

## Case Report: Guillain–Barré Syndrome after Zika Virus Infection in Brazil

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**Abstract.** Zika virus (ZIKV) is an emerging flavivirus, which has caused a widespread outbreak in the Americas. Shortly after its introduction in 2015, a cluster of cases with Guillain–Barré syndrome was detected in Brazil. Herein, we describe two cases from the city of Salvador, who developed ascending paresis after an acute exanthematous illness. The patients were admitted to the intensive care unit with tetraparesis and cranial nerve palsy, which resolved after intravenous administration of human immunoglobulin. Serological evaluation detected IgM-specific ZIKV antibodies. In regions of Zika virus transmission, health-care workers must be aware of the potential severe neurological complications associated with ZIKV infection and be prepared to provide prompt diagnosis, treatment, and supportive care.

### INTRODUCTION

Zika virus (ZIKV) is an emergent flavivirus transmitted by *Aedes aegypti* mosquitoes with a high potential for transmission in countries where infestation of the vector occurs.<sup>1</sup> The first documented human case of ZIKV infection was reported in Nigeria in 1954,<sup>2</sup> and a number of sporadic cases were reported in Africa and Asia in subsequent years.<sup>3</sup> ZIKV was first associated with a large outbreak beginning in 2007 in Micronesia,<sup>4</sup> and later at French Polynesia in 2013,<sup>5,6</sup> and New Caledonia in 2014.<sup>7</sup> ZIKV was initially detected in northeastern Brazil on March 2015,<sup>8,9</sup> and has rapidly spread throughout South and Central America and the Caribbean.<sup>10</sup>

Human ZIKV infection was considered as a benign and self-limited illness, with clinical manifestations represented by low-grade fever, maculopapular rash, myalgia, arthralgia, headache, and conjunctivitis.<sup>4</sup> However, neurological complications were observed in patients during a ZIKV outbreak in French Polynesia in 2013, where several individuals presented with Guillain–Barré Syndrome (GBS).<sup>5</sup> A subsequent investigation found evidence of association between GBS and ZIKV infection.<sup>11</sup>

Similarly, after detection of ZIKV transmission in Brazil,<sup>8</sup> a cluster of GBS cases was identified.<sup>10</sup> Herein, we describe two patients presenting with GBS associated with ZIKV infection during the outbreak in Salvador, situated in the northeast region of Brazil. These patients presented severe complications of GBS requiring admission to the intensive care unit.

### CASE REPORT

**Patient 1.** A 49-year-old female presented with transient symptoms of generalized pruritic maculopapular rash and myalgia without fever or arthralgia, which lasted one day on May 15, 2015 (Day –10). On May 25 (Day 0: onset of neuro-

logical symptoms), she presented paresthesia on both hands and feet. Four days later, she noticed generalized fatigue and lower right limb paresis, followed by upper limb paresis. On Day 9, she developed diplopia and dysphagia appeared, and presented to an emergency room by Day 11, when she developed bilateral facial nerve palsy. She was hospitalized on Day 20 with worsening extremity weakness and ataxia.

She had weakness of her four limbs (Medical Research Council, MRC grade 4), areflexia, impairment of all sensitivity modalities and moderate bifacial nerve palsy (House–Brackmann grade 3). A lumbar puncture yielded cerebrospinal fluid (CSF) with 10 cells/mm<sup>3</sup>, with a predominance of lymphocytes, and protein and glucose level of 214 and 70 mg/dL, respectively. Diagnosis of GBS with tetraparesis and bifacial palsy was established according to international criteria,<sup>12</sup> and treatment was initiated on Day 23 with 0.4 g/kg/day of intravenous human immunoglobulin (IVIG) for 5 days. The patient's clinical and laboratory data are summarized in Table 1. Rapid clinical response was observed with improvement of muscular strength and bifacial palsy (House–Brackmann grade 2) by Day 26. Hughes functional grade was used to access the improvement of disability.<sup>13</sup> This patient improved from grade 4 to grade 2 by day 28.

