Rev Soc Bras Med Trop 51(3):347-351, May-June, 2018
doi: 10.1590/0037-8682-0327-2017

Short Communication

Neurologic manifestations in emerging arboviral diseases in Rio de Janeiro City, Brazil, 2015-2016

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Abstract

Introduction: Dengue has affected Rio de Janeiro City since the 1980s. The sequential Zika and chikungunya virus introductions during 2015 aggravated the health scenario, with 97,241 cases of arboviral diseases reported in 2015-2016, some with neurological disorders. **Methods**: Arbovirus-related neurologic cases were descriptively analyzed, including neurological syndromes and laboratory results. **Results**: In total, 112 cases with non-congenital neurologic manifestations (Guillain-Barré syndrome, 64.3%; meningoencephalitis, 24.1%; acute demyelinating encephalomyelitis, 8%) were arbovirus-related; 43.7% were laboratory-confirmed, of which 57.1% were chikungunya-positive. **Conclusions**: Emerging arbovirus infections brought opportunities to study atypical, severe manifestations. Surveillance responses optimized case identification and better clinical approaches.

Keywords: Neurologic disorder. Arbovirus. Emerging infectious disease.

Emerging mosquito-borne arboviral infections are widespread in the world, causing severe systemic and neurologic disorders that are virus- or immune-mediated[1]. Dengue has been endemic in Rio de Janeiro City (RJC) since the 1980s. In January 2015, the Zika virus (ZIKV) was introduced in the city, followed by the chikungunya virus (CHIKV) in November of the same year[2]. Other countries were affected earlier and reported congenital syndrome related to the ZIKV and other neurologic conditions, mainly Guillain-Barré syndrome (GBS), due to the ZIKV and CHIKV[3,4].

The first report on the increase in GBS occurrence originated from the French Polynesia in 2013, with a median time between acute ZIKV infection and neurologic signs and symptoms of 6 days, requiring supportive respiratory assistance in 1/3 of cases, not resulting in death[4,5]. In the Brazilian Northeast region, a GBS increase was detected, with 62% of cases reporting previous Zika virus-related symptoms[6]. El Salvador, Suriname, and Venezuela published similar case reports. There seems to be a greater risk of GBS when ZIKV infection occurs after a previous dengue infection[7].

Atypical presentation of CHIKV infection occurs as neurologic (meningoencephalitis, GBS, seizures, cerebellar syndrome), cardiovascular (myocardiopathy, pericarditis, heart failure, cardiac arrhythmia), eye, renal (nephritis and acute renal failure), and other (hepatitis, pancreatitis, adrenal insufficiency) disorders. Neurologic-related conditions cause death and disabilities following CHIKV infection. Neurologic symptoms after CHIKV infection onset occur within a shorter period than after Zika infection onset, like within 2 or 3 days, with seizures and mental confusion[8-10].

The gold-standard laboratory test for the ZIKV is the polymerase chain reaction (PCR) assay, but its relatively short presence in both serum and urine hampers its use[11], coupled with the fact that an antibody cross-reaction occurs with dengue. CHIKV infection can be diagnosed based on both PCR and serology results[7,12].

In this study, we describe the non-congenital neurologic disorders related to Zika virus and CHIKV, discovered through enhanced hospital-based surveillance reported both to the national disease reporting system [*Sistema de Informação de Agravos de Notificação* (SINAN)] and to the Arboviral Neurologic Manifestations Report Form, developed by the Health Surveillance Branch of RJC Health Secretariat. Besides reporting the presumptive case, blood and/or urine collection for dengue, Zika, and CHIKV (PCR and serology); cerebrospinal fluid (CSF); neuroimaging; and electroneuromiography results were informed by healthcare personnel.

The GBS case definition followed the Pan American Health Organization (PAHO) criteria[13]. Neurological manifestations

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Received 25 August 2017
Accepted 17 November 2017

other than GBS were classified based on laboratory and image results and previous presumptive arbovirus infections, with no other proven diagnoses.

