ORIGINAL ARTICLE

Factors Associated with Prognosis After-treatment in Guillain–Barré Syndrome

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ABSTRACT

Background: Guillain–Barré syndrome (GBS) is an autoimmune identity against nervous system structures. There are two main variants, the demyelinating injury and the axonal injury. In general, post-infection, in Mexico, the axonal variant is highly prevalent. The diagnosis is clinical, neurophysiological, and serum autoantibodies. The treatment is the administration of intravenous immunoglobulin or plasma exchange. The different variants respond in another way to treatment, and therefore, in the disability. **Objective:** The objective of the study was to evaluate the answer to immunoglobulin administration according to the severity and time of administration in GBS. **Materials and Methods:** We reviewed the medical records of 67 patients diagnosed with GBS from January 1, 2011, to January 31, 2017, over 18 years old, treated with immunoglobulin. They were classified into two groups: Patients with acute motor axonal neuropathy (AMAN) and patients with other variants. The days from onset of symptoms until treatment were recorded and compared with Hughes Scale at the moment of their hospitalization and in their follow-up appointment after hospital discharge to assess disability improvement. **Results:** We found that the frequency of AMAN is 40%. The functional prognosis with Hughes Scale >3 is 25.38%. In AMAN, functional prognosis expressed in Hughes Scale score is closely related to the treatment onset delay. **Conclusions:** Patients who received treatment before the 3rd day of the onset of the symptoms had significant improvement compared to those who started it after this time, $P = 0.036$.

Key words: Guillain–Barré syndrome, immunoglobulin treatment, acute motor axonal neuropathy, Hughes scale, treatment, functional prognosis

INTRODUCTION

In 1856, Landry described the first reported case of an acute polyneuropathy; it was a patient with distal sensory formication, ascending weakness, fever, who progressed to paralysis, and dying shortly after due to respiratory failure.[1,2] Guillain, Barré, and Strohl described 2 cases (infantrymen) more in 1916, with areflexic paralysis and high protein levels in cerebrospinal fluid.[1-4] After this report, Guillain himself reported ten more cases with motor alterations, loss of deep tendon reflexes, preservation of superficial cutaneous reflexes, paresthesia with a discrete decrease in objective sensitivity, increased sensitivity to muscle touch, discrete changes in the electrical response of the nerves, and increase of proteins in cerebrospinal fluid in the absence of lymphocytic reaction.[1,3,4]

It was then known as Guillain–Barré syndrome (GBS), and various treatment strategies were proposed, among them, steroids at high doses, adrenocorticotropic hormone, among others. In the second half of the last century, the syndrome's pathogenesis has been characterized and variants also. It has been established that there are two significant sections, on the one hand,

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the demyelination acute inflammatory demyelinating polyneuropathy (AIDP) that is given as a result of the antibodies attack against Schwann cells. On the other hand, the axonal membrane injury is mediated by GM1a, GM1b, and GD1a. This one can be presented as a pure motor modality acute motor axonal neuropathy (AMAN), sensorimotor modality acute motor-sensory polyneuropathy (acute motor-sensory axonal neuropathy [AMSAN]), pharyngeal-cervical-brachial variant (related to anti-GT1a and Gq1b antibodies), or the Miller-Fisher variant (related to anti-Gq1b antibodies).

The acute monophasic immune-mediated polyradiculoneuropathy incidence is 1.1–1.8/100,000, with a mean age of onset of 40 years, and although it is more common in adults over 50, the incidence in children is 0.34–1.34/100,000. In the United States, it is reported that 80% of GBS cases are due to demyelinating injury AIDP.[2] Some authors report a frequency of 30% of AIDP and 30–65% of AMAN in Asia and Central and South America, besides AMAN epidemics.[5,6]

A history of infection is frequent in such patients, characteristically the upper respiratory tract infection of viral etiology, such as Epstein–Barr virus, cytomegalovirus, and mycoplasma, is related to AIDP. Instead, mostly by *Campylobacter jejuni*, infectious diarrhea is related to AMAN;[1,2,4-15] maybe this explains the high prevalence of this variety in developing countries, where health conditions are not ideal (Mexico, China, India). Finally, several cases of viral etiologies, such as Dengue, Chikungunya, and Zika, have been reported.[4]

