Neurologic manifestations of Zika virus infection

Manifestaciones neurológicas de la infección por el virus zika

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Abstract

Zika virus is a flavivirus transmitted via mosquito bite, blood transfusion, sexual intercourse or from mother-to-child during gestation. Although neurologic complications of Zika virus infection are rare, Guillain-Barré syndrome (GBS) is the most common manifestation and typically develops soon after the initial systemic manifestations of Zika virus infection. This syndrome typically starts in the distal limbs with symmetric sensory abnormalities and progresses to involve weakness and decreased or absent deep tendon reflexes. Severe cases may also involve respiratory and cardiovascular impairment requiring care in an intensive care unit, and ventilator or circulatory support. A review of 166 published cases of GBS associated with Zika virus is notable for lower mortality than seen with sporadic GBS, but limited data regarding long-term outcome. When available, treatment with intravenous IgG (IVIg) or plasmapheresis, can reduce the severity and duration of symptoms.

Keywords: Zika Virus; Neurologic Manifestations; Central Nervous System Infection; Guillain-Barré Syndrome.

Resumen

El virus zika es un flavivirus transmitido a través de la mordedura de mosquito, transfusión de sangre, la relación sexual o de madre a hijo durante la gestación. Aunque las complicaciones neurológicas de la infección por el virus zika son raras, el síndrome de Guillain-Barré (GBS) es la manifestación más común y normalmente se desarrolla poco después de las manifestaciones sistémicas iniciales de la infección por el virus. Este síndrome comienza en las extremidades distales con alteraciones sensoriales simétricas y progresa hasta involucrar la debilidad y la disminución o ausencia de reflejos tendinosos profundos. Los casos graves pueden implicar deterioro respiratorio y cardiovascular, requiriendo atención en una unidad de cuidados intensivos, así como ventilador o soporte circulatorio. Una revisión de 166 casos publicados de GBS asociados con el virus zika se caracteriza por una menor mortalidad que los observados con GBS esporádica, pero los datos son limitados con respecto a resultados a largo plazo. Cuando esté disponible, el tratamiento con IgG intravenoso (IVIg) o plasmaféresis puede reducir la gravedad y duración de los síntomas.

Palabras clave. Virus Zika; Manifestaciones Neurológicas; Infección del Sistema Nervioso Central; Síndrome de Guillain-Barré.

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INTRODUCCIÓN

Zika virus is an arthropod-borne RNA virus in the *flaviviridae* family, a family that includes other neurotropic viruses such as dengue, yellow fever, Japanese encephalitis, West Nile and Saint Louis encephalitis viruses. Although Zika virus was first described in Uganda in 1947, it was not identified as a cause of neurologic disorders until Guillain-Barré syndrome (GBS) was reported in French Polynesia in 2013 [1,2]. Since then, Zika virus infection has also been associated with microcephaly, encephalitis and myelopathy. Microcephaly in Brazil was initially reported in early 2016 and will be discussed in a separate manuscript. Encephalitis or meningoencephalitis associated with Zika virus infection has been reported in four patients, with Zika virus detected in cerebrospinal fluid (CSF) of three of the four patients and anti-Zika antibodies detected in CSF of the fourth patient [3-5]. Acute myelitis has also been reported in one patient, also confirmed through detection of Zika virus in CSF [6]. As GBS associated with Zika virus infection is currently the most common neurologic manifestation in adults, this review will focus on the clinical features, diagnosis and management of GBS.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) is a common cause of acute flaccid paralysis throughout the world. The syndrome is rare and most often follows a bacterial or viral infection, or less frequently, vaccination. Symptoms typically include weakness and sensory abnormalities but may also include cranial nerve abnormalities, such as ophthalmoplegia (the Fisher syndrome). Weakness starts in the distal limbs, then progresses proximally, and can progress to paralysis; is typically associated with decreased or absent deep tendon reflexes as well as sensory loss, paresthesia or dysesthesia that starts in the peripheral limbs and ascends proximally.

