Clinical-Epidemiological Characterization of Guillain Barré Syndrome in a Cuban Case Series

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ABSTRACT

The broad spectrum of Guillain Barré Syndrome (GBS) includes different pathological phenotypes, with a heterogeneous distribution. The reports, by country and region, have shown its great variability and clarified its behavior.

Objective: Characterize GBS and define the most frequent phenotypes.

Methods: A time series was constructed to analyze the epidemiological behavior of GBS. The demographic, epidemiological, clinical, and complementary aspects of 167 patients were retrospectively described. The severity was analyzed and the patients were classified.

Results: The mean age was 33 years, 22.8% were children. The incidence decreased with age and a seasonal preference was seen for the month of August, that usually coincides with higher rates of respiratory and digestive infections. Dengue preceded some GBS outbreaks. The Acute Inflammatory Demyelinating Polyradiculopathy (AIDP) variant predominated and was most severe. Regional variants, a recurrent GBS and a family one were detected. Age, personal history of autoimmune disease, preceding infectious phenomenon, latency between the preceding phenomenon and the onset of the clinical picture, the extent of the motor disorder, facial involvement, gait impairment, ventilatory compromise, and degradation of the osteotendinous reflexes, significantly correlated with the severity.

Conclusions: The predominance of AIDP coincides with some countries in the area, with varying geographical location and climatic conditions. The incidence decreases with age. The relationship between the severity and the personal history of autoimmune disease, the preceding infectious phenomenon, and the latency between the preceding phenomenon and the onset of the clinical picture, could be reflecting an underlying autoimmune mechanism in each case.

Introduction

GBS is the most common, rapidly evolving, and potentially fatal acute neuropathy. It is an autoimmune, self-limited, monophasic disease, generally triggered by an infectious process, in which the spinal and cranial peripheral nervous systems are widely affected, and courses with somatic (motor and sensory) and dysautonomic manifestations.[1]

In the first few days, the diagnosis is clinical, which can later be reinforced by the presence of albumin-cytologic disassociation in the cerebrospinal fluid (CSF) and the neurophysiological alterations.

This kind of paralysis, over the last century has motivated continuous reports of cases in the literature. Over time, it was associated with anatomical damage to the peripheral nervous system and the typical alteration in the cerebrospinal fluid (CSF) was demonstrated. Clinical descriptions have been numerous, from Landry (1859) and Osler (1982) to 1916, "year 0" of the GBS history.[2]

This year, Guillain, Barré and Strohl reported the "radiculoneuritis with acellular hyperalbuminemia of the cerebrospinal fluid". But, in the middle of the 20th century, the controversy over whether it was or not Guillain-Barre syndrome continued and it was argued that Guillain-Barre syndrome was easy to diagnose but impossible to define.[3] The pathological findings of the disease were reported (Haymaker and Kernohan) and its autoimmune pathogenesis were considered (Waksman and Adams), which was later confirmed by Asbury.[4] Since then, various classification systems have been proposed and numerous reports show the other sides of GBS (non-classical forms). In this way, the spectrum of GBS has been markedly broadened and includes different pathological phenotypes.

GBS is known to be a worldwide-recognized disease with the geographic distribution of the different GBS variants highly variable. Most authors report that in North

America and Europe the classical demyelinating form or AIDP represents up to 90%[5] and only about 5% of patients have the axonal subtypes. Whereas in China, Japan, and some countries within Central and South America, the axonal subtype predominates.[6] In the Latin American region, information is scarce and variable. In general, a predominance of demyelinating forms is reported, such as Chile,[7] Colombia[8] and many others; while some countries report a predominance of axonal forms, such as Mexico, [9 10] Peru[11] and a few others. In this article, we will describe the clinical-epidemiological behavior of GBS in a series of Cuban patients.

Objectives

Describe the demographic-epidemiological, clinical and complementary exam variables of GBS.

Methodology

The files from the Institute of Neurology and Neurosurgery (INN) were reviewed over a period of 30 years, from 1967 to 1997, a period in which the INN was the national reference center for GBS. A total of 409 patients were admitted. With the admission dates of patients, a time series was developed to analyze the epidemiological behavior of GBS. A total of 167 of the most complete medical records were selected for a detailed description of the demographic, epidemiological, clinical and complementary exam features of the disease. Multivariate analysis was carried out exploring the existence of correlation between the different variables that could explain the etiopathogenical aspects of the disease. The correlation, according to Spearman, of severity and demographic, epidemiological, clinical and complementary exam variables were analyzed. The cases were classified according to their clinical and neurophysiological characteristics.

Results and Discussion

Demographic Variables

The mean age in the case series was 33 years, with a minimum age of 2, a maximum age of 84, and a standard deviation of 20,407. Most of the authors similarly report a wide range of age of occurrence, but with a mean age around 50 years.[12] However, some authors report lower, younger mean ages[13]. Figure 1 shows the age distribution, with classes of 10 years. It appears to be a bimodal distribution, with two peaks: one before 40 years of age and another after 50 (the lower of the two), with an intermediate class between 40 and 50 years that shows the lowest number of patients. Figure 2 shows the age distribution, with classes of 20 years. In this, a frank decrease of incidence with age was observed, with a striking decrease after the 70s.

