Guillain–Barré Syndrome and Chikungunya: Description of All Cases Diagnosed during the 2014 Outbreak in the French West Indies

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Abstract. The Guillain–Barré syndrome (GBS) has been reported as a possible complication of acute chikungunya infection. The chikungunya epidemics, which occurred in Martinique and Guadeloupe in 2014, affected 308,000 people in these two islands. GBS occurred during or immediately after acute chikungunya infection in 13 patients (10 men, three women; mean age: 61 years). Median time from acute chikungunya to GBS onset was 9 days. Twelve patients were treated with intravenous polyvalent immunoglobulins, nine of whom improved within 7 days. Five of 13 patients required mechanical ventilation. Two patients with severe GBS died. At 6 months of follow-up, 7/13 achieved a good functional recovery with no or minor residual symptoms. A 2-fold increase in incidence was observed during the year of chikungunya outbreak. This study supports prior reports suggesting that GBS may be a complication of chikungunya.

INTRODUCTION

Chikungunya infection (CHIK) is a viral disease caused by chikungunya virus (CHIKV), an arthropod-borne RNA alphavirus of the *Togaviridae* family, mostly transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes.

In November 2013, the first autochthonous cases of CHIKV infection were identified in Saint-Martin, French West Indies (FWI).¹ Since then, local transmission of the virus has been identified in virtually all Caribbean islands as well as in Central and South America. From December 2013 to January 2015, a major outbreak of CHIK occurred in Guadeloupe and Martinique, FWI, involving 308,000 suspected CHIK cases (39% of the 783,336 inhabitants of both islands).

CHIKV infection, after an incubation period of 2–6 days, results in an abrupt febrile illness and is characterized by severe polyarthralgia, maculopapular rash, headache, myalgia, and fatigue. While CHIKV infection is considered to be a relatively benign condition, many atypical clinical manifestations resulting in significant morbidity and mortality have been documented in the literature, including Guillain–Barré syndrome (GBS).²

GBS is an autoimmune polyneuropathy that presents with acute and rapidly progressive flaccid peripheral paralysis. GBS is a heterogeneous syndrome, each form has distinctive clinical, pathophysiological, and pathological features.³ The most common form of GBS in the United States and Europe is the acute inflammatory demyelinating polyradiculoneuropathy (AIDP). GBS is more common in men

(ratio 3:2), and the annual incidence ranges between 0.89 and 1.89 cases per 100,000 population.³

GBS is a postinfectious illness that develops within 3 weeks after an acute infection, as a result of an aberrant immune response, which causes damage to the peripheral nerve.^{3,4} The most common GBS-causing infection is *Campylobacter jejuni* enteritis. Other agents associated with the development of GBS include cytomegalovirus, Epstein–Barr virus (EBV), *Myxovirus influenzae*, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*.³ Different arboviral diseases have been reported to trigger the development of GBS including dengue fever,⁵ West Nile encephalitis,⁶ CHIK,^{2,7,8} and Zika.⁹

The objectives of this study were to describe all the cases of CHIKV-related GBS that were diagnosed during the recent outbreak of chikungunya in the FWI and to estimate the incidence of this complication.

PATIENTS AND METHODS

Twenty-seven patients were admitted at the Martinique and Guadeloupe University Hospitals during the chikungunya outbreak (January 2014 to January 2015) with a diagnosis of GBS according to Asbury and Cornblath criteria, which include 1) typical signs and symptoms of acute polyradiculoneuropathy, 2) albuminocytologic dissociation on cerebrospinal fluid (CSF) analysis, 3) electromyography typical for GBS, and (4) absence of other possible causes of neuropathy.¹⁰ We reviewed the medical records of all cases of CHIKV-related GBS, defined by a laboratory confirmation of recent CHIKV infection (anti-CHIKV IgM antibodies in the serum and/or a positive CHIKV reverse transcription polymerase chain reaction in the plasma). Serologies for human immunodeficiency virus, hepatitis B virus, cytomegalovirus,

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TABLE 1
Subtypes of Guillain-Barré syndrome

