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Guillain–Barré syndrome in Colombia: where do we stand now?

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Abstract Guillain–Barré syndrome (GBS) is a rapid-onset muscle weakness disease caused by the immune-mediated damage of the peripheral nervous system. Since there is an increase incidence of GBS cases in Latin America, particularly in Colombia, and most of them are currently preceded by Zika virus (ZIKV) infection, we aimed to assess the available evidence of the disease in Colombia through a systematic literature review. Out of 51 screened abstracts, only 16 corresponded to articles that met inclusion criteria, of which 15 were case reports or case series. A total of 796 cases of GBS were reported in the included articles. The majority of patients were males (66.8 %) and younger than 50 years old (94 %). An infectious disease before the onset of GBS was registered in 31 % of patients, with gastrointestinal or respiratory symptoms being the most frequently observed. In those cases in which electrodiagnostic tests were performed, the most common subphenotype was acute inflammatory demyelinating polyneuropathy (17 %). Death was reported in 15 % of patients. Data regarding GBS in Colombia is scant and heterogeneous. Taking into account the burden of the disease and the recent rise of GBS cases associated with ZIKV, a careful patient evaluation and a systematic collection of data are warranted. A form to data gathering is proposed.

Keywords Guillain–Barré syndrome · Zika virus · Anti-gangliosides antibodies · Latin America

Abbreviations

AIDP	Acute inflammatory demyelinating polyneuropathy
AMAN	Acute motor axonal neuropathy
AMSAN	Acute motor sensory axonal neuropathy
GQ1b	Anti-ganglioside Q1b
BBE	Bickerstaff's brainstem encephalitis
CHIKV	Chikungunya virus
GBS	Guillain–Barré syndrome
ICU	Intensive care unit
IVIg	Intravenous immunoglobulins
MFS	Miller–Fisher syndrome
MCN	Multiple cranial neuropathy
NCS	Nerve conduction studies
ZIKV	Zika virus

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Introduction

In 1916, Guillain, Barré and Strohl fully described a syndrome of radiculoneuritis with increased albumin in the cerebrospinal fluids without cellular reaction. They reported the cases of two patients who presented with "motor difficulty, abolition of deep tendon reflexes with

preservation of cutaneous reflexes, paresthesias without demonstrable objective sensory loss, pain on deep palpation of large muscles, minor modifications in electrical reactions of nerve and muscle, and increased albumin in the cerebrospinal fluid with, most notably, absence of cellular reaction (albuminocytological dissociation)" [1]. Currently, one hundred years after Guillain, Barré and Strohl's description publication, Guillain–Barré syndrome (GBS) diagnosis is still based on similar criteria [2, 3].

It is globally accepted that GBS is an immune-mediated peripheral neuropathy affecting both the myelin sheath and axons, in which cellular and humoral immune responses are involved in the pathogenesis of the disease [4]. Serum anti-ganglioside antibodies represent a major player in the induction and perpetuation of GBS pathology [5] and are associated with a preceding infection, vaccination, or exposure to toxic substances [6]. The most common pathogen associated with GBS is *Campylobacter jejuni* [4]. In addition, GBS cases have been reported following cytomegalovirus [7], Epstein–Barr virus [8], *Mycoplasma pneumoniae* [9], Haemophilus influenza [10], influenza virus [11], Hepatitis E [12], Dengue [13], Chikungunya (CHIKV) [14] and Zika virus (ZIKV) infections [15], among others. Moreover, vaccination campaigns against influenza A (H1N1) [4] and rabies prophylactic vaccination [16] were associated with a small risk of GBS.

The most common subphenotypes of GBS are acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) [4, 6]. Overall, the clinical course, severity, and outcomes of GBS are highly variable. However, with the identification of several new subphenotypes in the past 30 years, the conceptual framework of GBS has become increasingly complex. New diagnostic classification has been recently published in order to enable neurologists and non-neurologists to diagnose GBS and all its variants using a simple yet all-inclusive classification system [17].