The disease occurred in 38 children, between 2 and 15 years old, for 22.8%, with a mean of 8.37 years and a standard deviation of 4.149. The group between six and 10 years was the one with the highest frequency (16 cases for 42.1%), similarly to that reported by Maneesh Kumar et al.[14] Classes younger than six years old and older than 10 years old were presented with the same frequency in our study (11 patients for 28.9%). Four patients were 2 years old. Hung refers that the incidence in children increases with age and is rare before two years of age.[15] However, Sinan found five patients (13.8%) under two years of age.[16]

There was a predominance of whites, 134 patients (80.2%) over blacks, 28 patients (16.8%) and mixed race, 5 patients (3%). The disease was more common in men (88 patients/52.7%) than women (79 patients/47.3%).

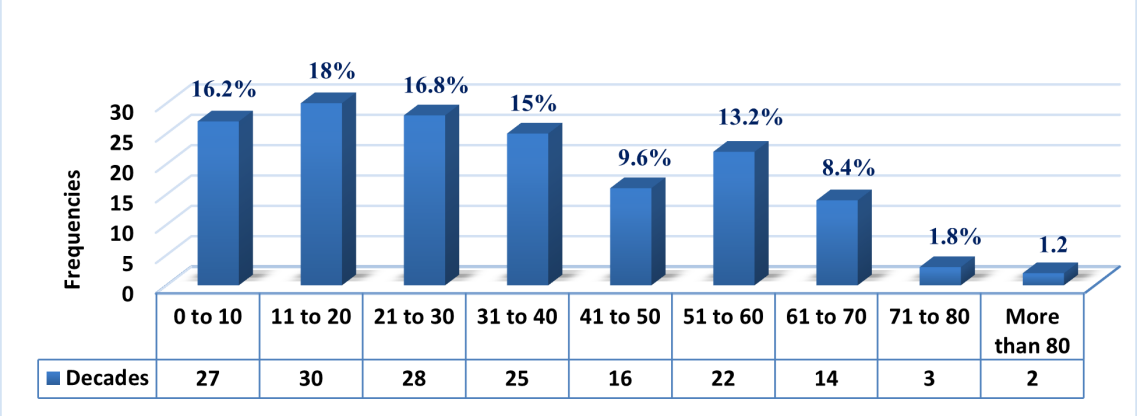


Figure 1. Frequency distribution of age (every 10 years).

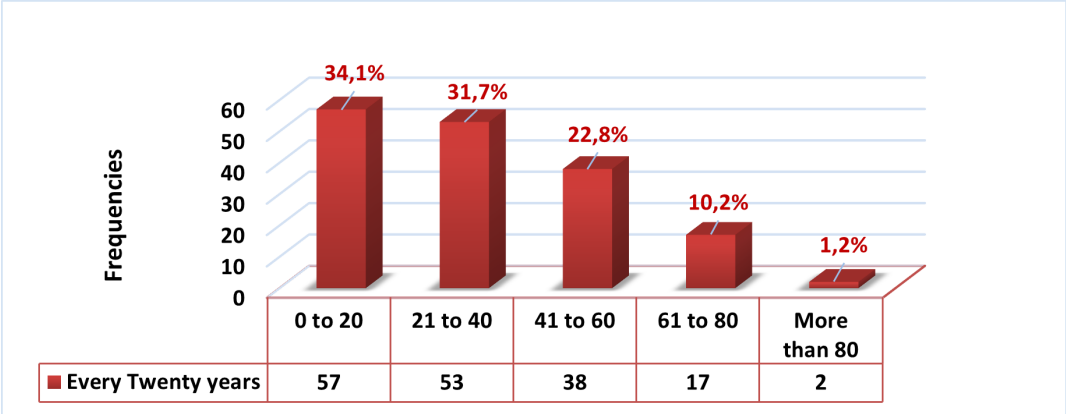


Figure 2. Frequency distribution of age (every 20 years).

Preceding Phenomenon

In 106 of the patients (63.5%) a preceding event was evidenced, which preceded the onset of the clinical picture in a mean time of 13.83 days. In 97 patients it was infectious, with respiratory infections (31.7%) more frequent than digestive ones (10.8%). One aspect of interest was Dengue as a preceding phenomenon. This was presented in 7 patients for 4.2%. In 9 patients (8.5%), the preceding event was non-infectious. In 3 patients there was a history of vaccination and in another 3 physical exercise was referred. Surgical intervention, head trauma and immediate postpartum were present in 1 patient each.

Time Series Analysis

In the annual time series, we observe the epidemic behavior of GBS in our country for 30 years (Figure 3). During this period, 409 patients were treated at the Institute, a minimum of 4 cases per year and a maximum of 31, with a mean of 13.06 and a deviation of 2.12.

