THE NEUROLOGIC CONSEQUENCES OF ARBOVIRUS INFECTIONS: ZIKA,DENGUE AND CHIKUNGUNYA

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Disclosure

NONE

Learning objective

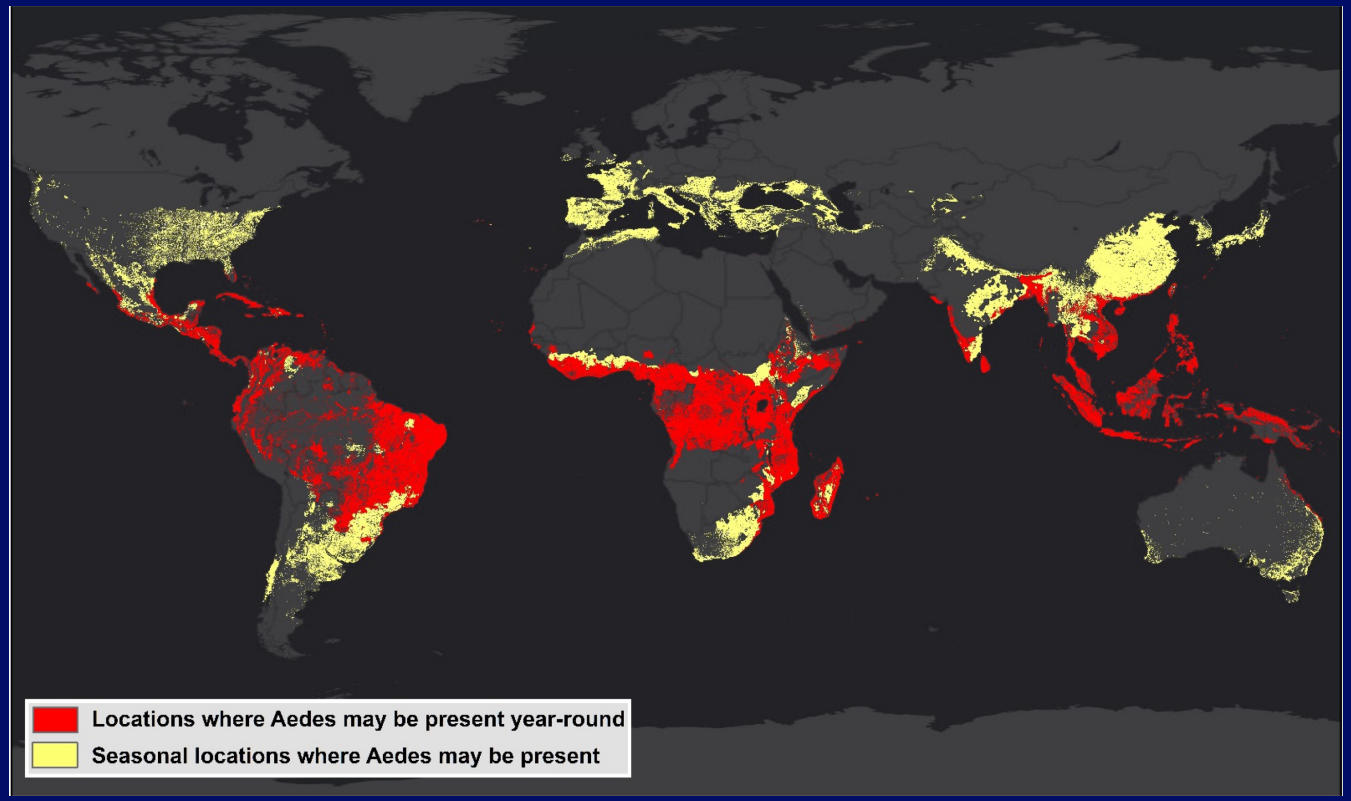
- To understand the spectrum of neurologic consequences of Arbovirus infections, mainly, Dengue, Zika and Chickingunya

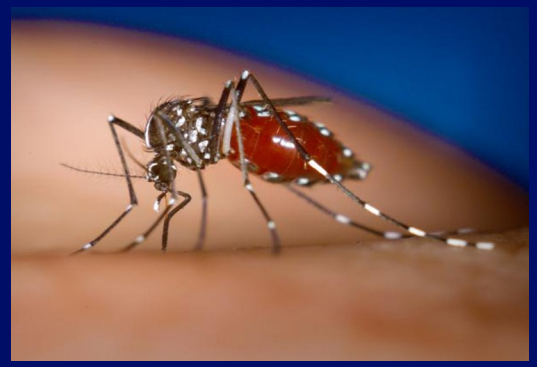
Arbovirus

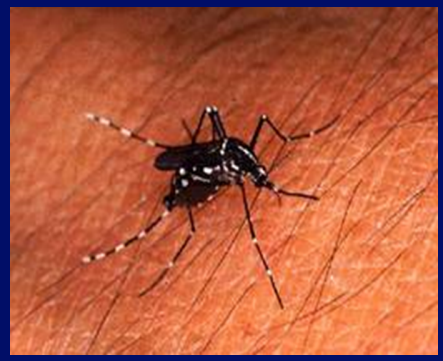
- The term arbovirus includes several families of RNA viruses that are spread by arthropod vectors, most commonly mosquitoes, ticks, and sand flies.
- The families of viruses included in the arbovirus group are Flaviviridae, Togaviridae, Bunyaviridae, and Reoviridae

- Beckham JD, Tyler KL. Arbovirus Infections. Continuum (Minneap Minn). 2015 Dec;21(6 Neuroinfectious Disease):1599-611.

Climate Change: Endemic and epidemic ranges of Aedes mosquito transmission (Aedes aegyptie and Aedes albopictus)







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Global risk model for vector-borne transmission of Zika virus reveals the role of El Niño 2015

Cyril Caminade[a,b,1], Joanne Turner[a], Soeren Metelmann[b,c], Jenny C. Hesson[a,d], Marcus S. C. Blagrove[a,b], Tom Solomon[b,e], Andrew P. Morse[b,c], and Matthew Baylis[a,b]

Caminade et al Global risk model for vector-borne transmission of Zika virus reveals the role of El Niño 2015 Proc Natl Acad Sci U S A. 2017 Jan 3; 114(1): 119–124.

Attaway et al Zika virus: Endemic and epidemic ranges of Aedes mosquito transmission Journal of Infection and Public Health 2017 10, 120-123

In 2016 WHO Declared Zika Virus a Global Public Health Emergency

On February 1st, 2016 the World Health Organization declared Zika virus infection an international public health emergency due to 2015 reports from Brazil of cluster of microcephaly cases and other neurological disorders , following a cluster of Guillain Barre Syndrome cases in French Polynesia in 2014.

AMERICA

WHO Declares A Global Public Health Emergency Over Zika Virus

February 1, 2016 · 1:45 PM ET

EYDER PERALTA

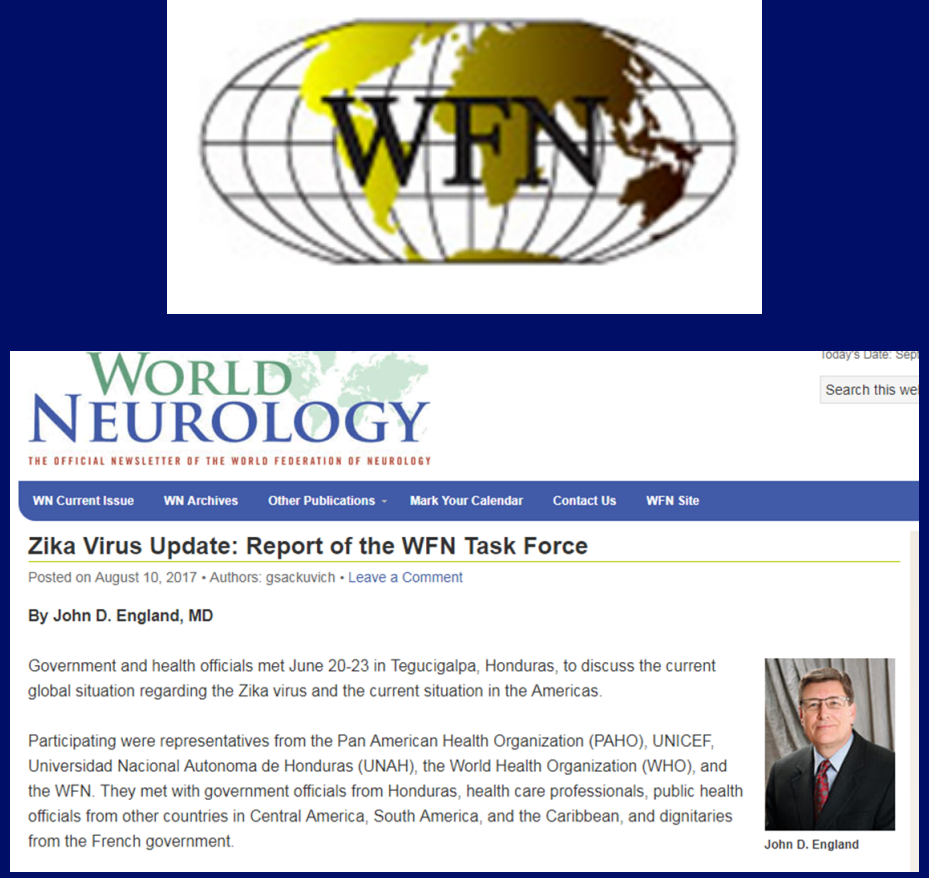
Dr. Margaret Chan, director-general of the World Health Organization, and Dr. David L. Heymann, WHO assistant director-general, announce the global emergency during a news conference Monday in Geneva.

Fabrice Coffrini/AFP/Getty Images

World Health Organization

WHO 2016

WFN Zika Working Group



WFN Zika Working Group

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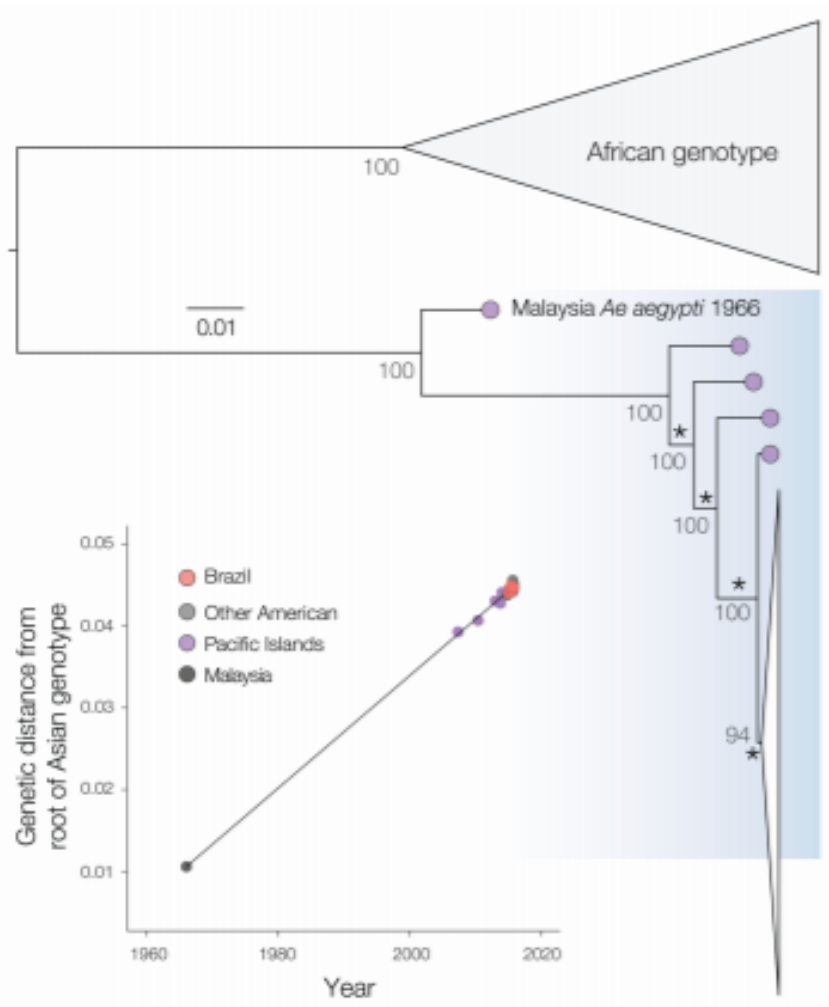
ZIKA: UGANDA IN 1947