An increasing number of severe neurological complications associated with ZIKV, mainly GBS and primary microcephaly, have led the World Health Organization to declare a global health emergency, which should provide impetus for collaborative research programs to evaluate the relations between ZIKV and these neurological conditions [18]. During the period of enhanced surveillance for neurological syndrome from December 2015 up to the 10th epidemiological week of 2016, Colombia detected 352 cases of neurological syndrome with history of ZIKV symptoms including 248 cases of GBS [19]. This prompted us to systematically review the available evidence based on GBS in Colombia and to propose a methodology to collect data regarding GBS associated with ZIKV infection in order to motivate physicians to report and study those cases.

Methods

Information sources and search strategy

On February 23, 2016 a systematic literature review was conducted, the search was performed in both international and Latin American electronic databases. We searched for "Colombia" AND "Guillain Barré" in OVID, Embase, Web of Science and Virtual Health Library platforms. We also hand-searched the references of the included articles in order to identify additional studies for inclusion. Additional information sources included personal communications and author's repositories. No date, language, or population limits were applied.

Eligibility criteria

To be included, the article had to have been conducted in Colombian population and to describe methods implemented to study, diagnose, treat or rehabilitate patients affected by GBS. Moreover, studies that compared the prevalence of GBS in two populations, factors associated with GBS, the prevalence of GBS before and after a specific intervention, or the clinical outcomes of patients affected by GBS were also included. Case reports, case series, clinical trials, cohort (prospective/retrospective), cross-sectional, and case–control studies were included.

Studies that did not include the population of interest, or that did not present relevant outcomes for the population of interest separately to outcomes for other population were excluded. We also excluded systematic literature reviews and meta-analyses.

Study selection and data extraction process

Eligibility assessment was done by a primary reviewer who screened all titles and abstracts of publications. Retrieved articles were rejected if eligibility criteria were not met, and a secondary reviewer was consulted in cases in which eligibility criteria were unclear.

A single author extracted the information regarding population, intervention, comparator, outcomes, and study design of all included studies; after that, a second reviewer verified the extracted information. Any discrepancies or missing information were resolved by consensus.

We followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses [20] during the data extraction, analysis, and reporting phases of our review.

Results

Search results

A total of 48 records were identified through databases searching. Three additional articles were identified from other resources. After deduplication, the titles and abstracts of 43 articles were screened. In the screening phase, seventeen studies were excluded. After that, 26 full-text articles were assessed for eligibility.

Six full-text articles written by Ortiz-Corredor et al. [21–26] were evaluated; however, only one [25] was included in the review because the rest of them studied patients from the same hospital and the same period of time that the included one.

Moreover, after full-text assessment, one study was excluded because it was not about Colombian population [27] and another one was excluded because it did not describe specific outcomes for Colombian patients [28].

Two articles whose titles contained the search terms were excluded because it was not possible to find out the full texts [29, 30].

Finally, sixteen studies were included for qualitative analysis (Fig. 1). Table 1 summarizes the main characteristics of all studies [14, 16, 25, 31–43].

Demographic data

A total of 796 cases of GBS in Colombian patients were reported in the included articles. The majority of patients were males (67 %). The studies included patients from a wide range of ages from 1 to 82 years old; however, the majority of cases were reported in patients younger than 50 years old (94 %). Near the 70 % of patients were younger than 20 years old.

Clinical classification and diagnosis

In 58 % of cases, nerve conduction studies (NCS) were not performed or were not reported. In those articles that described NCS results, the most frequent subphenotype of GBS was the AIDP. The NCS results and GBS subphenotypes described in the included articles are shown in Fig. 2.

