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Zika Virus–Associated Guillain-Barré Syndrome in a Returning US Traveler

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Abstract

Zika virus (ZIKV) infection has been associated with Guillain-Barré Syndrome (GBS). Roughly 60% of people in countries such as the U.S. live in areas at risk for seasonal spread of ZIKV. ZIKV belongs to a class of diseases that is not typically seen in hospital settings across the U.S. and Europe. We describe the case presentation, management, and treatment of ZIKV infection complicated by GBS. A 64-year-old woman with recent travel to the Dominican Republic presented with rash followed by an acute, ascending polyneuropathy consistent with GBS. She was confirmed to have an acute ZIKV infection by detection of ZIKV nucleic acid by reverse transcription-polymerase chain reaction. She met Brighton Collaboration criteria level 1 evidence for GBS. She received two courses of intravenous immunoglobulin and slowly improved, though still had weakness at discharge. More research is needed to identify the pathophysiology behind ZIKV-associated GBS and its optimal treatment. Prevention is fundamental to limiting infection and spread of ZIKV.

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Overview

Zika virus (ZIKV) infections in humans have been documented as early as 1956.[1–3] ZIKV is a Flavivirus which spread primarily through bites of certain *Aedes* species of mosquitoes and sexual contact with infected patients.[4, 5] Local transmission of ZIKV was first identified in Brazil in March, 2015, and has since rapidly spread throughout the Americas.[6–8] The World Health Organization declared the ZIKV outbreak a public health emergency in February, 2016.[9] A recent global infectious disease model estimated that Mexico, Colombia, and the United States are thought to have 31, 23, and 23 million people, respectively, living in areas at risk for year-round transmission of ZIKV.[10] In addition, it is estimated that more than 60% of populations in countries such as Argentina and the United States live in areas at risk for seasonal spread of ZIKV.[10]

Initially thought to be either asymptomatic or cause a mild acute febrile illness, ZIKV infection has now been associated with microcephaly and other birth defects, myelitis, and meningoencephalitis.[11–16] ZIKV has also been associated with Guillain-Barré syndrome (GBS), an acute autoimmune attack on the peripheral nerves and/or nerve roots resulting in progressive weakness with significant morbidity and potential mortality.[17–23] The full clinical range and optimal management of ZIKV-associated GBS is not known. We present a case, including clinical course, management, and outcome, of ZIKV-associated GBS in a traveler returning to the United States from the Dominican Republic.

Case Presentation

A 64-year-old female office worker who resided and worked in New York City, with hypothyroidism and hypertension first developed a facial maculopapular rash, which spread caudally to her chest. She also reported a subjective “low grade” fever, malaise, arthralgias, conjunctivitis, headache, cough and rhinorrhea 6 days after her return to the US from the Dominican Republic. She did not have any sexual exposure risk factors for over one year. A family member she had been travelling with had developed a similar febrile illness. On post symptom onset day (PSOD) 3 she presented to an outside hospital where she was evaluated. An arboviral molecular and serologic panel was sent, and she was discharged home.

On PSOD 10, she presented to our institution with paresthesias in her hands and feet, weakness in her legs, and difficulty walking. On admission examination, she was afebrile with normal vital signs. Her mental status and cranial nerve exams were normal. She had normal muscle bulk and tone in all four extremities. There was symmetric, bilateral, proximal greater than distal weakness in her upper and lower extremities (grade 3 power in bilateral deltoids, hip flexors, and hip extensors; grade 4 power in biceps and triceps; trace weakness in intrinsic hand muscles). Prior immunization status was not clear. Her sensory examination revealed mild pinprick and vibratory loss in her great toes. Her deep tendon reflexes were normal (2+) in her upper extremities, but absent in the lower extremities. She did not have a Hoffman’s sign or Babinski responses. There was no dysdiadokinesis or dysmetria in her upper extremities. She was unable to perform heel-knee-shin testing because of proximal leg weakness. She had difficulty sitting up, standing, and walking,

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largely due to proximal leg weakness. Electrodiagnostic studies on PSOD 10 showed a widespread, predominantly demyelinating, sensorimotor polyneuropathy with some secondary axonal involvement.