Several peaks of more than 15 cases per month are observed (above the mean of 13.06 cases). The first peak, of 31 patients, in 1969, was in relation to a serious influenza epidemic. The second peak comprises years 77 and 78, with a total of 38 patients, (18 and 20 patients, respectively). This is the first report in the national and international literature of post-Dengue GBS, it was related to a serious epidemic of Dengue hemorrhagic fever, serotype 1.[17] Then another increase is observed in years 81 and 82 (23 patients in each year). This increase was reported in the national literature,[18] also after Dengue outbreak. The series highlights another increase in 1984 (20 patients), another Dengue outbreak in Cuba, followed by other increases in the number of cases, of lesser quantity, where we do not have a clear relationship with frank dengue epidemics or other preceding. In 1994, there was an increase in GBS cases in the Arroyo Naranjo municipality (200 patients). It was preceded by an epidemic of gastroenteritis, caused by an enterobacteria, due to the ingestion of contaminated water. A similar situation occurred in Florida in 1986.[19]

GBS Seasonality

It is reported in the literature that GBS seasonality is related to the epidemiological situation of the country. Cuba has a tropical climate, with a dry season, with cooler temperatures (from late November to mid-April) and a rainy, hot and humid season (mid-April to early November, mainly from May to October). In our series of cases, two annual peaks of GBS were evidenced. One small in the

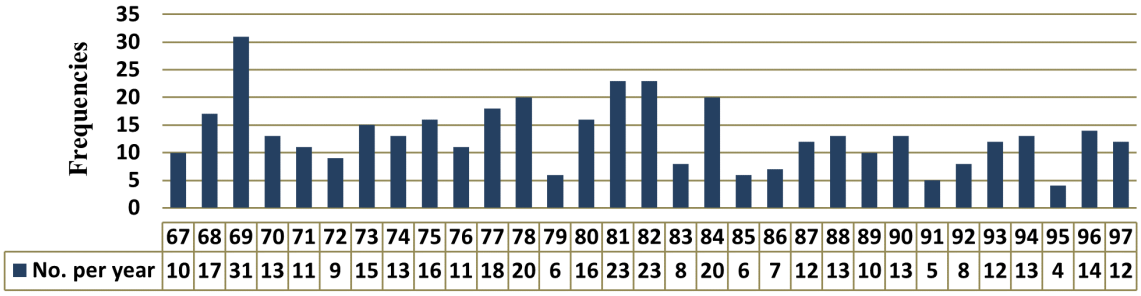


Figure 3. Number of cases per year. Serie of 30 years and 409 patients.

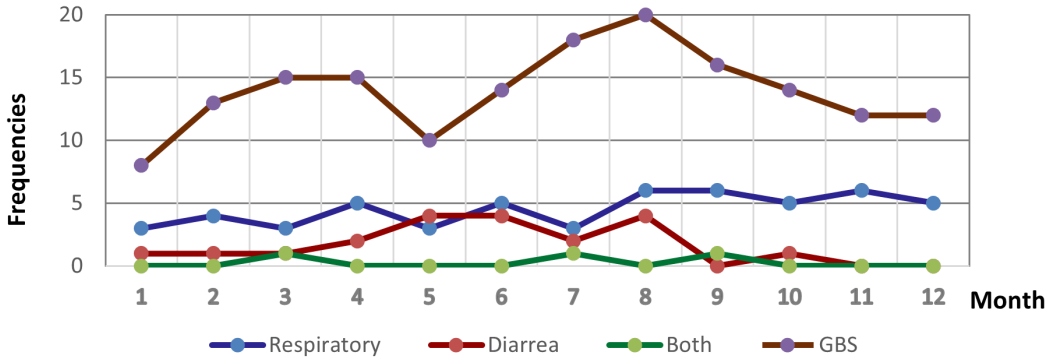


Figure 4. GBS seasonality and preceding infections.

months of March-April (at the end of the dry season) and another, larger, in the month of August (rainy season) (see Figure 4). The highest incidence of the syndrome occurred in the month of August, such that it can be clearly said that GBS in Cuba has a seasonal preference for that month. During this month there is a coincidence in the increased incidence of respiratory and digestive processes. The month of August is a rainy month, such that it also favors the growth stages of arboviruses, frequent in our country as a precedent.

Family and Personal History of Interest

Regarding the family history, we found the occurrence of GBS in two siblings, two months apart. The familial occurrence of GBS reinforces the genetic hypothesis.[20 21] One patient presented GBS on two occasions. Although exceptional, there are isolated reports in the literature of recurrent GBS.[22 23]

Time Elapsed Between the First Symptom and Admission

The average time it takes patients to see the doctor, after starting with the first symptoms of the disease is 11.82 days, with a standard deviation of 10.989 and a range that ranges from less than 24 hours to 61 days. Almost half of the patients (47.3%) attend before the first week and 88.6%, before the month.

First Symptoms

Muscle weakness was the first symptom and the most relevant reason for consultation in our study (59 patients for 35.3%), followed by sensory disorders (53 patients for 31.7%), while in 31 patients (18, 6%) pain was the first symptom and anticipated motor and sensory symptoms. In 23 (13.8%) the disease began due to combinations of two or more symptoms (motor and / or sensory and / or pain and / or dysautonomia). Only one patient (0.6%) presented from the beginning, and as cardinal manifestations, ataxia and diplopia, being a Miller Fisher syndrome (MFS).

Clinical Picture

As can be seen in Table 1, at the nadir of the disease, muscle weakness (100%), hypo / areflexic (99.4%), with significant compromise of gait (98.2%) predominated. It was followed in frequency by ventilatory disorders (32.9%), radicular signs (29.9%) and sensory disorders (26.9%). Autonomic signs were present in only 13 patients (7.8%), eight patients had ataxia for 4.8% (6 proprioceptive and 2 cerebellar) and fasciculations were found in 2 patients (1.2%).