On Day 58, during outpatient visit, she was able to walk unaided, had normal strength, sensitivity, and reflexes, and a mild residual bifacial palsy (House–Brackmann grade 2) on physical examination. The electromyogram, performed on Day 75, confirmed multifocal segmental demyelinating commitment with prolonged distal latencies and F-waves, with no reduction of compound motor action potential (CMAP). Reduction of sensory action potential amplitudes of median and ulnar nerves suggested secondary axonal injury (Table 1).

**Patient 2.** A 22-year-old male presented with fever, maculopapular generalized rash, and moderate arthralgia on May 30, 2015 (Day –8), which persisted for 5 days. These symptoms resolved and 3 days later (Day 0: onset of neurological symptoms), he had paresthesia on both feet and hands. On Day 3, he was tetraparetic and developed right-sided peripheral facial nerve palsy, dysarthria, urinary and fecal incontinence, and a transient blurred vision. On Day 4, he developed bifacial palsy and dysphagia, and he was admitted.

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TABLE 1  
Clinical and laboratory characteristics of two patients with Guillain-Barré syndrome from Salvador, Brazil

Characteristics	Case 1	Case 2
Age	49	22
Sex	Female	Male
Acute prodrome (duration)	Myalgia, rash, pruritus (1 day)	Fever, arthralgia, rash, pruritus (5 days)
Onset of neurological symptoms after prodrome	10 days	8 days
Neurological findings	Tetraparesis, bifacial palsy, ataxia, paresthesias, and other sensory disturbances	Tetraparesis, bifacial palsy, paresthesias, and other sensory disturbances
Cerebrospinal fluid findings	10 cells/mm <sup>3</sup> ; protein, 214 mg/dL; glucose, 70 mg/dL	5 cells/mm <sup>3</sup> ; protein, 67 mg/dL; glucose, 53 mg/dL
Electromyogram and nerve conduction study findings	Ulnar nerve: DL = 6.2 ms (RV < 3.0); CMAP = 7.4 mV (> 8.0 mV); NVC elbow = 52.1 m/s (> 50 m/s); F-wave: 32.6 ms (< 27 ms) Tibialis nerve: DL = 7.7 ms (< 5.0 ms); CMAP = 7.7 mV; NVC = 4.4 m/s Facial nerve: DL = 9.6 ms (< 3.0 ms); CMAP = 0.2 mV (> 1.5 mV)	Ulnar nerve: DL = 3.4 ms (RV < 3 ms); CMAP = 13.9 mV (> 8.0 mV); NVC elbow = 30.3 m/s (> 50 m/s); F-wave = 40.2 ms (< 29 ms) Median nerve: DL = 7.5 ms (< 3.7 ms); CMAP = 11.1 mV (> 8 mV); NVC = 54.2 m/s (> 50 m/s) Tibialis nerve: DL = 47 ms (< 5.0 ms); CMAP = 15.2 mV (> 4.0 mV); NVC = 49.7 m/s (> 40 m/s); Facial nerve: DL = 4.0 ms (< 3.0 ms); CMAP = 1.1 mV (> 1.5 mV); R1 = 20.0 ms/R2 = 47.8 ms (< 10.0/< 30.0 ms);
Treatment (duration)	Intravenous human gamma globulin (5 days)	Intravenous human gamma globulin (5 days)
Days of hospitalization	9	24

CMAP = conduction motor action potential; DL = distal latency; NVC = nerve conduction velocity; RV = reference value.

He became bedridden due to severe tetraparesis on Day 7 (MRC grade 2, upper limbs; grade 3, lower limbs) and was transferred to the neurological intensive care unit. He was alert, there was areflexia in all extremities, severe sensory impairment on all modalities, and moderately severe bifacial palsy (House-Brackmann grade 6). A nasogastric tube was inserted because of severe dysphagia. Examination of CSF revealed 5 cells/mm<sup>3</sup> with a predominance of lymphocytes and levels of protein and glucose of 67 and 53 mg/dL, respectively. The patient's clinical and laboratory findings are summarized in Table 1.