Initial laboratory studies revealed normal complete blood count, basic metabolic panel, liver function tests, erythrocyte sedimentation rate, C-reactive protein, and thyroid function tests (Table 1). Computed tomography (CT) scan of the brain showed no acute intracranial abnormality. The patient was given intravenous immunoglobulin (IVIG) 2g/kg over 5 days starting on PSOD 10 for presumed GBS. On PSOD 12 she was transferred to the intensive care unit (ICU), where she was intubated for airway protection after complaining of throat tightness, increasing dyspnea, and development of facial weakness. The arboviral panel collected by the outside hospital on PSOD 3 showed a positive urine and serum ZIKV reverse transcription-polymerase chain reaction (RT-PCR) (Table 2). Arbovirus plaque reduction neutralization testing (PRNT) was negative for ZIKV but positive for Dengue virus. Dengue and chikungunya virus immunoglobulin (Ig) M testing on serum were negative. Dengue virus IgG testing on serum was positive at 7.72 immune status ratio (ISR) (Normal < 1.65), suggesting prior infection with an unspecified *Flavivirus*. She had no confirmed past history of dengue virus disease. Further viral studies including neutralizing antibody for St. Louis Encephalitis Virus were not performed given Zika virus nucleic acid was detected which confirmed Zika virus infection.

Lumbar puncture on PSOD 13 showed mildly elevated cerebrospinal fluid (CSF) white blood cells of 6 cells/mm^3 (78% lymphocytes), normal CSF glucose of 71 mg/dL, and mildly elevated CSF protein of 51.5 mg/dL (Table 2). There were no oligoclonal bands in CSF. Other CSF studies including herpes simplex virus PCR, John Cunningham virus PCR, and Venereal Disease Research Laboratory tests were negative. CSF and repeat serum testing on PSOD 13 for ZIKV nucleic acid by RT-PCR were negative, however repeat urine RT-PCR from PSOD 13 was positive. Initial serum Zika IgM enzyme-linked immunosorbent assay (ELISA) on PSOD 3 was negative, however, on PSOD 13 resulted presumptive positive, as did CSF ZIKV IgM ELSIA. PRNT on PSOD 13 was positive for both ZIKV and Dengue virus. New Zika infection is supported this new conversion to a positive ZIKV PRNT of 320.

Over the next several days, her weakness worsened to the point she was unable to sit-up or lift her arms or legs off the bed. Vibration and pin-prick sensory loss progressed up to both knees in the lower extremities and in the fingers and hands. She lost her upper extremity deep tendon reflexes. She developed methicillin sensitive *Staphylococcus aureus* pneumonia while intubated and was treated with a course of cefazolin. A tracheostomy was performed on PSOD 21. Given persistent respiratory failure and weakness, she was given a second course of IVIG 2g/kg over 5 days starting on PSOD 22.

Her respiratory status and weakness slowly improved to where she was transitioned to tracheostomy collar on PSOD 23, transferred out of the ICU PSOD 25, and discharged to acute rehabilitation on PSOD 35. Her neurologic exam at discharge revealed grade 3 strength in the bilateral upper extremities and grade 4 strength in the bilateral lower extremities; deep tendon reflexes were still absent throughout her upper and lower

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extremities at discharge. Follow-up PRNT on PSOD 63 was positive for ZIKV and Dengue virus, and serum ZIKV IgM ELISA returned presumptive positive. Patient continued to improve, was able to walk, tracheostomy was decanulated and she was eventually able to return to work after four months.

Discussion

Our patient had confirmed acute ZIKV infection by detection of ZIKV nucleic acid in serum and urine at the time of initial presentation after[24] travel to the Dominican Republic (a family member who traveled with her was also confirmed to have an acute ZIKV infection). She also met Brighton Collaboration criteria level 1 epidemiologic evidence for GBS given her neurologic exam, CSF analysis, and electrodiagnostic results.[25] Therefore, this case represents one of the first confirmed clinical cases of likely ZIKV-associated GBS diagnosed and treated in the U.S. states.

Our patient's onset of GBS symptoms occurred 10 days after acute ZIKV symptom onset, consistent with the limited literature on ZIKV-associated GBS suggesting a shorter time from acute infection to onset of GBS when compared to GBS associated with other etiologies (Ref – French Polynesian article). Additionally, our case was consistent with a rapid progression to nadir and a severe course requiring ICU admission and mechanical ventilation, as noted in the literature from other settings.

