Guillain–Barré syndrome and Zika virus outbreaks

Osvaldo J.M. Nascimento[a] *and Ivan R.F. da Silva*[b]

Purpose of review
Arboviruses have been associated with central and peripheral nervous system injuries, in special the flaviviruses. Guillain–Barré syndrome (GBS), transverse myelitis, meningoencephalitis, ophthalmological manifestations, and other neurological complications have been recently associated to Zika virus (ZIKV) infection. In this review, we aim to analyze the epidemiological aspects, possible pathophysiology, and what we have learned about the clinical and laboratory findings, as well as treatment of patients with ZIKV-associated neurological complications.

Recent findings
In the last decades, case series have suggested a possible link between flaviviruses and development of GBS. Recently, large outbreaks of ZIKV infection in Asia and the Americas have led to an increased incidence of GBS in these territories. Rapidly, several case reports and case series have reported an increase of all clinical forms and electrophysiological patterns of GBS, also including cases with associated central nervous system involvement. Finally, cases suggestive of acute transient polyneuritis, as well as acute and progressive postinfectious neuropathies associated to ZIKV infection have been reported, questioning the usually implicated mechanisms of neuronal injury.

Summary
The recent ZIKV outbreaks have triggered the occurrence of a myriad of neurological manifestations likely associated to this arbovirosis, in special GBS and its variants.

Keywords
acute polyneuropathy, chronic inflammatory demyelinating polyradiculoneuropathy, Guillain–Barré syndrome, imaging, zika

INTRODUCTION

Zika virus (ZIKV) is a relatively new entrant to an extensive list of viruses that have alerted the world over the last decades. Arboviruses have been previously associated with central nervous system (CNS) and peripheral nervous system injuries, especially flaviviruses, such as the dengue virus (DENV), Japanese Encephalitis virus, and West Nile virus [1], and an alphavirus, the chikungunya virus (CHKV) [2].

Frequent reports of severe neurological complications likely to be associated with ZIKV infection have been published over the last 2 years, culminating on 1 February 2016, with a declaration from the WHO of a public health emergency of international concern [3]. The most notable of these reports were those pertaining to microcephaly in fetuses and newborns, and Guillain–Barré syndrome (GBS) in adults. The aim of this review was to focus on the relationship of ZIKV infection as a trigger for GBS.

HISTORY AND EPIDEMIOLOGY

ZIKV is an enveloped, single-stranded RNA arbovirus, belonging to the *Flaviviridae* family, being first isolated in 1947 from a Rhesus monkey in the Zika forest (Uganda) [4]. The virus is mostly transmitted by mosquitoes of the *Aedes aegypti* genus, but evidence suggests possible transmission by *Aedes albopictus* mosquitoes as well [4]. During previous outbreaks, it has become evident that intrauterine transmission might play an important role in cases of microcephaly [5]. There are reports of possible transmission via sexual intercourse, laboratories, and blood transfusions [6].

Approximately, 14 cases of an acute febrile exanthematous disease associated with ZIKV infection in humans were reported before the first large outbreak occurred in 2007, in the Yap Islands of Micronesia

[a]Neurology Department, Universidade Federal Fluminense, Rio de Janeiro, Brazil and [b]Neurocritical Care Section, Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA

Correspondence to Osvaldo J.M. Nascimento, MD, PhD, Rua Siqueira Campos, 53/1204, Copacabana, RJ, 22031071 Brazil.
Tel: +55 21 999846044; e-mail: osvaldo_nascimento@hotmail.com

[4]. In 2013–2014, another large outbreak of ZIKV occurred in the French Polynesia, leading to an increased incidence of neurological complications, most notably, GBS [5]. In 2015–2016, ZIKV infected individuals in South America, first in Northeast Brazil, rapidly disseminating to other South American, Caribbean, and Central American countries, finally reaching North America by the end of 2016 [7]. Imported cases of ZIKV infection (some with neurological injuries [8]) were reported in Europe [9,10].