Guillain-Barré syndrome associated with Zika virus infection

The onset of neurologic symptoms typically follows a prodromal illness that may include rash, fever, arthritis and conjunctivitis. The median onset of neurologic symptoms of GBS following transient illness with Zika virus is 6-10 days, which is similar to the median interval of 9 days reported between onset of neurologic symptoms of GBS and diarrhea due to *Camphylobacter jejuni* infection [7-10]. Given the lack of prior reports of GBS in Uganda, some experts have postulated that prior exposure to another arboviral infection, specifically dengue or chikungunya, is necessary for Zika to produce GBS through an immune-mediated mechanism. In one study, evidence of prior dengue infection was present in 32 (86%) of 37 patients with GBS [9]. In this same study, 20 (29.4%) of 68 patients with Zika virus-associated GBS had onset of neurologic symptoms during or immediately following the viral prodrome, suggesting a portion of the GBS symptoms could be due to direct effects of viral infection [9]. Neuropathologic studies in human and non-human primate fetuses have detected Zika virus in brain tissue [11,12]. Immunohistochemical assays have further localized Zika virus infection to neurons and glial cells [13]. Neuropathologic studies of patients with Zika-associated GBS have not been published.

The clinical symptoms associated with GBS due to Zika virus infection are similar to those due to other etiologies of GBS. Table 1 provides an overview and summary of specific symptoms, neurologic findings and frequency of respiratory and intensive care unit support required for patients with Zika-associated GBS. Although there is no particular neurologic finding that would suggest Zika virus over an alternate etiology, clinical symptoms typically appear distally and symmetrically, as opposed to West Nile virus infection, which typically produces an asymmetric flaccid paralysis similar to polio [14].

Diagnosis

Diagnosis of GBS requires confirmation of a peripheral neuropathy by neurophysiologic testing [15]. There are multiple potential types of peripheral nerve dysfunction associated with GBS (acute inflammatory demyelinating polyneuropathy, AIDP; acute motor and sensory axonal neuropathy, AMSAN; acute motor neuropathy, AMAN; acute sensory neuronopathy, acute pandysautonomia and overlap syndrome) and criteria for electrodiagnosis vary with the subtype of GBS. Measurement of nerve conduction velocity and needle electromyography are used to characterize and confirm the presence of demyelinating polyradiculoneuropathy or axonal damage in affected limbs. Specific guidelines are available to help diagnose and differentiate between the various forms of GBS [15]. The likelihood of detecting abnormalities with neurophysiologic testing is maximal at 7 or more days following onset of illness.

Lumbar puncture in patients with GBS should demonstrate less than 50 white blood cells/µl in CSF and, when CSF is obtained at least two days after symptoms develop, often reveals a "cytoalbuminologic dissociation" – an elevation of CSF protein greater than 45 mg/dL (this level may vary by local laboratory). Lumbar puncture is also useful for excluding other infectious causes of acute flaccid paralysis. The Brighton criteria were developed to provide guidelines for diagnosing GBS with four levels of diagnostic certainty (Table 2) [16]. These criteria incorporate clinical, electrodiagnostic and CSF findings and provide a useful tool for case ascertainment of GBS.

As is the case for many viral infections of the central nervous system (CNS), detection of virus in CSF is transient and is often absent by the time neurologic symptoms develop. As GBS is often an immune-mediated response to the CNS initiated by a bacterial or viral infection, detection of Zika virus in CSF is not necessary, but is more likely if neurologic symptoms start during the prodromal stage with systemic symptoms, such as rash and arthralgia. Current assays can directly detect Zika virus RNA or the immune response developed by the immune system against the Zika virus (Table 3) [17].

During the initial viremic period, real-time reverse transcriptase polymerase chain reaction (rRT-PCR) can be used to detect virus in blood, CSF, saliva or urine up to a week after onset of symptoms [18]. A positive rRT-PCR confirms the presence of Zika virus infection, but as vire-

Table 1. Clinical features of Guillain-Barré Syndrome associated with Zika virus infection. Compiled from references (1, 7-9, 24, 25).