GBS can occur after infections with various pathogens, including *Campylobacter jejuni*, *Mycoplasma pneumoniae*, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus (HIV), typically within two to six weeks.[26–28] Certain arboviral infections (e.g., dengue and chikungunya virus infection) have also preceded the development of GBS.[29–32] The reasons why certain people develop GBS after an infection (whether it be from Zika, influenza, or *Campylobacter*) and others do not is currently unknown. It is suspected that people who develop GBS have a genetic susceptibility and require certain exposures, but what those are is not known at this time. Prior infection with dengue virus has not been proved a risk factor for ZIKV-associated GBS as of yet. [33] Nonetheless, cross-reactivity between dengue virus and ZIKV has been demonstrated, with prior dengue infection possibly leading to increased ZIKV severity. This interaction is not unexpected as infection with related flaviviruses is known to produce a cross-reactive, non-neutralizing serum antibody response, and offers an explanation for the steep rise in dengue virus antibodies observed in the patient via PRNT.[34]

Recently, GBS has been associated with ZIKV infection, an emerging arbovirus in the *Flavivirus* genus.[17–23] A case-control study from French Polynesia showed GBS cases had 34 times the odds of having ZIKV-neutralizing antibodies compared to controls; 88% of cases had an illness compatible with ZIKV infection a median of 6 days prior to the development of GBS.[17] These results are highly suggestive of recent ZIKV infection in most of the cases, but since the virus nor its nucleic acid was found, it wasn't absolute proof that the cases were infected with ZIKV recently. Acute axonal motor neuropathy (AMAN) was the predominant GBS variant among those who had electrodiagnostic studies. Additionally, a prospective surveillance study from Puerto Rico identified 34 cases of GBS

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with either presumptive or confirmed preceding ZIKV infection a median of 5 days before GBS onset.[22] Acute inflammatory demyelinating polyneuropathy (AIDP) was the most common variant described in this series. Our patient developed GBS on PSOD 10 which is within the time frame of ZIKV-associated GBS already described in the literature. She also had a predominantly demyelinating polyneuropathy consistent with the AIDP variant, though there were some mixed secondary axonal features.

Zika testing is often available through commercial laboratories, the local, and/or state health departments who can facilitate, track, and prioritize testing. Investigations may include serologic (antibody) or molecular (nucleic acid) tests, depending on the sample type and timing of the sample acquisition. The optimal treatment of ZIKV-associated GBS is not known, as there have been no controlled trials.

For more classically-described GBS, both IVIG and plasmapheresis have been shown to equally limit long-term weakness and disability[35], but there is no advantage to combining both treatments.[36] The vast majority of ZIKV-associated GBS cases in the literature have been treated with IVIG over plasmapheresis, likely because IVIG was logistically easier to administer. IVIG might also be theoretically less immunosuppressive than plasmapheresis (which removes circulating antibodies), which might be advantageous given that direct ZIKV infection of peripheral nerves has not yet been excluded pathophysiologically. Our patient showed little improvement after the first course of IVIG, but improved significantly after the second course of IVIG. Whether this improvement was due to the natural course of the disease, treatment with IVIG, or both is unclear.

In addition to disease modifying therapy, complications of GBS including respiratory failure, autonomic instability, neuropathic pain, and deep vein thrombosis should be managed.[37, 38] Our patient required mechanical ventilation for respiratory failure, was monitored with telemetry and frequent vital sign checks in case of autonomic instability, and was given unfractionated heparin for deep vein thrombosis prevention.

The full clinical spectrum and optimal management of ZIKV-associated GBS are not completely known. Prevention is fundamental to limiting infection and spread of ZIKV. Key components of prevention include limiting exposure to mosquitoes which are key vectors in transmission and limiting sexual transmission. Suspected ZIKV-associated GBS cases should be reported to local, state, or territorial public health authorities. Finally, directed ZIKV vaccines are being investigated by several groups.[39, 40] More research is needed to better understand ZIKV pathophysiology, clinical course, and optimal management.