In 164 patients the spinal musculature was affected (98.2%), in isolation in 70 patients for 41.9% and associated with cranial muscle involvement in 94 patients for 56.3%. Cranial involvement occurred in 97 patients, in 3 of them in an isolated manner (1.8%).

Of the patients with spinal implication, 22 presented a motor clinical picture limited to the lower limbs (13.2%) and in 142 both limbs were affected (85%). The cranial muscles most involved were the facial (67 patients for 40.1%), pharyngeal (55 patients for 32.9%) and extraocular (14 patients for 8.4%). Of the cases with isolated cranial compromise, one presented with a multiple cranial mononeuropathy, with bilateral facial and pharyngeal involvement, ophthalmoparesis and areflexia. The second patient presented unilateral facial weaknees, with paresthesia. We find a similar report in the literature.[24] The third case was a complete MFS (ophthalmoparesis, ataxia, and areflexia).

Table 1. Clinical manifestations of GBS, at nadir

SIGNS				TOTAL	
	Details	**No**	**%**	**No**	**%**
Weakness	Spinal	70	41,9	**167**	**100,0**
	Spinal and Cranial	94	56,3		
	Cranial	3	1,8		
Hypo/areflexia	Areflexia	114	68,3	**166**	**99,4**
	Hyporeflexia	52	31,1		
Gait impairment	Impossible	89	53,3	**164**	**98,2**
	With support	61	36,5		
	Independent	14	8,4		
Impaired ventilation	Assisted	34	20,4	**55**	**32,9**
	Controlled	21	12,6		
Radicular signs				**50**	**29,9**
Sensitive signs	Hypopalestesia	17	10,2	**45**	**26,9**
	Global Hypoesthesia	17	10,2		
	Superficial Hypoesthesia	11	6,6		
Autonomic signs				**13**	**7,8**
Ataxia	Proprioceptive	6	3,6	**8**	**4,8**
	Cerebellar	2	1,2		
Fasciculation				**2**	**1,2**

The facial involvement was bilateral in 52 patients (31.1%), symmetric rather than asymmetric (17.4% vs 13.8%). Only 15 patients presented unilateral facial involvement. According to reports, cranial nerve involvement occurs in 25% of cases, with bilateral implication being the most characteristic.[25]

A single patient had a typical clinical picture of GBS but with preservation of the deep tendon reflexes (DTRs), as reported in the literature.[26]

The percentage of patients who needed ventilatory support (32.9%/55 patients), coincides with that reported in the literature where it is stated that up to 30% of patients in the progression phase develop respiratory failure.[27] Lawn ND et al report progression to mechanical ventilation was highly likely to occur in those patients with rapid disease progression, bulbar dysfunction, bilateral facial weakness or dysautonomia. In our cases ventilatory compromise was significantly correlated (α of 0.01) only with older ages and cranial extension of the weakness.

Complementary Diagnostics

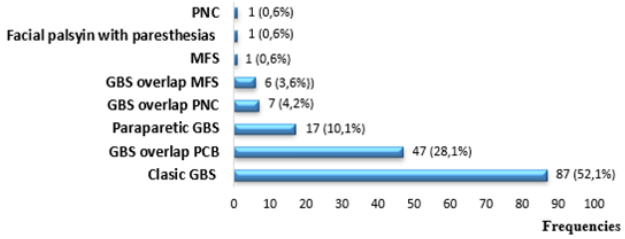
CSF data was obtained in 163 patients, conforming increased protein in 110, for 67.5%. In 85 patients (52.1%), rupture of the Blood-brain Barrier was found and in 27 (16.6%), intrathecal synthesis of IgG. Hypercellularity (less than 10 cells, lymphocytic type) was observed in 22 patients for 13.5%. These results coincide with the literature.[28] According to authorities on the subject,[29] albumin-cytological dissociation is detected in the CSF, initially in 50% of patients and is found in more than 90% of patients, if they are at the clinical nadir. In a previous study, carried out at the INN, it was found that all patients whose CSF was studied after the ninth day of evolution of GBS, presented a breakdown of the blood-CSF barrier.[30]

The result of the Nerve Conduction Studies (NCS) of 66 patients was obtained. Compromise of the peripheral nerves was evident in 50 patients (75.8%) and in 16, was normal (24.2%). Myelin involvement frankly predominated (35 patients/53%) over the axonal (2 patients/3%). In 13 patients (19.7%) the NCS showed mixed damage.

Electromyography showed signs of denervation in 50 studies of the 71 performed (70.4%). In 21 patients, the affectation was mild (29.6%), moderate in 16 (22.5%) and severe in 13 patients for 18.3.

Periods of the Disease

The average time of disease progression was from 11.46 days, with a minimum of half a day and a maximum of 60 days. The 70.7%, 118 patients, reached nadir in less than 15 days. The recovery stage lasted from a few hours to a maximum of 158 days, for an average of 22.4 days. 80.8% (135 patients) recovered within 28 days.



GBS: Guillain Barré syndrome. PCB: Pharyngeal-Cervical-Brachial. MFS: Miller Fisher syndrome. PNC: Polyneuritis cranialis. In parenthesis the relative frequency for each absolute frequency value.

Figure 5. Clinical classification of patients.