Zika virus Phenotype and Genotype findings



AMERICAN SOCIETY FOR MICROBIOLOGY | mSphere®

RESEARCH ARTICLE
Host-Microbe Biology

Phenotypic Differences between Asian and African Lineage Zika Viruses in Human Neural Progenitor Cells

Fatih Anfasa,[a,b] Jurre Y. Siegers,[a] Mark van der Kroeg,[c] Noreen Mumtaz,[a] V. Stalin Raj,[a] Femke M. S. de Vrij,[c] W. Widagdo,[a] Gülsah Gabriel,[d] Sara Salinas,[e] Yannick Simonin,[e] Chantal Reusken,[a] Steven A. Kushner,[c] Marion P. G. Koopmans,[a] Bart Haagmans,[a] Byron E. E. Martina,[a,f] Debby van Riel[a]

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Rodriges-Faria et al. Zika virus in the Americas: Early epidemiological and genetic findings Science. 2016 Apr 15;352(6283):345-349

Anfasa F, et al Phenotypic Differences between Asian and African Lineage Zika Viruses in Human Neural Progenitor Cells. mSphere. 2017 Jul 26;2(4)

Zika Clinical Manifestations of the Asian Lineage

ORIGINAL ARTICLE

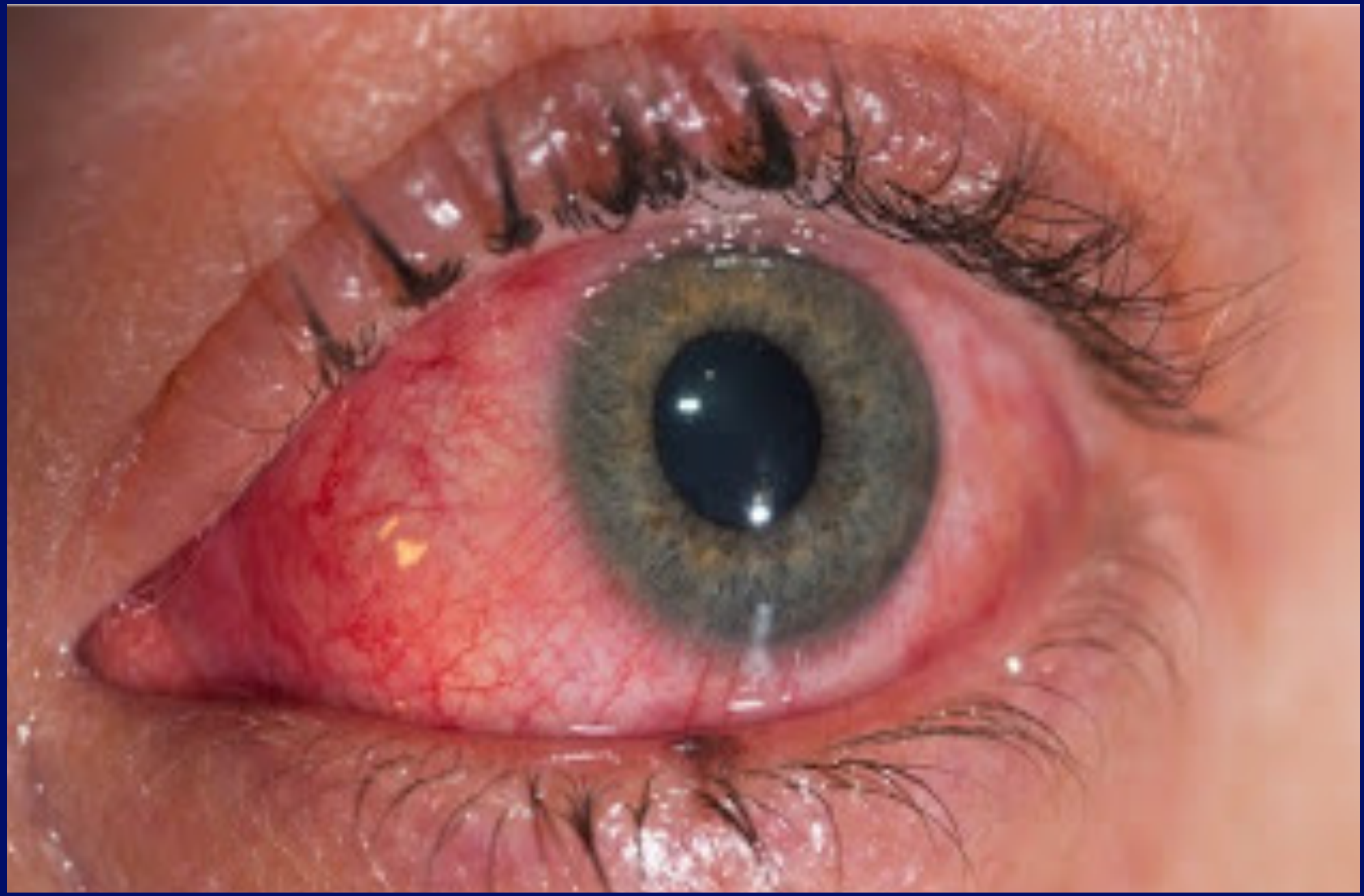
Zika Virus Outbreak on Yap Island, Federated States of Micronesia

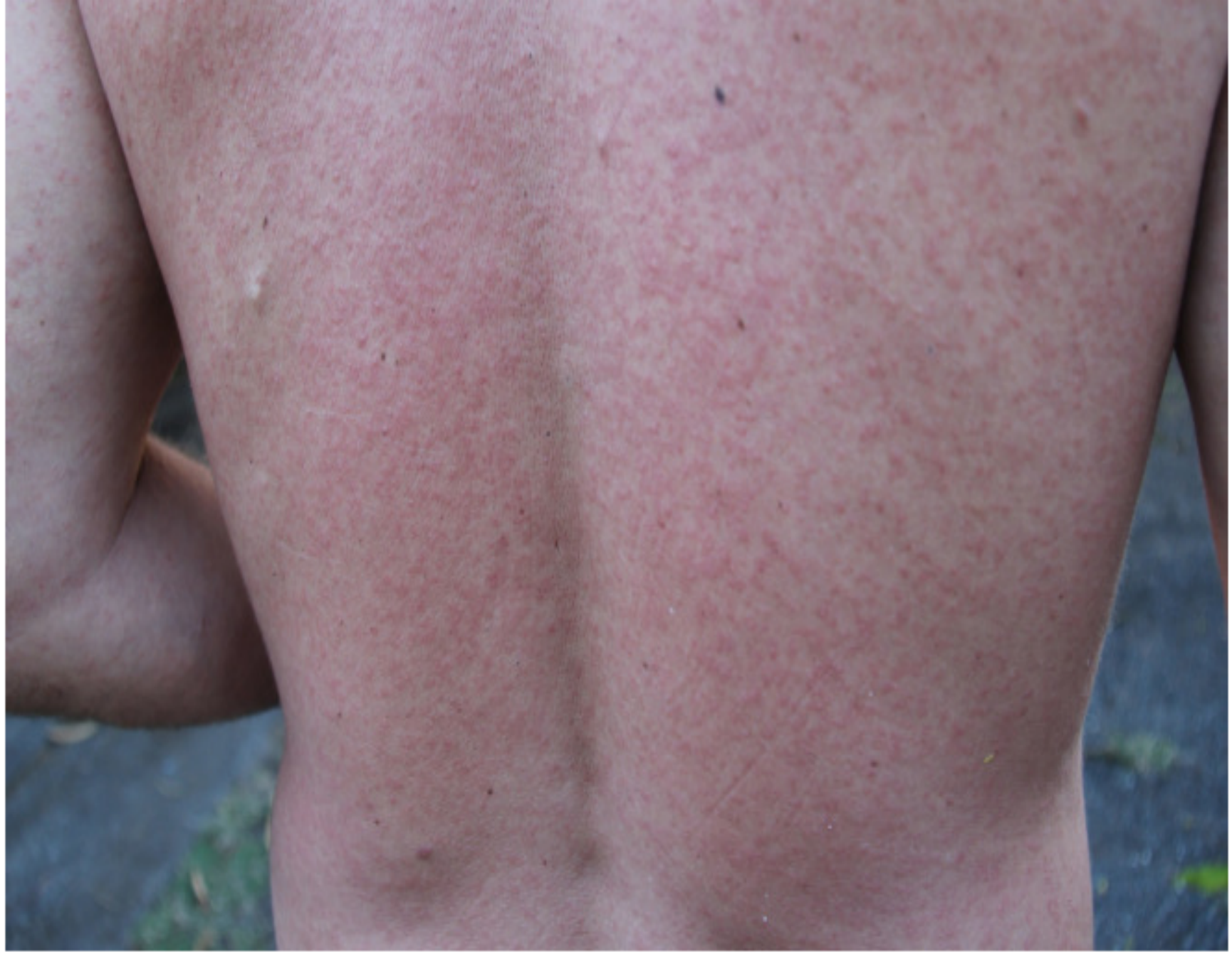
Table 1. Clinical Characteristics of 31 Patients with Confirmed Zika Virus Disease on Yap Island during the Period from April through July 2007.

Sign or Symptom	No. of Patients (%)
Macular or papular rash	28 (90)
Fever*	20 (65)
Arthritis or arthralgia	20 (65)
Nonpurulent conjunctivitis	17 (55)
Myalgia	15 (48)
Headache	14 (45)
Retro-orbital pain	12 (39)
Edema	6 (19)
Vomiting	3 (10)

* Cases of measured and subjective fever are included.

- Duffy et al Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009 Jun 11;360(24):2536-43





World Federation of Neurology

PAFNS
Panamerican Federation of Neurological Societies

Journal of the Neurological Sciences 383 (2017) 214–215

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Editorial

New spectrum of the neurologic consequences of Zika

ARTICLE INFO

Keywords:
Zika
Neurologic complications
Childhood
Arterial ischemic stroke

ABSTRACT

Zika virus infection represents a new neuropathological agent with association to a wide spectrum of neurological complications: a) Congenital Zika Syndrome by affecting the neural stem cells of the human fetal brain; b) Guillain-Barré Syndrome by an autoimmune response against peripheral myelin and/or axonal components or probable direct inflammatory reaction; c) Encephalitis/meningoencephalitis and myelitis by a direct viral inflammatory process on the central nervous system; d) Sensory neuropathy by infecting directly the peripheral neurons and causing substantial cell death and pathogenic transcriptional dysregulation; e) Acute Disseminated Encephalomyelitis and optic neuropathy; f) Seizures and Epilepsy and g) childhood arterial ischemic stroke by probable inflammatory reaction and endothelial injury.

NEW SPECTRUM OF THE NEUROLOGIC CONSEQUENCES OF ZIKA

Zika virus infection has become a new emergent neuropathological agent with several neurological complications.

