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Guillain-Barré Syndrome Associated With Zika Virus Infection in Martinique in 2016: A Prospective Study

Benoît Rozé,[1,2] Fatiha Najioullah,[3] Jean-Louis Fergé,[2] Frédérique Dorléans,[4] Kossivi Apetse,[5] Jose-Luis Barnay,[6] Elise Daudens-Vaysse,[4] Yannick Brouste,[7] Raymond Césaire,[3] Laurence Fagour,[8] Ruddy Valentino,[2] Martine Ledrans,[4] Hossein Mehdaoui,[2] Sylvie Abel,[1] Isabelle Leparc-Goffart,[9] Aissatou Signate,[10] and André Cabié[11]; for the Guillain-Barré Syndrome Zika Working Group of Martinique[a]

[1]Infectious and Tropical Diseases Unit, University Hospital of Martinique, [2]Intensive Care Unit, University Hospital of Martinique, and [3]Laboratory of Virology, University Hospital of Martinique, Université des Antilles EA4537, Fort de France; [4]French National Public Health Agency, Regional Unit Antilles Guyane, Saint-Maurice; [5]Electrophysiological Department, [6]Rehabilitation Unit, [7]Emergency Department, and [8]Laboratory of Virology, University Hospital of Martinique, Fort de France; [9]French Armed Forces Biomedical Research Institute, Marseille; [10]Neurology Department, University Hospital of Martinique, and [11]Infectious and Tropical Diseases Unit, University Hospital of Martinique, Université des Antilles, EA4537, INSERM CIC1424, Fort de France, France

Background. Guillain-Barré syndrome (GBS) has been reported to be associated with Zika virus (ZIKV) infection in case reports and retrospective studies, mostly on the basis of serological tests, with the problematic cross-reacting antibodies of the *Flavivirus* genus. Some GBS cases do not exhibit a high level of diagnostic certainty. This prospective study aimed to describe the clinical profiles and the frequency of GBS associated with ZIKV during the ZIKV outbreak in Martinique in 2016.

Methods. We recorded prospective data from GBS meeting levels 1 or 2 of diagnostic certainty for the Brighton Collaboration, with proof of recent ZIKV infection and negative screening for etiologies of GBS.

Results. Of the sample of 34 patients with suspected GBS during the outbreak, 30 had a proven presence of GBS, and 23 had a recent ZIKV infection. The estimated GBS incidence rate ratio (2016 vs 2006–2015) was 4.52 (95% confidence interval, 2.80–7.64; $P = .0001$). Recent ZIKV infection was confirmed by urine reverse-transcription polymerase chain reaction (RT-PCR) analysis in 17 cases and by serology in 6 cases. Patients, 65% of whom were male, had a median age of 61 years (interquartile range, 56–71 years) and experienced severe GBS. Electrophysiological tests were consistent with the primary demyelinating form of the disease.

Conclusions. ZIKV infection is usually benign, when symptomatic, but in countries at risk of ZIKV epidemics, adequate intensive care bed capacity is required for management of severe GBS cases. Arbovirus RNA detection by RT-PCR should be part of the management of GBS cases.

Keywords. Guillain-Barré syndrome; Zika virus infection; Martinique; vector-borne infections; outbreaks.

The Zika virus (ZIKV) was discovered in Uganda in the course of mosquito and primate surveillance during research on yellow fever in 1947. It has now circled the tropical and subtropical countries of the globe [1]. The increasing population density and mobility, proliferation of breeding sites for *Aedes* mosquitoes, and difficulties in producing effective mosquito control measures could explain this emergence.

In March 2015 [2], Brazil confirmed autochthonous transmission of ZIKV. Local transmission of the virus was then detected in Central America and the Caribbean, bringing, in January 2017, the total to 48 countries or territories reporting vector-borne transmission of ZIKV across the Americas, with >540 000 cases [3]. In 2016, an outbreak of ZIKV infections occurred in Martinique, a French Caribbean island. The epidemic was declared on 20 January 2016 by health authorities and spread through the island until 13 October 2016, with >35 600 patients having presented to their physicians for symptomatic cases [4, 5].