Clinical Classification of Patients

Figure 5 shows the clinical classification. Classic GBS expressed by neuropathic involvement of the upper and lower limbs, with or without facial involvement, without cranial involvement, occurred in 87 patients (52.1%). Myelin damage was confirmed in 20 patients (AIDP), 9 had normal nerve conduction and 1 (0.6%), axonal damage. This patient expressed as Axonal Motor Sensory Neuropathy (AMSAN). In the rest of these patients the data was not available.

In 47 patients (28.1%), GBS overlapped with the Pharyngeal-Cervical-Brachial variant (PCB). These patients had neuropathic compromise of the lower or upper limbs or both, with or without facial weakness and pharyngeal involvement. In patients with this overlap, who had the nerve conduction study result, 11 showed myelin damage, 3 had mixed damage and in the remaining 4, the studies were normal. The paraparetic form manifested itself in 17 patients (10.1%), in isolation in 7, with facial weakness in 4 and associated with neuropathic sensory disorders in 6 cases. Four patients had myelin damage and one, mixed damage.

GBS superimposed with PNC (Polyneuritis cranialis) was present in seven patients (4.2%). All had limb weakness, oropharynx participation and ophthalmoplegia. We found no involvement of other cranial nerves. Only one case had NCS, which was normal. GBS superimposed with Miller Fisher Syndrome was present in six patients (3.6%). In five patients, the associated MFS was incomplete (ophthalmoplegic GBS) and in 1 patient, complete. We only had a nerve conduction study in two of these patients, one showed axonal damage and the other mixed. Only one patient presented the classic symptoms of complete MFS (0.6%). Another presented acute unilateral facial weakness, accompanied by distal paresthesia in the extremities, hyporeflexia and electromyogram showing moderate denervation. This case is similar to the one reported by Verma et al.[24] Isolated cranial weakness, expression of the regional form of Polyneuritis cranialis of GBS, was present in only 1 patient who presented facial, pharyngeal and ophthalmoplegia weakness, without skeletal muscle involvement, with areflexia and alterations in the CSF. The hyperacute variant was presented in one case, which reached its nadir in one day. Two cases presented with very mild clinical forms: an MFS superimposed with a PCB and a classic demyelinating GBS, type AIDP. There was a recurrent GBS and a family case.

Functional Assessment or Severity of GBS

According to the Hughes score, GBS took severe forms in 153 patients for 91.6%. Patients with grades 4 and 5 predominated (Table 2).

Table 2. Functional evaluation of the GBS according to the Hughes Scale

GRADE	HUGHES SCALE				
	No	%		No	%
Grade 1	3	1,8	**Mild**	14	8,4
Grade 2	11	6,6			
Grade 3	35	21,0	**Severe**	153	91,6
Grade 4	63	37,7			
Grade 5	55	32,9			
TOTAL	**167**	**100,0**	**TOTAL**	**167**	**100,0**

Spearman's correlation was calculated between severity and demographic, clinical and complementary variables. It was evidenced that the severity increased with age. Neither sex nor skin color were shown to be related to severity. Within the epidemiological variables, a correlation was sought between the history of having suffered an autoimmune disease prior to GBS and the severity, and this was not significant. However, it was found that patients who had presented with a prior infectious phenomenon had a more severe neuropathic presentation. It was of interest that in patients who had antecedents preceding GBS, the longer the time between this event and the onset of GBS, coincided with greater severity.

The clinical variables that positively correlated with severity were gait disorder, compromised ventilation, and extension of weakness to the upper limbs and cranial muscles. These correlations have obvious clinical significance. However, the relationship between facial involvement and severity was interesting. Patients with bilateral and symmetric facial weakness developed

more severe GBS than those with unilateral or bilateral asymmetric facial weakness. In the same way, a positive correlation, although weaker, was evidenced between the greater compromise of the osteotendinous reflexes and the severity (Table 3).

Discussion

In our series, the behavior of the incidence according to age differs from many of the reports. The authors frequently report that the incidence increases with age[31] and consider that this behavior is related to a failure in the immunosuppressive mechanism,[32] which increases, in turn, the susceptibility to autoimmune disorders. Another relevant aspect is the bimodal aspect of the age distribution. The bimodality and age peaks found in our series have been detected in other series.[33]

The mean age of presentation and the groups with the highest incidence, found in our children, coincides with those reported in the literature.[14 34] The disease predominated in males and whites, as traditionally reported in the literature.[35] GBS is considered one of the few autoimmune disorders where the incidence is higher in men;[36] similarly, it occurs in CIDP and in multifocal motor neuropathy with conduction blocks.

The preceding infectious, respiratory rather than digestive phenomenon, predominated. One aspect of interest was Dengue as a preceding phenomenon. Dengue epidemics preceded several GBS outbreaks in our time series. Cuba was the first country in the region to report post-Dengue GBS, at a time when Dengue was an endemic disease in the region and there were few worldwide reports of GBS as a neurological complication of the disease. Already in the last decade the reports of GBS secondary to arboviruses have been highlighted; first, Dengue then Chikungunya and finally Zika and even combinations thereof.[37]

The average time between the preceding phenomenon and the onset of symptoms in our series (13.83 days) coincides with that reported by some authors (between 11 and 13 days).[32]