There are some other risk factors already characterized; for example, 60% of the cases are males, there are two seasonal peaks, spring, and winter, where the incidence increases by 15%.[1,2,5-10] The risk of suffering this syndrome after a surgical event is 13 times higher.[2]

For its diagnosis, there are criteria: (1) It is imperative, progressive weakness of more than one limb, as well as hyporeflexia or areflexia, (2) supportive criteria: (a) Progression occurs in <4 weeks, (b) symmetric weakness, (c) symptoms or sensitive signs in the case of AMSAN or AIDP, (d) cranial neuropathy, especially of the VII, (e) autonomic dysfunction, (f) protein elevation fluid with less of 20/mm^3, and (g) electrophysiological characteristics of demyelination in the case of AIDP and axonal injury in the case of AMAN or AMSAN, (3) other characteristics should raise doubt, such as marked asymmetry, sphincter dysfunction at onset, or during the entire evolution, more than 50 lymphocytes per cubic millimeter in cerebrospinal fluid, polymorphonuclear cells in cerebrospinal fluid and sensory level. And the exclusion criteria were: evidence of exposure to toxins, botulism, diphtheria, or porphyria.[1,2,5-17]

AMAN variant, as already mentioned, also starts with an infectious insult, usually *C. jejuni*; molecular imitation leads to pathology in the nodal and paranodal axolemma mediated by anti-GM1/GD1a antibodies and the membrane attack complexes, different from the segmental demyelination in AIDP.[5-9] It is known that if the AMAN variant is treated promptly, the prognosis is favorable. However, if the axonal damage is prolonged, it can lead to axonal degeneration, and the diagnosis will be bleak.

Poor prognostic factors have been described in GBS, including sensorimotor AIDP or AMAN electrophysiological patterns associated with late recovery.[16] Some other poor prognostic factors are age over 60 years, history of diarrhea, the earlier requirement of ventilatory support, muscle weakness severity, and the electrophysiological finding of excitable nerves.[4,5,17,18-21] It has also been seen that electrophysiological characteristics of demyelination in evaluating the median, ulnar, and peroneal nerves with frankly diminished motor potentials are related to an increased risk of requiring mechanical ventilation.[18]

The Erasmus GBS Respiratory Insufficiency Score model tries to predict the dependence of mechanical and can be applied at the patient's admission; it evaluates the days between the symptomatology onset and the admission to the emergency department, bulbar or cranial nerve VII compromise, and the sum of the strength evaluation of the four limbs with the Medical Research Council Scale (MCR) for muscle power.[22,23] The modified Erasmus GBS Outcome Score model uses age at the onset of symptoms, the sum of the strength in the four limbs, and if it was preceded by diarrheal disease in the previous 4 weeks (this is indirectly related to *Campylobacter* infection and the AMAN variant), and it evaluates the probability of walking after treatment.[22]

According to the American Academy of Neurology guidelines and the Clinical practice guidelines, treatment is carried out by intravenous immunoglobulin infusion or plasmapheresis. Immunoglobulin administration should be carried out in hospitalized patients, and 2 g per kilogram of weight are calculated, divided into five doses; in the case of plasmapheresis, the placement of a central catheter is required will require from 5 to 7 sessions.[1,2,6-15] Both procedures generate high institutional, social, and personal costs and carry risks and adverse effects; in the case of immunoglobulin, anaphylaxis due to the formula may occur, or infectious complications related to its administration.[23-26] In the case of plasmapheresis, the risk of catheter placement and hemodynamic instability, bleeding, or infection during the procedure are the most prevalent risks.[25]

There is the Hughes scale for the patient's follow-up, in which disability secondary to GBS is evaluated. It is divided into seven grades, with 0 being the lowest score and its represented

by the asymptomatic patient, and six as the highest score represented by death; between these values, it evaluates the requiring of assisted ventilation,[5] the ability or not to walk 5 m with or without help[2,3,4] and the ability to run.[1,22,27,28]

It has been reported that the delay in diagnosis or treatment of GBS is a factor that overshadows the prognosis.[29-36]

With the increase in the incidence of viral infection by Zika, Chikungunya, and Dengue, as well as those prevalent in our environment, due to our socioeconomic conditions, it is necessary to extensively characterize one of the most severe associated complications or nosological entities, such as the GBS. The current economic situation, as well as the economic forecasts, does not pose an increase in the well-being of the population, especially the majority with few resources; these, due to overcrowded conditions, promiscuity, and malnutrition, are the most susceptible to contracting infectious diseases and, therefore, they have a higher risk of suffering from the said syndrome. Given that it is a disabling disease, it increases the precariousness of these same families' resources.