Guillain-Barré syndrome (GBS) is an acute polyneuropathy that occurs after an infectious disease in two-thirds of the cases [6]. The most frequently identified infectious agent associated with the consecutive development of the GBS is *Campylobacter jejuni* [6]. Epstein-Barr virus (EBV), varicella zoster virus, *Mycoplasma pneumoniae* [6–10], and arboviruses (including dengue virus [DENV], West Nile virus, Japanese encephalitis virus, and chikungunya virus [CHIKV]) are also reported [11–15].

The first reports of human neurological complications following ZIKV infections were described during the French Polynesia outbreak of 2013. A 10-fold increase in GBS incidence and 25 cases of other neurological disorders, suspected to be triggered by the ZIKV, were reported [16, 17]. A temporal relationship between these 2 diseases was made on the basis of serological and anamnestic data.

Since October 2015, while ZIKV was spreading through the Americas and Caribbean islands, several countries have reported increase in GBS incidence and some neurological manifestations [18, 19]. In November 2016, the reported

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[a]Members of the GBS Zika Working Group of Martinique are listed after the References.

Correspondence: B. Rozé, Service de maladies Infectieuses et Tropicales, CHU de Martinique, site PZQ, CS 90632, 97261 Fort-de-France cedex (benoit.roze@chu-martinique.fr).

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neurological complications of ZIKV infections totaled >1580 cases for the countries and territories of Brazil, Colombia, Dominican Republic, El Salvador, French Guiana, Honduras, Surinam, Venezuela, and the French West Indies [4, 20–24]. Detection of ZIKV from GBS cases was introduced by the GBS Working Group of the University Hospital of Martinique (UHM) in March 2016 [25].

This prospective study aimed to describe the clinical profiles of ZIKV-associated GBS cases to assess the hypothesis of an increased incidence of GBS cases during the ZIKV outbreak compared to the non-ZIKV outbreak period (from 2006 to 2015) and to document the value of molecular biology in the screening of GBS cases etiologies by excluding the other infections associated with GBS.

METHODS

Background Information

Martinique is an overseas territory of the French West Indies. This island of 1100 km^2 has a population of 378 243 inhabitants; 19% are <15 years old, 59% between 15 and 60 years old, and 22% >60 years old. The UHM is a tertiary referral center providing healthcare, teaching, and research programs on this island. Martinique has experienced several outbreaks of dengue fever since 2001 and in 2011, a prospective study of adult blood donors reported a 93% seroprevalence for DENV antibodies [26].

Between January 2006 and December 2015, 105 GBS cases were recorded, with a median age of 56.5 years (interquartile range [IQR], 46.5–68.7 years). The mean incidence of GBS was 8.2 cases per year, with extremes of 4–15 cases per year. The estimated average annual incidence rate was 2.1 cases per 100 000 person-years (PY). The highest incidence rate was attained in 2014 (estimated incidence rate of 3.9 cases per 100 000 PY), concomitantly with an outbreak of CHIKV, with a cumulative incidence of symptomatic CHIKV in the total population of 40% (Figure 1).

Since November 2015, a healthcare track has been organized for patients suffering from GBS, through the establishment of cooperation with relevant experts (neurologists, intensivists, infectious diseases specialists, microbiologists, and rehabilitation specialists). Because it was the only place on the island to find intravenous immunoglobulin (IVIG) or plasmapheresis, all patients with GBS were referred to this specialized multidisciplinary center.

Case Definitions

All the patients with an acute flaccid paralysis diagnosed by a neurologist, without cytological reaction of the cerebrospinal fluid (CSF), and meeting levels 1 or 2 of diagnostic certainty for the Brighton Collaboration criteria case definitions for GBS, were recruited [27]. Electrodiagnostic studies (EDSs) were performed by the same practitioner with a Medtronic KeyPoint version 5.05 electromyograph. The first EDSs were performed at 2 weeks, the second at 3 months, after the neurological

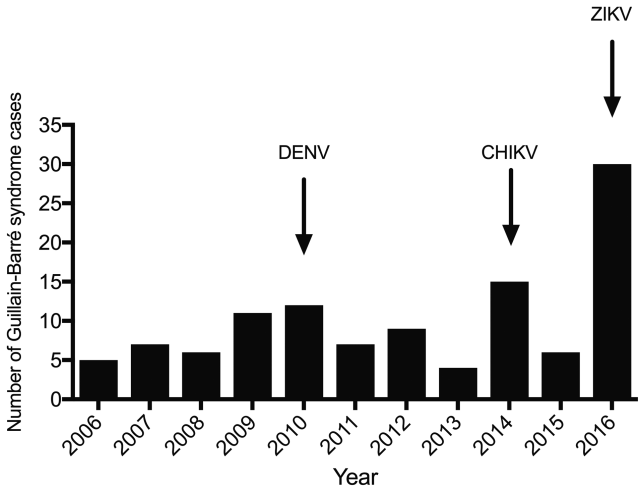

Figure 1. Number of Guillain-Barré syndrome cases per year during 10 years at the University Hospital of Martinique (2006–2016). Abbreviations: CHIKV, chikungunya virus; DENV, dengue virus; ZIKV, Zika virus.