Table 3. Variables that showed significant correlations with severity

SPEARMAN RHO		HUGHES SCALE
Age	Corr. Coeff	,229**
	Sig.	,003
	N	167
Personal history of autoimmune disease	Corr. Coeff	-,132
	Sig.	,090
	N	167
Preceding infectious phenomenon	Corr. Coeff	,205**
	Sig.	,008
	N	167
Latency between preceding phenomenon and the onset of the clinical picture	Corr. Coeff	,235**
	Sig.	,002
	N	167
Gait impairment	Corr. Coeff	,841**
	Sig.	,000
	N	167
Ventilatory compromise	Corr. Coeff	,842**
	Sig.	,000
	N	167
Muscle weakness (espinal, craneal or both)	Corr. Coeff	,348**
	Sig.	,000
	N	167
Facial weakness	Corr. Coeff	,158*
	Sig.	,042
	N	167
Degradation of the deep tendon reflexes	Corr. Coeff	,191*

* Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

The GBS seasonal preference in our series (August) coincides with the highest incidence of respiratory and digestive infections in this month. From the meta-analysis carried out by Webb et al., we can summarize that the seasonal variation of GBS may depend on: the seasonal preference of the prodromal disease, the preferential existence of some infections in rural communities, local economic factors (health) and the differences in ethnic groups with genetic susceptibility to develop GBS or immunological tolerance due to a previous viral infection.[38]

The predominance of demyelinating forms in our series is similar to that reported by most authors, especially from North America, Europe and some South American countries, such as Chile[7] and Colombia.[8] However, other countries in South America, such as Peru,[11] and Central America such as Mexico,[9 10] the axonal subtypes predominate.[6] It cannot be said that there are geographical conditions (latitude, climatic conditions, etc.) that justify this preference. Between the classical forms, AIDP was the most frequent, followed by other variants, superimposed and regional. Only two patients (3%) had axonal damage, one case with AMSAN and the other with GBS superimposed on MFS. Verboon et al. reported differences in the spectrum of MFS overlapped with SGB.[39] On the other hand, overlapping presentations, such as those found in this series, are frequent reports today.[40 41]

According to the Hughes score, the disease was predominantly severe. Age, coinciding with what other authors report,[42 43]significantly correlated with severity, but not sex or skin color. This is possibly the reason why age is one of the variables contained in the Erasmus prognostic scale (EGOS). We only found one report where the severity was greater in women.[44]

Other variables that correlated with age and that could be better studied as prognostic determinants in GBS are: the antecedent of previous autoimmune disease, prior infections, the latency between the preceding phenomenon and the onset of neuropathic manifestations, the extension of the motor disorder, the presence and severity of facial compromise, gait impairment, the severity of ventilatory compromise, and the degradation of deep tendon reflexes.

Factors that determine a worse prognosis for GBS have been established. It can be mentioned the advanced age (57 years or older),[42 43] marked weakness on presentation and fundamentally if the upper limbs are weak (with MRC sum score below 40), hyperacute cases, infectious precedent, especially diarrhea, detection of antibodies against *Campylobacter jejuni*[42] or cytomegalovirus, the axonal variety, presence of anti-ganglioside GM1 antibodies, need for ventilatory support[43] and severe axonal neurophysiological damage.

On the other hand, biomarkers of worsening prognosis, prolonged disease or slow recovery from GBS have been studied,[45 46] such as levels of high weight neurofilaments (above 0.73 ng / ml);[47] increased levels of neuronal-specific enolase and S-100 protein,[48] as well as long-lasting increments in IgM-type antibodies against GM1 gangliosides[49] Van der Pol et al. state that future research is needed to determine whether mortality in GBS can be reduced if monitoring is intensified in patients with a high-risk profile.[50]

Conclusions

The incidence of GBS in our series decreases with age. The respiratory rather than digestive infections as preceding phenomena, predominated, and in a peculiar way, the Dengue. GBS in Cuba has a seasonal preference for the month of August. The most frequent clinical form was classic GBS and prevail the myelin damage (AIDP). Regional variants were detected: overlapping, complete and incomplete, as well as one recurrent case and another with familial GBS. The variables that showed to be linked to the greater severity were: the increase in age, the personal antecedent of previous autoimmune disease, having suffered a previous infectious disease, the increase in the average time between suffering the preceding phenomenon and the onset of the clinical manifestation, the greater corporal extension of the motor disorder, the presence and severity of the facial compromise, the deterioration of the gait, the severity of the ventilatory compromise and the degradation of the deep tendon reflexes.

References

1. Lestayo O´Farrill Z, Hernández Cáceres J.L. Guillain Barre Syndrome behavior. Agreements and discrepancies. Rev Neurol 2008; 46(4):230-237.

2. Mathis S, Soulages A, Vallat JM and Le Masson G. History of acute polyradiculoneuropathy (part 1) The prehistory of Guillain-Barre Syndrome. Neurology 2020; 94:1-8.

3. Theodore L. Munsat and James E. Barnes. Relation of multiple cranial nerve dysfunction to the Guillain-Barre Syndrome. Neurol. Neurosurg. Psychiat. 1965; 28:115.

4. Asbury AK, Arnason BG, Adams RD. The inflammatory lesion in idiopathic polyneuritis. Its role in pathogenesis. Medicine (Baltimore) 1969; 48(3):173-215.

5. Hadden RD, Cornblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV, et al. Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. Plasma Exchange/ Sandoglobulin Guillain-Barré Syndrome Trial Group. Ann Neurol. 1998;44(5):780–8.