Medina and Medina-Montoya Journal of the Neurological Sciences 2017

Neurologic Consequences of Zika

- A) Congenital Zika Syndrome by affecting the neural stem cells of the human fetal brain

- B) Guillain-Barré Syndrome by an autoimmune response against peripheral myelin and/or axonal components or probable direct inflammatory reaction;

Neurologic Consequences of Zika

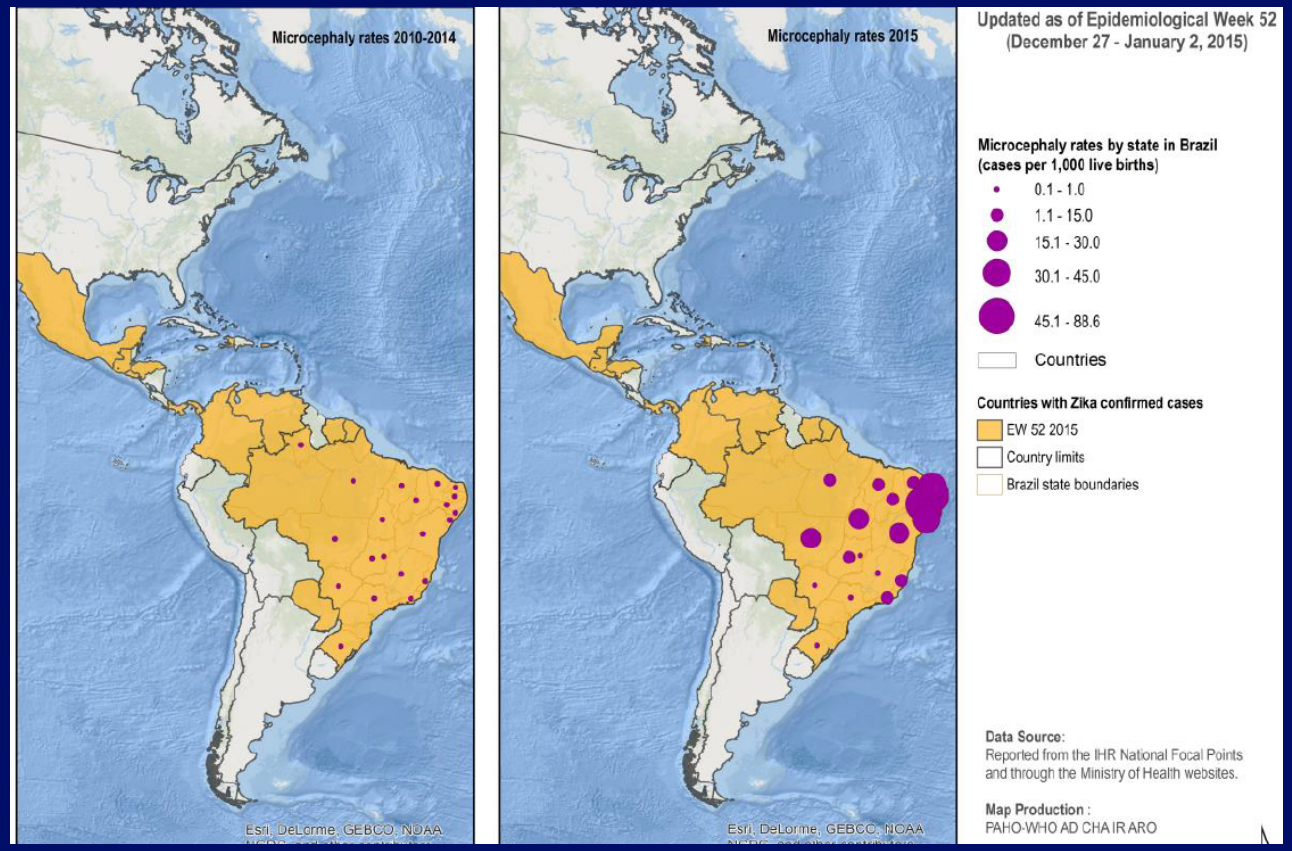
- C) Encephalitis/meningoencephalitis and myelitis by a direct viral inflammatory process on the central nervous system;

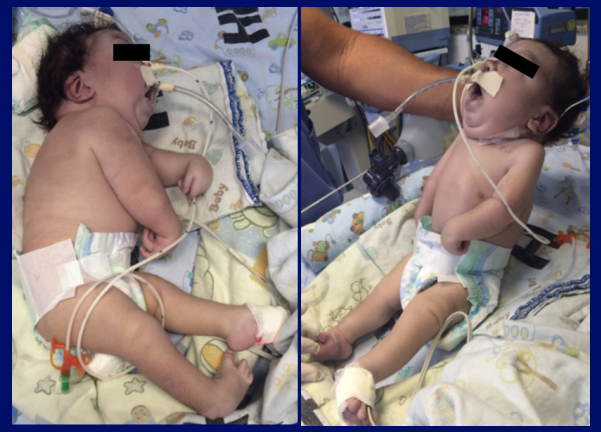
- D) Sensory neuropathy by infecting directly the peripheral neurons and causing substantial cell death and pathogenic transcriptional dysregulation;

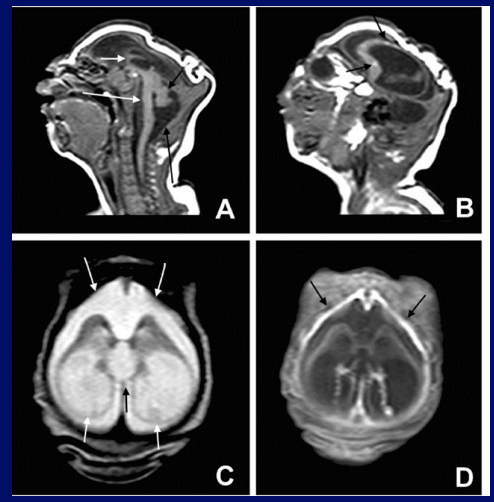
Neurologic Consequences of Zika

- E) Acute Disseminated Encephalomyelitis and optic neuropathy;
- F) Seizures and Epilepsy
- G) Childhood arterial ischemic stroke by probable inflammatory reaction and endothelial injury.

Microcephaly in Brazil
2010-2014 rates versus 2015 rates







PAHO 2016

Miranda-Filho et al. Initial Description of the Presumed Congenital Zika Syndrome. Am J Public Health. 2016 Apr;106(4):598-600

Congenital Zika virus Syndrome

- The WHO estimates that nearly 100 million people, and more than 1 million pregnant women in the Americas, could be infected, suggesting that tens of thousands of children may have the congenital Zika virus syndrome and a main concern is the Non-microcephalic infants (the"Iceberg" worst-case scenario)

England J. World Neurology Aug 2017

Aragao et al . Nonmicrocephalic Infants with Congenital Zika Syndrome Suspected Only after Neuroimaging Evaluation Compared with Those with Microcephaly at Birth and Postnatally: How Large Is the Zika Virus "Iceberg"? AJNR Am J Neuroradiol. 2017 Jul;38(7):1427-1434

Zika virus associated with microcephaly

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Zika Virus Associated with Microcephaly

Jernej Mlakar, M.D., Misa Korva, Ph.D., Nataša Tul, M.D., Ph.D., Mara Popović, M.D., Ph.D., Mateja Poljšak-Prijatelj, Ph.D., Jerica Mraz, M.Sc., Marko Kolenc, M.Sc., Katarina Resman Rus, M.Sc., Tina Vesnaver Vipotnik, M.D., Vesna Fabjan Vodušek, M.D., Alenka Vizjak, Ph.D., Jože Pižem, M.D., Ph.D., Miroslav Petrovec, M.D., Ph.D., and Tatjana Avšič Županc, Ph.D.

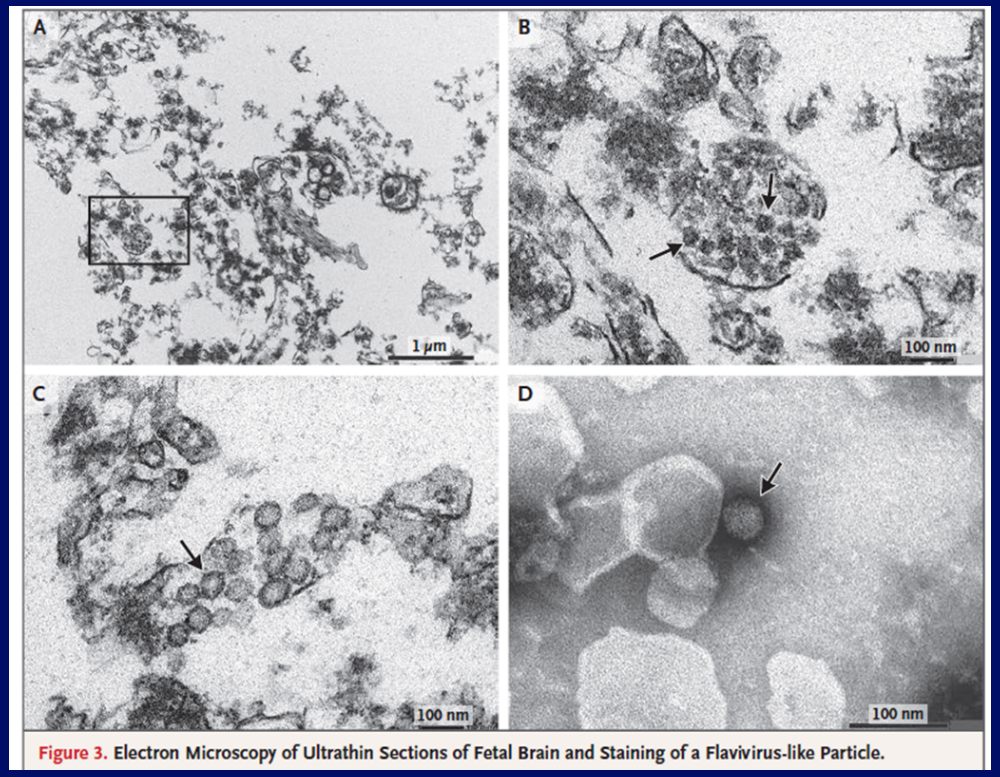


Figure 3. Electron Microscopy of Ultrathin Sections of Fetal Brain and Staining of a Flavivirus-like Particle.

Mlakar et al Zika Virus Associated with Microcephaly. N Engl J Med. 2016 Mar 10;374(10):951-8

Stem Cell Reports
Article
OPEN ACCESS

Differential Responses of Human Fetal Brain Neural Stem Cells to Zika Virus Infection

Erica L. McGrath,[1,10] Shannan L. Rossi,[2,3,10] Junling Gao,[1,10] Steven G. Widen,[4] Auston C. Grant,[1] Tiffany J. Dunn,[1] Sasha R. Azar,[2,3,5] Christopher M. Roundy,[2,3,5] Ying Xiong,[6] Deborah J. Prusak,[7] Bradford D. Loucas,[6] Thomas G. Wood,[7] Yongjia Yu,[6] Ildefonso Fernández-Salas,[8] Scott C. Weaver,[2,3,5] Nikos Vasilakis,[2,3,*] and Ping Wu[1,9,*]

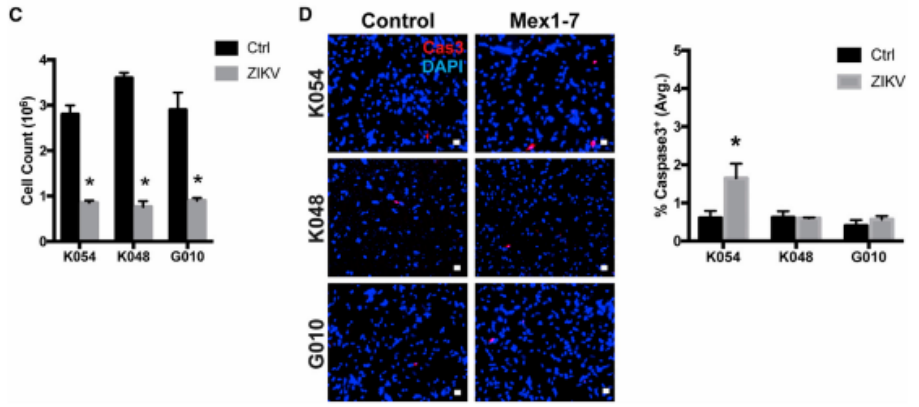


Figure 2. Reduction of hNSCs by Mex1-7

(A) Four hours of BrdU pulse labeling in three hNSC strains at 7 days post ZIKV infection.
(B) Immunocytochemical staining with Ki-67 proliferation marker at 7 days post infection.
(C) Total number of cells in three Mex1-7-infected hNSC strains after 11 days of proliferation, all starting at 1 million cells.
(D) Activated caspase 3 (Cas3, red) staining of hNSCs with or without Mex1-7 infection after differentiation.
DAPI, blue nuclear staining. Scale bars: 15 μm in (A), (B), and (D). Quantitative data are presented as means ± SEM. *$p < 0.05$ compared with control, $n = 3$. See also Figure S2.