symptom onset (NSO). Compound muscle action potentials and sensitive nerve action potentials were recorded with surface electrodes. Electromyographic features were assessed using concentric needles. For each patient, at least 1 median; ulnar; common peroneal and tibial motor; and sural, radial, ulnar, and median-sensitive component was tested. Patients were classified into main GBS subtypes according to conventional electrodiagnostic criteria for GBS [28].

At hospital admission, all patients diagnosed with acute flaccid paralysis were immediately screened for the etiologies of GBS. Before the administration of IVIG, blood, CSF, and urine samples were taken from each patient; then new serum samples were taken 8 weeks after treatment with IVIG. CSF analysis was used as part of the differential diagnostic investigation of GBS and was required to investigate an infection of the central nervous system. We performed serological tests for *Campylobacter jejuni*, *Campylobacter fetus* (RFC Virion, AES), *Mycoplasma pneumoniae* (immunoglobulin G [IgG], immunoglobulin M [IgM], enzyme immunoassay [EIA], Theradiag), human immunodeficiency virus (HIV) (HIV Combi PT, Roche, Meylan), Epstein–Barr virus (EBV VCA IgG, EBV VCA IgM, EBNA IgG ELISA, Platelia Bio-Rad), cytomegalovirus (CMV IgG, CMV IgM, Roche, Meylan), influenza virus (Grippe RFC Virion, AES), rubella and measles (EIA, Vidas, bioMérieux, France), and direct detection in the CSF for enterovirus (Enterovirus R-gene kit from bioMérieux), herpes simplex virus, varicella zoster virus (RealStar alpha Herpesvirus PCR 1.0 kit from Altona), and CMV by polymerase chain reaction (PCR) (CMV R-gene kit from bioMérieux). We used reverse-transcription PCR (RT-PCR) assays to detect nucleic acid from ZIKV, DENV, and CHIKV in the CSF, urine and plasma. For detection of viral RNA, we used the Simplexa Dengue RT-PCR assay (Focus Diagnostics, Cypress, California) and the RealStar

Chikungunya RT-PCR kit 1.0 (Altona Diagnostics, Hamburg, Germany). For ZIKV, we used an in-house RT-PCR from January to February, and we then changed to the RealStar Zika Virus RT-PCR kit 1.0 (Altona Diagnostics). Serum samples were also tested by IgM enzyme-linked immunosorbent assay (MAC-ELISA) for all 3 arboviruses. Dengue-specific IgM and IgG were detected with MAC-ELISA kits (Panbio, Brisbane, Australia). For CHIKV serology, we used EUROIMMUN Chikungunya IgM and IgG ELISA kits (Luebeck, Germany). All the serological tests against ZIKV (IgM, IgG, and neutralizing antibodies) were done by the French National Reference Laboratory for arboviruses in Marseille, France. IgM antibodies were captured with rabbit anti-human IgM antibodies (Interchim, Montluçon, France). ZIKV antigens, prepared on Vero cells, precipitated and inactivated by β-propiolactone (Sigma-Aldrich, St Quentin Fallavier, France), was added. Specific binding was demonstrated by using a ZIKV mouse hyperimmune ascitic fluid virus and a goat antimouse peroxidase-labeled conjugate (Interchim). For IgG detection, ZIKV antigens were coated, followed by test sera; and specific binding was demonstrated by using a peroxidase-labeled goat antihuman IgG conjugate. Serum samples were considered positive if the optical density at 450 nm was >3-fold the mean of negative sera with a Sunrise spectrophotometer (Tecan, Lyon, France). Detection of neutralizing antibodies against ZIKV was performed in serum samples when RT-PCR and IgM MAC-ELISA results were negative or when IgM was positive against both DENV and ZIKV. Laboratory methods were calibrated using internal and external quality controls.