6. Hughes RA, Cornblath DR: Guillain-Barre syndrome. Lancet 2005; 366:1653–1666.

7. CEA Gabriel, Jara Paula, Quevedo Fernando. Epidemiological characteristics of Guillain Barre Syndrome in the Chilean population: hospital study in a period of 7 years. Rev. Med. Chile 2015; 143(2):183-189.

8. Palmezano Díaz JM, Rodríguez Amaya RM, Rangel Rivera Diego Alejandro, Galvis Blanco Silvia Juliana, Camargo Ariza William Alejandro, Figueroa Pineda Claudia Lucia. Clinical profile of Guillain Barre Syndrome in a university hospital in Colombia. Archivos de Medicina 2017; 13(4):1-6.

9. De la O-Peña D, Robles-Figueroa M, Chávez-Peña Quetzalcóatl, Bedolla-Barajas Martín. Characteristics of Guillain Barre Syndrome in adults: results from university hospital. Rev Med Inst Mex Seguro Soc. 2015; 53(6):678-85.

10. Jackson B. R., Alomía Zegarra J., López-Gatell H, Sejvar J., Arzate F., Waterman S. Binational outbreak of Guillain–Barré syndrome associated with Campylobacter jejuni infection, Mexico and USA, 2011. Epidemiol. Infect. 2014; 142:1089–1099.

11. Ballón-Manrique Benigno, Campos-Ramos Neptalí. Clinical and paraclinical characteristics of Guillain Barre Syndrome in the regional hospital of Lambayeque. Rev Neuropsiquiatr. 2017; 80(1):22-26.

12. Levison L.S, Thomsen R.W, Christensen D.H, Mellemkjær T, Sindrup SH, Andersen H. Guillain-Barré Syndrome in Denmark: validation of diagnostic codes and a population-based nationwide study of the incidence in a 30-year period. Clinical Epidemiology [Internet] 2019; 11:275-283.

13. Mohammad Ali Arami, Mohammad Yazdchi, Reza Khandaghi. Epidemiology and characteristics of Guillain-Barré Syndrome in the northwest of Iran. Ann Saudi Med 2006; 26(1):22-27.

14. Kumar M, Aroor S, Mundkur S, Kumar S. Guillain-barré syndrome: a clinical study of twenty children. J Clin Diagn Res. 2015; 9(1):9-12.

15. Hung P-L, Chang W-N, Huang L-T, Huang S-C, Chang Y-C, Chang C-J, et al. A clinical and electrophysiologic survey of childhood Guillain-Barré syndrome. Pediatr Neurol. 2004; 30(2):86-91.

16. Akbayram S, Doğan M, Akgün C, Peker E, Sayın R, Aktar F, et al. Clinical features and prognosis with Guillain-Barré syndrome. Ann Indian Acad Neurol. 2011; 14(2):98-102.

17. Estrada González J.R., Goyenechea Ángel, Herrera C. Outbreak of Polyradiculoneuritis, LGBS type, during a Dengue epidemic. Rev Cub Hig Epidem. 1981; 19(3):252-265.

18. Rafael Estrada González. On the neurological syndromes that have occurred during our two recent Dengue virus epidemics and their possible relationships. Rev. Cub. Hig Epid 1983; 21:105-113.

19. Sacks JJ, Lieb S, Baldy LM, Berta S, Patton CM, White MC, et al. Epidemic campylobacteriosis associated with a community water supply. Am J Public Health. 1986; 76(4):424-8.

20. Naik KR, Saroja AO, and Patil BP. Familial Guillain-Barré syndrome: First Indian report. Ann Indian Acad Neurol. 2012; 15(1):44-47.

21. Pandey Shweta, Garg Ravindra Kumar, Malhotra Hardeep Singh, Kumar Neeraj and Uniyal Ravi. Simultaneous Occurrence of Axonal Guillain–Barré Syndrome in two siblings following Dengue infection. Ann Indian Acad Neurol. 2018; 21(4):315–317.

22. Gunatilake SSC, Gamlath Rohitha and Wimalaratna Harith. An unusual case of recurrent Guillain-Barré syndrome with normal cerebrospinal fluid protein levels: a case report. BMC Neurology 2016; 161(16):1-5.

23. Hernandez BA, Mendez FM, Elosegui IM. Recurrent Guillain Barre Syndrome. J Neurol Neurosci 2018; 9(4):266.

24. Verma Rajesh, Chaudhari Tejendra S, Giri Prithvi. Unilateral facial palsy in Guillain-Barre syndrome (GBS): a rare occurrence. BMJ Case Reports 2012; doi:10.1136/bcr-2012-007077.

25. Dimachkie MM. and Barohn RJ. Guillain-Barré Syndrome and Variants. Neurol Clin. 2013; 31(2):491–510.

26. Yuki N, Kokubun N, Kuwabara S, Sekiguchi Y, Ito M, Odaka M, et al. Guillain-Barré syndrome associated with normal or exaggerated tendon reflexes. J Neurol. 2012; 259(6):1181-90.

27. Lawn ND, Fletcher DD,Henderson RD, Wolter TD, Wijdicks EF. Anticipating mechanical ventilation in Guillain-Barre Syndrome. Arch Neurol 2001; 58:893-8.