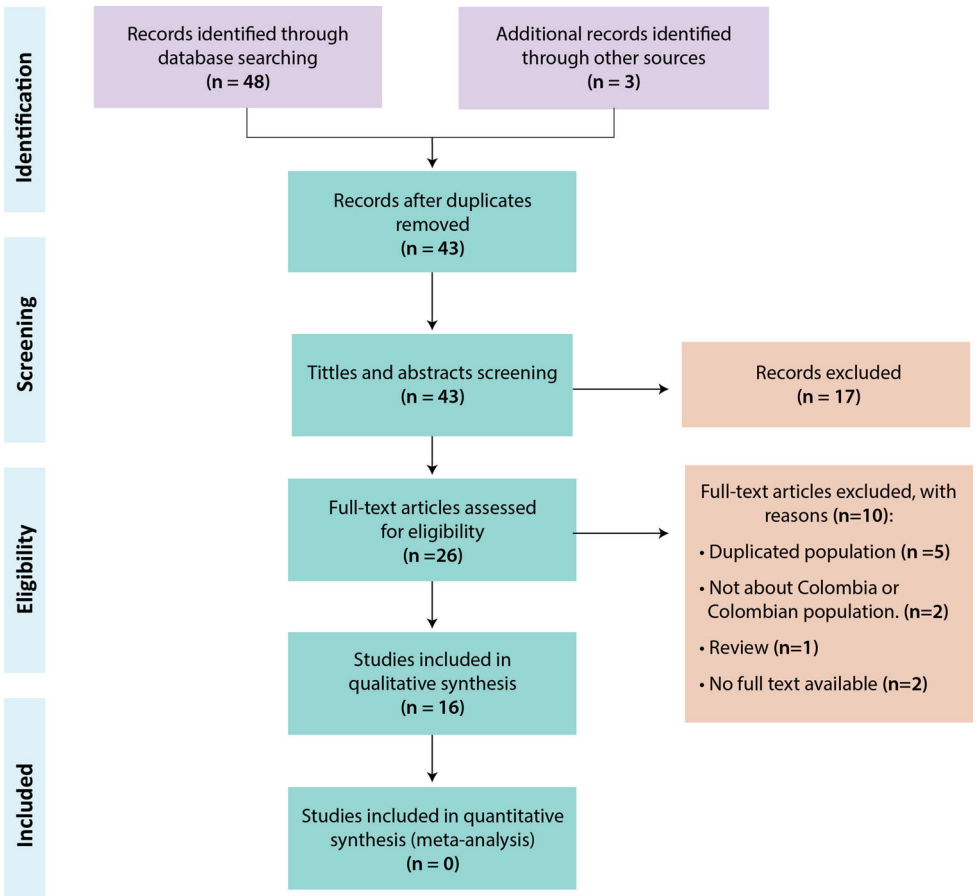

Fig. 1 Selection process. We followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses [20]

Table 1 Summary of included studies

Author	Type of study	GBS cases (*n*)	GBS subphenotype and NCS findings (*n*)	History of previous infection (*n*)	History of recent vaccination (*n*)	Treatment (*n*)	Outcomes (*n*)
Lopez et al. [38]	Case series	17	Not described* (17)	Gastrointestinal or respiratory tract infection (10)	No	Symptomatic treatment exclusively (7) Intravenous ACTH (3) Prednisone 30 mg QD (3) ACTH + Prednisone: (3)	Deaths (3) Four months after the illness, 8 patients completely recovered 1 patient recovered after 8 months After 18 months two patients remained with wasting of the small muscles of the hand
Toro et al. [40]	Case series	16	Not described (16)	Rabies encephalitis (1)	SMB rabies vaccination (16) Neurological symptoms occurred on average after 13 doses of the vaccine (range 4–18 injections) The latent period between the first dose of the vaccine and the onset of neurological symptoms (GSB or others) averaged 14 days	Corticosteroids and respiratory assistance (16)	Deaths (6) Three patients left the hospital without major sequelae after an average stay of 42 days 7 out of13 cases survived after respiratory insufficiency. They left the hospital with severe sequelae after a mean hospital stay of 89 days
Vergara et al. [16]	Case report	1	Not described (1)	No stated	SMB rabies vaccination (1) The patient received seven subcutaneous doses. The symptoms appeared 6 days after termination of the vaccination	High dose of corticosteroids and respiratory assistance (1)	Deaths (1)
Palacios [42]	Case series	339	MFS (3) Not described (336)	Gastrointestinal or respiratory tract infection (198)	Not stated	Respiratory assistance	Deaths (51) 27 patients required tracheostomy 37 patients presented respiratory tract infections or atelectasis 8 patients recidivated, 4 of them died
Escobar et al. [32]	Epidemiologic report	11	Not described (11)	Gastrointestinal or respiratory tract infection (6)	Polio vaccine (1). The patient had received 3 doses of the vaccine 12, 11 and 10 months before developing GBS	Respiratory assistance (5)	Deaths (4)
Delgado et al. [31]	Case report	1	MFS (1)	Gastrointestinal or respiratory tract infection (1) Salmonella—Serotype D: 12–9 was identified in patient stools	Not stated	Respiratory assistance (1)	No post-discharge outcomes were described