A recent infection with ZIKV was proven when ZIKV nucleic acid was detected by RT-PCR in any specimen, or serum antibodies to ZIKV detected by ZIKV IgM MAC-ELISA if IgM MAC-ELISA results against DENV were negative or neutralizing antibodies against ZIKV were positive. Serums containing only neutralizing IgG antibodies against ZIKV detected by neutralization testing (NT) were considered positive for a nonrecent ZIKV infection, and were deleted from the final analysis.

Other Laboratory Methods

As serum antibodies to many peripheral nerve antigens have been found in GBS [29], we tested the patients sera by ELISA for IgG or IgM reactivity to the glycolipids GM1, GA1, GM2, GD1a, GD1b, and GQ1b (Bühlmann-Gangliocombi, Schönenbuch, Switzerland). According to the kit instructions, the results were considered positive, equivocal, and negative when showing >50%, 30%–50%, and <30% binding, respectively.

Study Population

Before this study, we analyzed data of the past 10 years on adult GBS cases (January 2006 to December 2015) in the UHM discharge database.

During this observational prospective study, we aimed to describe only the GBS cases associated with ZIKV. We analyzed patients living in Martinique, with proof of recent ZIKV infection, and diagnosed as developing a case of GBS with a negative screening for recent infection associated with other etiologies of GBS.

Statistical Analysis

GBS baseline data for the preepidemic Zika period were estimated for the period covering the years from 2006 to 2015, the 10-year period preceding the Zika epidemic in Martinique. Data were extracted from the hospital data information system (PMSI) whose classification is based upon the *International Classification of Diseases, Tenth Revision* (*ICD-10*). Hospital data codes for GBS diagnostic were selected into PMSI databases and based upon the information from the databases to estimate incidence rates and incidence rate ratios. The average annual incidence rate of GBS hospitalized cases was estimated by reporting the total cumulative number of GBS hospitalized cases occurring over the 10-year preepidemic period to the census population for the same period and subsequently reported to a theoretical population of 100 000 PY. We estimated the GBS cases incidence rate by reporting the total cumulated number of GBS cases detected over the 10-month epidemic period to

Table 1. Zika Virus and Dengue Virus Virological Patterns Associated With Guillain-Barré Syndrome From 30 Patients on Martinique, 2016

	ZIKV IgM								
	Negative[a]			Flavivirus[b]			ZIKV[c]		
	ZIKV IgG Positive	ZIKV IgG Negative	ND	ZIKV IgG Positive	ZIKV IgG Negative	ND	ZIKV IgG Positive	ZIKV IgG Negative	ND
RT-PCR ZIKV on Urine									
Negative	4	3	0	2	0	0	—	—	4
Positive	—	—	4	—	—	3	—	—	10

Detection of neutralizing IgG antibodies against ZIKV were proceed by neutralization testing when RT-PCR ZIKV and ZIKV IgM were negative, or when RT-PCR ZIKV was negative and both ZIKV IgM and dengue virus IgM were positive.

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; ND, not determined; RT-PCR, reverse-transcription polymerase chain reaction; ZIKV, Zika virus.

[a]Negative: Both IgM against Zika virus and IgM against dengue virus were negative.

[b]Flavivirus: Both IgM against Zika virus and IgM against dengue virus were positive.

[c]ZIKV: IgM against Zika virus was positive and IgM against dengue virus was negative.

the total population and subsequently reported to a theoretical population of 100 000 PY.

An incidence rate ratio can be considered as an approximation of a relative risk. We will then estimate the incidence rate ratio by reporting the estimated GBS average annual incidence rate during the preepidemic period (per 100 000 PY) to the estimated GBS incidence rate (100 000 PY) during the Zika epidemic.

Ethics

Since the emergence of ZIKV in Martinique (December 2015), patients with GBS were included, after informed consent was obtained, in the Cohort of Patients Infected by an Arbovirus (CARBO; ClinicalTrials.gov identifier NCT01099852). This ethically approved study allowed us to make prospective biological and clinical data collections during a follow-up of 18 months.

