

Neurologic Manifestations of Zika Virus Infection

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Zika Virus and Neurologic Manifestations

- Zika virus (ZIKV): recently associated with several neurologic manifestations
 - Guillain-Barré syndrome (GBS)
 - Meningoencephalitis
 - Myelitis
 - Ocular manifestations
- ZIKV – related to other neurotropic flaviviruses
 - Japanese encephalitis virus
 - West Nile virus
 - Dengue virus

Zika Virus and Guillain-Barré Syndrome

- ❑ Historically, sporadic cases or small outbreaks of mild rash illness
- ❑ 2007: Large outbreak in Yap, South Pacific
 - Largest 'modern' outbreak of ZIKV
 - No neuro manifestations reported
- ❑ 2013: Outbreak of ZIKV in French Polynesia
 - Reports of large numbers of GBS cases (*EuroSurveill 2014*)
 - Subsequent publication (*Lancet 2016*)
- ❑ 2014: Outbreak of GBS in Fiji (*Fiji MOH, WHO, & CDC, unpublished*)
 - Commensurate with large dengue outbreak
 - 10 GBS cases over 2 month period; extremely high incidence (7-8 x 'expected')
 - Unable to document ZIKV infection, but evidence of recent flavivirus infection greater in cases than controls (unrecognized ZIKV infection?)

Zika Virus and GBS (2)

- ❑ December 2014: First recognition of ZIKV in Brazil
 - June 2015: PAHO notified of increase in reports of GBS
 - Brazil MOH / CDC / PAHO case control investigation conducted January 2016
- ❑ October / November 2015: Zika explosion
 - Reports of increase in GBS cases following introduction of ZIKV reported from at least 12 Central / South American, Caribbean countries
 - Some with laboratory evidence of ZIKV infection
- ❑ February 2016: Prospective GBS surveillance established in Puerto Rico, in anticipation of 'GBS outbreak'

Guillain-Barré Syndrome(s) (GBS)

- Para- or post-infectious syndrome; follows an antecedent infection or vaccination
- Autoimmune response to infection / immunization / antigenic stimulus
 - Antecedent antigenic stimulus leads to autoreactive antibodies / T-cells that damage peripheral nerve epitopes
- Nonspecific response—may be triggered by many different agents
- Damage to peripheral nerves / nerve roots leads to weakness, sensory abnormalities
- Incidence 1-2 / 100,000 persons / year in North America, Europe
- Several subtypes of GBS

ZIKV / GBS in French Polynesia

- ❑ **Oct 2013 – Apr 2014: largest outbreak of ZIKV infection to date in FP**
 - Subsequent increasing reports of GBS
 - Nov 2013 – Feb 2014: 42 GBS cases presented to CHPF – orders of magnitude greater than prior years
- ❑ **Case control study**
 - Cases (n=42): GBS patients presenting to CHPF; clinical and demographic data; electrophysiologic studies; biological specimens
 - Controls: two groups
 - Group 1 (n=98): hospitalized with non-febrile illness
 - Matched by age, sex, island of residence
 - Serum median 13 days from admission date of matching GBS case
 - Group 2 (n=70): PCR-confirmed ZIKV infection, no neurologic illness
 - Matched by 10-year age groups; assess role of past dengue infection in GBS cases
 - ZIKV infection determined by PCR, immunofluorescent assay, serum IgM / IgG, PRNT
 - DENV assessed (same assays)
 - Anti-ganglioside antibodies assessed

ZIKV / GBS in French Polynesia

- ❑ 42 GBS cases identified Oct 2013 – March 2014
 - Median age 42 yrs; 74% male
- ❑ Infectious prodrome in 88%, median 6 days before neuro onset
 - Rash (81%), arthralgia (74%), fever (58%)
- ❑ Features of GBS illness
 - Rapid progression to nadir (median 6 days), short plateau (median 4 days)
 - 38% admitted to ICU, 29% required ventilation
 - Electrophysiologic studies – acute motor axonal neuropathy (AMAN)
 - Reactivity to anti-ganglioside antibodies in <50% at 3 months
 - Median duration of hospitalization 11 days; no deaths
- ❑ Epidemiologic evidence of association
 - ~3 week interval between ZIKV and GBS epidemic peaks respectively

