Oswaldo J.M.
Nascimento, MD, PhD
Jennifer A. Frontera, MD
Daniel A. Amtrano, MD,
PhD
Ana M. Bispo de Filippis,
PhD
Ivan R.F. Da Silva, MD,
PhD
On behalf of the
RIO-GBS-ZIKV
Research Group

ZIKA VIRUS INFECTION-ASSOCIATED ACUTE TRANSIENT POLYNEURITIS

Zika virus (ZIKV) has been associated with various neurologic complications in adults, including Guillain-Barré syndrome (GBS), transverse myelitis, meningoencephalitis, and ophthalmologic manifestations. Though some of these syndromes may be due to a postinfectious (molecular mimicry) mechanism, a direct viral pathogenic mechanism may be responsible in others. We present 3 cases of a newly described syndrome of ZIKV-associated acute transient polyneuritis.

Methods. This article describes a case series of 3 patients admitted to a tertiary hospital in Rio de Janeiro during the 2016 outbreak of Zika virus infection in Brazil.

Standard protocol approvals, registrations, and patient consents. This study was approved by the HUAP-UFF institutional review board. All patients or their surrogates were consented for participation in this study.

Zika virus diagnosis. Blood and CSF collected at admission were tested in duplicate using real-time reverse transcriptase PCR (rRT-PCR) for ZIKV following published methods at the Oswaldo Cruz Foundation Flavivirus Laboratory. Urine rRT-PCR was tested in one case.

Other diagnostics. Electrophysiology studies (EMG and nerve conduction studies) were performed by certified neurologists with specialty training in neuromuscular disease using criteria endorsed by the European Federation of Neurological Societies/Peripheral Nerve Society and American Association of Neuromuscular and Electrodiagnostic Medicine (e-Methods at Neurology.org). All examinations included nerve testing in both upper and lower extremities and F wave testing. Nerve ultrasound was performed of the bilateral median nerves (1–2 cm proximal to the carpal tunnel) and bilateral superficial peroneal nerves (5 cm above the medial malleolus). Brain and spine 3T MRI with gadolinium administration and nerve ultrasound were interpreted by independent, board-certified neuroradiologists. Other blood testing was conducted to rule out alternative causes of muscular/peripheral nerve disease (e-Methods).

Results. Three patients presented to the Antonio Pedro University Hospital of Universidade Federal Fluminense in Rio de Janeiro, Brazil, with signs and symptoms of distal pain, stocking-glove hyposthesia, mild distal weakness, and hyporeflexia within 1–2 days of ZIKV symptom onset. Clinical examination, imaging, electrophysiologic, and outcome findings for these patients are delineated in the table. Nerve ultrasound demonstrated bilaterally enlarged median nerves in patients 1 and 2 (figure e-1). Mental status, cranial nerves, and cerebellar examination were normal for all patients, as were muscle enzyme testing, inflammatory serology testing, and other routine laboratory studies. No patient met Brighton¹ or electrophysiologic criteria for GBS.

Discussion. We report acute ZIKV infection accompanied by clinical findings consistent with a mild, self-limited, distal, sensorimotor neuropathy. Because nerve ultrasound in 2 patients demonstrated enlargement of symptomatic nerves, followed by concomitant improvement in symptoms and nerve diameter on serial ultrasound, the mechanism of this syndrome may be related to nerve swelling. It has been described that some forms of infections might result in segmental nerve inflammation with edema, compromising nerve function in an acute fashion.^{2,3} For the most part, the Schwann cells are the target of the infectious agent resulting in demyelination, which could evolve into a rapid resolution or further progress, depending on the host's immune response.^{2,3} Since symptoms and imaging findings tracked closely with ZIKV viremia, we hypothesize that there may be a direct neuropathic effect of ZIKV leading to inflammation and nerve swelling. Others have published reports of weakness developing soon after the first few days of ZIKV infection symptoms, considered early for postinfectious molecular mimicry mechanism of nerve injury, but in this case series the patients developed clinical, laboratory, and electrophysiologic findings highly suggestive of GBS.⁴ We report 3 cases that do not fit the usual criteria for GBS, as weakness was mild and limited to the extremities, a predominance of sensory symptoms was observed, and rapid improvement of symptoms within the first

Supplemental data
at Neurology.org

Table Clinical and laboratory findings in patients with Zika virus-associated polyneuritis