A diagnosis of GBS with bifacial palsy, tetraparesis, and brainstem involvement was established, and treatment with 0.4/kg/day of human IVIG for 5 days was initiated on Day 8. He recovered over the following 20 days with gradual improvement of muscular strength, dysphagia, dysphonia, and ability to walk with unilateral assistance. He improved from Hughes functional grade 4 to 3, and was discharged on Day 28. Electromyogram performed on Day 31 showed bilateral demyelinating impairment of median and ulnar nerves at wrist and ulnar nerve impairment at elbow, with prolonged distal motor latencies, reduced sensory conduction velocities in distal segments, and reduced motor conduction velocities of ulnar nerves with prolonged latencies of the F-waves and normal amplitudes of CMAP. Proximal demyelinating commitment of right facial nerve, with increase in blink reflex latencies (R1 = 20 ms/R2 = 55 ms), and mild reduction in the amplitude of CMAP was also noted (Table 1).

On Day 47, the patient did not have sensitivity or muscular strength abnormalities but had a mild/moderate right facial palsy (House-Brackmann grade 3) and areflexia in upper and lower limbs.

**Laboratory evaluation.** Serological tests for human immunodeficiency virus, hepatitis B and C were negative in both cases, as well as an IgM enzyme-linked immunosorbent assay (ELISA) for cytomegalovirus and herpes simplex virus type 1 and 2. Reverse transcription polymerase chain reaction (RT-PCR) for ZIKV, chikungunya virus (CHIKV), and

TABLE 2  
Serological evaluation of two patients with Guillain-Barré syndrome from Salvador, Brazil

Test	Case 1	Case 2
IgM ELISA*		
ZIKV	<b>0.765</b>	<b>1.357</b>
CHIKV	0.092	0.093
DENV	0.062	0.181
YFV	0.041	0.094
HI (IgG + IgM)		
ZIKV	≥ 1:1,280	≥ 1:1,280
CHIKV	Negative	Negative
DENV-1	1:320	≥ 1:1,280
DENV-2	1:640	≥ 1:1,280
DENV-3	1:320	≥ 1:1,280
DENV-4	1:640	≥ 1:1,280
YFV	1:160	≥ 1:1,280
PRNT <sub>90</sub>		
ZIKV	320	> 2,560
CHIKV	< 20	< 20
DENV-1	> 640	ND
DENV-2	320	> 2,560
DENV-3	160	1,280
DENV-4	80	160
YFV	< 20	< 20

CHIKV = chikungunya virus; DENV = dengue virus; ELISA = enzyme-linked immunosorbent assay; HI = hemagglutination inhibition; ND = not determined; PRNT<sub>90</sub> = plaque reduction neutralization test with a 90% neutralization cutoff; YFV = yellow fever virus; ZIKV = Zika virus. Positive values are in bold.

\*Optical densities, cutoff = 0.200.

dengue viruses (DENV) were negative on blood samples collected on Day 23 for case 1 and on Day 8 for case 2.

Specific anti-ZIKV IgM antibodies were detected in patients 1 and 2 when acute-phase serum samples collected on Days 23 and 8 respectively, before administration of IVIG, were tested in an in-house IgM antibody capture ELISA (MAC-ELISA) (Table 2). Evaluation of these samples in CHIKV, DENV, yellow fever virus (YFV), and Mayaro virus MAC ELISA yielded negative results. A hemagglutination inhibition (HI) assay performed using a panel of 18 arboviruses, which included alphaviruses, orthobunyaviruses, and flaviviruses, demonstrated prior exposure to flavivirus infection (ZIKV and DENV1–4). These findings were confirmed by testing serum samples from the patient in a plaque reduction neutralization test (PRNT) against ZIKV, CHIKV, YFV, and DENV (serotypes 1–4) (Table 2). Taken together, the serological findings of both patients indicated a recent infection by ZIKV and argued for resolute infections by DENV1–4.