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Table 1

Laboratory Data

Variable		Reference	PSOD			
			10	13	17	25
Hemoglobin (g/dL)		12.0–16.0	13.2	13.3	11.1	10.5
Hematocrit (%)		37–47	39.9	39.8	32.8	30.5
Platelet (per nl)		150–450	290	334	318	416
White Blood Cell Count (per nl)		4.8–10.8	5.4	7.3	16.0	11.1
Differential Count (%)	**Neutrophils**	44–70	67.5	79.2	86.9	75.9
	Lymphocytes	20–45	24.4	12.2	5.7	15.2
	Monocytes	2–10	6.7	7.8	6.5	5.1
	Eosinophils	1–4	1.1	0.3	0.6	3.3
	Basophils	0–2	0.3	0.3	0.3	0.5
Protein (g/dl)	**Total**	6.3–8.2	8	8.8	7.7	8.7
	Albumin	3.7–5.1	4.2	3.7	3.2	3.4
Aspartate Aminotransferase (U/L)		11–39	45	42	36	33
Alanine Aminotransferase (U/L)		11–35	14	22	28	21
Alkaline Phosphatase (U/L)		25–100	71	67	74	87
Bilirubin (mg/dl)	**Total**	0.2–1.3	0.4	0.5	0.9	0.5
	Direct	0.0–0.2	0.2	0.2	0.3	0.2
Sodium (mmol/L)		137–147	141	128	118	131
Potassium (mmol/L)		3.6–5.2	4.1	3.4	4.1	4.7
Chloride (mmol/L)		99–112	103	89	83	96
Carbon Dioxide (mmol/L)		23–32	24	30	26	31
Urea Nitrogen (mg/dl)		6–22	9	8	16	14
Creatinine (mg/dl)		0.1–1.1	0.5	0.5	0.4	0.4
Glucose (mg/dl)		70–99	103	113	106	100
Calcium (mg/dl)		8.0–10.4	9.2	8.6	8.2	9.8
Free T3 (pg/mL)		2.3–4.2	2.2			
Free T4 (ng/dL)		0.9–1.9	1.49			

Infect Dis Clin Pract (Baltim Md). Author manuscript; available in PMC 2019 November 01.

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Variable		Reference	PSOD			
			10	13	17	25
TSH (μIU/mL)		0.35–4.8	1.88			
ESR (mm/hr)		0–20	20			
Wide Range CRP (mg/L)		≤3	6.84			
Coagulation	Prothrombin Time (sec)	8.8–12.3	10.8	11.9	12.5	
	Partial Thromboplastin Time (sec)	23.6–35.8	26.7	24.2	24.7	
	INR	0.8–1.13	0.96	1.06	1.11	

Reference values reflect ranges for female adults without medical conditions. The values may therefore not be appropriate for all patients

PSOD 13 First full day in the MICU, had LP and repeat ZIKV testing

PSOD 17 developed pneumonia

PSOD 25 transferred to the floor

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Table 2

Arboviral Studies and Cerebrospinal Fluid

Variable (reference)[a]			PSOD 3 (Presentation OSH)	PSOD 13	PSOD 63
Arboviral Studies					
Zika	**PCR**	**Serum**	ZIKV RT-PCR (+)	ZIKV RT-PCR (−)	
		Urine	ZIKV RT-PCR (+)	ZIKV RT-PCR (+)	
		Cerebrospinal Fluid		ZIKV RT-PCR (−)	
	IgM ELISA	**Serum**[b]	Negative	Presumptive Positive	Presumptive Positive
		Cerebrospinal Fluid		Presumptive Positive	
Serum	**PRNT**[c]	**Zika**	Negative (<10)	Positive (320)	Positive (320)
		Dengue	Positive (160)	Positive (20,480)	Positive (2,560)
	Dengue	(<1.65)	IgM 1.58 ISR		
		(<1.65)	IgG 7.72 ISR		
	West Nile	(−)			
	Chikungunya		IgM (−)		
			IgG (−)		
Cerebrospinal Fluid[d]					
Glucose	(40–80)			71	
Protein	(15–45)			51.5	
Red Blood Cell	(0–3)			4	
White Blood Cell	(0–5)			6	
Differentials (%)	**Neutrophils**	(0–7)		12	

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Variable (reference)[a]		PSOD 3 (Presentation OSH)	PSOD 13	PSOD 63
Lymphocytes	(28–96)		78	
Monocytes	(16–56)		10	

[a] Human Immunodeficiency Virus, Herpes Simplex Virus Type 1 and 2, Hepatitis C, Syphilis antibody, Lyme, oligoclonal bands, John Cunningham virus in Cerebrospinal Fluid negative. Epstein-Barre Virus and Cytomegalovirus were IgG positive, IgM negative.

[b] Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA)

[c] Arbovirus Plaque Reduction Neutralization Test (PRNT)

[d] Cerebrospinal Fluid- only 50 white blood cells seen on cytospin smear Gram stain, Varicella-Zoster and Lyme Total Antibody screen- negative.

Infect Dis Clin Pract (Baltim Md). Author manuscript; available in PMC 2019 November 01.