	Subtype	Literature	Our cases series
Demyelinating polyneuropathy			
AIDP	Sensorimotor GBS, often combined with cranial nerve deficits and frequent autonomic dysfunction	Predominant subtype (60–80% of patients) in North America and Europe	54%
Axonal polyneuropathy			
AMAN	Pure motor form but cranial nerves rarely affected	From 6–7% in Europe and North America to 30–65% in Asia, Central America, and South America	0%
AMSAN	Clinically, AMSAN resembles the AMAN variant but has more sensory symptoms, and more severe than AMAN		15%
Uncommon subtype of GBS			
MFS	Clinical triad of ophthalmoplegia, ataxia, and areflexia	5% Europe and 20–25% in Asia	15%
Bickerstaff's brainstem encephalitis	Encephalopathy and hyperreflexia with features of MFS such as ophthalmoplegia and ataxia	Rare	8%
Pharyngeal–cervical–brachial variant	Weakness of oropharyngeal, facial, neck, and shoulder muscles with swallowing dysfunction. Leg strength and leg reflexes are usually preserved	Rare	8%

Adapted from Ref 3. AIDP = Acute inflammatory demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor and sensory axonal neuropathy; GBS = Guillain-Barré syndrome; MFS = Miller Fisher Syndrome.

and EBV were either negative or excluding recent infection in all CHIKV-related GBS cases. The medical records of patients with CHIKV-related GBS were abstracted using a standardized case report form (CRF). Once completed, CRFs were reviewed by a neurologist who assigned each one a category of the GBS classification proposed by van den Berg and others (Table 1).³ Severe GBS was defined by the presence of at least one of the following events: severe autonomic dysfunction, respiratory failure requiring mechanical ventilation (MV), or death. Patients' functional status at 6 months and 1 year was assessed using the GBS disability score.¹¹

We measured the annual incidence of GBS of each calendar year from 2011 to 2015, given that the span of the chikungunya outbreak coincided exactly with the year 2014. The number of cases was obtained by retrieving all those with GBS as a primary diagnosis from each hospital database. The annual incidence of GBS was calculated by dividing the number of confirmed GBS cases each year by the population size and expressed as a number of cases per 100,000 population. The incidence rates observed in 2011, 2012, and 2013 were compared with the 2014 incidence rate using a two-sample test of proportions (Stata 12[®]). In addition, we calculated the rate of CHIKV-related GBS in patients who had been infected by CHIKV by dividing the number of confirmed CHIKV-related GBS diagnosed in 2014 by the estimated number of CHIKV infection cases that occurred in 2014.

RESULTS

Thirteen cases of CHIKV-related GBS (seven cases in Martinique, six in Guadeloupe) were identified in 10 men and three women. Table 2 shows the main characteristics of these patients. Their mean age was 61 years (range: 48–80). Eleven patients had presented with typical symptoms of CHIKV infection within 4 weeks before the onset of GBS, one patient only reported a headache and fatigue, and one could not be interviewed because of severe dysarthria.

Median time from acute CHIKV infection to the first symptoms of GBS was 9 days (range: 1–22).

Cases were categorized in seven AIDP, two acute motor and sensory axonal neuropathy, two Miller Fisher syndrome, and two variant forms (one pharyngeal-cervical-brachial weakness and one Bickerstaff's brainstem encephalitis).

Twelve patients received intravenous immunoglobulins (IVIg). Nine of these patients showed a marked improvement neurologically within 7 days. Of the three patients who had no clinical response to IVIg, two received plasma exchange (PE). PE resulted in a slight improvement in one patient and no clinical response in the other. One patient received no specific treatment and completely recovered.

Six patients had severe GBS: four required MV and had severe autonomic dysfunction, one required MV but had no autonomic dysfunction, and one had severe autonomic dysfunction but did not require MV. Two of the 13 patients, both with severe GBS forms, died. One patient was 70 years old and bedbound, who received MV and died 8 days after IVIg initiation. The other patient had a Bickerstaff's brainstem encephalitis with severe autonomic dysfunction and required MV. They did not respond to specific GBS treatments (IVIg followed by PE) and died of complications of tetraplegia after 7 months. At 4 weeks of follow-up, seven patients were able to walk without aid. At 6 months, seven had achieved a good functional recovery with no or minor residual symptoms (GBS disability score ≤ 1), three had a GBS disability score of 2, and two had a score of 4. At 1 year of follow-up, one patient was lost to follow-up, and of the remaining 10 patients, eight had persisting non-disabling foot and/or hand paresthesia (GBS disability score ≤ 1), one had severe residual symptoms (GBS disability score of 3), and one developed a chronic inflammatory demyelinating polyneuropathy after initial cure of GBS symptoms. Finally, no relapse occurred in any patient.