CAUSAL INFERENCE

Several studies, varying from case reports to prospective studies in the population have tried to elucidate a probable association between ZIKV infection and the development of GBS (ZIKV–GBS). The first reported case of ZIKV–GBS was that of a female patient during the French Polynesian outbreak in 2014 [11]. Later, in 2015–2016, some studies in South America have reported chronologically related significant increases in the hospital admissions for GBS and ZIKV outbreak [12–16]. A case–control study utilizing samples from the 2013–2014 outbreak in the French Polynesia revealed that 41 out of 42 patients with GBS had evidence of recent ZIKV infection using serological testing [immunoglobulin M (IgM) and/or immunoglobulin G (IgG)] and Plaque reduction neutralization test (PRNT) [17]. A major limitation of this study relies on the fact that, approximately 95% of patients with GBS tested positive for serum dengue IgG and 19% for dengue IgM, and even though all 41 patients had PRNT neutralizing antibodies to ZIKV, only one patient had titers at least four times higher than

dengue titers, making it extremely difficult to eliminate the possibility of cross-reactivity. A large cohort of GBS cases from Colombia tested using ZIKV real-time reverse transcriptase PCR (rRT-PCR) and serological techniques studied 66 patients with symptoms compatible with ZIKV infection before the onset of acute weakness suggestive of GBS [18]. Among the 42 patients who had their samples tested for ZIKV using RT-PCR, the results were positive in 17 patients (40%). A major problem was the fact that, the investigators were able to definitively diagnose both ZIKV infection (using rRT-PCR) and GBS (respecting level 1 Brighton criteria) in 14/68 (20%) patients alone, initially. Finally, the only prospective cohort study conducted to date that analyzed the neurological complications following ZIKV infection, revealed that among 40 patients admitted to a tertiary neurological referral center in Rio de Janeiro, Brazil, 35 (88%) had molecular and/or serological evidence of recent ZIKV infection, based on serum and/or cerebrospinal fluid (CSF) testing [19]. Compared to historical records from the same institution, the GBS admissions had increased from an average of 1.0/month to 5.6/month [19]. Table 1 describes the studies associating ZIKV and GBS [11,12,17–30].

PATHOPHYSIOLOGY

GBS is generally considered an immune-mediated, postexposure neuropathy, usually developing up to 4 weeks after an infection or any other stimuli, leading to an increased immune response and molecular mimicry between an inciting agent and nerve antigens, targeting peripheral nerves and their respective spinal roots [31,32]. ZIKV–GBS has defied some of the current knowledge, as in most studies, the weakness developed roughly 6–10 days after the initial viral symptoms [17–19]; this is relatively too rapid to be an autoimmune reaction to a first exposure to a virus. Also, the antigens involved in molecular mimicry might be different from the ones usually involved in GBS. Analysis of blood samples from the French Polynesia study revealed that less than 50% of the sera at admission had a significant autoimmune response against glycolipids, including gangliosides or glycolipid complexes, and that complementary analysis of reactivity against ganglioside GA1 did not show any competition between this antigen and the ZIKV proteins [17]. A recent study has demonstrated that, there is a high peptide overlap between the ZIKV polyprotein and human proteins related to myelin, demyelination, and axonal neuropathy [33]. Finally, we have performed a fascicular sural nerve biopsy in a male patient with ZIKV–GBS, which showed

