%. Most patients responded to treatment, which is evidenced by long-term follow-up. Finally, axonal impairment is corroborated as a factor associated with long-term disability.

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