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Co-infection ZIKV and HSV-1 associated with meningoencephalitis: Case report and literature review

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ABSTRACT

A man, 26 years-old, presented fever, mental confusion and a progressively worsening headache 6 days prior to admission. The CSF study was suggestive of meningoencephalitis, the PCR study revealed presence of HSV-1 and ZIKV, while other immunology tests were negative. ZIKV was also identified in serum. The MRI showed temporal lobe hyper-intensity in FLAIR-weight sequence with areas of contrast enhancement and the electroencephalogram showed slow wave activity in such region. Patient was treated with acyclovir and supportive measures and had good clinical outcome at evaluation after 6 months. Neurological spectrum of ZIKV manifestations is wide, but meningoencephalitis is not frequent. Co-infection HSV-1 plus ZIKV was not yet related in humans, but there is increased cellular damage caused by association of ZIKV and herpes virus family infection. ZIKV may facilitate infection or recrudescence by other viruses or cause concurrently neuronal injury by direct or indirect mechanisms. We suggest that clinicians attempt new manifestations related to ZIKV and include this agent in differential diagnosis of neurological diseases even when other agents were identified.

Introduction

Recently, zika virus (ZIKV) outbreak affecting a novel population, in a different environment, brought new clinical manifestations that caused this virus to change from an otherwise innocent agent to a public health issue, demanding a high priority status of surveillance. This was mainly due to congenital malformations and Guillian–Barré syndrome associated with ZIKV, but other neurological manifestations are also described [1]. Encephalitis is a condition that was already related to ZIKV in a temporal and biologic potential contexts, but its frequency is lower than these syndromes.

Here we describe a case of co-infection of ZIKV + human herpes simplex virus (HSV)-1, which led to meningoencephalitis with markedly brain structural changes, although the clinical outcome was favourable.

Case presentation

A man, 26 years-old, previously healthy, with a history of fever (38.8 °C), nausea, mental confusion and progressively worsening headache six days prior to the admission in an emergency room during the 2016 outbreak of ZIKV in Pernambuco (northeast of Brazil). No neck stiffness was observed and neurological examination was otherwise unremarkable. MRI of the brain showed anterior-mesial right temporal lobe hypo-intensity in T1-weighted imaging, hyper-intensity in FLAIR and no restriction on diffusion imaging, and there were areas of contrast enhancement (Fig. 1). Cerebrospinal fluid (CSF) revealed a cellularity of 95 cell/mL (100% of lymphomononuclear cells), proteins of 180 mg/dL, glucose levels of 41 mg/dL, immunology testing for HIV, VZV, EBV and toxoplasmosis resulted negative, and HSV-1 and -2 IgG were positive (Elisa). Real time polymerase chain reaction (qPCR, iCyclear iQ) in CSF revealed the presence of HSV-1 DNA and the conventional reverse transcription-PCR (RT-PCR) was positive for ZIKV RNA while negative for dengue virus (DENV). RT-PCR in serum was also positive for ZIKV. Serology for HIV, B and C hepatitis and syphilis were negative. The electroencephalogram showed slow wave activity in

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Table 1
Literature review of all cases of meningoencaphalitis/encephalitis associated with zika virus infection.

