Zika virus detection in cerebrospinal fluid from two patients with encephalopathy, Martinique, February 2016

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We report two cases of encephalopathy (one with seizures, one with electroencephalogram changes) in patients with Zika virus infection. The cases occurred on Martinique in February 2016, during the Zika virus outbreak. Awareness of the various neurological complications of Zika virus infection is needed for patients living in areas affected by Zika virus infections or for travellers to these areas.

We describe two cases of encephalopathy in patients with Zika virus infection detected on Martinique in February 2016. In both patients, Zika virus RNA was detected in their cerebrospinal fluid (CSF), plasma, and urine.

Description of the cases

Case 1

At the end of February 2016, two months after the detection of the first Zika virus-positive cases on Martinique, a previously healthy young adult was admitted to the University Hospital of Martinique, after having experienced an episode of convulsive seizures that occurred six hours after the onset of a dengue-like syndrome (fever, arthralgia, asthenia and headache). Upon initial clinical evaluation, the patient was febrile, with a low level of consciousness (Glasgow coma scale (GCS) 9) and no neurological focal signs. After direct intravenous injection of clonazepam (one milligram), the patient recovered to a normal level of consciousness (GCS 15). The patient was hospitalised for three days, then returned back home with symptomatic treatment of acetaminophen and codeine against headache and arthralgia. One week later, clinical assessment found no new neurological symptoms, but headache and arthralgia persisted for 45 days.

Brain magnetic resonance imaging (MRI) and video-electroencephalogram (EEG) performed on day 5 after onset of neurological symptoms, were normal.

Laboratory findings at onset of neurological symptoms showed normal blood count and a sterile CSF with no white blood cells (norm: ‹10/ml), and 0.20 g/L protein (norm: 0.15–0.40). The glycorachia/glycaemia ratio was normal (norm: ›0.5).

The patient was screened for the common aetiologies of viral encephalitis: test results for herpes simplex virus, varicella zoster virus and cytomegalovirus (CMV) by PCR were negative in CSF. Direct detection in CSF of enterovirus, dengue virus (DENV) and chikungunya virus by real-time RT-PCR were negative. Serological tests for HIV, CMV and venereal research disease laboratory (VDRL) were negative. Serology for toxoplasmosis was positive in IgG. Direct detection of *Leptospira* sp. in plasma by PCR was negative. *Cryptococcus* sp. antigenemia in serum was negative. Detection of Zika virus by real-time RT-PCR in plasma, cerebrospinal fluid and urine were positive (Table).

Case 2

In the last week of February 2016, a patient in their late 70s was brought to the University Hospital of Martinique by their family who reported symptoms including acute mental confusion, speech disorder,

Table

Clinical, neuroimaging, electroencephalography and microbiological findings in two cases of encephalopathy associated with Zika virus infection, Martinique, February 2016

Clinical features upon hospital admission		Case 1	Case 2
Body temperature		40 °C	37.2 °C
Headache		Yes	Yes
Conjunctivitis		No	Yes
Whole body maculopapular rash		No	No
Arthralgia		Yes	Yes
Myalgia		Yes	Yes
Altered mental status		Yes	Yes
Seizures		Yes	No
Focal neurologic findings		No	Yes
Additional tests			
CSF WBC count ≥ 5/mm³		No	No
Neuroimaging (magnetic resonance imaging)		Normal (day 5)	Leukoaraiosis (day 1)
Electroencephalography		Normal (day 5)	Focal activity (day 1)
Microorganism	**Detection**		
Mycoplasma spp.	Serology	IgM: 3,606.74 IU/mL (norm: <950 IU/mL) IgG: 2,412.94 IU/mL (norm: <1,200 IU/mL)	IgM: 193.58 IU/mL (norm: <950 IU/mL) IgG: 478.24 IU/mL (norm: <1,200 IU/mL)
Cryptococcus spp.	Antigen (serum)	Negative	Negative
Epstein–Barr virus	Serology	IgM anti-VCA: 0.11 IU/mL (norm: <0.9 IU/mL) IgG anti-VCA: 2.78 IU/mL (norm: <0.9 IU/mL) IgG anti-EBNA: 1.23 IU/mL (norm: <0.9 IU/mL)	IgM anti-VCA: 0.06 IU/mL (norm: <0.9 IU/mL) IgG anti-VCA: 2.82 IU/mL (norm: <0.9 IU/mL) IgG anti-EBNA: 3.09 IU/mL (norm: <0.9 IU/mL)
Human immunodeficiency virus	Serology	Ratio: 0.30 (norm: <0.9)	Ratio: 0.30 (norm: <0.9)
Herpes simplex virus	CSF (PCR)	Negative	Negative
Cytomegalovirus	Serology	Ratio IgM<0.7 (norm: <0.7) Ratio IgG<0.15 (norm: <0.5)	Ratio IgM: 0.20 (norm: <0.7) Ratio IgG: 0.163 (norm: <0.5)
	CSF (PCR)	Negative	Negative
Varicella zoster virus	CSF (PCR)	Negative	Negative
Enterovirus, including poliovirus	CSF (real-time RT-PCR)	Negative	Negative
Dengue virus	Serology	Ratio IgM: 4.37 (norm: <0.9) Ratio IgG: 5.65 (norm: <1.8)	Ratio IgM: 0.46 (norm: <0.9) Ratio IgG: 4.29 (norm: <1.8)
	Plasma (real-time RT-PCR)	Negative	Negative
	CSF (real-time RT-PCR)	Negative	Negative
Chikungunya virus	Serology	Ratio IgM: 0.239 (norm: <0.8) Ratio IgG: 5.403 (norm: <0.8)	Ratio IgM: 0.284 (norm: <0.8) Ratio IgG: 5.161 (norm: <0.8)
	Plasma (real-time RT-PCR)	Negative	Negative
	CSF (real-time RT-PCR)	Negative	Negative
Zika virus	Plasma (real-time RT-PCR)	Positive	Positive
	CSF (real-time RT-PCR)	Positive	Positive
	Urine (real-time RT-PCR)	Positive	Positive