From June 2015 to December 2016, 97,241 cases of dengue, ZIKV infection, and CHIKV infection were reported among the residents of RJC, of which 184 cases included neurologic manifestations (**Figure 1**). After a thorough investigation and discussion by a referral committee, 112 (72.7%) cases were considered related to arbovirus infection, with a rate of 1.3/1,000 cases. Previous exanthema was referred by 72.3%. The most common presentations were GBS (64.3%) and meningoencephalitis (24.1%), followed by acute demyelinating encephalomyelitis [(ADEM), 8%], transverse myelitis (2.7%), and optic neuritis (0.9%). The fatality rates were greater among

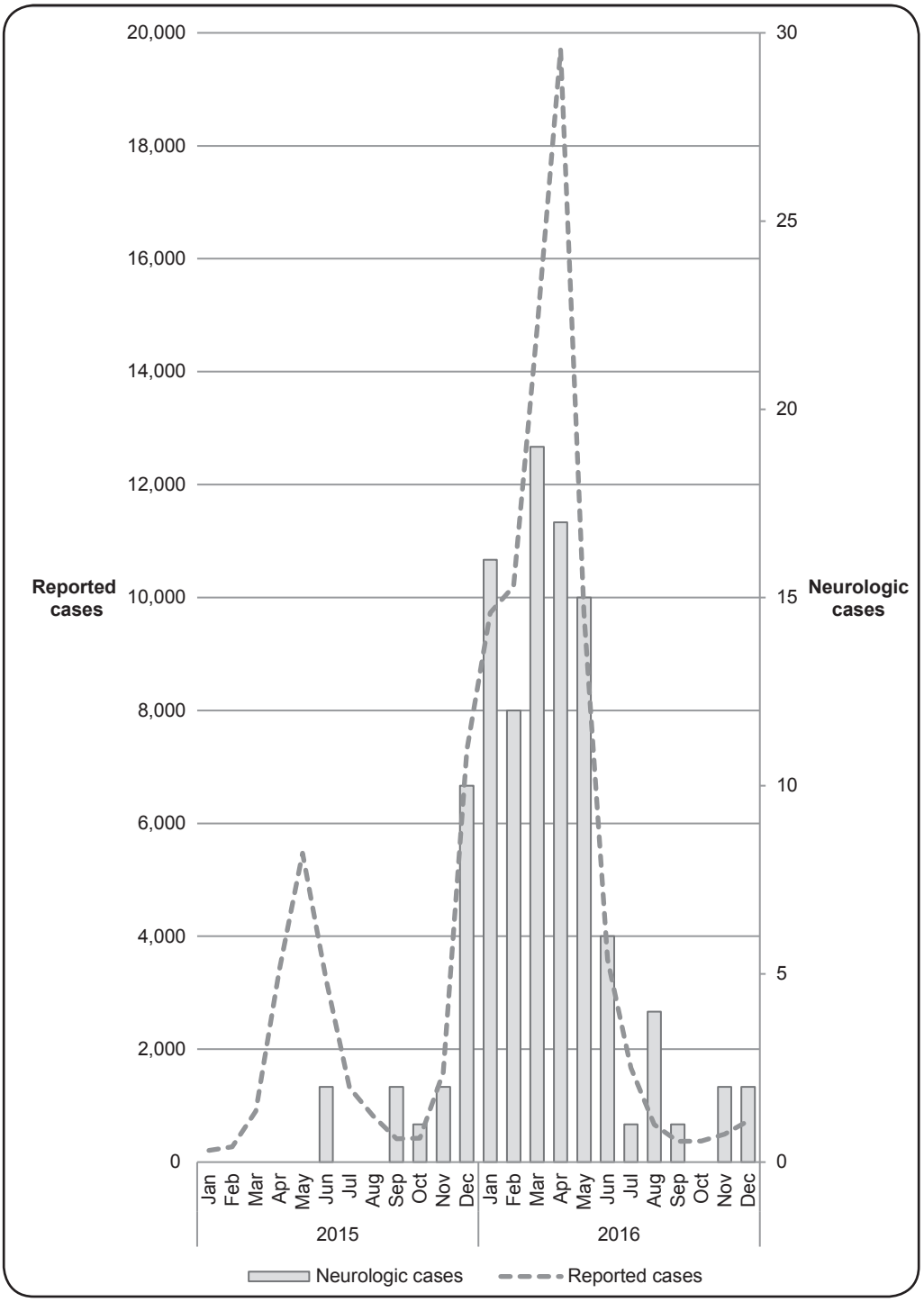

FIGURE 1: Distribution of reported cases of dengue, Zika virus, and chikungunya virus and cases involving neurologic manifestations in Rio de Janeiro City, 2015-2016. **SINAN**: *Sistema de Informação de Agravos de Notificação*; **RJC:** Rio de Janeiro City. **Source: SINAN** and **RJC**.