RESULTS

The first case of ZIKV-associated GBS was diagnosed at the UHM during the second week of the emergence of ZIKV in Martinique in January 2016. In the third week of 2016, the epidemic was declared by the French public health services, with >1000 estimated cases of new symptomatic ZIKV patients who consulted their general practitioner per week. It lasted until the second week of October 2016, with >36 500 patients who consulted their general practitioner for symptomatic ZIKV infections. During week 16, we observed a maximum of 4 new cases of ZIKV GBS. We have not had new ZIKV GBS cases since the end of the epidemic.

From January 2016 through October 2016, 34 patients with clinically suspected GBS were admitted to our center. Four were excluded after electromyography study (3 with isolated facial diplegia, and 1 without electrophysiological anomaly). The estimated incidence rate during the Zika epidemic was 9.5 cases per 100 000 PY, and the estimated incidence rate ratio (2016 vs 2006–2015) was 4.52 (95% confidence interval, 2.80–7.64; $P = .0001$).

Among the 30 patients with a proven presence of GBS, 27 had a ZIKV infection, of whom 23 were recent. ZIKV nucleic acid was detected by RT-PCR in the urine of 17 cases, antibodies to ZIKV were detected by ZIKV IgM MAC-ELISA with negative DENV IgM MAC-ELISA in the sera of 4 other cases, and both positive ZIKV IgM MAC-ELISA and DENV IgM MAC-ELISA with positive neutralizing antibodies against ZIKV were detected in 2 additional patients (Table 1).

Characteristics of the Patients

Characteristics of study participants are shown in Table 2. The patient group consisted of 15 male patients and 8 female patients, with a median age of 61 years (IQR, 56–71 years). The median age of male patients (61 years [IQR, 55–71 years]) was the same as that of female patients (62.7 years [IQR, 56.4–70 years]) ($P = .95$).

Table 2. Clinical Characteristics of Patients With Zika Virus–Associated Guillain-Barré Syndrome (n = 23) on Martinique, 2016

Characteristic	No. (%) or Median (IQR)
Demographic factors	
Age, y	61 (56–71)
Male sex	15 (65)
Previous viral syndrome	16 (70)
Conjunctivitis	8 (35)
Rash	11 (48)
Fever	5 (22)
Arthralgia	10 (43)
Myalgia	8 (35)
Headache	8 (35)
Time between reported viral syndrome and onset of neurological symptoms, d	5.9 (1.5–6.5)
Symptoms at admission	
Paresthesia	22 (96)
Hyporeflexia	23 (100)
Arm weakness	16 (70)
Leg weakness	20 (87)
Incapacity of walking	19 (83)
Facial palsy	9 (39)
Dysphagia	16 (70)
Time between onset of neurological symptoms and diagnosis of GBS, d	6.3 (2–9)
Time between onset of neurological symptoms and peak of illness, d	8.8 (7–12)
Duration of plateau phase of illness, d	7.9 (3–12)
Treatment	
Intravenous immunoglobulin	23 (100)
Plasmapheresis	0
Time between onset of neurological symptoms and treatment, d	6.7 (3–12)
Patients admitted to intensive care	14 (61)
Respiratory assistance	10 (43.5)
Duration of hospitalization in intensive care, d	20 (7–23)
Duration of hospital stay, d	60 (36–83)
Lumbar puncture results	
Proteins, g/L	1.08 (0.64–1.39)
White blood cells/μL	5.9 (0–3)
First electrophysiological examination	
Time between onset of neurological symptoms and first electrophysiological examination (n = 21), d	18.6 (10–19)
AIDP	20 (95)
Inexcitable	1 (5)
AMAN	0
Second electrophysiological examination	
Time between onset of neurological symptoms and second electrophysiological examination (n = 12), d	74.6 (51–97.5)
AIDP	4 (33.33)
AIDP with secondary axonal damages	7 (58.33)
Inexcitable	0
AMAN	0
Recovery	1 (8.33)

Abbreviations: AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; GBS, Guillain-Barré syndrome; IQR, interquartile range.

Preceding arbovirus-like syndrome, characterized by fever, headache, retro-orbital pain, nonpurulent conjunctivitis, maculopapular rash, arthralgia, or myalgia, was observed in 16 of 23 cases (70%). Symptomatic patients (median age, 63.9 years [IQR, 58–70.9 years]) were of the same age as nonsymptomatic patients (median age, 56.4 years [IQR, 47.4–71.2 years]) (P = .32). The median duration from first symptoms of ZIKV infection to the onset of GBS was 5.9 days (IQR, 1.5–6.5 days).