Table 1. Studies associating Zika virus and Guillain–Barré syndrome

Country	Year	No. of patients	Symptom	Sample tested	ZIKV detection method	EMG findings	References
French Polynesia	2013	1	GBS	Serum	Anti-ZIKV IgG ELISA and PRNT	AIDP	Oehler et al. [11]
Brazil	2015	4	GBS	Serum or CSF	RT-PCR and/or anti-ZIKV IgM ELISA	Not reported	Araujo et al. [12]
French Polynesia	2013–2014	42	GBS	Serum	Seroneutralization assay and anti-ZIKV IgM/IgG ELISA	AMAN	Cao-Lormeau et al. [17]
Colombia	2016	68	GBS	Blood, urine, and CSF	RT-PCR and antiflavivirus antibody ELISA	36 with AIDP, 4 equivocal, 2 normal, 3 unexcitable, and 1 AMAN	Parra et al. [18]
Brazil	2017	35	GBS, Encephalitis, Myelitis	Serum and CSF	RT-PCR/MAC-ELISA	18 with AIDP, 2 AMAN, 6 AMSAN, and 1 MFS	Da Silva et al. [19]
Colombia	2015–2016	19	GBS	Serum	RT-PCR	AMAN	Arias et al. [20]
Canada	2015–2016	2	GBS	Not reported	RT-PCR, anti-ZIKV IgM ELISA, and seroneutralization assay	Not reported	Boggild et al. 2017 [21]
Brazil	2014	1	GBS	Serum, saliva, CSF, and urine	RT-PCR and anti-ZIKV IgM/G ELISA	Without findings	Brasil et al. [22]
Puerto Rico	2015–2016	5	GBS	Serum	RT-PCR and/or anti-ZIKV IgM ELISA	AIDP	Dirlikov et al. [23]
Brazil	2015	2	GBS	Not reported	RT-PCR, anti-ZIKV IgM ELISA, and PRNT	AIDP	do Rosario et al. [24]
United States	2016	1	GBS	Urine	RT-PCR	AIDP	Fabrizius et al. [25]
Brazil	2016	1	GBS	Not reported	Not reported	AIDP	Fontes et al. [26]
Suriname	2016	3	GBS	Urine	RT-PCR, seroneutralization assay, and anti-ZIKV IgG ELISA	AIDP	Langerak et al. [27]
New Zealand	2016	1	GBS	Serum	RT-PCR and Anti-ZIKV IgM/G ELISA	AIDP	Siu et al. [28]
Colombia	2016	16	GBS	Not reported	RT-PCR	Not reported	Villamil-Gomez et al. [29]
Martinique	2015	2	GBS	Urine	RT-PCR	AIDP	Roze et al. [30]

AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory axonal neuropathy; CSF, cerebrospinal fluid; EMG, electromyography; GBS, Guillain–Barré syndrome; IgG, immunoglobulin G; IgM, immunoglobulin M; MAC, IgM antibody capture; MFS, miller fisher syndrome; PRNT, plaque reduction neutralization test; RT-PCR, reverse transcriptase PCR; ZIKV, Zika virus.

predominantly nerve fiber demyelination and some fibers with axonal degeneration, associated with the presence of mononuclear inflammatory cells, consistent with the classical GBS findings reported by Ritter *et al.* [34]. Special techniques applied to the sample disclosed no direct viral infection (including RT-PCR), suggesting a cross-reactive immune response.

Finally, in a case series of three patients from Brazil, the patients developed acute ZIKV infection accompanied by clinical findings consistent with a mild, self-limited, distal, sensorimotor neuropathy [35]. All patients presented with weakness and frank clinical viral symptoms with positive ZIKV RT-PCR results. Electrophysiological, MRI, and CSF studies were normal in all patients; however, the nerve ultrasonography revealed significant nerve edema that subsided weeks after the resolution of symptoms. This phenomenon was named the ZIKV infection-associated acute transient polyneuritis, possibly caused by the direct action of the ZIKV on the peripheral nerves.

VIRAL DIAGNOSIS

ZIKV infection can mimic the clinical signs and symptoms of DENV and CHKV, and there is a lack of a simple laboratory test for a prompt diagnosis. These three viral infections might present with an acute exanthematous fever, normally associated with a maculopapular skin rash, conjunctivitis, and edema, along with headache, myalgia, and arthralgia, with subtle differences in the presentation. The rash might be more prominent with ZIKV, whereas DENV leads to more pronounced headaches and generalized pain, with CHKV frequently causing incapacitating arthralgia and/or arthritis.

Recommendations for the diagnosis of ZIKV infection have been suggested by the Pan American Health Organization and the WHO [36].

rRT-PCR for ZIKV is the gold standard test to prove acute ZIKV infection; however, its positivity is very transient, usually persisting no longer than 5–7 days in the blood and CSF [37]. Its positivity might be observed in urine samples for a few weeks [18].