Clinical feature	Publication						
	Arias (n=19)	Dirilikov (n=34)	Oehler (n=1)	Cao-Lorameau (n=42)°	Do Rosario (n=2)	Parra (n=68)	Total (n=166)
Male gender	12 (63.2%)	14 (41%)	-	31 (74%)	1 (50%)	38 (565)	96/165 (58%)
Median onset days (Range)	10 (2-20)	5 (0-17)	7	6 (4-10)	9 (8-10)	7 (3-10)	-
Rash	17 (89%)	18 (56%)	1 (100%)	29/36 (81%)	2 (100%)	40 (59%)	107/160 (67%)
Fever	15 (79%)	12 (30%)	1 (100%)	18/31 (58%)	1 (50%)	47 (69%)	94/155 (61%)
Arthritis	14 (74%)	-	1 (100%)	23/31 (74%)	2 (100%)	15 (22%)	55/121 (45%)
Conjunctivitis	7 (37%)	-	1 (100%)	15/31 (48%)	0 (0%)	17 (25%)	40/121 (33%)
Diarrhea	-	7/21 (34%)	-	-	-	-	
Facial palsy	8 (42.1%)	20/32 (63%)	1 (100%) Bilateral	33 (79%) Bilateral 25 (60%)	2 (100%) All Bilateral	34 (50%) All Bilateral	98/164 (60%)
Dysphagia	5 (26%)	19/32 (59%)	-	19 (45%)	2 (100%)	-	45/95 (47%)
Paresthesias	14 (73.7%)	Leg 24/32 (75%)	1 (100%)	35 (83%)	2 (100%)	52 (76%)	128/164 (78%)
Limb paresis	Upper 13 (68.4%) Lower 19 (100%)	Upper 24/32 (75%) Lower 31/32 (97%)	1 (100%)	33 (79%) Lower 17 (40%)	2 (100%)	66 (97%)	152/164 (93%)
Areflexia	18 (95%)	31/32 (97%)	1 (100%)	20 (48%)	2 (100%)	64 (94%)	136/164 (83%)
Increased CSF protein	8 (42.1%)	25/25 (100%)	1 (100%)	39 (93%)	2 (100%)	45/55 (82%)	120/144 (83%)
Respiratory assistance	15 (79%)	12/32 (29%)	-	12 (29%)	-	21 (31%)	60/161 (37%)
Labile blood pressure Hypotension	15 (79%)	-	1 (100%)	-	-	41 (31%)	57/88 (65%)
ICU stay	19 (100%)	21 (62%)	0 (0%)	16 (30%)	0 (0%)	40 (59%)	56/95 (59%)
Disability (3 months)	-	-	*	24/57	**	-	-
Death	0/19 (0%)	1/34 (3%)	0/1 (0%)	0/42 (0%)	0/2 (0%)	3/68 (4%)	4/166 (2.4%)

* Day 4: Walking without assistance.
** Day 28: House-Brackmann Grade 2, Day 47: House-Brackmann Grade 3.

mia is transitory, a negative test does not exclude the diagnosis. Presence of Zika virus RNA in urine has been reported to start approximately two weeks after onset of viral symptoms and in one patient persisted for 48 days, suggesting that duration of detection of viral RNA by rRT-PCR may vary across body fluids [9,19].

The detection of specific IgM antibodies or a significant rise in the anti-Zika IgG titer in a pair of samples taken at least two weeks apart provides evidence of an acute infection. Anti-Zika virus IgM can be detected by enzyme-linked immunosorbent assay (ELISA) in CSF or serum following the initial viremic phase until about 12 weeks after infection. Neutralizing antibodies to Zika virus develop following appearance of IgM antibodies, are primarily IgG, and typically persist for years. Unfortunately, Zika virus antibody assay results can be obscured due to cross-reactivity with other flaviviruses, which can prevent identification of the specific infecting virus, especially in a person previously infected with or vaccinated against a related flavivirus [20]. The plaque reduction neutralization test (PRNT) allows discrimination of anti-Zika virus antibodies from other potential cross-reacting antibodies due to other flavivirus infections. Although a PRNT ≥ 4-fold titer is typically used to confirm an infection, the U.S. Centers for Disease

Table 2. Key diagnostic criteria and Brighton case definitions for Guillain-Barré syndrome.

Diagnostic criteria	Level of diagnostic certainty			
	1	2	3	4
Bilateral and flaccid weakness of limbs	+	+	+	+ / -
Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+ / -
Monophasic course and time between onset-nadir 12 h to 28 days	+	+	+	+ / -
CSF cell count <50 white blood cells/mL	+	+ [(a)]	-	+ / -
CSF protein concentration > 45 mg/dL	+	+ / - [(a)]	-	+ / -
Nerve conduction study consistent with one of the subtypes of GBS	+	+ / -	-	+ / -
No alternative diagnosis for weakness	+	+	+	+

+ present; - absent; + / - present or absent.
(a) If CSF results not available, nerve conduction study must be consistent with diagnosis of Guillain-Barré syndrome.

Table 3. Key clinical and laboratory diagnostic criteria for Zika virus infection with and without Guillain-Barré Syndrome.