The median length of hospitalization in the UHM was 60 days (IQR, 36–83 days). A great majority of patients had severe GBS at hospital admission, 70% (16/23) had swallowing disorders, and 83% (19/23) were unable to walk. Sixty-one percent (14/23) of the patients were hospitalized in the intensive care unit, with a median duration of 20 days (IQR, 7–23 days), and 43.5% (10/23) required mechanical ventilation due to paralysis of the respiratory musculature leading to respiratory failure. The median time between ONS and peak of illness was 8.8 days (IQR, 7–12 days), and the median duration of the plateau phase of illness was 7.9 days (IQR, 3–12 days). Two patients died due to the illness.

Assessment of Laboratory Diagnostic Testing Strategies

We were able to discover the trigger of GBS, within a few hours, in 17 GBS cases by conducting RT-PCR of urine samples. For patients with negative ZIKV direct detection, serological tests were consistent with a recent ZIKV infection in 6 cases (serum antibodies to ZIKV detected by ZIKV IgM MAC-ELISA and IgM MAC-ELISA results against DENV negative), and ZIKV infection was only proven by NT for 4 other cases. All blood and CSF specimens were negative for ZIKV amplification.

First EDSs were performed for 21 patients at a median delay of 18.6 days (IQR, 10–19 days). On the basis of the conventional electrodiagnostic criteria for GBS [28], motor abnormalities were consistent with inexcitable form in 1 patient and with acute inflammatory demyelinating polyradiculoneuropathy (AIDP) in all others (20/21). At the second EDS, performed on 12 patients, at a mean time of 74.6 days (IQR, 51–97.5 days) after NSO, slow components characteristic of remyelination were recorded in all patients, as well as signs of secondary axonal damage in 7 patients. One patient (1/23) did not have any EDS.

The sera from all patients were tested for IgM and IgG reactivity to glycolipids. As previously described in the majority of GBS patients suffering from the AIDP subtype, we identified only 1 case exhibiting autoantibodies (GD1b + GM1) [29].

All the patients were treated with IVIG, with a mean dose of 147 g (daily dose of 0.4 g/kg over 5 days), started with a median delay of 6.7 days (IQR, 3–12 days) from NSO. Plasmapheresis was available at UHM, but we preferred using IVIG for reasons of simplicity.

DISCUSSION

In this prospective series of GBS cases, we implemented another proof that demonstrates the role of ZIKV in triggering GBS [24]. We described only certain GBS with recent ZIKV infection, and added evidence of a link for 17 patients with positive PCR in urine. This series occurred in Martinique in 2016, with a 4-fold increase in GBS incidence during this ZIKV epidemic, while ZIKV GBS represented 77% of all GBS cases recorded during this period (23/30) (Figure 2).

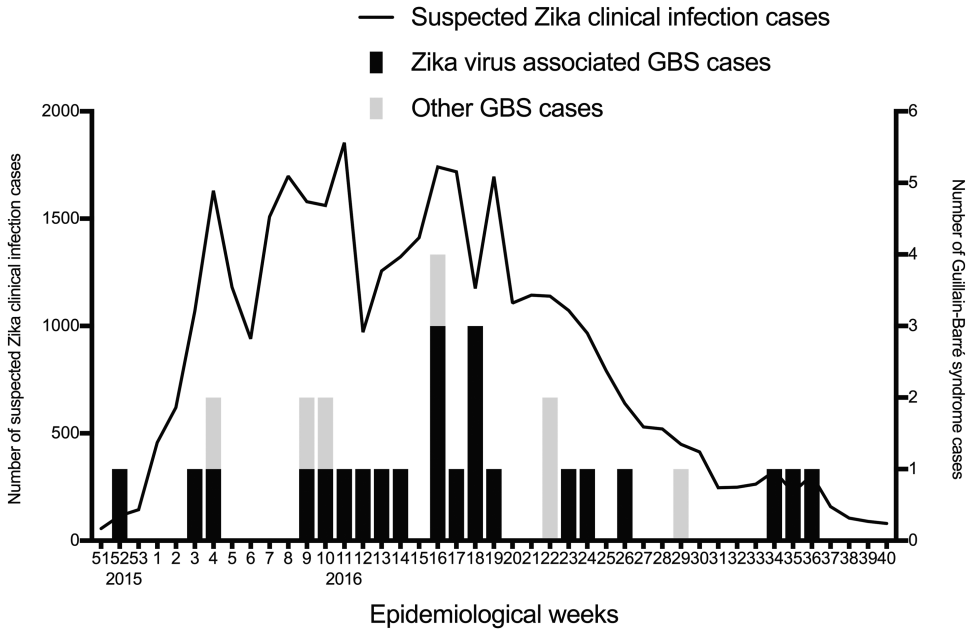

Figure 2. Weekly cases of patients with suspected Zika virus clinical infection consulting general practitioners and Guillain-Barré syndrome (GBS) in Martinique between January 2016 and October 2016.