The annual incidence rate of GBS in the FWI general population was 3.45/100,000 in 2014, compared with 1.77/100,000 over the 2011–2013 period (Table 3), which demonstrates a significant 2-fold increase during the year of the chikungunya outbreak ($P = 0.006$). The overall rate of CHIKV-related GBS among CHIKV-

TABLE 2
Summary of clinical characteristics of the 13 CHIKV-related GBS cases

Patients	Sex	Age (year)	Relevant medical history	Clinical forms	Severe autonomic dysfunction	Preceding event and diagnosis tests	Time from preceding event to onset of neurological defects (days)	MV	Treatment	Outcome (days after IVIg treatment)	Walk, 4 weeks unaided	6-month outcome (GBS disability scale)	1-year outcome
GBS1	M	53	Type 2 diabetes	AIDP	No	CHIKF IgM+ PCR S ND PCR CSF-	21	No	IVIg	Partial recovery (1 day)	Yes	1/6	1/6
GBS2	M	48	BPH	AIDP	No	CHIKF IgM+ PCR S ND PCR CSF-	8	No	IVIg	Partial recovery (1 day)	Yes	1/6	1/6
GBS3	M	59	None	MFS	Yes	CHIKF IgM+ PCR S ND PCR CSF-	1	Yes	IVIg followed by PE	No recovery	No	4/6	3/6
GBS4	M	58	Chronic HCV infection since 1984 Prior history of dengue-related GBS in 2010	AMSAN	Yes	CHIKF IgM+ PCR S+ PCR CSF+	3	Yes	IVIg	Partial recovery (6 days)	Yes	1/6	2/6 CIDP
GBS5	M	49	Alcoholism	AIDP	No	CHIKF IgM+ PCR S- PCR CSF ND	4	No	IVIg	Partial recovery (3 days)	Yes	1/6	ND
GBS6	F	53	Type 2 diabetes	AIDP	No	CHIKF IgM+ PCR S- PCR CSF-	15	No	IVIg	Partial recovery (7 days)	Yes	1/6	1/6
GBS7	F	62	Depressive syndrome	MFS	No	CHIKF IgM+ PCR S- PCR CSF-	10	Yes	IVIg	Partial recovery (12 days)	No	2/6	1/6
GBS8	M	70	Hypertension AIS with left hemiplegia and epilepsy sequelae	AIDP	Yes	Anamnesis impossible IgM+ PCR S ND PCR CSF-	ND	Yes	IVIg	Death 8 days after IVIg	No	6/6	6/6
GBS9	F	66	None	BE	Yes	CHIKF IgM+ PCR S- PCR CSF ND	8	Yes	IVIg followed by PE	No recovery	No	4/6	6/6 (death at 7 months)
GBS10	M	64	Hypertension	AIDP	No	No specific IgM+ PCR ND	19	No	IVIg	Partial recovery (9 days)	Yes	2/6	1/6
GBS11	M	80	AIS without sequel	AIDP	Yes	CHIKF IgM+ PCR S- PCR CSF+	22	No	No treatment	NA	Yes	1/6	1/6

(continued)

TABLE 2
Continued

Patients	Sex	Age (year)	Relevant medical history	Clinical forms	Severe autonomic dysfunction	Preceding event and diagnosis tests	Time from preceding event to onset of neurological defects (days)	MV	Treatment	Outcome (days after IVIg treatment)	Walk, 4 weeks unaided	6-month outcome (GBS disability scale)	1-year outcome
GBS12	M	66	AVB/PM	PCB variant	No	CHIKV IgM+ PCR S+ PCR CSF+	4	No	IVIg	Partial recovery (15 days)	No	1/6	1/6
GBS13	M	62	Hypertension	AMSAN	No	CHIKV IgM+ PCR S+ PCR CSF ND	13	No	IVIg	Partial recovery (9 days)	No	2/6	1/6
Total	3,3/1	Mean: 61 (range: 48–80)		7 AIDP, 2 AMSAN, 2 MFS, and 2 variant forms	5/13	13/13 IgM+ 4/13 PCR S+ 3/13 PCR CSF+	Median 9	5/13	12 IVIg 2 PE		7/13		