	Zika virus disease Clinical AND Laboratory		Zika associated GBS Clinical AND Laboratory	
Suspected*	Patient with rash with two or more of the following signs or symptoms: 1) Fever <38.5° C 2) Conjunctivitis (non-purulent/ hyperemic) 3) Arthralgia 4) Myalgia 5) Peri-articular edema	No laboratory confirmation	Bilateral and flaccid weakness of the limbs AND Decreased or absent deep tendon reflexes in weak limbs AND Monophasic illness pattern, with interval between onset and nadir of weakness between 12 hours and 28 days, and subsequent clinical plateau AND Absence of identified alternative diagnosis for weakness**	No laboratory confirmation
Probable		Zika IgM antibodies without evidence of other flavivirus infection		Detection of anti-Zika antibodies by enzyme-linked immunosorbent assay (ELISA) in CSF, serum, or urine and exclusion of the four dengue virus serotypes
Confirmed		RNA or Zika virus antigen detected in serum, urine, saliva, tissue or whole blood; OR Positive Zika IgM antibodies AND Plaque reduction neutralization (PRNT90) for Zika virus titers = 20 and ≥ four times greater than titers for other flaviviruses; AND exclusion of other flavivirus; OR detection of Zika viral genome in autopsy specimen (fresh or paraffin tissue) by molecular techniques or immunohistochemistry		Detection of Zika virus RNA by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay in blood, CSF or urine

*Adapted from PAHO Zika: Case Definition (7). Suspected case requires potential exposure through 1) Zika virus disease in geographic areas with autochthonous transmission and vectors are present; OR 2) travel to or residing in, a geographic area with known vector presence or Zika virus transmission within 2 weeks prior to onset of symptoms; OR 3) un-protected sex, in the 2 weeks prior to onset of symptoms, with a person who traveled, in the previous 8 weeks, to a geographic area with (a) known local transmission of the Zika virus or (b) an area with known vector presence.
** See Table 1 for levels of diagnostic certainty.

Control and Prevention has suggested a more conservative approach using a titer of ≥ 10 against Zika virus and PRNT < 10 against other flaviviruses to confirm infection [17].

Similar to the Brighton Criteria developed to provide levels of diagnostic certainty for GBS, the World Health Organization has developed criteria to determine level of certainty for diagnostic assays for Zika virus infection [21]. These levels of diagnostic certainty have been further modified to include CSF testing by Parra and colleagues [9], with definite infection requiring detection of Zika virus RNA by rRT-PCR assay in blood, CSF or urine; probable infection requiring detection of anti-Zika antibodies by ELISA in the CSF or serum, as well as exclusion of dengue virus serotypes; and suspected infection requiring two or more features of the PAHO case definition without laboratory confirmation (Table 3).

Treatment

Treatment of GBS is often symptomatic, but as respiratory and cardiovascular systems can also be affected, experts recommend monitoring in an intensive care setting where respiratory and blood pressure support are available. In addition to symptomatic treatment, GBS can be treated with plasmapheresis or high dose intravenous immunoglobulins (IVIg). As plasmapheresis requires specialized equipment for plasma exchange, this procedure is often limited to specialized reference centers and to patients affected by respiratory compromise or hypotension. Although IVIg is easier to administer, cost of treatment is high, typically costing over $US10 000 for a five-day course of 0.4 g/kg bodyweight.

Although outcome of GBS is generally quite good, 5-15% of patients die and 20% remain disabled at one year [22]. Factors associated with poor prognosis include requiring mechanical ventilation, rapid onset of weakness and severe weakness at nadir of illness [23]. Although long-term neurologic outcome following Zika-associated GBS is not yet clear, reports suggest mortality from Zika-associated GBS, when appropriate intensive care services and treatment are available, is less than 5%. Reports of long-term outcome following Zika-associated GBS are few, but suggest the majority of patients recover the ability to walk without assistance (Table 1).

CONCLUSIONS

The neurologic complications of Zika virus infection in adults include Guillain-Barré syndrome (GBS), meningitis, encephalitis and myelitis. The most common of these complications is GBS.

The clinical presentation and course of illness of GBS due to Zika virus infection appears to be very similar to GBS caused by other etiologies. Healthcare providers in areas where Zika is endemic, or who evaluate patients who have recently traveled through an endemic area or had sex with a person who may have had Zika infection, should consider Zika virus as a possible etiology of GBS. Treatment frequently requires an intensive care unit to provide support for respiratory and cardiovascular decompensation. In addition, IVIg and plasmapheresis, where available, can reduce duration and severity of symptoms.

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