Table 1 continued

Author	Type of study	GBS cases (*n*)	GBS subphenotype and NCS findings (*n*)	History of previous infection (*n*)	History of recent vaccination (*n*)	Treatment (*n*)	Outcomes (*n*)
Ortiz-Corredor et al. [25]	Retrospective cohort	332	AIDP (104) AMAN (102) Other** (51) Not described (75)	Not stated	Not stated	Respiratory assistance. (86) IV-immunoglobulin (122)	Muscular strength at day 10 of the disease was the most important predictor to determine motor recovery
Isaza et al. [37]	Case series	46	AIDP (24) AMAN (14) AMSAN (5) Other (1) Not described (2)	Gastrointestinal or respiratory tract infection (5)	Not stated	Plasmapheresis (11) IV-immunoglobulin (12)	Deaths (3) 66.7 % of patients treated with immunoglobulin and 40 % of patients treated with plasmapheresis, improved their Hughes scale score Dysautonomia and pneumonia were the most frequent complications
Toro et al. [43]	Case report	1	MCN (1)	Gastrointestinal or respiratory tract infection (1)	No	IV-immunoglobulin (1)	Tracheostomy and gastrostomy tubes were placed Patient was discharged 3 months after the admission with a Hughes scale of 2
Guerra et al. [34]	Case report	1	BBE (1)	No	No	Respiratory assistance and IV-immunoglobulin (2)	Tracheostomy and gastrostomy tubes were placed The patient was discharged 1 month after the admission
González et al. [33]	Case series	25	AIDP (8) AMAN (7) AMSAN (7) MFS (3)	Gastrointestinal or respiratory tract infection (21)	Not stated	IV-immunoglobulin (3) Plasmapheresis (22) Respiratory assistance (12)	Deaths (1) Complications: Dysautonomia (36 %) Hyponatremia (40 %) Urinary tract infection (16 %) Tracheitis (12 %) Ventilator associated pneumonia (20 %) Vasopressor requirement (24 %)
Córdoba et al. [39]	Case series	1	Not described (1)	No stated	Not stated	Plasmapheresis (1)	After the completion of the treatment the patient recovered the ability to swallow and to walk without assistance