- McGrath et al Differential Responses of Human Fetal Brain Neural Stem Cells to Zika Virus Infection. Stem Cell Reports, 2017; DOI: 10.1016/j.stemcr.2017.01.008

Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study

Van-Mai Cao-Lormeau*, Alexandre Blake*, Sandrine Mons, Stéphane Lastère, Claudine Roche, Jessica Vanhomwegen, Timothée Dub, Laure Baudouin, Anita Teissier, Philippe Larre, Anne-Laure Vial, Christophe Decam, Valérie Choumet, Susan K Halstead, Hugh J Willison, Lucile Musset, Jean-Claude Manuguerra, Philippe Despres, Emmanuel Fournier, Henri-Pierre Mallet, Didier Musso, Arnaud Fontanet*, Jean Neil*, Frédéric Ghawché*

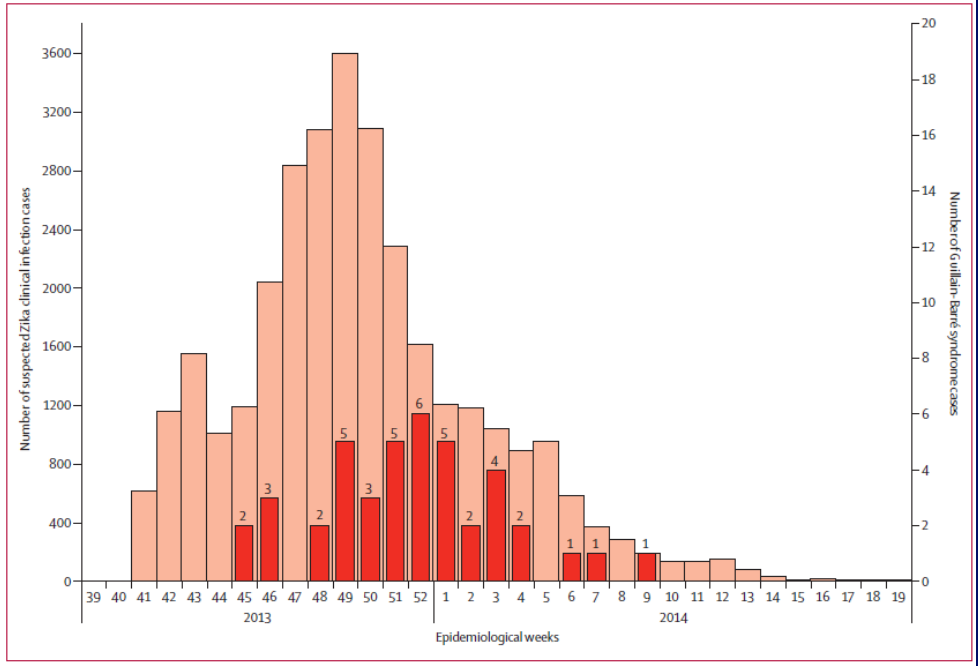


Figure: Weekly cases of suspected Zika virus infections and Guillain-Barré syndrome in French Polynesia between October, 2013, and April, 2014

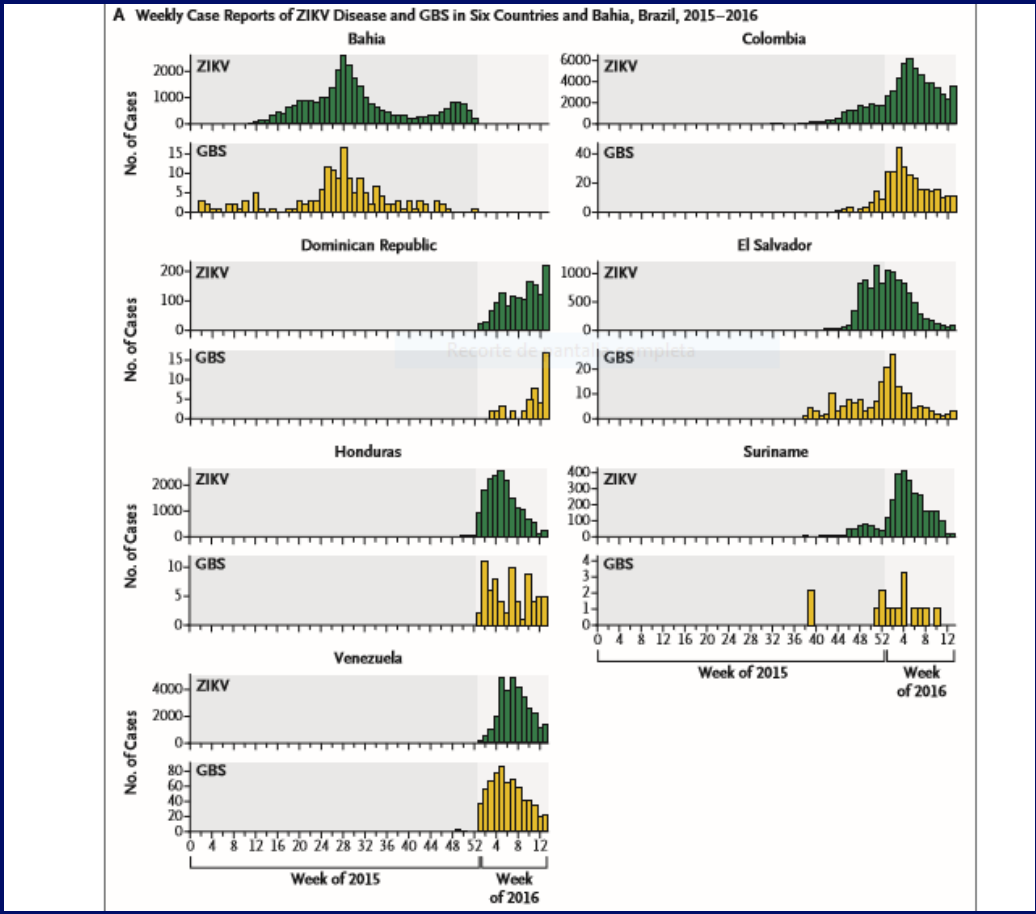
	Guillain-Barré syndrome at onset (n=42)	Guillain-Barré syndrome at 3 months (n=31)	Controls* (n=20)
GM1	0	8 (26%)	0
GA1	8 (19%)	10 (32%)	0
GM2	2 (5%)	1 (3%)	0
GD1a	5 (12%)	9 (29%)	0
GD1b	3 (7%)	9 (29%)	0
GQ1b	0	0	0
Any	13 (31%)	15 (48%)	0

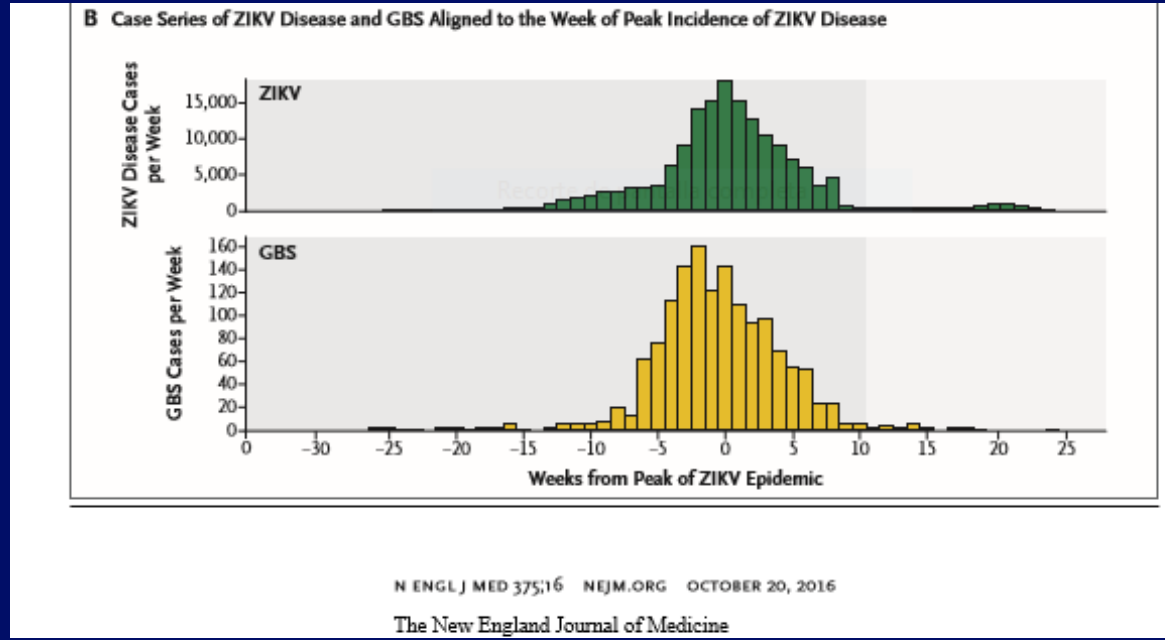
Data are n (%). *Blood donors.

Table 6: **Positive (>50%) reactivity to glycolipids in sera of patients with Guillain-Barré syndrome (n=42) and controls (n=20) in French Polynesia 2013–14**

Cao-Lormeau et al Guillain-Barré Syndrome outbreak associated wit Zika virus infection in French Polynesia: a case-control study. Lancet. 2016 Apr 9;387(10027):1531-1539

ZIKV and GBS





The NEW ENGLAND JOURNAL of MEDICINE

Zika Virus and the Guillain–Barré Syndrome — Case Series from Seven Countries

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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Letter to the editor

Zika virus associated with sensory polyneuropathy

Keywords:
Zika virus
Polyneuropathy
Small fiber sensory neuropathy

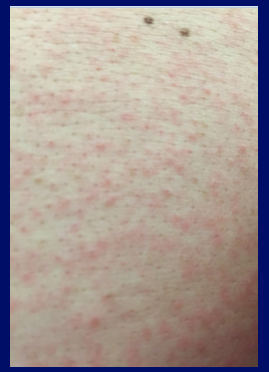
Dear Editor,

pattern, and a nerve conduction study showed reduction of velocity on the left sural nerve.

The patient returned to Honduras and had a second neurological evaluation on 15 February 2016 (MTM) which demonstrated persistent distal asymmetric hypoalgesia on arms, hands, legs and feet. The patient complained of having an intermittent "electric-like" sensation on both legs, and feet. The "electric-like" sensation progressively ascended in a patch-like-pattern to thighs, gluteal region, abdomen and in a less intense form to both arms. "Patchy" areas of numbness were also described in these regions. Neurological examination otherwise was normal. Repeat nerve conduction studies confirmed normal motor nerve conduction studies and F waves on median, ulnar, tibial and peroneal nerves. The sensory nerve conduction studies were abnormal showing a decreased velocity of both sural nerves (32.0 m/s on the

Zika Sensory Polyneuropathy (August 2016)

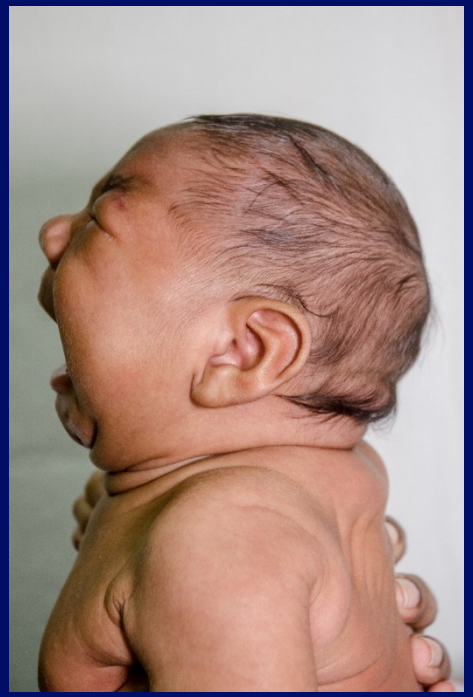
A 62 year old male Honduran resident was neurologically evaluated in Venezuela with complaints of an erythematous papular rash and mild fever that started on 27 January 2016. He experienced intense pruritus on chest, abdomen, upper and lower limbs that lasted for four days. Additionally, he had arthralgias and edema of both hands and feet. Neurological examination during the first week of February 2016 was remarkable for hypoalgesia in a glove stocking pattern, and a nerve conduction study showed reduction of velocity on the left sural nerve.