Epidemiologic Curves, Suspected Zika Virus Infections and GBS, French Polynesia

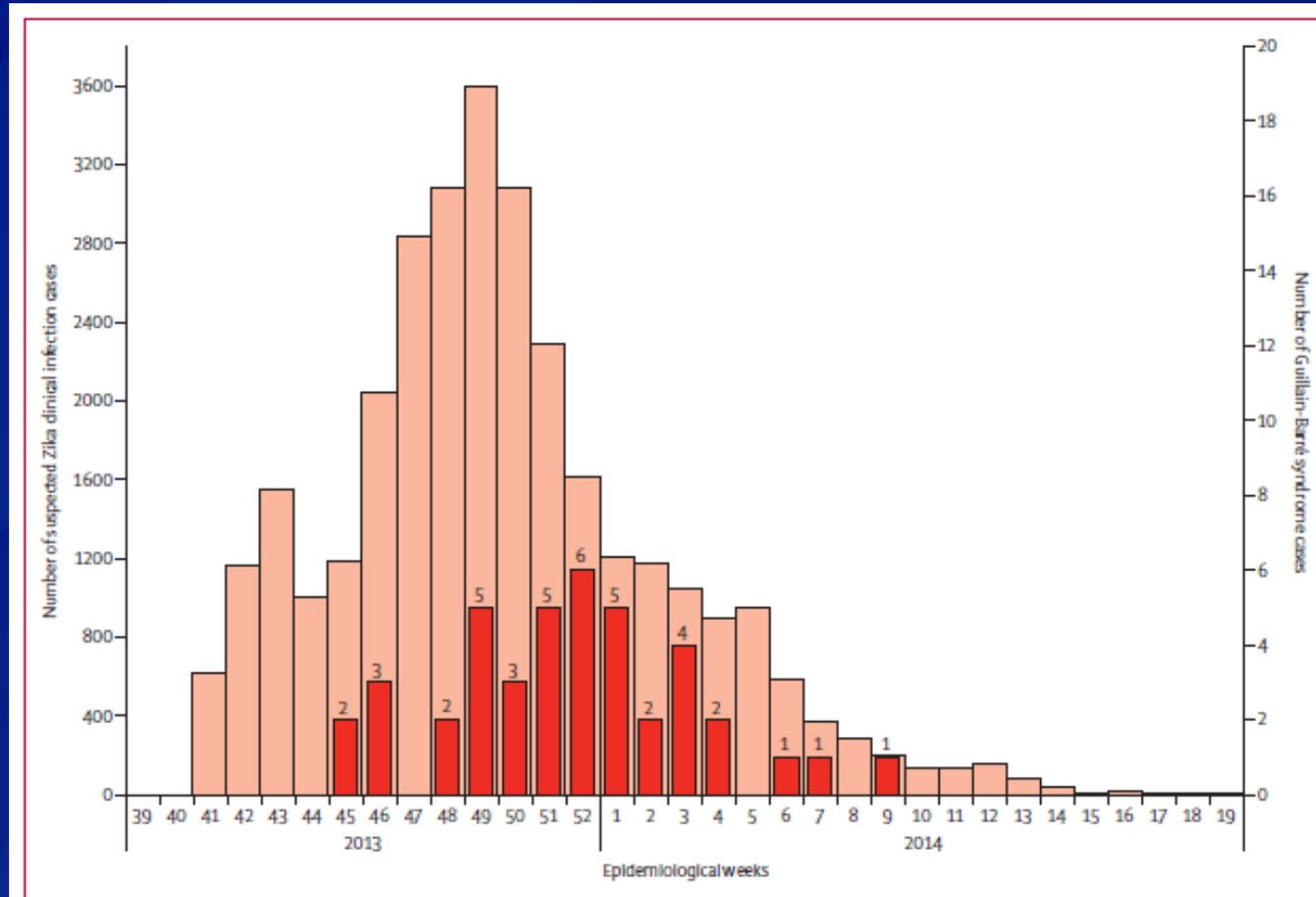


Figure: Weekly cases of suspected Zika virus infections and Guillain-Barré syndrome in French Polynesia between October, 2013, and April, 2014

ZIKV / GBS in French Polynesia

□ Virologic assays

- Serum PCR: All negative in GBS cases
- Anti-Zika IgM antibodies: 93% GBS cases, 17% Group 1 patients
- Immunofluorescence performed to assess serologic cross-reactivity
 - GBS group – 74% with IgM against ZIKV but not DENV
- 98% GBS cases had evidence of prior ZIKV infection, compared to 36% Group 1 controls [OR 59.7, $p < 0.0001$]
- However, concomitant transient boost of anti-DENV IgG, anti-ZIKV IgG -- confusing picture