28. Soysal A, Aysal F, Calıskan B, Dogan Ak P, Mutluay B, Sakallı N, Baybas S, Arpacı B. Clinico-electrophysiological findings and prognosis of Guillain-Barre syndrome - 10 years' experience. Acta Neurol Scand 2011; 123: 181–186.

29. Ropper AH. The Guillain-Barre Syndrome. NEJM 1992; 326 (17):1130-1136.

30. González-Quevedo A, Carriera RF, O'Farrill ZL, Luis IS, Becquer RM, Luis Gonzalez RS. An appraisal of blood-cerebrospinal fluid barrier dysfunction during the course of Guillain Barré syndrome. Neurol India 2009; 57(3):288-94.

31. Hense S, Schink T, Kreisel SH, Marcelon L, Simondon F, Tahden M, Garbe E. Estimation of background incidence rates of Guillain-Barré syndrome in Germany - a retrospective cohort study with electronic healthcare data. Neuroepidemiology. 2014; 43(3-4):244-52.

32. Hahn AF. Guillain-Barré syndrome. Lancet. 1998; 352(9128):635-41.

33. Al-Hakem Helle, Sindrup Soren H, Andersen Henning, Dornonville de la Cour Charlotte, Lassen Lisbeth L, Bianca Van den Berg et all. Guillain–Barré syndrome in Denmark: a population-based study on epidemiology, diagnosis and clinical severity. J Neurol. 2019; 266(2):440-449.

34. Varkal MA, Uzunhan TA, Aydınlı Nur, Ekici Barış, Çalışkan Mine and Özmen Meral. Pediatric Guillain-Barré syndrome: Indicators for a severe course. Ann Indian Acad Neurol. 2015; 18(1):24-28.

35. Willison HJ, Jacobs BC, Van Doorn PA. Guillain-Barré syndrome. Lancet 2016; 388:717-27.

36. Govoni V, Granieri E. Epidemiology of the GuillainBarre syndrome. Curr Opin Neurol. 2001; 14 (5): 605-13

37. Hariharan U, Chaudhary L and Bhasin N. Guillain-Barre Syndrome following combined Chikungunya and Dengue Infection: Critical Care Management and Future Research. Exploratory Research and Hypothesis in Medicine 2017; 2(1):30-32.

38. Webb AJ, Brain SA, Wood R, Rinaldi S, Turner MR. Seasonal variation in Guillain-Barré syndrome: a systematic review, meta-analysis and Oxfordshire cohort study. J Neurol Neurosurg Psychiatry 2015; 86(11):1196-201.

39. Verboon C, van Berghem H, van Doorn PA., Ruts L and Jacobs BC. Prediction of disease progression in Miller Fisher and overlap syndromes. Journal of the Peripheral Nervous System 2017; 22:446–450.

40. Chae CS, Kwon KM, Lee JS and Kim YH. A Case Report of Overlapping Miller Fisher Syndrome de Guillain-Barré Syndrome and the Bickerstaff Brainstem Encephalitis.The Neurologist 2018; 23:128–130.

41. Sekiguchia Y., Moria M., Misawaa S., Sawaia S., Yuki N., Beppua M. et al. How often and when Fisher syndrome is overlapped by Guillain-Barre sndrome or Bickerstaff brainstem encephalitis? European Journal of Neurology 2016; 23:1058-1063.

42. Walgaard C., Lingsma H.F., Ruts L., Van Doorn P.A., Steyerberg E.W., and Jacobs B.C. Early recognition of poor prognosis in Guillain-Barré syndrome. Neurology. 2011; 76(11):968–975.

43. Soo-Hyun Park, Nam-Hee Kim. Early Prediction Factors of Poor Outcome in Guillain-Barre Syndrome. Soonchunhyang Medical Science 2016; 22(2):79-82.

44. Van Koningsveld R, Van Doorn PA, Schmitz PIM, et al. Mild forms of Guillain-Barre syndrome in an epidemiologic survey in the Netherlands. Neurology 2000; 54(3):620-625.

45. Altaweel YA, Abdelaziz S, Fathy HA, AbdelBadea S. Correlative study between C-reactive protein, clinical severity, and nerve conduction studies in Guillain-Barrè syndrome. Egypt J Neurol Psychiatr Neurosurg. 2018;54(1):4.

46. J Kalita, UK Misra, Goyal G, Das M. Guillain-Barré syndrome: subtypes and predictors of outcome from India. JPNS. 2014; 19(1):36-43.

47. Petzold A., Hinds N., Murray N.M.F., Hirsch N.P., Grant D., Keir G. et all. CSF neurofilament levels: A potential prognostic marker in Guillain-Barré syndrome. Neurology 2006; 67:1071-1073.

48. Mokuno K, Kiyosawa K, Sugimura K, et al. Prognostic value of cerebrospinal fluid neuron-specific enolase and S-100b protein in Guillain-Barré syndrome. Acta Neurol Scand 1994; 89:27-30.

49. Bech E, Orntoft TF, Andersen LP. IgM anti-GM1 antibodies in the Guillain-Barré syndrome: a serological predictor of the clinical course. J Neuroimmunol 1997; 72:59-66.

50. Van der Pol W.L., Van den Berg L.H., Scheepers R.H. M., Van der Bom J.G., Van Doorn P.A., Van Koningsveld R. et all. IgG receptor IIa alleles determines susceptibility and severity of Guillain-Barré syndrome. Neurology 2000; 54(8):1661-1665.