CSF: cerebrospinal fluid; EBNA: Epstein–Barr nuclear antigen; IU: international unit; VCA: viral capsid antigen; WBC: white blood cell count.

and right facial palsy, which had started three hours before hospital admission. Upon initial clinical evaluation the patient was afebrile and aphasic; conjunctivitis, bilateral hands oedema, and peripheral arthritis were present. Facial palsy was not noticed upon clinical examination. Aphasia resolved spontaneously 45 minutes after the first clinical evaluation.

Upon initial clinical evaluation, brain MRI was only consistent with leukoaraiosis, and EEG revealed an unequivocal asymmetry with abnormal left frontotemporal slow waves. These waves were consistent with the presence of a pathological process, but had no specific pattern. The EEG performed one week later showed almost complete regression of the slow waves.

The analysis of CSF showed a protein count of 0.40 g/L and a white blood cell count of 2/mL. The glycorachia/glycaemia ratio was normal. PCR for common aetiologies of encephalitis was negative. Detection of Zika virus by real-time RT-PCR in plasma, CSF and urine gave a positive result (Table).

Discussion

Since December 2015, an outbreak of Zika virus infections has been ongoing on Martinique, a French West Indies island of 390,000 inhabitants. It spread rapidly, with more than 15,400 cases estimated as at 31 March 2016 [1]. Zika virus infection is usually benign, when symptomatic. The disease resembles uncomplicated dengue fever and lasts for four to seven days and is self-limiting. In Martinique, *Aedes aegypti* is assumed to be the unique vector of flaviviruses. Recent Zika virus epidemics in French Polynesia, Brazil, Central America and the French West Indies have been associated with neurological complications [2].

Over the past five years, there have been between one and three patients with encephalitis hospitalised monthly in the University Hospital of Martinique.

In this report, we present two cases of encephalopathy fulfilling the diagnostic criteria of the Consensus Statement of the International Encephalitis Consortium [3]. Based on the laboratory findings, we consider these cases as Zika virus-associated. In keeping with neurological findings in other arbovirus infections, the presentations were of non-specific nature; the spectrum of arboviral neurological disease may even lead to ischemic stroke [4]. Moreover, in arbovirus-related neurological disorders, imaging findings may be normal and different EEG abnormalities can be seen [5]. Zika virus is known as a neurotropic microorganism [6], however, both structural imaging and EEG can be normal in acute infection [5]. The mechanism of flavivirus infection of the central nervous system (CNS) is not clearly understood and pathology depends on the virus. Neurological involvement can be caused by direct damage of the nerve by the virus but also be immune mediated. For example, dengue virus can infect human astrocytes and brain microvascular endothelial cells, whereas West Nile virus infection could lead to a blood-brain barrier dysfunction [7].

Awareness of the wide spectrum of neurological symptoms of Zika virus infection is needed for patients living in, or travelling to areas affected by Zika virus infections. Knowledge of the pathophysiology of Zika virus infection and the reasons behind its predilection for the CNS is needed to design treatment strategies to mitigate significant morbidity.

Neuro-Zika Working Group

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Conflict of interest

None declared.

Authors' contributions

BR, KA, FN, SA, PH, AC wrote the manuscript.

BR, PH, AS, KA, YB, SG and the Neuro-Zika Working Group took part in the clinical management of the patients.

FN, RC collaborated in molecular biology techniques.

LF, RC, FN collaborated on the serological techniques.

All authors participated in the outbreak investigation.

All authors read and approved the final manuscript.

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