Regarding the postinfectious syndromes, rRT-PCR might be negative, but ZIKV IgM antibody capture ELISA might remain positive in the blood and CSF samples for a longer period [37,38]. Diagnosing acute ZIKV infection with the aid of serological testing is complicated in regions with endemic DENV as cross-reactivity is known to occur [36]. PRNT can be performed to help differentiate anti-ZIKV antibodies from cross-reacting antibodies

that originate by exposure to other flaviviruses, but with a low specificity. ZIKV titers must be at least four-fold higher than any other flavivirus to be considered indicative of ZIKV infection [36]. PRNT also is expensive, and requires cell culture and specialized, experienced laboratories, as no commercial kit is available [39]. Therefore, since December 2016, the centers for disease control and prevention no longer recommend the use of PRNT in areas with endemic presence of other flaviviruses, owing to its low accuracy [37]. Recently, a Brazilian study has shown that cross-reactivity might be overcome by using ZIKV IgM antibody capture ELISA of both CSF and serum in cases of ZIKV-associated neurological complications [19]. The IgM pentamer is considered too large to cross the blood–brain barrier and its positivity in the CSF suggests recent intrathecal antibody synthesis and direct CNS penetration of ZIKV [40,41]. In areas endemic for DENV, a serum dengue IgM for serotypes 1–4 should be performed to check for cross-reactivity. However, if the serum ZIKV and dengue IgM are positive, then CSF IgM for both viruses must be tested; the results are considered diagnostic if ZIKV alone is positive. A recent study using CSF and blood samples from newborns with ZIKV-associated microcephaly has supported these findings, showing a 100% correlation between positive CSF ZIKV serologies and PRNT [42]. Fig. 1 shows a suggested algorithm for ZIKV diagnosis.

Guillain–Barré syndrome–Zika virus clinical aspects

ZIKV–GBS seems to occur more frequently in young adults and is slightly more prevalent in male individuals. The median ages were 47, 42, and 42 years in Colombian, French Polynesian, and Brazilian cohorts, respectively [17–19]. Neurological symptoms were present 6–10 days on an average after the initial symptoms of ZIKV infection in all studies. Lower extremity weakness predominates as the inaugural symptom, followed by pain, autonomic dysfunction, and facial palsy. Hyporeflexia or areflexia was seen in 89% of the Brazilian patients and in 95% of the Cucuta's cohort [19,20]. Facial palsy was present in eight (42%) and 16 (60%) patients, respectively, in Colombian and Brazilian series [18,19]. In Brazil, an ataxic proprioceptive component was observed in 19 (70%) cases [19]. Finally, dysautonomia is a commonly observed phenomenon in patients with GBS. In a study involving six Colombian hospitals, it was observed in 21 patients (31%) [18]. Labile blood pressure and ileus were noticed in all the 29 patients from Cucuta [20]. Cardiac arrhythmias and urinary retentions were
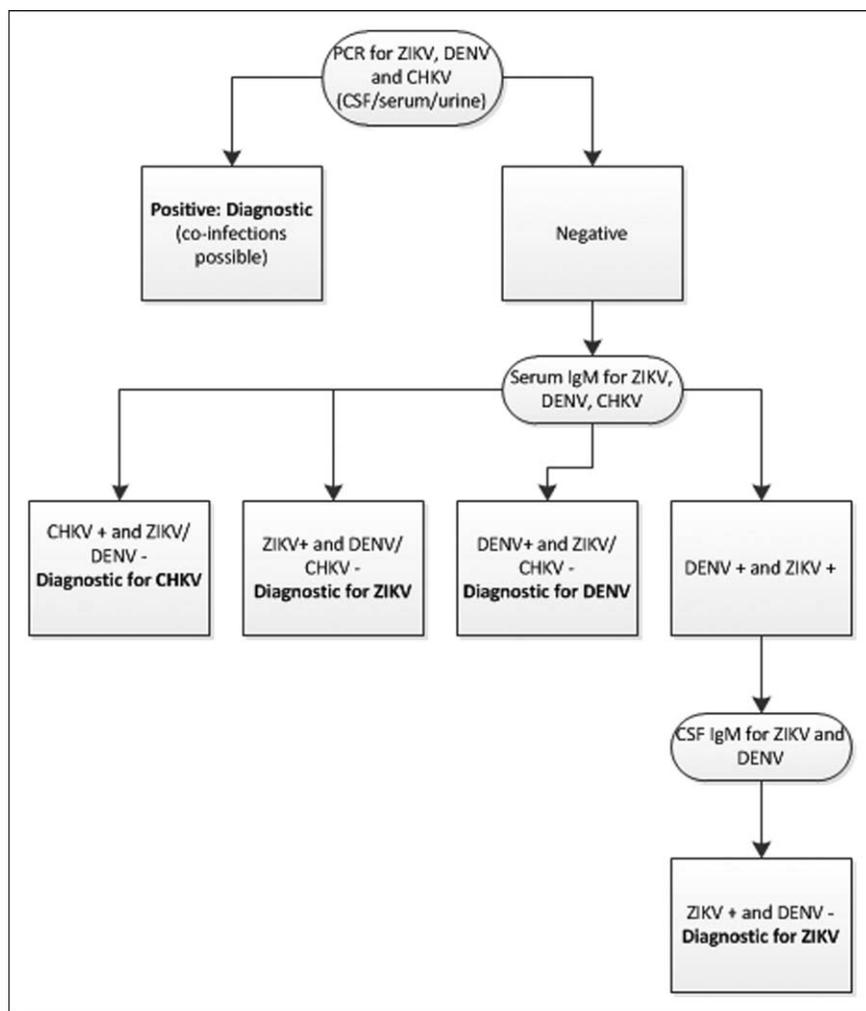
FIGURE 1. Suggested algorithm for ZIKV diagnosis. CHKV, chikungunya virus; CSF, cerebrospinal fluid; DENV, dengue virus; ZIKV, Zika virus.