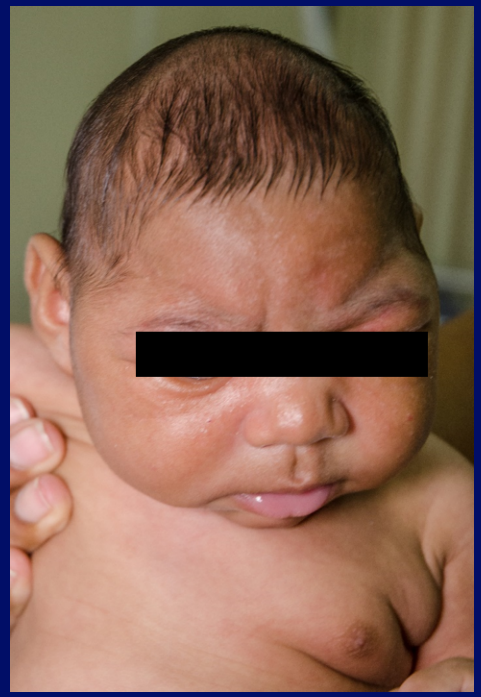


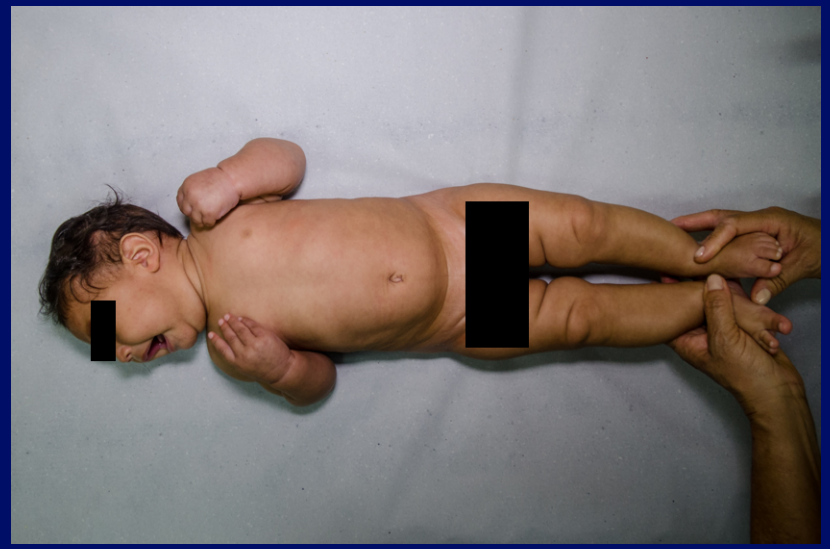
Medina MT, England JD, Lorenzana I, Medina-Montoya M, et al Zika virus associated with sensory polyneuropathy. J Neurol Sci. 2016 Oct 15;369:271-2

Zika congenital infection syndrome

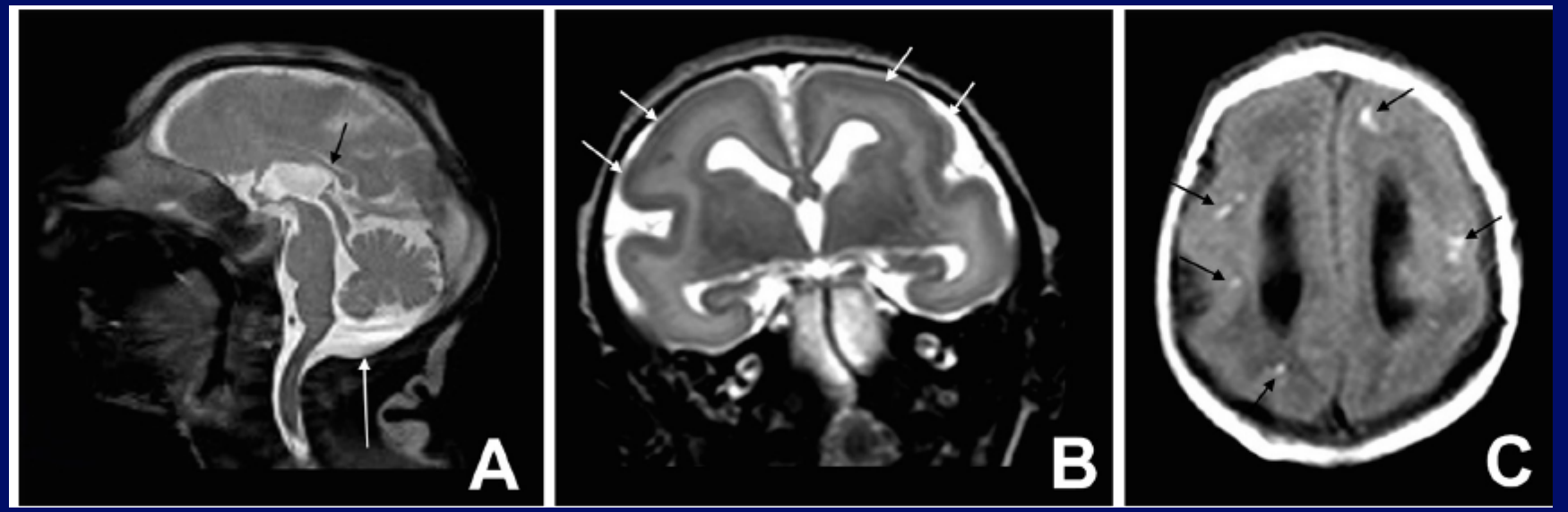
microcephaly, arthrogryposis in arms and or legs etc

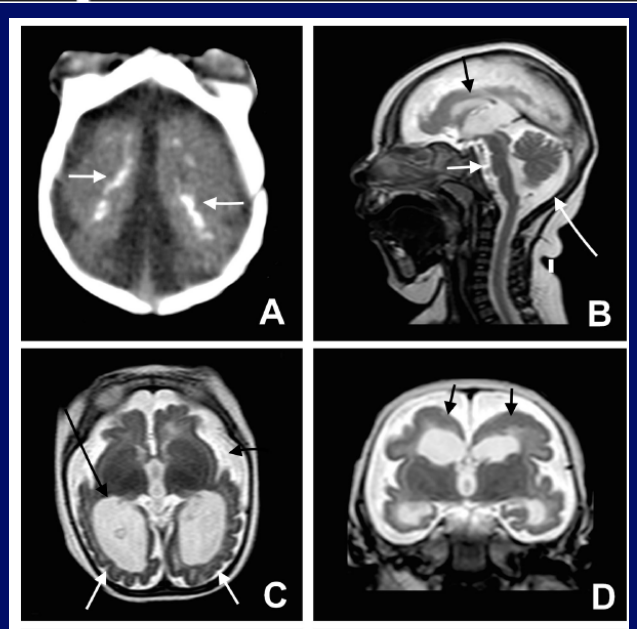






Brain Malformations

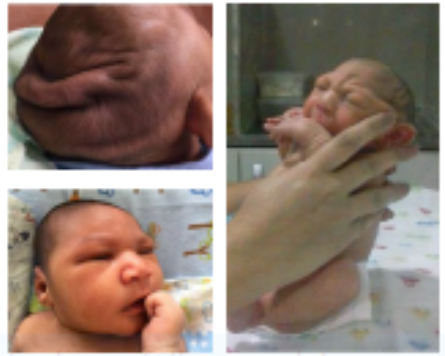




NEWBORN AND ZIKA from WHO 2017

FIG 2. INITIAL EVALUATION OF A NEWBORN POTENTIALLY EXPOSED TO ZIKV

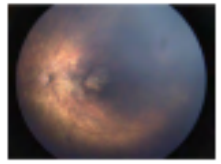
a. Dysmorphic features in CZVS: Note the severe microcephaly and cutis gyrata in the infant shown in the top and right-hand images, and craniofacial disproportion without microcephaly in the image on the bottom.



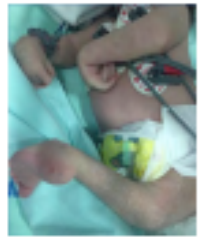
a.

b. Ophthalmological abnormalities in CZVS: Note the optic nerve with increased disc cupping, discrete vascular attenuation and chorioretinal scar with pigmented mottling in the macular region.

c. Arthrogryposis in CZVS

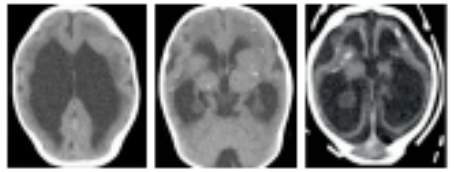


b.



c.

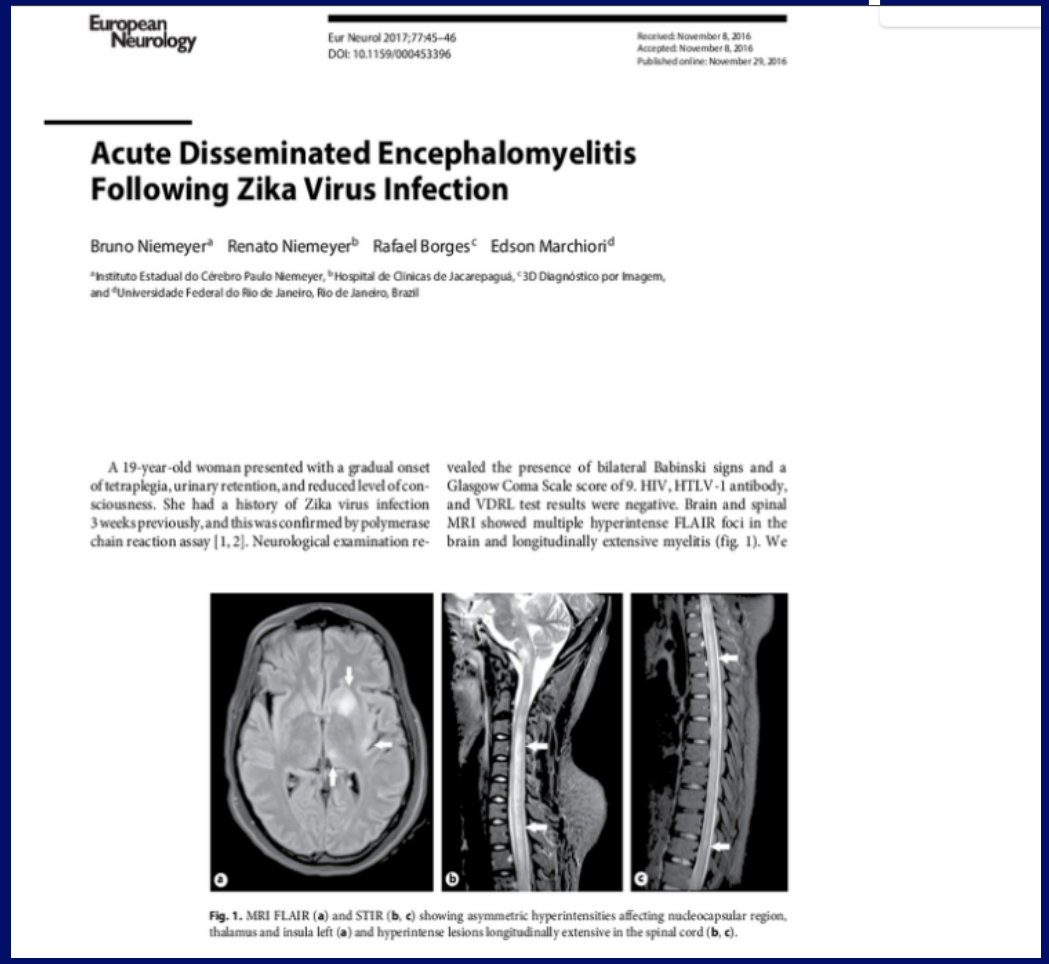
d. Neuroradiology features of CZVS (computed tomographt scans are for different infants)



d.