The use of human immunoglobulin is an expensive and relatively safe procedure; there are reports of complications related to its use; if we manage to identify the risk factors for its failure in the treatment of GBS, we could reduce the risk of complications in the patient, as well as the costs for the said patient and the institution.

Much has been described in the literature about whether the AMAN variant itself a poor prognostic factor is, but no if it influences the prognosis when treatment with immunoglobulin is started early.

The impact of delay in treatment has been described in general, not in combination with the AMAN variant or the other variants.

The purpose of this study is to evaluate if the AMAN variant and the treatment onset are factors associated with deterioration in the Hughes scale after treatment with IV human immunoglobulin in the treatment of patients with GBS.

MATERIALS AND METHODS

According to the availability of records in the file, a search of medical records was conducted from January 1, 2011, to January 31, 2016, in search of patients diagnosed with GBS, only the patients' records over 18 years of age were included in the review. The following exclusion criteria were applied to this group: (1) That it was a chronic polyneuropathy and (2) that had been treated with plasmapheresis. Besides, the records that did not have a subsequent evaluation, at least 3 months after discharge, were removed. For all included subjects, the Hughes scale was applied, and the following variables were reported: Age, gender, infection history, type of variant (AMAN or others), and delay of treatment (days between symptoms onset and treatment) [Table 1].

The total number of patients in the universe that met the selection criteria was included, so no sample size was determined. In the way to evaluate the primary objective, a linear regression analysis was performed with the following model: Initial Hughes scale–Final Hughes scale ~ GBS variant + delay on treatment + Infectious history + Age + Sex.

An intentioned search of patients diagnosed with GBS was performed in the extensive archive of the Hospital Central of San Luis Potosí. Covering the dates already commented, which showed 141 patients in this period, the patients over 18 years were identified, resulting in 81 subjects. The exclusion criteria were applied to this population: with which three patients were excluded, leaving 78 subjects remaining; to have been treated with plasmapheresis, with which two more patients were excluded, resulting in 76 subjects, of those there were nine medical records without follow-up, so these were removed from the analysis, leaving 67 records.

In the review of the medical records, the following variables were searched: Age, sex, infectious history, GBS variant, delay in treatment (days from the onset of the symptoms to

Table 1: General properties of the studied population

Characteristics of the patients	
Variable	***n*=67**
Initial Hughes scale*	3.5 (3.0) [2.0, 7.0]
Hughes scale at 3 months	1.73 (2) [1, 2.5] (0–5)
Δ Hughes scale	–1.8 (–2.0) [–2, –1] (–4–0)
AGE	43.6 (41) [30.5, 53.5] (18–83)
Sex	
Female (0)	30 (45%)
Male (1)	37 (55%)
History of previous infection	
(Si = 0)	28 (42%)
GBS variant	
AMAN = 1	27 (40)
Others = 0	40 (60)
Delay in treatment (days)*	
(Starting–treatment)	5.2 (3) [2,7] (1–30)
Delay in treatment (days)*	
(Admission–treatment)	1.2 (0) [0,1] (0–15)

AMAN: Acute motor axonal neuropathy, GBS: Guillain–Barré syndrome

the immunoglobulin treatment onset), and the Hughes scale at diagnosis and the follow-up appointment after hospital discharge. The time elapsed between arrival at the emergency department, the GBS diagnosis and immunoglobulin administration were also reviewed.

Ethics

The present study was carried out following the standards established by the WHO regarding human research and, because it was a retrospective study, it did not represent a risk for the patients involved. The protection of sensitive patient data privacy is the head of the division, who will be the custodian of the information, records, and names. Research participants will have access to statistical information, keeping confidential information under the person in charge, so the consent letter is not required. The protocol was approved by the Research and the Ethics in Research Committees of the Hospital Central Dr. Ignacio Morones Prieto, granting it the authorization record 105–15.