those with meningoencephalitis (37%), ADEM (22.2%), and GBS (16.%). The median age of the patients was 45.5 years (**Table 1**) and the male gender accounted for 53.6%.

CSF was analyzed in 76.8% of patients, with protein levels >40mg/dL in 76% and cell counts >10 cells/mL in 30.3%. Elevated CSF protein was present in 100% of transverse myelitis and optic neuritis, 77.3% of meningoencephalitis, 75% of GBS, and 66.7% of ADEM cases. Increased CSF cell counts occurred in 69.6% of meningoencephalitis, 66.7% of ADEM, and 6.8% of GBS cases.

Etiologic diagnosis was possible in 49 (43.7%) cases, with CHIKV infection being the most common (57.1%), followed by Zika virus infection (18.4%), dengue (14.3%), and dual infections like CHIKV infection/dengue (6.1%), Zika virus infection/dengue (2%), and Zika virus infection/CHIKV infection (2%) (**Table 2**). The presence of the Zika virus was confirmed based on PCR assay results; CHIKV based on PCR assay (21.4%), immunoglobulin M (IgM) serology (64.3%), and immunoglobulin G (IgG) serology (10.7%) results; and dengue only based on IgM serology results, which could not be distinguished from the Zika virus due to cross-reactivity and could be referred as a flavivirus infection[14].

The time lag between the viral infection and the neurologic signs and symptoms was greater among GBS (mean=12 and median=10 days) than among meningoencephalitis (mean=7 and median=5 days) cases. This was in agreement with other reports of CHIKV-related meningoencephalitis. The differentiation of neurological syndrome is very important for the management and prognosis of patients. Moreover, the time lag predicts the ability to yield an etiological diagnosis, because of the shorter Zika viremia and the lack of access to proper Zika virus serology in our setting.

Seizures and altered levels of consciousness were more frequent in meningoencephalitis, pointing to a greater encephalic involvement. The need for intensive care and Ig were more frequent for patients with GBS (63.8% and 55.1%, respectively), with ventilatory support more common for patients with ADEM (42.9%) and meningoencephalitis (40.7%).

Although the occurrence of neurological complications were less frequent in RJC than in other places, those cases attracted attention for their related morbidity and mortality, especially regarding meningoencephalitis presentation, as there is no specific recommended therapy besides clinical support[9,10]. Treatment with Ig or plasmapheresis is indicated only in patients with GBS, and Ig and intravenous methylprednisolone therapy in patients with myelitis[8,15]. However, the lethal outcome and need for intensive care contrasted with the benign evolution observed in other viral meningitis cases, reinforcing the great potential for brain damage of arboviruses. Although we noted greater health resource expenditures, like toward the use of intensive care units, mechanical ventilation, and advanced life support, in patients with GBS, more severe presentation of meningoencephalitis was observed, with a poor therapeutic response, seizures, and altered levels of consciousness, sometimes with brain death, as observed in other studies.

The case fatality rate of neurologic disorders in CHIKV infection varied from 6.1% to 20% in different studies in India[9,10]. In the French Polynesia, a case-control study did not observe any deaths[5]. In RJC, the case fatality rate for neurological complications, regardless of the causative arbovirus, was 21.4%. However, this rate was 50% in individuals older than 60 years of age. The high case fatality rate found herein was probably due to the occurrence of severe meningoencephalitis due to direct damage to the brain by the CHIKV[16].

In India, researchers reported a high frequency of neurologic complications after CHIKV infection (16.3%), mainly encephalitis (55.1%), almost exclusively in men (95.9%) and in the age group over 20 years old (97.9%)[9]. Our results were similar for the age group regarding CHIKV infection, except for the male gender prevalence, which were more common only among meningoencephalitis cases. The CSF findings were in accordance with those from India.