Images courtesy of Dr Vanessa van der Linden (a, c, d) and Dr Camilla Ventura (b), Recife, Brazil

Acute Disseminated Encephalomyelitis



European Neurology

Eur Neurol 2017;77:45–46
DOI: 10.1159/000453396

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Accepted: November 8, 2016
Published online: November 29, 2016

Acute Disseminated Encephalomyelitis Following Zika Virus Infection

Bruno Niemeyer[a] Renato Niemeyer[b] Rafael Borges[c] Edson Marchiori[d]

[a]Instituto Estadual do Cérebro Paulo Niemeyer, [b]Hospital de Clínicas de Jacarepaguá, [c]3D Diagnóstico por Imagem, and [d]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

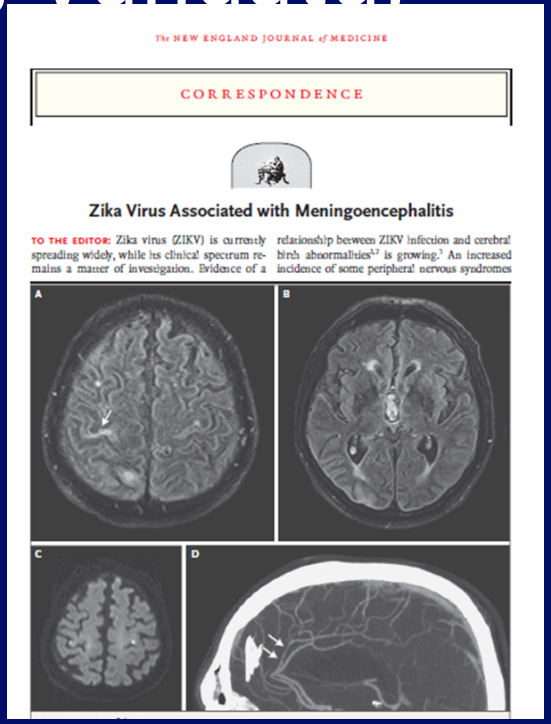
A 19-year-old woman presented with a gradual onset of tetraplegia, urinary retention, and reduced level of consciousness. She had a history of Zika virus infection 3 weeks previously, and this was confirmed by polymerase chain reaction assay [1, 2]. Neurological examination revealed the presence of bilateral Babinski signs and a Glasgow Coma Scale score of 9. HIV, HTLV-1 antibody, and VDRL test results were negative. Brain and spinal MRI showed multiple hyperintense FLAIR foci in the brain and longitudinally extensive myelitis (fig. 1). We

Fig. 1. MRI FLAIR (**a**) and STIR (**b**, **c**) showing asymmetric hyperintensities affecting nucleocapsular region, thalamus and insula left (**a**) and hyperintense lesions longitudinally extensive in the spinal cord (**b**, **c**).

- Niemeyer B, Niemeyer R, Borges R, Marchiori E. Acute Disseminated Encephalomyelitis Following Zika Virus Infection. Eur Neurol. 2017;77(1-2):45-46

Zika Virus associated with Meningoencephalitis

- An 81-year-old man was admitted to the intensive care unit (ICU) 10 days after he had been on a 4-week cruise in the area of New Caledonia, Vanuatu, the Solomon Islands, and New Zealand.

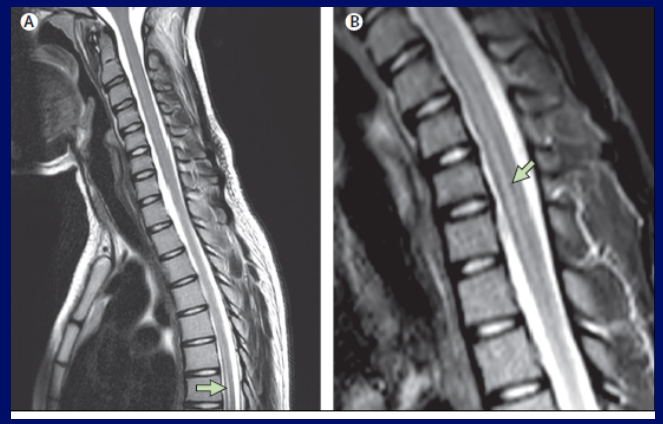


Carteaux G et al Zika Virus Associated with Meningoencephalitis. N Engl J Med. 2016 Apr 21;374(16):1595-6

Acute Myelitis

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



- January, 2016, a 15-year-old girl was admitted to hospital in Pointe-à-Pitre, Guadeloupe, with left hemiparesis.

Mécharles et al. Acute myelitis due to Zika virus infection. Lancet. 2016 Apr 2;387(10026):1481

Seizures/Epilepsy and Zika

Seizure 43 (2016) 13–13

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Letter to the Editor

Zika virus-associated seizures

To the Editor,

Recently, a few review articles have been published on Zika virus discussing many aspects of Zika virus infection eloquently; however, they did not mention the evidence on Zika virus-associated seizures [1,2]. The potential for worldwide Zika virus spread is large [1,2]. About 80% of people infected by Zika virus appear to be without symptoms. When symptoms occur, they are described as "dengue-like". Zika virus has a strong neurotropism [1–3]. Zika virus may impair growth in cerebral organoids from human embryonic stem cells by targeting neural progenitors [4]. It may cause dysregulation of the genes involved in neurogenesis [4]. Association between maternal Zika virus infection and infantile microcephaly has been reported [1–3]. In a series of 35 infants with Zika-associated microcephaly, neurological abnormalities (other than microcephaly) were reported in 49% of the cases, including hypertonia/spasticity (37%) and seizures (9%). In that series, neuroimaging was available in 27 patients and it was abnormal in all of them. Widespread brain calcifications and evidence of cell response to limit its impact through the development of better preventative, diagnostic, and therapeutic approaches.

Conflict of interest statement

Ali A. Asadi-Pooya, M.D., consultant: Cerebral Therapeutics, LLC and UCB Pharma; Honorarium: Hospital Physician Board Review Manual; Royalty: Oxford University Press (Book publication).

Acknowledgments

This work is not funded.

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[1] Araujo AQ, Silva MT, Araujo AP. Zika virus-associated neurological disorders: a review. Brain 2016;139(Pt 8):2122–30.
[2] Boeuf P, Drummer HE, Richards JS, Scoullar MJ, Beeson JG. The global threat of Zika virus to pregnancy: epidemiology, clinical perspectives, mechanisms, and impact. BMC Med 2016;14(1):112.
[3] Valentine G, Marquez L, Pammi M. Zika virus-associated microcephaly and eye lesions in the newborn. J Pediatric Infect Dis Soc 2016;5(3):323–8.
[4] Dang J, Tiwari SK, Lichinchi G, Qin Y, Patil VS, Eroshkin AM, et al. Zika virus depletes neural progenitors in human cerebral organoids through activation of the innate immune receptor TLR3. Cell Stem Cell 2016;19(2):258–65.

Zika y Epilepsia

Table 1. Clinical and Electroencephalographic Findings Associated with Congenital Zika Virus Infection.

Variable	Study Cohort (N=141)
	no./total no. (%)
Prevalence of epilepsy	95/141 (67)
Seizure type*	
Epileptic spasms	68/95 (72)
Focal motor	20/95 (21)
Tonic	4/95 (4)
Tonic–clonic	2/95 (2)
Myoclonic	1/95 (1)
Use of antiepileptic drugs	95/141 (67)
Monotherapy†	42/95 (44)
Polytherapy	53/95 (56)
Two antiepileptic drugs	42/53 (79)
Three antiepileptic drugs	11/53 (21)
Electroencephalographic features	
Abnormal background	84/89 (94)
Abnormal or absent sleep patterns	83/84 (99)
Diffuse slowing	73/84 (87)
Asymmetry with slowing over one hemisphere	3/84 (4)
Epileptiform activity	73/89 (82)
Multifocal epileptiform discharges	32/73 (44)
Focal epileptiform discharges	37/73 (51)
Generalized epileptiform discharges	4/73 (5)
Hypsarrhythmia	8/73 (11)
Burst-suppression pattern	6/73 (8)

* Seizure types were classified according to the guidelines of the International League against Epilepsy

was not associated with tonic seizures. Remission occurred in one patient in the group of patients with a burst-suppression pattern or hypsarrhythmia.

The prevalence of epilepsy in this referral center–based cohort was higher than in previous series in which the prevalence ranged from 9 to 50%.[1-4] In our study, patients had early-onset, often drug-resistant, epilepsy. The background was abnormal in most EEGs, as previously observed.[5] However, some EEG features, such as a burst-suppression pattern and hypsarrhythmia, were predictive of severe epilepsy. Epilepsy may complicate congenital ZIKV infection.