	Case 1	Case 2	Case 3
Clinical presentation			
Age, y	23	39	24
Sex	Female	Female	Female
Medical history	None	None	None
Viral prodrome	Fever, rash, malaise	Fever, rash, arthralgias	Fever, rash, conjunctival injection
Neurologic symptoms	Burning pain in hands and feet, distal weakness of upper and lower extremities bilaterally	Paresthesias in hands and feet, pain with joint motion, and distal > proximal weakness in arms and legs bilaterally	Numbness, pain, and mild weakness of hands and feet bilaterally
Time from viral prodrome to neurologic symptoms, h	24	48	48
Neurologic examination			
Motor	MRC 4 muscle strength distally (wrist extensors and flexors, intrinsic muscles of the hand, foot, dorsiflexion and plantar flexion, foot inversion and eversion); MRC 5 strength proximal upper and lower extremities	MRC 3 muscle strength distally (wrist extensors and flexors, intrinsic muscles of the hand, foot, dorsiflexion and plantar flexion, foot inversion and eversion); MRC 4 muscle strength proximally (deltoids, biceps, triceps, hip flexors, quadriceps, hamstrings)	MRC 4 muscle strength distally (wrist extensors and flexors, intrinsic muscles of the hand, foot, dorsiflexion and plantar flexion, foot inversion and eversion); MRC 5 strength proximal upper and lower extremities
Sensory	Hypoesthesia to light touch and pain in a stocking-glove distribution	Hypoesthesia to light touch and pain in a stocking-glove distribution	Hypoesthesia to light touch and pain in hands and feet bilaterally and circumferentially
Reflexes	1 + Patella and ankle, 2 + biceps and triceps; negative Babinski sign	1 + Patella, ankle, biceps, and triceps; negative Babinski sign	1 + Patella and ankle, 2 + biceps, triceps; negative Babinski sign
Diagnostic studies			
ZIKV RT-PCR results (time from rash to collection)	CSF and blood positive (24 h); urine not tested	Blood and urine positive (48 h); CSF not tested	CSF and blood positive (96 h); urine not tested
EMG/NCS (time from symptom onset)	Normal motor and sensory amplitudes, distal latency, conduction velocities, and F waves; normal needle study (days 3 and 60 post viral symptom onset)	Normal motor and sensory amplitudes, distal latency, conduction velocities, and F waves; normal needle study (days 4 and 90 post viral symptom onset)	Normal motor and sensory amplitudes, distal latency, conduction velocities, and F waves; normal needle study (days 5 and 30 post viral symptom onset)
MRI brain and spine with gadolinium	Normal	Normal	Normal
Nerve ultrasound cross-sectional area (time from symptom onset) ^a	Day 5	Day 6	Not performed
Median nerve, mm²			
Left	18	20	
Right	16	27	
Superficial peroneal, mm²			
Left	5	6	
Right	5	5	
	Day 52	Day 65	
Median nerve, mm²			
Left	11	15	
Right	10	18	
Superficial peroneal, mm²			
Left	3	3	
Right	2.5	3	
CSF	Cell count: 0, protein: 27 mg/dL, glucose: 75 mg/dL	Cell count: 1, protein: 38 mg/dL, glucose: 87 mg/dL	Cell count: 0, protein: 22 mg/dL, glucose: 81 mg/dL

Continued

Table	Continued		
	Case 1	Case 2	Case 3
Management and outcome			
Treatment	Supportive	IV gammaglobulin for 5 d	Supportive
Time to resolution of neurologic symptoms, d	7	10	8
3-Month reexamination	Asymptomatic with normal strength and reflexes	Asymptomatic with normal strength and reflexes	Asymptomatic with normal strength and reflexes

Abbreviations: MRC = Medical Research Council; NCS = nerve conduction studies; RT = reverse transcriptase; ZIKV = Zika virus.

^aNormal values: median nerve 9–11 mm², superficial peroneal 2–3 mm².

7–10 days with associated unrevealing electrophysiologic and CSF testing (repeated weeks later) was noted.

Preliminary research using human neural progenitor cells have shown that ZIKV infection increases cell death and dysregulates cell cycle progression.⁵ Other flaviviruses, such as West Nile virus, can lead to direct neurotropic injuries as well.

Though nerve conduction studies were normal, mild syndromes with clinical manifestations may manifest with minimal electrophysiologic abnormalities.^{6,7} Since the syndrome we describe primarily involves distal nerves, normal electrophysiologic studies are not inconsistent with an acute neuropathy. Negative serum and CSF laboratory studies and normal gadolinium-enhanced MRI of the brain and spine diminish the likelihood of a brain, spinal cord, or muscular etiology for our patients' clinical presentations.