RESULTS

For the AMAN variant group, the average age was 40.1 years, ranging from 18 to 77. Of them, 65% (15) were males. The subjects with an infectious history were 10 (37%). The delay in treatment was 6.5 days on average, with a range of 1–30 days; the delay between diagnosis and treatment onset was 1.3 days. The initial Hughes scale was 3.5 (range 2–5), the score after discharge was 1.92 on average, with a range from 0 to 4, with a difference of 1.6, when it is compared with the evaluations of the Hughes scale in the other variants (initial 3.5 and 1.6 at discharge) gives 1.92 resulting in $P = 0.124$. Regarding the delay in treatment, comparing the variant AMAN with the other variants, we found a $P = 0.05$, with a delay of 6.5 versus 4.4 days, respectively.

Of the total number of patients, the Hughes scale scores were divided as follows, ten patients with a score of 0, asymptomatic; 20 patients with a score of 1, able to even run; 20 patients with a score of 2, able to walk at least 5 m without help; 13 patients with a score of 3, able to walk 5 m, but with help; 3 patients with a score of 4, unable to walk; and 1 patient with a score of 5, requiring assisted ventilation. No deaths were recorded in this study [Figure 1].

In the AMAN population (27 patients), there were obtained 1 (3.7%) healthy patient, 9 (33.3%) patients able to run, 9 (33.3%) patients able to walk at least 5 m without help, 7 (25.9%) patients able to walk at least 5 m with help, and 1 (3.7%) patient unable to walk [Figure 2].

The final multivariate linear regression model was statistically significant for the onset time of intravenous immunoglobulin ($P = 0.005$), explaining 24% of the Hughes scale variation. Figure 3 shows that there is a direct relationship between the decrease in the Hughes scale and the elapsed days between the symptom's onset and the treatment onset.

In the post-discharge evaluation, patients were classified according to the Hughes scale, and it was observed that most of the patients that resulted with a score of 0 (healthy) were found in the group of other variants; instead, in the AMAN group, only one patient was found, this resulted in a significant difference with $P = 0.04$. Paradoxically, the only patient who, in our study, required mechanical ventilation was found in the group of other variants. The number of patients by variant and by Hughes is summarized in Table 2.

In the AMAN group, when comparing the improvements in the Hughes scale in patients with five or fewer delay days with those with more than five delay days, we found that the first group's improvement was, on average, 1.94 points versus 0.88 of the second group. When the same exercise is done but comparing those who received treatment in 3 days

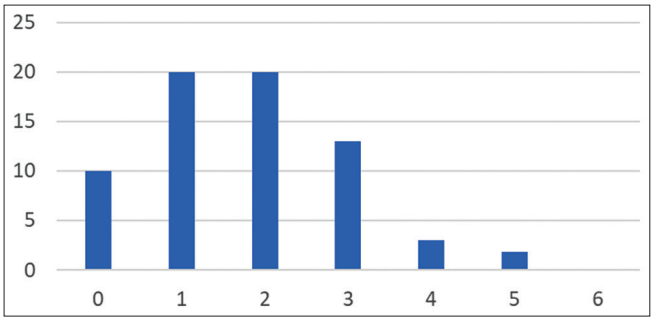

Figure 1: Patients in Hughes scale groups.

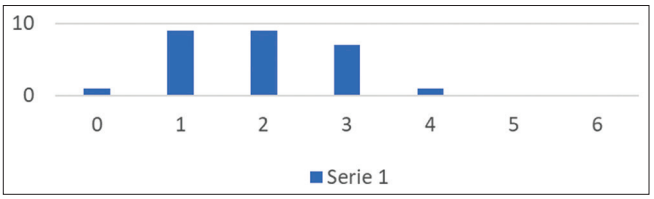

Figure 2: Patients with acute motor axonal neuropathy variant in Hughes scale groups