Most cases were severe GBS; this is consistent with the median patients' age of 61 years (IQR, 56–71 years). It has already been described in GBS population-based studies that old age was associated with a less favorable outcome, such as being bed bound or requiring artificial ventilation at nadir [30, 31]. The severity is also linked with the short time of 9 days between NSO and peak of illness, as GBS cases with a rapid onset phase are more believed to be worse [32]. Contrary to the Polynesian cohort EDS [16], our patients had findings consistent with the AIDP pattern, the most common subtype of GBS reported in patients with ZIKV in Colombia [22] and in Puerto Rico [23]. Whether the same virus triggers AIDP rather than acute motor axonal neuropathy remains unclear.

GBS is a postinfectious inflammatory disease, but research is confounded by difficulties in isolating the organism from infected patients [33]. Arboviruses could have triggered GBS [11–15], and their RNA is detectable in urine at higher load and for longer time than in plasma [34, 35]. Some GBS cases had viral excretion in urine >15 days after NSO [25], whereas RNA detection in blood and CSF was negative. To perform the microbiological diagnosis, we believe that arbovirus viruria needs to be investigated in GBS cases.

Molecular mimicry is well described for anti-ganglioside-mediated disorders [36], but considering ZIKV as a highly neurotropic virus [37], and the short delay of 6 days observed between ZIKV infectious symptoms and neurological deficiencies, without autoimmune response against gangliosides, we think the hypothesis of a direct link between ZIKV infection and neurological manifestations must be explored in ZIKV-associated GBS. Another explanation could be found in the >200 ZIKV peptide sequences matching throughout 99 human proteins that, when altered, are associated with myelin disorders and/or neuropathies [38]. Here is a challenge for the scientific community to find a way to immunize ZIKV-susceptible populations safely to protect people from neurological complications of this emerging arboviral infection.

CONCLUSIONS

This prospective study documents a series of patients who developed certain GBS following ZIKV infections. The incidence rate ratio indicates an increased likelihood of GBS syndrome occurrence between the Zika epidemic period compared to the preepidemic Zika period. Most cases were severe GBS, 43.5% required mechanical ventilation, and 2 patients died due to the illness. In countries at risk of ZIKV epidemics, adequate intensive care unit bed capacity is required for management of severe GBS cases. Arbovirus RNA detection by RT-PCR should be part of the management of GBS cases.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Gwenole Jean Abgrall, Véronique Aïm, Alessandro Arrigo, Philippe Cabre, Cyrille Chabartier, Sylvie Colombani, Julien Cuziat, Christophe Deligny, Nicole Desbois, Anne-Laure Dessoy, Gaëlle Dunoyer, Régis Duvauferrier, N'Guyen Duc, Mireille Edimonana, Pierre Garrigou, Stéphane Gaucher, Sarah Gourgoudou, Karine Guitteaud, Patrick Hochedez, Gwladys Ivanes, Yolène Jacquens, Sandrine Julié, Armelle Jean-Etienne, Séverine Jeannin, Joux Julien, Pasquier Jérémie, Jean-Louis Lamaignère, Ingrid Laudarin, Maud Le Gall, Véronique Legris-Allusson, Mehdi Mejdoubi, Corinne Michel, Franck Michel, Charline Miossec, Florence Moinet, Cervantes Minerva, Claude Olive, Pascale Olive, Karine Pailla, Céline Paysant, Sandrine Pierre-François, Mathilde Pircher, Katlyne Polomat, Alain Putot, Patrick René-Corail, Dabor Resiere, Christiane Richer, Jean-Romain Risson, Karen Rome, Marie Sabia, Michel Schloesser, Pauline Simonnet-Vigeral, Rafaelle Théodose, Rosalie Vilain.