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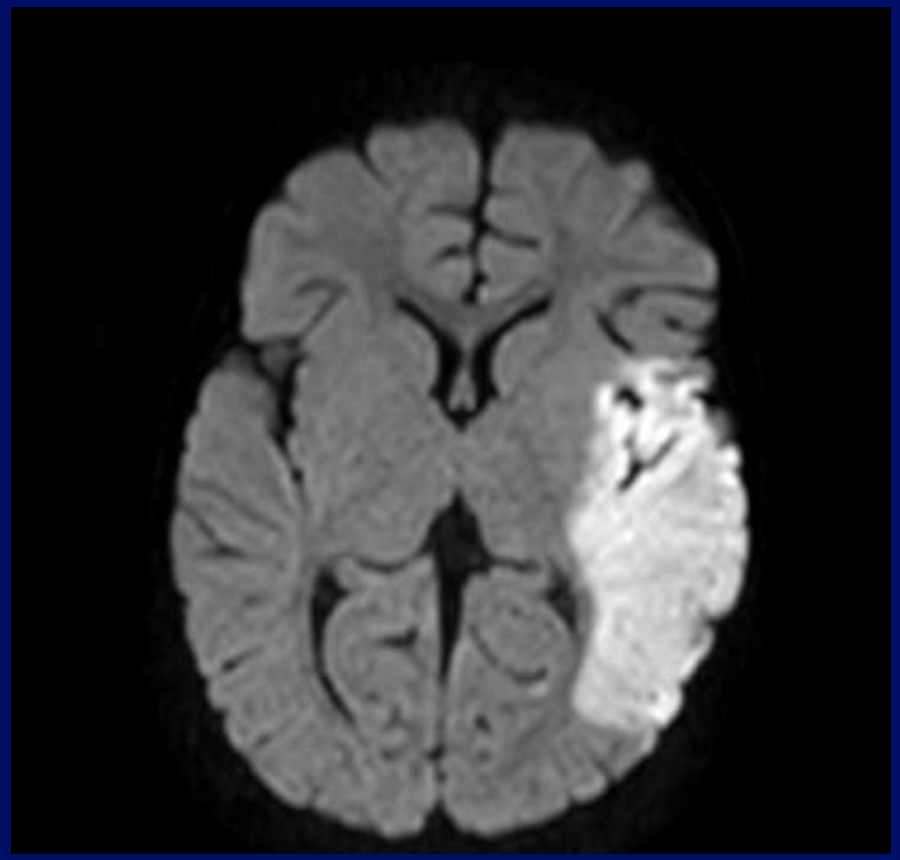
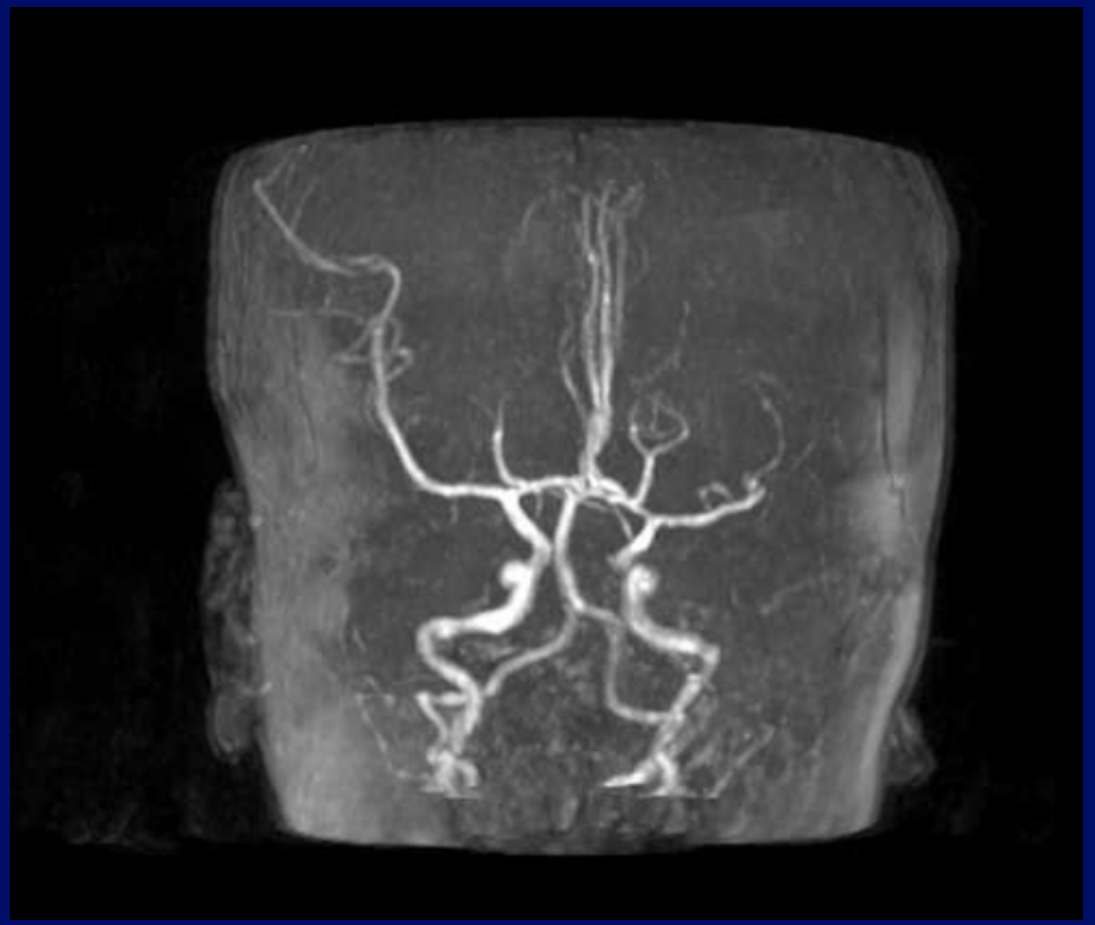
ZIKA vasculitis: a new cause of stroke in children?

By: Anne Landaisa, Audrey Césaireb, Manuel Fernandezc , Sébastien Breurecdef ,
Cécile Herrmannd, Fréderique Delionb Philippe Desprezb

Journal of the Neurological Sciences 2017 In Press





- Frequent Co-circulation of multiple virus and serotypes (hyperendemnicity)

Journal of Infection and Public Health (2016) xxx, xxx–xxx

ELSEVIER

http://www.elsevi

Estimating and mapping the incidence of dengue and chikungunya in Honduras during 2015 using Geographic Information Systems (GIS)

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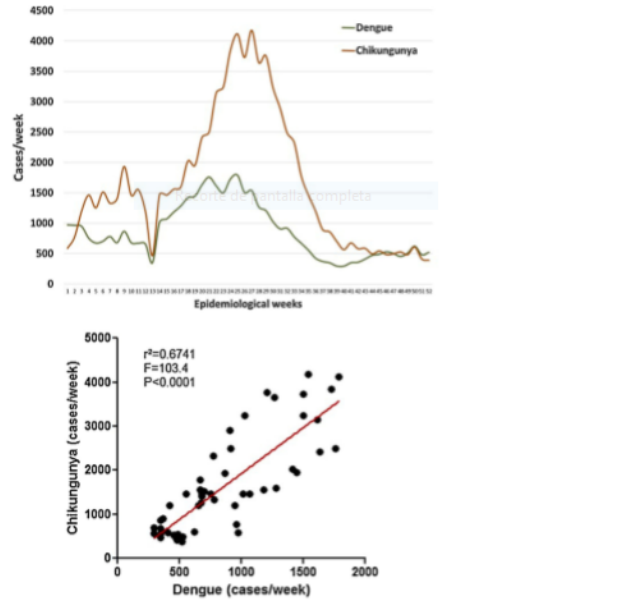
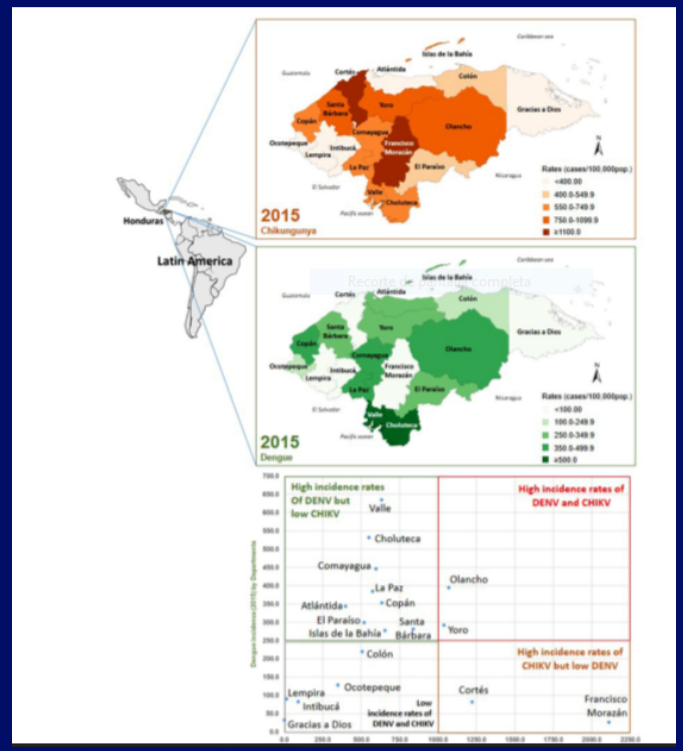


Figure 1 Temporal distribution by epidemiological weeks of number of cases of dengue and chikungunya in Honduras, 2015, and its relation in a linear regression model.



Neurologic Complications Chikungunya Virus

- The Chikungunya virus (CHIKV) is a single-chain linear RNA arbovirus that is transmitted to humans primarily by the Aedes aegypti and Aedes albopictus mosquitoes

1.Samra et al Journal of Child Neurology 2017

2.Gutierrez-Saravia E, Guitierrez CE. J Pediatr Infect Dis Society. 2015;4:103.

3. Ritz N, Hufnagel M, Gerardin P. Pediatr Infect Dis J. 2015;34:789-791.

Chikungunya

- CHIKV infection was first detected in southern Tanzania in 1952. The name Chikungunya is Swahili for “that which bends up,”3 since the classic clinical symptoms include fever and joint pain. Joint pain can persist for months to years after infection, causing patients to adopt a bent, stooping posture.

1. Gutierrez-Saravia E, Guitierrez CE. J Pediatr Infect Dis Society. 2015;4:103. 2. Ritz N, Hufnagel M, Gerardin P. Pediatr Infect Dis J. 2015;34:789-91

Chikungunya

- Following the bite of an infected mosquito, chikungunya virus causes a characteristic febrile syndrome manifested by headache, rash, and severe arthralgia. Patients can develop a poly-articular large-joint arthritis during acute infection, and symptoms of joint pain can linger for months following infection

1.Samra et al Journal of Child Neurology 2017

2.Gutierrez-Saravia E, Guitierrez CE. J Pediatr Infect Dis Society. 2015;4:103.

3. Ritz N, Hufnagel M, Gerardin P. Pediatr Infect Dis J. 2015;34:789-791

Chikungunya

- By the end of 2014, 1 million suspected and 20, 000 confirmed cases of autochthonous transmission of CHIKV were identified in 15 countries in North, South, and Central America.
- International travel exposures have contributed to the spread of the virus, and confirmed autochthonous cases have been identified in the United States.

1.Samra et al Journal of Child Neurology 2017

2.Gutierrez-Saravia E, Guitierrez CE. J Pediatr Infect Dis Society. 2015;4:103.

3. Ritz N, Hufnagel M, Gerardin P. Pediatr Infect Dis J. 2015;34:789-791

Chikungunya

- Associated neurologic clinical manifestations of chikungunya virus have included meningitis, encephalitis, and encephalomyeloradiculitis. Diagnosis of chikungunya virus infection can be made with serology using acute and convalescent serum, and cases of chikungunya virus–associated CNS disease have been confirmed following detection of Reverse Transcription-PCR and anti–chikungunya virus IgM in the CSF.

1.Samra et al Journal of Child Neurology 2017

2.Gutierrez-Saravia E, Guitierrez CE. J Pediatr Infect Dis Society. 2015;4:103.

3. Ritz N, Hufnagel M, Gerardin P. Pediatr Infect Dis J. 2015;34:789-791

Chikungunya

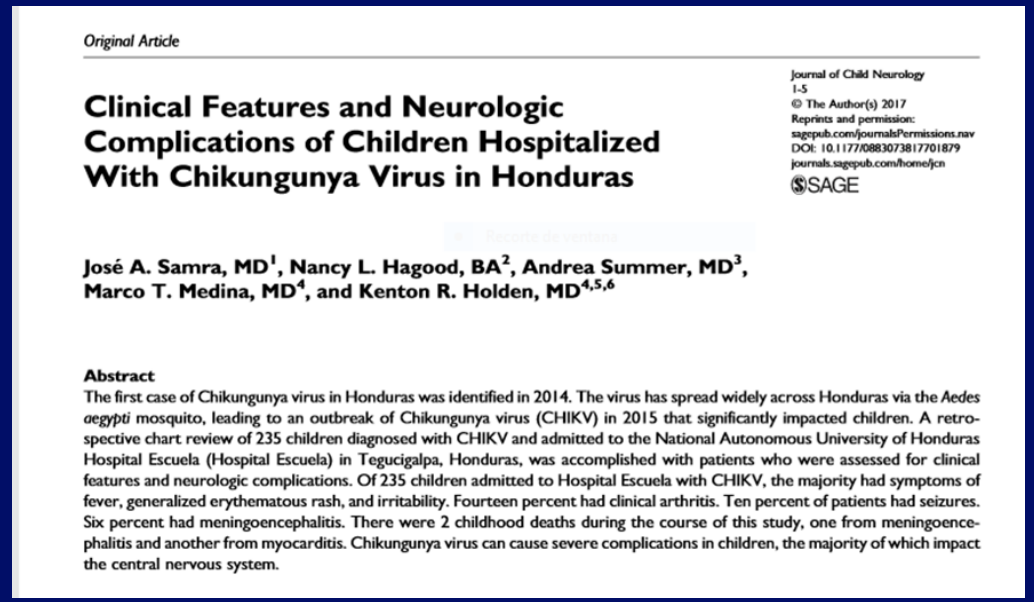
- Chikungunya virus has been identified as an infection that can cause significant nervous system morbidity globally, especially in young children.
- The 2006 CHIKV outbreak in India revealed the neurologic manifestations of CHIKV, including meningoencephalitis, seizures, Guillain-Barre´ syndrome, and myelopathy or myeloneuropathy.

1.Gutierrez-Saravia E, Guitierrez CE. J Pediatr Infect Dis Society. 2015;4:103.