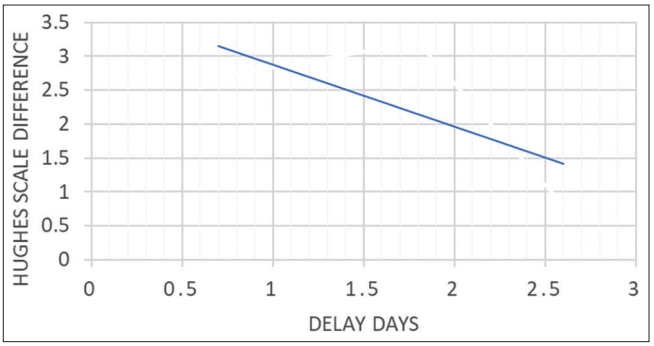

Figure 3: Relationship between treatment delay and improvement

Table 2: Hughes post-discharge by groups

Hughes post-discharge by groups			
Hughes scale	**AMAN variant *n*=27**	**Others *n*=40**	***P***
0	1 (3.7)	9 (22.5)	0.04
1	9 (33.3)	11 (27.5)	NS
2	9 (33.3)	11 (27.5)	NS
3	7 (26)	6 (15)	NS
4	1 (3.7)	2 (5)	NS
5	0	1 (2.5)	NS
6	0	0	NS

AMAN: Acute motor axonal neuropathy

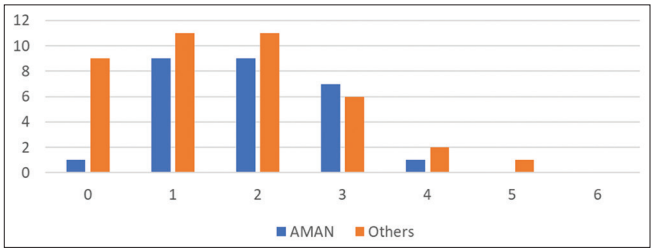

Figure 4: Hughes post-discharge by groups

or less versus those, who received it after the 3rd day, the average improvement for the first group is 2 points, while for the second group was 1.31 points [Figure 4].

When the Chi-squared TEST is applied in these two groups, we find that, in the group with a delay of fewer than 3 days, it results in $P = 0.036$. Instead, when evaluated with a delay of fewer than 5 days, it shows a $P = 0.376$.

DISCUSSION

In this study, 40% of the AMAN variant is found in a population of 67 patients, compared to that reported by McLauchlan10 (33%). We also found 25.38% of patients with a three or more score on the Hughes scale than Van Doorn *et al*.[11] reports (20%). Due to our population's socioeconomic and cultural characteristics, the history of infection is identified in less than half of cases (42%), compared to 70% reported by Pasanen,[1] but 58% of the subjects did not identify an infectious antecedent. Hence, it represents a significant challenge to identify possible etiologies; this search could be expanded with the viral etiologies of Dengue, Zika, and Chikungunya that in our country has had a critical incidence, the last two with a recent appearance, but the first, with prevalence in our country for several years. Although the expected clinical presentation would have some differences, we do not observe in the population studied.

According to Kuwabara and Yuki,[5] who in 2013 did a review about the AMAN form, this variant has a worse functional prognosis and a longer time for recovery. While it has been determined that the axonal variant has a worse prognosis, which we have replicated in this study, we can realize that due to the timely intervention in several cases. The prognosis approached the rest of the variants; it will be necessary to consider that the patient with more delay in treatment arrived outside the treatment time, which decisively modified the response to the treatment.

The opportunity to offer an early treatment of the axonal variant is a better prognostic factor, especially for the AMAN variant that, if not treated promptly, is the most disabling, and that leaves more sequels of the Guillain–Barré variants.

Since, in previous years, our hospital did not have an electrophysiology department, the study of reported cases can be considered incomplete since few of them had a study within the first 30 days of the condition. This same data encourages the continuation of the registry of patients' clinical characteristics with GBS, now with the necessary complement of electrophysiology.

CONCLUSIONS

In this study, we were able to identify that the AMAN variant is frequent in our population. During the case review, we have also found that infectious history is less prevalent or not determined. Timely administration of standard intravenous immunoglobulin treatment results in a significant improvement in functional prognosis. We found that patients with the administration in the first 3 days of the onset of symptoms improve up to 2 points of the functional scale than those who receive it after those 3 days.

Although our sample is not large, it is enough to affirm that the first 3 days, from the onset of symptoms, are the ideal ones to influence the quality of the recovery of the patients, as well as, to reduce the time of disability and, therefore, reduce the costs generated by complications, treatment, rehabilitation, and lack of economic productivity.

Therefore, we can affirm that the hypothesis raised at the beginning of this investigation is correct; the delay in immunoglobulin treatment in patients with GBS in its axonal motor variant negatively affects functional recovery. We have also managed to establish an optimal time for the treatment onset.

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