AIDP = acute inflammatory demyelinating polyneuropathy; AIS = acute ischemic stroke; AMSAN = acute motor sensory axonal neuropathy; AVB = atrioventricular block; BE = Bickerstaff's brainstem encephalitis; BPH = benign prostatic hyperplasia; CHIKV = chikungunya fever; CHIKV = chikungunya virus; CIDP = chronic inflammatory demyelinating polyneuropathy; F = female; GBS = Guillain-Barré syndrome; HCV = hepatitis C virus; IgM = immunoglobulin M; IVIg = intravenous immunoglobulin; M = male; MV = mechanical ventilation; ND = not done; PCB = pharyngeal-cervical-brachial; PCR CSF = CHIKV RNA in cerebrospinal fluid; PCR S = CHIKV RNA in serum; PM = plasma exchange; + = positive; – = negative.

infected subjects in FWI was 13/308,000, that is, one case of GBS per 24,000.

DISCUSSION

Chikungunya is usually a benign illness. However, atypical, complicated, and/or severe forms have been described, including neurological, cardiac, renal, dermatological, and ocular manifestations.^{12–14}

In this case series of CHIKV-related GBS, several features differed from those of other case series already published. Patients were older, with a mean age of 61 years compared with 50 years.^{15,16} The time from infection to GBS was shorter, except in the case of GBS secondary to Zika where this time was similar.^{4,9} Interestingly, five patients still had detectable CHIKV viremia at GBS diagnosis, which has not been reported in other post-arbovirus GBS,¹⁷ including in the recently reported post-Zika GBS outbreak in French Polynesia.⁹ However, these five patients were indistinguishable from the other eight patients in terms of clinical or temporal patterns. Compared with previously published data, we observed a higher rate of MV and cardiovascular autonomic dysfunction.¹⁸ Despite an initially severe presentation, most patients had a rapid improvement as 54% of them were able to walk unaided at 4 weeks. However, 6-month³ and 1-year recovery rates¹⁹ were similar to those already described.

Our study strongly suggests a link between chikungunya and GBS, based on the clinical and virological evidence of recent CHIKV infection. The comparison of annual incidence rates before and after the epidemic provides an epidemiological argument for causality. We thus confirm prior reports suggesting that GBS may be a complication of chikungunya.^{2,7,8,14} Our data add to those recently acquired from Polynesia and La Réunion island on the mounting evidence regarding the links between CHIKV and severe neurological disease.^{8,12} To our knowledge, this is the largest series of GBS temporally associated with a chikungunya outbreak. Our data show that although the rate of CHIKV-related GBS was relatively low (one case of GBS per 24,000), CHIKV infection contributed to a 2-fold increase of the overall incidence of GBS in the Caribbean. CHIKV may belong to three main genotypes, the West Africa, East/Central/South African (ECSA), and Asian. The latter two genotypes have been associated with neurological disease in La Réunion¹² and the Caribbean, respectively.¹⁴ Recent clinical and experimental data indicate differences in the pathogenicity between the Asian and ECSA lineages.^{20,21} However, GBS is an acute autoimmune neuropathy resulting most likely from an epigenetic modification or environmental trigger in a genetically susceptible host.²²

Whether some arboviruses have a greater ability than others to induce GBS remains unclear. Indeed, a large number of Zika-related GBS has been described during the Zika outbreak in French Polynesia (42 cases/268,270 inhabitants, a 20-fold increased incidence),⁹ which contrasts with the rarity of other arboviral-related GBS.^{5–7,17} A previous exposure to dengue virus may have predisposed to GBS, and this hypothesis deserves further investigation.

In conclusion, our data strongly suggests the existence of a relationship between CHIKV and GBS. CHIKV may therefore be added to the list of viruses associated with GBS, especially in the context of an epidemic.

TABLE 3
Annual incidence rate of GBS in FWI in the general population from 2011 to 2015

	2011		2012		2013		2014		2015	
	Martinique	Guadeloupe	Martinique	Guadeloupe	Martinique	Guadeloupe	Martinique	Guadeloupe	Martinique	Guadeloupe
Adults GBS	9	5	12	3	6	7	17	10	6	9
Total GBS cases	14		15		13		27		15	
Total FWI population	796,926		791,678		787,670		783,336		778,375	
GBS incidence (n/100,000 population)	1.76		1.89		1.65		3.45		1.93	

FWI = French West Indies; GBS = Guillain-Barré syndrome.

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