Table 1 continued

Author	Type of study	GBS cases (*n*)	GBS subphenotype and NCS findings (*n*)	History of previous infection (*n*)	History of recent vaccination (*n*)	Treatment (*n*)	Outcomes (*n*)
Guzmán et al. [35]	Case report	1	AIDP (1)	Gastrointestinal or respiratory tract infection (1)	Not stated	Plasmapheresis (1)	After the last session of plasmapheresis, the patient gradually recovered the strength of lower limbs The patient required additional treatment with methimazole in order to control the hyperthyroidism
Villamil-Gómez et al. [14]	Case report	1	AIDP (1)	CHIKV infection (1)	Not stated	IV-immunoglobulin (1)	The patient was discharged on day 30 post-admission. Eight weeks after onset of symptoms, the patient reported a satisfactory full recovery
Hernández-Beltrán et al. [36]	Case report	1	AMAN (1)	*Trypanosoma cruzi* infection—Chagas disease (1)	Not stated	IV-immunoglobulin (1)	The patient was discharged on day 15 post-admission
Gonzalez et al. [41]	Case report	2	AIDP (1) Not described (1)	Dengue (2)	Not stated	IV-immunoglobulin (2) Respiratory assistance (1)	Ventilator associated pneumonia (2) Tracheitis (1) Bilateral deep venous thrombosis (1) Submassive pulmonary embolism (1) Dysautonomia (1) Acute renal failure (1) Urinary tract infection (1)

ACTH adrenocorticotrophic hormone, *AIDP* acute inflammatory demyelinating polyneuropathy, *AMAN* acute motor axonal neuropathy, *AMSAN* acute motor sensory axonal neuropathy, *BBE* Bickerstaff's brainstem encephalitis, *CHIKV* chikungunya virus, *GBS* Guillain–Barré syndrome, *IV* intravenous, *MCN* multiple cranial neuropathy, *MFS* Miller–Fisher syndrome, *SMB* suckling mouse brain, *QD* once a day

* In this category, we included electrodiagnostic results classified as equivocal ($n = 14$), inexcitable ($n = 26$), normal ($n = 1$), and without diagnostic criteria ($n = 1$)

** In this category, we included reports that did not describe nerve conduction studies results or that did not performed it

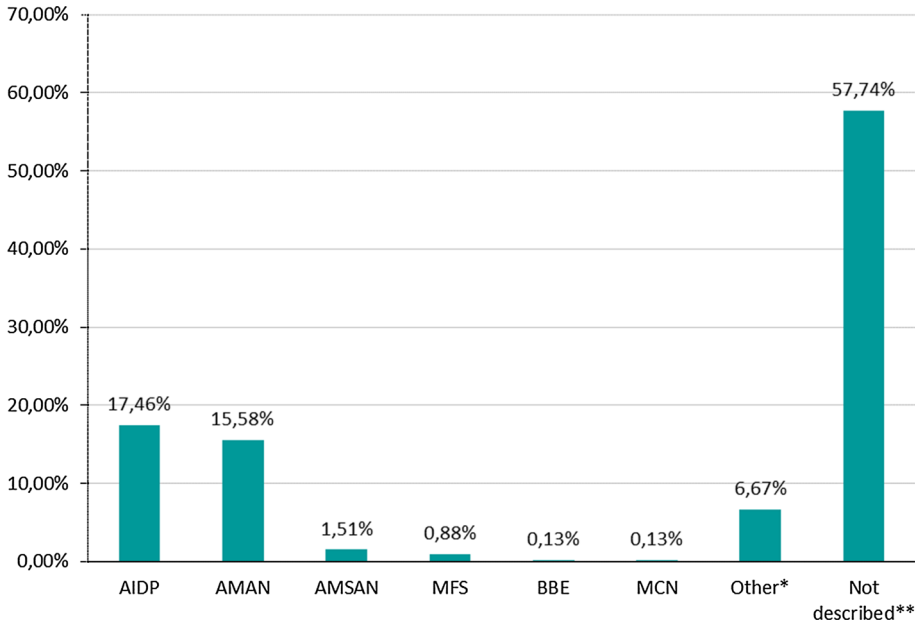

Fig. 2 GBS subphenotypes in Colombian patients. *GBS* Guillain–Barré syndrome, *AIDP* acute inflammatory demyelinating polyneuropathy, *AMAN* acute motor axonal neuropathy, *AMSAN* acute motor sensory axonal neuropathy, *MFS* Miller–Fisher syndrome, *BBE* Bickerstaff's brainstem encephalitis, *MCN* multiple cranial neuropathy. *In this category, we included electrodiagnostic results classified as equivocal ($n = 14$), inexcitable ($n = 26$), normal ($n = 1$), or without diagnostic criteria ($n = 1$). **In this category, we included reports that did not describe electromyography—nerve conduction studies results or that did not performed it