## DISCUSSION

ZIKV is a reemerging pathogen, which poses new and unforeseen challenges for regions with recent outbreaks, representing an important threat for Latin America and other regions at risk.<sup>14</sup> Aside from the expected burden of an acute febrile illness to the health-care systems in the regions affected, the identification of potential causality between ZIKV and neurological complications results in an urgent concern with dramatic consequences to public health.

The term GBS is used to describe a broad spectrum of acute autoimmune neuropathies.<sup>12</sup> About two-thirds of the patients report an antecedent acute infectious illness and numerous infectious agents are associated with GBS.<sup>12</sup> An association with arboviruses, such as DENV<sup>15</sup> and CHIKV,<sup>16</sup> have been reported but are believed to be rare events. GBS cases were associated with ZIKV infection during the French Polynesia outbreak in 2013.<sup>11</sup>

This report describes two cases that were identified during a large outbreak in the city of Salvador, Brazil, in 2015, where 17,440 cases of suspected ZIKV infection were reported.<sup>17</sup> Concomitantly, 44 GBS cases, were identified, of which 32 (73%) reported having an acute prodromal illness, compatible with ZIKV infection.<sup>17</sup> Our patients had acute prodromal illness of pruritic rash, fever, myalgias, or arthralgias, which occurred 8–10 days before the onset of the neurological manifestations of GBS. Diagnosis of recent ZIKV infection was made based on detection of anti-ZIKV-specific IgM antibodies. Of note, like the GBS cases from French Polynesia,<sup>11</sup> RT-PCR analysis of serum samples at the time of the onset of neurological manifestations yielded negative results, indicating, presumably, the development of an anti-ZIKV immune response.

Underlying factors that influence the association of GBS and a recent ZIKV infection presumably involves an autoimmune process as described for other viral infections.<sup>12</sup> It has been speculated that the simultaneous epidemics of DENV and ZIKV may be a predisposing factor for GBS after a recent ZIKV infection, perhaps as a result of sequential arboviral immune stimulation and triggering of an immunopathogenic process.<sup>11,18</sup> We found that the two GBS cases, who are residents of a region of high DENV-endemic transmission,<sup>19</sup> had high HI and PRNT<sub>90</sub> (PRNT with a 90% neu-

tralization cutoff) to DENV serotypes, indicating that the patients had a distant infection with this virus, before their recent ZIKV infection. However, in a case-control study at French Polynesia, the authors could not find evidence of an association between previous dengue infection and development of GBS.<sup>11</sup> They also observed the absence of typical patterns of antiglycolipid antibodies and suggested that onset of GBS may be attributed to unidentified autoantibodies in post-Zika virus exposure.<sup>11</sup> Thus, further immunopathologic studies are still required for better understanding of this issue.

Both patients had clinical and laboratory findings of GBS, with albuminocytologic dissociation. Electromyogram pattern showed distal demyelinating disorder with accentuated prolonged distal latencies and minimal reduction of CMAP amplitudes, suggesting an acute inflammatory demyelinating polyneuropathy (AIDP) GBS subtype,<sup>20</sup> with secondary axonal injury. The patients received and tolerated human IVIG treatment with no relevant adverse effects. The better prognostic of AIDP GBS subtype<sup>20</sup> along with prompt implementation of human IVIG treatment may have had an important role in clinical recovery. As illustrated, patients with severe GBS require intensive supportive management in intensive care settings. Yet, despite the severity of their clinical presentations, none of them needed mechanical ventilation or died.

The investigation of these two cases provides additional evidence in support of the association of GBS and ZIKV infection. Furthermore, it also serves as an alert to clinicians in regions of South and Central America and the Caribbean, where the virus has recently spread, of the potential risk for GBS and the need for timely detection, diagnosis, and initiation of treatment and supportive care to prevent mortality and long-term sequelae.

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