TABLE 1: Distribution of cases by clinical form and age group in Rio de Janeiro City, 2015-2016.

Age group (years)	ADEM	Meningo-encephalitis	Transverse myelitis	Optic neuritis	Guillain-Barré syndrome	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<10	2 (22.2)	3 (11.1)	0 (0.0)	1 (100.0)	3 (4.2)	9 (8.0)
10–19	0 (0.0)	4 (14.8)	0 (0.0)	0 (0.0)	3 (4.2)	7 (6.3)
20–29	1 (11.1)	4 (14.8)	0 (0.0)	0 (0.0)	7 (9.7)	12 (10.7)
30–39	1 (11.1)	3 (11.1)	0 (0.0)	0 (0.0)	12 (16.7)	16 (14.3)
40–49	0 (0.0)	1 (3.7)	1 (33.3)	0 (0.0)	17 (23.6)	19 (17.0)
50–59	2 (22.2)	2 (7.4)	2 (66.7)	0 (0.0)	15 (20.8)	21 (18.7)
60–69	1 (11.1)	5 (18.6)	0 (0.0)	0 (0.0)	7 (9.7)	13 (11.6)
70–79	1 (11.1)	4 (14.8)	0 (0.0)	0 (0.0)	5 (6.9)	10 (8.9)
≥80	1 (11.1)	1 (3.7)	0 (0.0)	0 (0.0)	3 (4.2)	5 (4.5)
Total	**9 (100.0)**	**27 (100.0)**	**3 (100.0)**	**1 (100.0)**	**72 (100.0)**	**112 (100.0)**

ADEM: acute demyelinating encephalomyelitis; **SINAN**: *Sistema de Informação de Agravos de Notificação*; **RJC:** Rio de Janeiro City. **Source:** SINAN and Arboviral Neurologic Manifestations Report Form, RJC.

TABLE 2: Distribution of cases with laboratory-proven etiology by clinical form in Rio de Janeiro City, 2015-2016.

Etiology	ADEM	Meningo-encephalitis	Transverse myelitis	Optic neuritis	Guillain-Barré syndrome	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Chikungunya	1 (25.0)	15 (71.4)	0 (0.0)	1 (100.0)	11 (52.4)	28 (57.2)
CHIKV/dengue	0 (0.0)	1 (4.8)	1 (50.0)	0 (0.0)	1 (4.8)	3 (6.1)
Dengue	0 (0.0)	1 (4.8)	1 (50.0)	0 (0.0)	5 (23.8)	7 (14.3)
Zika	3 (75.0)	3 (14.2)	0 (0.0)	0 (0.0)	3 (14.2)	9 (18.4)
Zika/dengue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	1 (2.0)
Zika/CHIKV	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Total	**4 (100.0)**	**21 (100.0)**	**2 (100.0)**	**1 (100.0)**	**21 (100.0)**	**49 (100.0)**

ADEM: acute demyelinating encephalomyelitis; **CHIKV**: chikungunya virus; **SINAN**: *Sistema de Informação de Agravos de Notificação*; **RJC:** Rio de Janeiro City.
Source: SINAN and Arboviral Neurologic Manifestations Report Form, RJC.

The dual circulation of the Zika virus and CHIKV in RJC in the period allowed us to identify a variety of neurologic disorders related to both arboviruses, as it was possible to describe the GBS case increase in the French Polynesia[17].

The emerging arbovirus infections brought an opportunity to study atypical and severe manifestations of those diseases. The quick surveillance response, coupled with alerting the healthcare teams, optimized the identification of cases and a better clinical approach, aimed at reducing mortality among those cases.

Our laboratory performance was a clear limitation in this study. We would have benefited from a readily available serology method for the Zika virus. Hopefully, we will soon be able to tackle this problem of cross-reactivity between dengue and the ZIKV, with the production and distribution of IgM- or non-structural protein 1-based tests, including rapid tests, in new cases of Zika virus infections or dengue epidemics.

Ethical considerations

The Institutional Ethics Review Board of the RJC Health Secretariat approved the study under the number CAAE 63971716.3.0000.5279.

Conflict of interest

The authors declare that there is no conflict of interest.

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