Pathophysiology and immunopathology

An infectious disease previous the onset of GBS was reported in 248 (31 %) patients. Eight articles [31–33, 35, 37, 38, 42, 43] reported patients who had respiratory and/or gastrointestinal infections before the start of GBS symptoms. Only one article described the cause of the gastrointestinal infection (i.e., *Salmonella*) [31]. Moreover, four patients were diagnosed with CHIKV, Chagas disease, or Dengue virus ($n = 2$) infection in the workup done during the course of GBS [14, 36, 41].

Suckling mouse brain (SMB) rabies vaccination preceded the onset of neurological symptoms in 17 patients included in two studies [16, 40]. Moreover, a two-year-old patient had received three doses of polio vaccine 12, 11, and 10 months before developing GBS [32]. No other cases of vaccination before the onset of GBS symptoms were reported.

Anti-Ganglioside Q1b (GQ1b) antibodies were found in one patient presenting with BBE [34]. In another patient, who presented with multiple cranial neuropathy variant of SGB, the serum anti-GQ1b antibodies were negative [43]. In addition, one patient presented with GBS concomitant with Graves' disease [35]. No other autoantibodies or autoimmune diseases were reported in patients with GBS.

Treatment and outcomes

With the information provided in the included articles was not possible to establish differences between the clinical outcomes of patients from different age or sex groups.

Regarding the therapeutic strategies implemented, articles published before 1980 described treatment approaches that included respiratory assistance and symptomatic treatment, intravenous adrenocorticotropic hormone, or corticosteroids [16, 38, 40]. Later articles described treatment with intravenous immunoglobulins (IVIg) or plasmapheresis along with respiratory assistance [14, 25, 31–37, 39, 41–43]. The evaluation of the effectiveness of those therapeutic approaches is over the scope of this review.

Reported complications included tracheostomy or gastrostomy requirement, dysautonomia, hyponatremia, urinary or respiratory tract infections, tracheitis, atelectasis, GBS relapses, ventilator associated pneumonia, deep venous thrombosis, pulmonary embolism, and acute renal failure.

Only 13 articles reported the number of deaths within their studied population; 69 out of 462 patients died (15 %).

Discussion

This study systematically reviewed the available evidence based about GBS in Colombia. It was found that the majority of studies about GBS in Colombia are case series or case reports.

In accordance with the worldwide trend [44], the majority of patients included in our review were males. Because of the design of our study, we were not able to calculate the incidence rate of GBS in Colombia; however, it is noticeable that the majority of cases were reported in young patients. It is contrary to previous reviews that observed increases in incidence rates of GBS in people aged 50 years or more [44].

As it has been previously described in other countries, the majority GBS cases in Colombia were associated with the presence of gastrointestinal and/or respiratory tract symptoms in the weeks before the onset of neurological symptoms [4]. Tropical infections like *Trypanosoma cruzi* [36], CHIKV [14], and Dengue virus [41] were also associated with GBS cases in Colombia.

Regarding the association between GBS and vaccination, it is important to note that, until 40 years ago, GBS in Colombia was also associated with SMB rabies vaccination. Those neuroparalytic accidents were caused by the presence of animal myelin in the vaccines that caused sensitization in some recipients with the subsequent production of autoantibodies against myelin [45]. Currently, rabies vaccines used in Colombia are not produced in animals' brain but in human cells cultures [46], and the latter provide good immunogenicity with a better safety profile than the former [45].