Our cases suggest a newly described ZIKV-associated acute transient polyneuritis. It will be important for practitioners to recognize this benign syndrome and differentiate it from other ZIKV-related complications.

From the Universidade Federal Fluminense (O.J.M.N., D.A.A.), Niteroi, Brazil; Cerebrovascular Center of the Neurological Institute (J.A.F.), Cleveland Clinic, OH; the Flavivirus Laboratory (A.M.B.d.F.), Oswaldo Cruz Foundation, Rio de Janeiro, Brazil; and Rush University Medical Center (I.R.F.D.S.), Chicago, IL.

Coinvestigators are listed at Neurology.org.

Author contributions: Dr. Nascimento contributed with study design, data analysis, and manuscript writing. Dr. Frontera contributed with study design, data analysis, and manuscript writing. Dr. Amitrano contributed with study design, data analysis, and manuscript writing. Dr. Bispo de Filippis contributed with study design and samples testing. Dr. Da Silva contributed with data collection, study design, data analysis, and manuscript writing.

The authors wrote on behalf of the RIO-GBS-ZIKV Research Group (see supplemental data).

Acknowledgment: The authors thank Dr. Richard Hughes for his comments on this manuscript and acknowledge coauthor Dr. Daniel A. Amitrano who died prior to publication of this article.

Study funding: This study was funded by the Cleveland Clinic Foundation, award RPC194-S2.

Disclosure: O. Nascimento, J. Frontera, and D. Amitrano report no disclosures relevant to the manuscript. A. Bispo de Filippis receives grants from Conselho Nacional de Desenvolvimento e Pesquisa (CNPq), Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ). I. Da Silva reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received November 2, 2016. Accepted in final form March 22, 2017.

Correspondence to Dr. Nascimento: osvaldo_nascimento@hotmail.com

© 2017 American Academy of Neurology

1. Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2011;29:599–612.
2. Brizzi KT, Lyons JL. Peripheral nervous system manifestations of infectious diseases. *Neurohospitalist* 2014;4:230–240.
3. Nascimento OJ. Leprosy neuropathy: clinical presentations. *Arq Neuropsiquiatr* 2013;71:661–666.
4. Parra B, Lizarazo J, Jimenez-Arango JA, et al. Guillain-Barré syndrome associated with Zika virus infection in Colombia. *N Engl J Med* 2016;375:1513–1523.
5. Tang H, Hammack C, Ogden SC, et al. Zika virus infects human cortical neural progenitors and attenuates their growth. *Cell Stem Cell* 2016;18:587–590.
6. Gupta D, Nair M, Baheti NN, Sarma PS, Kuruvilla A. Electrodiagnostic and clinical aspects of Guillain-Barre syndrome: an analysis of 142 cases. *J Clin Neuromuscul Dis* 2008;10:42–51.
7. Kushnir M, Klein C, Pollak L, Rabey JM. Evolving pattern of Guillain-Barre syndrome in a community hospital in Israel. *Acta Neurol Scand* 2008;117:347–350.

Neurology[®]

Zika virus infection–associated acute transient polyneuritis

Osvaldo J.M. Nascimento, Jennifer A. Frontera, Daniel A. Amitrano, et al.
Neurology 2017;88;2330-2332 Published Online before print May 12, 2017
DOI 10.1212/WNL.0000000000004026

This information is current as of May 12, 2017

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2017 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/88/24/2330.full
Supplementary Material	Supplementary material can be found at: http://n.neurology.org/content/suppl/2017/05/12/WNL.0000000000004026.DC1 http://n.neurology.org/content/suppl/2017/05/12/WNL.0000000000004026.DC2
References	This article cites 7 articles, 0 of which you can access for free at: http://n.neurology.org/content/88/24/2330.full#ref-list-1
Citations	This article has been cited by 3 HighWire-hosted articles: http://n.neurology.org/content/88/24/2330.full##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Immunology http://n.neurology.org/cgi/collection/all_immunology All Infections http://n.neurology.org/cgi/collection/all_infections Burden of disease http://n.neurology.org/cgi/collection/burden_of_disease EMG http://n.neurology.org/cgi/collection/emg Peripheral neuropathy http://n.neurology.org/cgi/collection/peripheral_neuropathy Public health http://n.neurology.org/cgi/collection/public_health Ultrasound http://n.neurology.org/cgi/collection/ultrasound
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2017 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.