Variables	Age, sex	Main neurological finding	First CSF	ZIKV infection diagnosis	Brain imaging	Disease duration	Outcome	Commentaries
This study	26, M	Headache and mental confusion	95 cells (100% L), P = 180	CSF RT-PCR	Temporal hyperintensity in FLAIR, with anomalous contrast-impregnation	18 days	Good	Concomitant presence of HSV-1 (PCR)
Soares et al. [3]	47, F	Crural paresis, dysarthria and confusion	10 cells (80% L), P = 111	IgM positive in CSF, RT-PCR in urine	Massive brain swelling	15 days	Poor	Blood-CSF barrier dysfunction and intrathecal antibody synthesis
Carteaux et al. [2]	81, M	Left hemiplegia, coma	41 cells (98% PMN), P = 76	CSF RT-PCR, vero cell line culture	Slight hyperintensity of the right rolandic fissure	38 days	Good	Other MRI findings could be attributable to microangiopathy
Roze et al. [6] (1)	–	Headache, convulsive seizures	<10 cells, P = 20	qRT-PCR in serum, urine and CSF	Normal	45 days	Good	Video-EEG normal
Roze et al. [6] (2)	70, –	Aphasia, headache, confusion	2 cells, P = 40	qRT-PCR in serum, urine and CSF	Normal (leukoaraiosis)	–	Good	Abnormal left frontotemporal slow waves on EEG
Nicastri et al. [5]	32, F	Abnormal gait, crural paresis	<10 cells, P = 48	qRT-PCR in CSF, urine, serum and saliva	Normal	<60 days	Good	Impairment in memory, concentration and flexibility task tests
Acevedo et al. [4] (3)	23, M	Encephalo-pathy, asthenia, oliguria	5 cells (40% PMN), P = 51	qRT-PCR in CSF	Lenticular nucleus and periventricular thalamic nucleus ischemic-like lesions	–	–	PCR in CSF also positive for dengue and chikungunya. MRI suggestive of vasculitis
Acevedo et al. [4] (7)	47, M	Generalized tremor, convulsive seizures	6 cells (83% PMN), P = 76	qRT-PCR in CSF	Alterations in lenticular nucleus	–	–	PCR in CSF also positive for chikungunya

PMN = polymorphonuclear, L = lymphocytes, P = protein (mg/dL), RT-PCR = reverse transcription polymerase chain reaction, qRT-PCR = real time reverse transcription polymerase chain reaction, cells = cell/mL, EEG = electroencephalogram, – = no data available. Number in parenthesis relates to the order in a case series.

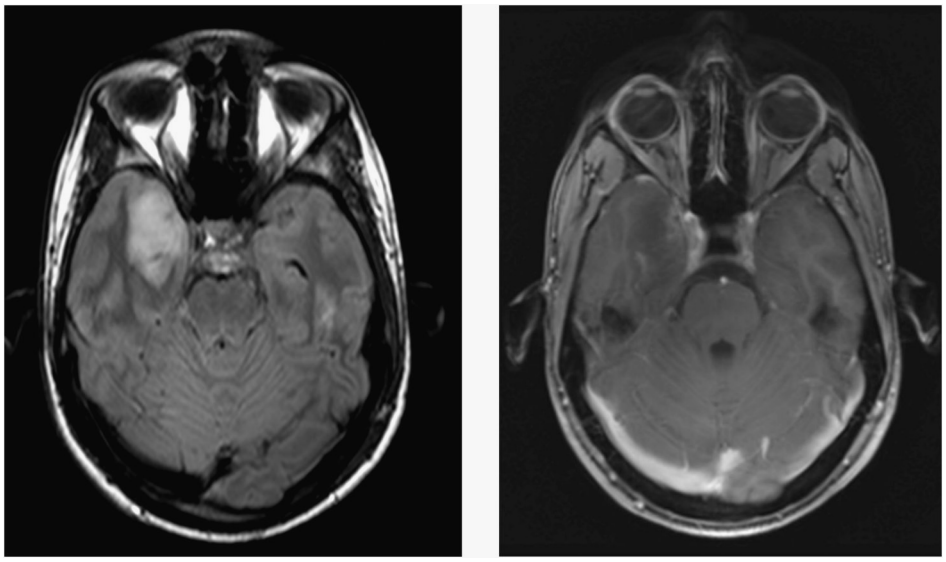

Fig. 1. Head MRI. Note right medial temporal pole hyper-intensity on FLAIR-weighted sequence suggestive of oedema (left) and areas of contrast enhancement in meninges and brain parenchyma (right).

right frontotemporal region. Treatment with venous acyclovir was started.

At the 4th day, the patient had no complaints, including headache nor fever. At the 12th day, CSF had 160 cell/mL (100% of lymphocytes), proteins 95 mg/dL, and PCR still positive for HSV-1 DNA (qPCR, iCyclear iQ). Due to these inflammatory characteristics of CSF, positivity of PCR and prominent imaging characteristics, acyclovir treatment was expanded up to 21 days.