also frequently reported. Autonomic derangements were also present in 22% of the Brazilian cases [19]. Autonomic dysfunction comprised the main risk factor for poor prognosis in patients with GBS [31,32]. Finally, some interesting findings were reported in the Brazilian cohort, such as two patients with preserved deep tendon reflexes (as previously described by Yuki *et al.* [43]) and two cases of GBS associated with encephalitis [19]. Figure 2 shows the clinical presentations of GBS in general [44].

The Brighton criteria apply levels of diagnostic certainty to aid in an accurate diagnosis of GBS, and are commonly used as a clinical and research tool [45]. The French Polynesian study did not report it for their cases [17]. The cohort from Cucuta reported five ZIKV–GBS cases with level 1 diagnostic certainty (highest level), 8 level 2, and 6 level 3 cases [20]. The largest Colombian series reported 30 level 1 (44%), 26 level 2 (38%), and 6 level 3 (9%) cases [18]. Finally, the Brazilian study reported that 90% of their cases had a level 1 diagnostic certainty [19].

Guillain–Barré syndrome analysis

In the ZIKV–GBS Colombian retrospective series, the CSF protein levels were increased in 45 out of 55 tested cases (82%), with a median of 0 cells/μl (0–2.5 cells/μl) [18]. The study from French Polynesia showed elevated CSF protein in 93% of the patients, with a median of 4 cells/μl (1–7 cells/μl) [17]. The Brazilian prospective cohort disclosed albuminocytologic dissociation in 28/29 (97%) of the cases, with a mean cell count of 3 cells/μl [19]. When compared to a pre-ZIKV era cohort of patients with GBS from the same institution, the Brazilian investigators disclosed a higher median cell count in the CSF of ZIKV-related GBS cases [19].