Heterogeneous classification systems were implemented to describe GBS cases in Colombia. As it has been previously reported in other South American countries [47–49], the most frequent subphenotype reported in Colombia was AIDP. Conversely, in Mexico AMAN subphenotype is the most frequently observed [50].

A clear distinction of GBS by means of clinical and electrodiagnostic tools may be difficult [49]. AIDP is sometimes mistaken for AMAN if conventional electrodiagnostic data are applied as patients with AMAN have a rapidly reversible conduction block or slowing evident on sequential studies. Such conduction blocks disappear with no electrophysiological evidence of remyelination in patients with AMAN [49, 51]. In non-tropical countries, a clear seasonal distribution of the cases of GBS has been reported [52]. It has been hypothesized that AMAN is more prevalent with poor hygiene infrastructures and higher incidence of diarrhea [49]. Genetic factors may also account for the different clinical patterns of the disease [53].

Just two studies in Colombia examined the presence of anti-ganglioside antibodies [34, 43]. Serum antibodies against many peripheral nerve antigens have been found in GBS. The clinical subphenotypes of GBS are related to the antigenic specificities of these antibodies, and the distribution of gangliosides in peripheral nervous tissues may help explain the heterogeneous clinical presentation of GBS, but an important number of patients with GBS have no identified autoantibodies [54]. Anti-GM1 antibodies are associated with distal muscle weakness, fewer sensory deficits, more axonal degeneration, and *C. jejuni* infection [55]. The presence of anti-ganglioside antibodies does not influence treatment [3].

Studies designed to identify the targets of the autoimmune response to molecules such as gangliosides and peptides sharing between ZIKV and human proteins may represent an underexploited opportunity to examine the increased incidence of neurological complications related to ZIKV infection [56, 57].

Although there are not conclusive data about the burden of GBS in Colombia, it is estimated to be high. Almost all the patients with this condition require hospitalization and one-third of them need to be admitted to the intensive care unit (ICU) because of respiratory failure, dysautonomia, or because of medical complications [58]. Most of the patients require therapeutic plasma exchange or intravenous immunoglobulin infusion therapy [59] and long-term disability, and change in their social status is not uncommon [60]. The mortality reported in the articles included in our review is still high (15 %). Reported mortality in GBS ranges between 1 and 18 % [61, 62]. Death results from pneumonia, sepsis, adult respiratory distress syndrome, and less frequently due to autonomic dysfunction or pulmonary embolism [62].

During a recent ZIKV outbreak in French Polynesia, 42 patients were diagnosed with GBS [63]. Of them, 88 % reported having experienced a transient illness about one week before the onset of neurological symptoms and <50 % disclosed the presence of anti-ganglioside antibodies [63]. Patients had electrophysiological findings compatible with AMAN subphenotype. The patients deteriorated rapidly with 38 % of them requiring ICU, most commonly owing to difficulty breathing or swallowing. The average length of ICU stay was 35 days. Most of the patients recovered relatively quickly, and 3 months after discharge from hospital, 57 % were able to walk. The risk of GBS was estimated to be 0.24 per 1000 ZIKV infections [63].

According to the Colombian National System for Public Health Surveillance, the number of cases of GBS in Colombia is increasing in recent years, with 837 and 1.037 cases registered in 2013 and 2014, respectively [64]. Taking into account, these numbers and the new ones

associated with ZIKV are probably that new studies will be published soon. In order to contribute to the study of the association between ZIKV and GBS, it is necessary that clinical data to be systematically collected and shared. We propose a methodology to collect data regarding GBS cases in order to motivate physicians to report and study those cases (Appendix A of Electronic supplementary material). We hope that those forms help to standardize the available data and to contribute to the study of the association between ZIKV and other infections and GBS.

Conclusions

Data regarding GBS in Colombia is scant and heterogeneous. Taking into account, the burden of the disease and the recent risen of GBS cases associated with ZIKV epidemic is recommend that clinical data from GBS cases be systematically collected and shared. A methodology to collect these data is proposed.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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