2. Ritz N, Hufnagel M, Gerardin P. Pediatr Infect Dis J. 2015;34:789-791

CHIKV

- Few observational studies have detailed the clinical manifestations of CHIKV in children, but those that do support the fact that children may have a clinical presentation different from adults.



Original Article

Clinical Features and Neurologic Complications of Children Hospitalized With Chikungunya Virus in Honduras

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1-5

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Abstract

The first case of Chikungunya virus in Honduras was identified in 2014. The virus has spread widely across Honduras via the *Aedes aegypti* mosquito, leading to an outbreak of Chikungunya virus (CHIKV) in 2015 that significantly impacted children. A retrospective chart review of 235 children diagnosed with CHIKV and admitted to the National Autonomous University of Honduras Hospital Escuela (Hospital Escuela) in Tegucigalpa, Honduras, was accomplished with patients who were assessed for clinical features and neurologic complications. Of 235 children admitted to Hospital Escuela with CHIKV, the majority had symptoms of fever, generalized erythematous rash, and irritability. Fourteen percent had clinical arthritis. Ten percent of patients had seizures. Six percent had meningoencephalitis. There were 2 childhood deaths during the course of this study, one from meningoencephalitis and another from myocarditis. Chikungunya virus can cause severe complications in children, the majority of which impact the central nervous system.

1.Samra et al Journal of Child Neurology 2017

Chikungunya

- Our study of the clinical features and neurologic complications of 235 pediatric cases of CHIKV needing hospitalization during the 2015 outbreak in Honduras

1.Samra et al Journal of Child Neurology 2017

CHIKV

Table 1. Ages of Pediatric Patients Admitted to Hospital Escuela in Tegucigalpa in 2015 With Chikungunya Virus.

Age	RT-PCR frequency (%)	Epidemiologic link frequency (%)	Total (%)
1-7 d	8 (3)	1 (1)	9 (4)
8-29 d	26 (11)	21 (9)	47 (20)
1-12 mo	54 (23)	69 (29)	123 (52)
1-2 y	17 (7)	4 (2)	21 (9)
3-5 y	10 (4)	7 (3)	17 (7)
6-11 y	7 (3)	2 (1)	9 (4)
12-18 y	6 (3)	3 (1)	9 (4)
Total	128 (54)	107 (46)	235 (100)

Abbreviations: RT-PCR, reverse transcription–polymerase chain reaction.

Table 2. Clinical Manifestations of Pediatric Patients Admitted to Hospital Escuela in Tegucigalpa in 2015 With Chikungunya Virus.

Clinical manifestation	RT-PCR (128 patients), %	Epidemiologic link (107 patients), %
Fever	100	100
Rash	90	86
Irritability	68	77
Arthralgia	27	14
Myalgia	27	11
Arthritis	23	3
Vomiting	21	23
Headache	15	6
Diarrhea	10	20
Bulging fontanelle	4	0

1.Samra et al Journal of Child Neurology 2017

Chikungunya

Table 4. Presence of Complications Among Pediatric Patients Admitted to Hospital Escuela in Tegucigalpa in 2015 With Chikungunya Virus.

Complication	RT-PCR (41 patients), %	Epidemiologic Link (12 patients), %
Seizures	59	0
Meningoencephalitis	34	58
Acute hepatitis	24	33
Myocarditis	10	8
"Sepsis"	7	25
Shock	2	8

Abbreviation: RT-PCR, reverse transcription–polymerase chain reaction.

Table 5. Clinical Manifestations of 14 Pediatric RT-PCR CHIKV Patients Admitted to Hospital Escuela in Tegucigalpa in 2015 and Presenting With Meningoencephalitis.

Clinical manifestation	Frequency, %
Fever	100
Rash	100
Irritability	100
Hyperalgesia	93
Seizures	57
Lethargy	50
Bulging fontanelle	36
Vomiting	21
Diarrhea	21

1.Samra et al Journal of Child Neurology 2017

Chikungunya

- Chikungunya virus has been known to cause mother-to child transmission since the first case of vertical transmission CHIKV was identified in 2005 on La Reunion Island in the Indian Ocean.

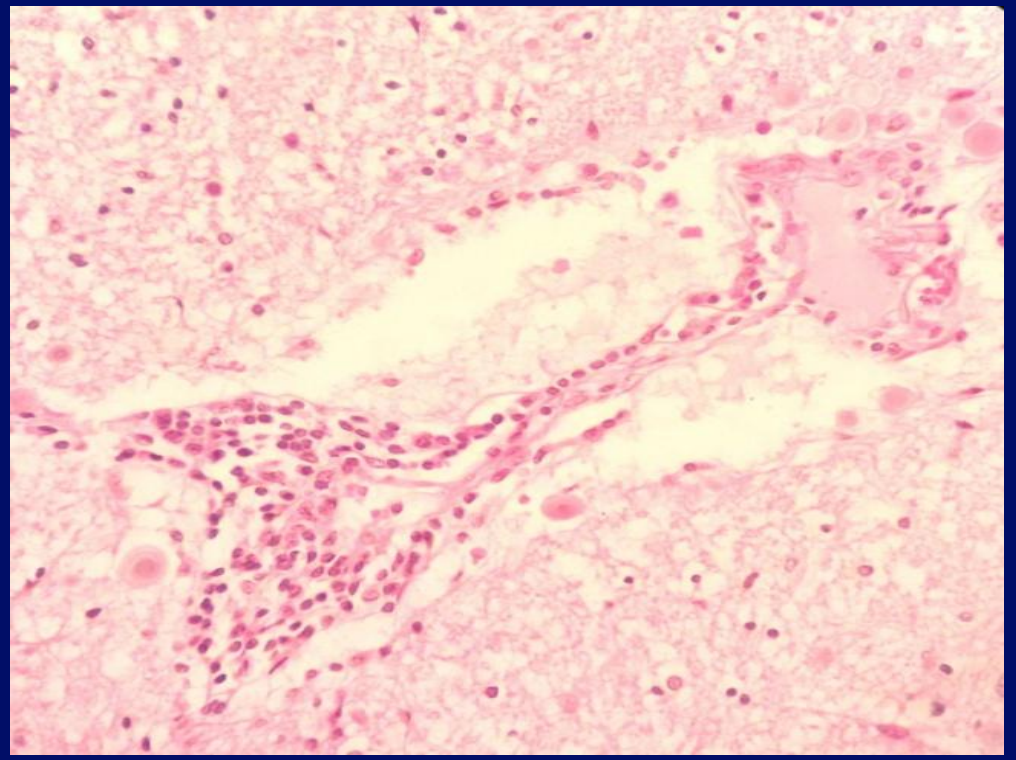
1.Samra et al Journal of Child Neurology 2017

2.Gutierrez-Saravia E, Guitierrez CE. J Pediatr Infect Dis Society. 2015;4:103.

3. Ritz N, Hufnagel M, Gerardin P. Pediatr Infect Dis J. 2015;34:789-791

Chikungunya Encephalitis in Adults

- Perivascular Inflamatory reaction in a Honduran patient



- Ortiz et al WCN 2017

Dengue

- Dengue virus is an Arbovirus member of the Flavivirus genus of the family Flaviviridae.
- There are 4 genetically and antigenically distinct serotypes of dengue (DENV 1–4).
- Frequent Co-circulation of multiple serotypes (hyperendemnicity)

- Gubler D. 2006. Dengue/dengue haemorrhagic fever: history and current status. NFS . Vol.277, pp.3–16.

Dengue

- In 2009, WHO adjustments in the classification of the disease resulted in the recognition of two main presentations of dengue:
- Dengue Fever and Severe Dengue.
- Neurological dengue is classified as a form of Severe Dengue

WHO Dengue: Guidelines for diagnosis, treatment, prevention and control. World Health Organization and Special Programme for Research and Training in Tropical Diseases, 2009.

Dengue

- Dengue virus infection causes an acute self-limited febrile syndrome characterized by headache, retroorbital pain, rash, nausea, vomiting, diarrhea, myalgia, and arthralgia. In individuals with prior exposure to dengue virus, reexposure to another serotype places the individual at increased risk for severe dengue

WHO Dengue: Guidelines for diagnosis, treatment, prevention and control. World Health Organization and Special Programme for Research and Training in Tropical Diseases, 2009.

Severe Dengue

- Severe Dengue (dengue hemorrhagic fever) is characterized by increased vascular permeability, thrombocytopenia, hypotension, and hemorrhagic manifestations.

WHO Dengue: Guidelines for diagnosis, treatment, prevention and control. World Health Organization and Special Programme for Research and Training in Tropical Diseases, 2009.

Lab methods for dengue diagnosis

Diagnostic Method	Specimen	Time of collection after onset of symptoms	Diagnosis of acute infection
Virus isolation Serotype confirmation	Whole blood, serum, Tissue	1 to 5 days	Confirmed
Nucleic acid detection	Whole blood, serum, plasma, Tissue	1 to 5 days	Confirmed
NS1 antigen detection	Serum Tissue	1 to 6 days	Confirmed
IgM ELISA -paired seroconversion	Serum, plasma, whole blood	Acute sera (1-5 days) Convalescent sera (>15 days)	Confirmed
IgM ELISA-Single sera	Serum, plasma, whole blood	>5 days	Probable
IgM rapid test	Serum, plasma, whole blood	>5 days	Probable
IgG single serum , HI titre>1280	Serum, plasma, whole blood	>5 days	Probable
IgG (paired sera) by ELISA, HI or Neutralization test (seroconversion or 4 fold rise)	Serum, plasma, whole blood	Acute sera (1-5 days) Convalescent sera (>15 days)	Confirmed

Table 1. Summary of laboratory methods used in the diagnosis of dengue infection

- WHO 2009
- Pok et al 2010

Diagnosis

- According to the CDC due to cross-reaction with other flaviviruses (i.e., Zika and Dengue infections) and possible nonspecific reactivity, results may be difficult to interpret. Consequently, presumed positive tests must be forwarded for confirmation by plaque-reduction neutralization test (PRNT)
- https://www.cdc.gov/zika/hc-providers/types-of-tests.html

DENGUE

- Outbreaks of dengue have been documented in the Eastern Mediterranean Region since 1799 in Egypt. William Smart documented descriptions of neurological manifestations of dengue as early as 1827.

Severe Dengue

- An example of such documentation is demonstrated in the excerpt which follows: “In children, the attack may be ushered in with convulsions, and the resolution may be attended by sensorial depression, approaching more or less to “dementia“, which last condition may attend the stage of resolution of the disease in elderly persons also” (Smart, 1877).

DENGUE AND NEUROLOGIC COMPLICATIONS

- Neurologic involvement occurs in 4%-5% of confirmed dengue cases (Puccioni-Sohler et al., 2009). The incidence of dengue infection in patients with suspected central nervous system (CNS) infection is noted to range from 4.2% in southern Vietnam (Solomon et al., 2000) to 13.5% in Jamaica (Jackson et al., 2008) mainly encephalitis, meningitis, mielitis, GBS, etc

Beckham JD, Tyler KL. Arbovirus Infections. Continuum (Minneap Minn). 2015 Dec;21(6 Neuroinfectious Disease):1599-611

Key messages

1. The Zika, Dengue and Chikungunya arbovirus infections and its neurologic consequences represent a major global health problem.
2. Zika, Dengue and Chikungunya arbovirus infections have a wide spectrum of neurologic consequences and represent neuropathological agent with several neurological complications.
3. 3. The ZVI, mainly the Asian lineage, has a neurotropism that affects the Human Fetal Brain Neural Stem Cells producing Congenital Zika Syndrome.

Key messages

4. The Zika, Dengue and Chikungunya infections can produce an autoimmune response (i.e., Glycolipids in GBS)
5. ZVI directly infects Peripheral Neurons and causes substantial cell death and pathogenic transcriptional dysregulation (i.e., Sensory neuropathy)
6. Zika, Dengue and Chikungunya infections have a direct viral inflammatory process on CNS (Meningoencephalitis, encephalitis, acute myelitis, etc)
7. Zika Virus infections may produces vasculitis by primary human brain microvascular endothelial cells damage