At the 18th day, CSF had 43 cell/mL, proteins = 138 mg/dL, glucose = 45 mg/dL, RT-PCR did not find HSV-1 DNA. RT-PCR for ZIKV could not be repeated at the end of treatment. In 6 months of follow-up, the patient had no complaints.

Informed consent was obtained from the patient for the publication of this report.

Discussion

We presented a case of co-infection of ZIKV (confirmed by RT-PCR in serum and CSF) and HSV-1, in a patient presenting mental confusion and progressive headache. Complementary exams showed lymphocytic pleocytosis and high protein concentration in CSF, besides brain imaging and EEG revealing right temporal lobe abnormalities. In a follow-up of 6 months, a favourable clinical outcome was achieved.

Although in our setting it was impossible to determine the impact of each virus individually over clinical manifestations, we found seven cases of ZIKV-related meningoencephalitis or encephalitis (Table 1), some in co-infection with chikungunya and DENV. The neurological clinical presentation may range from headache to coma [2], and previous constitutional symptoms are frequently present, mainly fever, but may also be absent [3]. In this review, we did not observe a relation between admission symptoms and outcome. Likewise, neither CSF protein count nor pleocytosis are proportional to the severity of the case at admission/evolution. Predominance of neutrophils in CSF differential count may be associated to samples obtained at early (first to second day) phases of symptoms [2,4], becoming lymphocytic in sequence. Some groups opted for treatment with pulse of intravenous immunoglobulins [5], while others had chosen for observation/supportive therapy [3,6].

Reports showed that encephalitis/meningoencephalitis due to ZIKV generally has a good prognosis [5,6], but one fatal case was already reported [3]. Although previously considered a clinically inoffensive agent, when ZIKV was exposed to new populations in different environments, severe manifestations were noted and a priority status was set for epidemiological and clinical surveillance.

Actual data shows a neurotropism of this virus (biological plausibility), but causal relation for encephalitis still is lost [1]. Adult animal models suggest encephalitis and myelitis after subcutaneous injection of ZIKV, characterized by neuronal death and apoptotic bodies; likewise, there was white matter degeneration [7]. Studies suggest that ZIKV disease may cause dysfunctions in the blood-brain barrier [3] and also stimulate memory immune response in individuals who have been exposed to other related viruses (cross reactivity), such as DENV — a mechanism of antibody-dependent enhancement of ZIKV [1]. DENV is endemic in Pernambuco and may provoke an immune response against ZIKV, leading to additional or more severe injuries.

The co-infection of ZIKV and other viruses (HIV, Epstein-Barr, DENV, chikungunya viruses) has already been reported and related to neurological symptoms [4]. Interaction between ZIKV and herpes virus family (HSV-2) facilitated the infection of placental cells and increased cellular damage [8]. We hypothesize that in our case a temporally immune depression caused by ZIKV asymptomatic infection led to susceptibility to HSV-1 meningoencephalitis and/or a concurrent mechanism of direct or indirect injury in neuronal cells from both viruses in an exposed individual.

Our case has some limitations. We could not repeat the RT-PCR for ZIKV, we also did not perform immunological tests in CSF because of high DENV cross-reactivity. Although the manifestations described maybe only due to HSV-1 and sensibility and specificity of RT-PCR for ZIKV are unknown [9], various studies describe a positive RT-PCR as diagnosis method for infection in addition to positivity occurred in CSF and serum.

Conclusion

We conclude that ZIKV should be part of differential diagnosis in neuroinfection setting, especially for susceptible individuals in an epidemiological context — its clinical spectrum is large and yet unknown. Nevertheless, the presence of ZIKV may play roles in development of infections and powering neuronal damage by other viruses.

Author contribution

PSRA evaluated the patient, conceived the study and acquired data. MLMSJ performed literature review and drafted the article, MT and FGTS helped in data acquisition and reviewed critically this paper.

All authors approve this final version.

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Competing interests

None declared.

Ethical approval

Not required.

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