□ Conclusions

- Outbreak of GBS in setting of ZIKV outbreak; tight geo-temporal clustering, high incidence
- Epidemiologic evidence suggestive of association
- Serologic evidence for association between GBS and ZIKV infection; challenges with interpretation of laboratory results due to cross-reactivity

Zika Virus and Other Neurologic Manifestations

- Anecdotal reports of other neurologic manifestations of ZIKV illness

Meningitis, encephalitis, myelitis, optic neuritis

Generally isolated case reports or small case clusters; difficult to discern from background

Nothing of magnitude seen with GBS

Possible association may become clear with time

- ZIKV as 'neurotropic' virus??

GBS: immune-mediated syndrome, not due to direct viral neuroinvasion

ZIKV Congenital Malformations: Fetal brain is 'different'; no evidence of inflammation in ZIKV – associated congenital anomalies

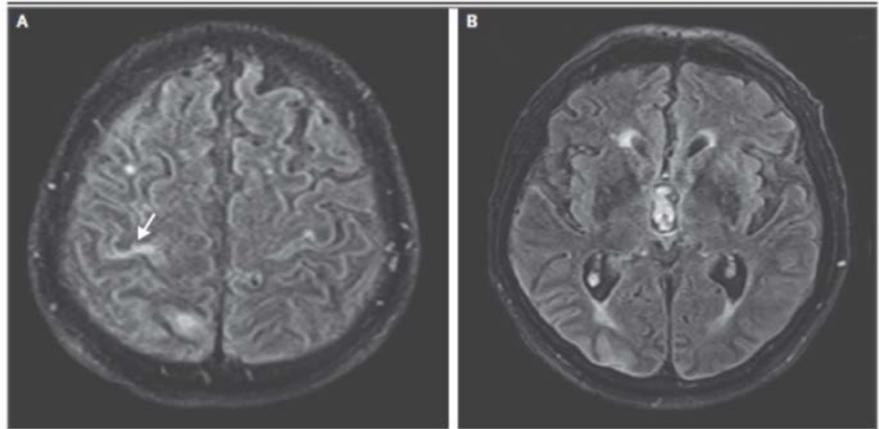
ZIKV does not 'appear' to have same neurotropism as some other flaviviruses

CORRESPONDENCE



Zika Virus Associated with Meningoencephalitis

TO THE EDITOR: Zika virus (ZIKV) is currently spreading widely, while its clinical spectrum remains a matter of investigation. Evidence of a relationship between ZIKV infection and cerebral birth abnormalities^{1,2} is growing.³ An increased incidence of some peripheral nervous syndromes



Case Report

Acute myelitis due to Zika virus infection

Sylvie Mécharles, Cécile Herrmann, Pascale Poullain, Tuan-Huy Tran, Nathalie Deschamps, Grégory Mathon, Anne Landais, Sébastien Breurec, Annie Lannuzel

In January, 2016, a 15-year-old girl with a history only of an ovarian cyst was admitted to hospital in Pointe-à-Pitre, Guadeloupe, with left hemiparesis. 7 days previously she had presented to the emergency department with left arm

myelitis suggests that this virus might be neurotropic. In addition to the usual clinical picture of myelitis she had severe pain. Absence of intrathecal immunoglobulins and normal brain MRI excluded acute disseminated encephalomyelitis. The neurotropic nature of ZIKV is



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Service de Neurologie

But Why??

- Why now?
- Why such stereotypic presentations?
- Why such rapid spread throughout Central / South America?



**Thank you!
Obrigada!**



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Brighton Collaboration Criteria for GBS

Levels of Diagnostic Certainty				
Level 1	Level 2	Level 3	Level 4	Level 5
Absence of an alternative diagnosis for weakness				NOT a case
Acute onset of bilateral and relatively symmetric flaccid weakness of the limbs			Lacking documentation to fulfill minimal case criteria	
Decreased or absent deep tendon reflexes in affected limbs				
Monophasic illness pattern with weakness nadir between 12 hours and 28 days, followed by clinical plateau				
Albuminocytologic dissociation (elevation of CSF protein level above laboratory normal value and CSF total white cell count < 50 cells/mm ³)	CSF with a total white cell count < 50 cells/mm ³ (with or without CSF protein elevation above laboratory normal value) or if CSF not collected or results not available, and electrodiagnostic studies consistent with GBS			
Electrophysiologic findings consistent with GBS				