Nerve conduction studies

There are some controversies in the nerve conduction studies reported in some ZIKV–GBS series regarding the most common electrophysiological pattern observed in ZIKV–GBS cases. The criteria
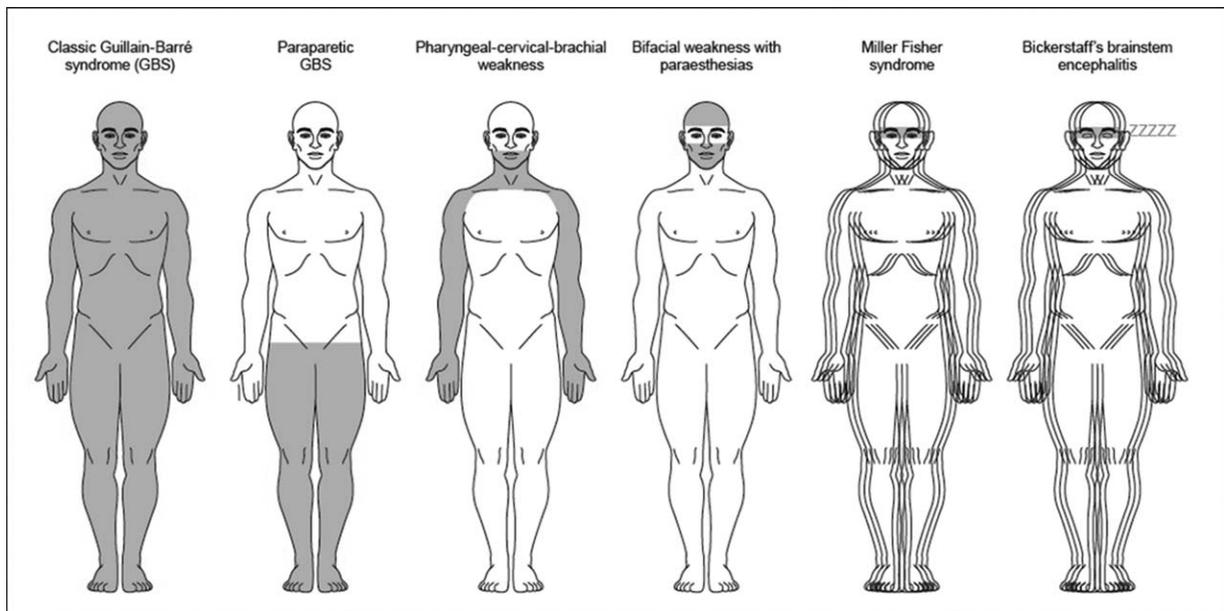
FIGURE 2. Clinical Presentations of GBS. Adapted with permission [44]. GBS, Guillain–Barré syndrome.

for acute motor axonal neuropathy (AMAN) were considered fulfilled in almost all nerve conduction studies performed in patients from a case series from Cucuta, Colombia [10 out of 14 (73%) patients]; moreover, two had unexcitable nerves (11%) and another two tests were within normal ranges [20]. In contrast, in the largest Colombian series, including 46 tested patients, 36 (78%) were considered to have acute inflammatory demyelinating polyradiculoneuropathy (AIDP), one patient (2%) AMAN and four patients (9%) were deemed as having equivocal studies that did not allow a subtype classification [18]. Within a large Brazilian cohort, out of 27 tested ZIKV–GBS cases, 18 (66.6%) were consistent with AIDP, two (7.4%) had AMAN, six (22.2%) had acute motor and sensory axonal neuropathy, and in one (3.7%) as miller fisher syndrome [19]. In the French Polynesia case–control study, all the 37 patients examined were diagnosed with the AMAN subtype [17].

A recent elegant review on the neurophysiological findings in ZIKV–GBS called for attention to the mean prolonged distal motor latencies (DMLs) and reduced distal compound muscle action potential amplitudes reported in the studies from Cucuta and French Polynesia, considering that the described results were more in resonance with the current criteria for AIDP and chronic inflammatory demyelinating polyneuropathy, instead of AMAN, as initially reported [46]. The 10 patients from Cucuta also presented with a sural-sparing pattern, usually observed in AIDP [46]. Improvement of DMLs and compound muscle action potentials were observed in 19 patients reexamined 4 months later in the

French Polynesia, and these cases were considered as having AMAN with reversible conduction failure as per the investigators [17], a fact questioned by other specialists [46]. Markedly prolonged DMLs, mostly in the upper limbs, were also observed in Brazil [19].

In general, AIDP is the most common pattern observed in patients with traditional GBS [32,47]. Some authors suggest that the variability of electrophysiological findings in different populations with ZIKV–GBS might be explained in part by differences in the distribution of HLA alleles and associated immunological response [17].

Neuroimaging

Neuroimaging of the CNS and peripheral nervous system might be useful in the setting of ZIKV–GBS (Fig. 3). In the Brazilian prospective cohort, two patients developed GBS with associated CNS lesions, notably located in bilateral cerebellar peduncles [19], resembling West Nile Virus encephalitis [48]. Moreover, in the same study, brain and spine MRI were performed in 21 of the ZIKV–GBS cases, with cranial nerve enhancement and cauda equine or nerve root contrast enhancement present in 19% [19]. These findings of nerve enhancement did not differ from what is occasionally observed in patients with GBS [49–51].

Guillain-Barré syndrome–Zika virus treatment and prognosis

Immunoglobulin was the most commonly used treatment in most series, usually administered within 7 days after onset of symptoms [17–20].
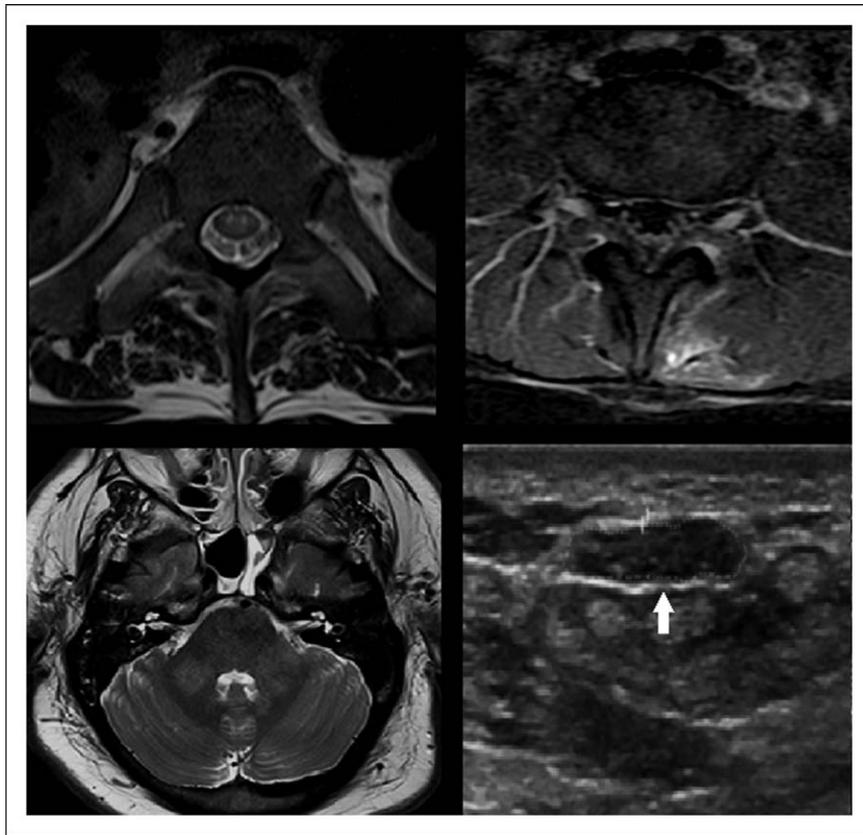
FIGURE 3. Radiological findings in ZIKV–GBS. Upper left: MRI of the thoracic spine (T2WI) disclosing hypersignal of the bilateral cortical-spinal tracts. Upper right: MRI of the lumbar spine (T1WI with gadolinium) showing enhancement of the nerve roots. Lower left: MRI of the brain (T2WI) showing hypersignal of the bilateral cerebellar peduncles. Lower right: Ultrasonography of the median nerve showing enlarged sectional area of the nerve (white arrow) of an acute infectious polyneuropathy ZIKV-PCR-positive case.

Admission to an ICU was needed for 59, 38, and 15% of the patients in the Colombian, French Polynesian, and Brazilian series, with fatal outcomes in 4, 0, and 4%, respectively [17–19]. Treatment-related fluctuations were observed in one case in the Brazilian series [19]. Mechanical ventilation was required in 29% of the French Polynesian patients [17], 31% in the Colombian series [18], and 7% in the Brazilian cohort [19].

The prognosis was generally favorable in all the series. In the French Polynesian study 57% of the patients were ambulatory at 3 months [17]; similar findings were noted in the Brazilian study. However, chronic pain was observed in 56% of the Brazilian patients [19]. Finally, the ZIKV-associated GBS combined outcomes of the three major studies did not significantly differ from what had been observed in the largest prospective cohort of patients from Europe with GBS secondary to other causes [45].

CONCLUSION

The recent ZIKV outbreaks have triggered the occurrence of a myriad of neurological manifestations that are likely to be associated with this arbovirosis, especially GBS and its variants. It is of high urgency that neurologists and practioners in general familiarize themselves with this new agent causing neuronal injury.

Conflicts of interest

There are no conflicts of interest.

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