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Short Communication

Neurological manifestations of dengue in Central Brazil

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Abstract

Introduction: The incidence of dengue has increased throughout the 2000s with a consequent global increase in atypical clinical forms**. Methods:** This study reports a series of cases of neurological dengue out of 498 confirmed cases of laboratory dengue in Goiânia, Brazil. Cases were confirmed based on viral RNA detection via polymerase chain reaction or IgM antibody capture. **Results:** Neurological symptoms occurred in 5.6% of cases, including paresthesia (3.8%), encephalitis (2%), encephalopathy (1%), seizure (0.8%), meningoencephalitis (0.4%), and paresis (0.4%). DENV-3 was the predominant circulating serotype (93%). **Conclusions:** We reported dengue cases with neurological manifestations in endemic area.

Keywords: Dengue. Neurological. Encephalopathy.

Dengue is an acute febrile infectious disease of viral etiology that can progress to severe disease and shock[1,2]. The incidence of dengue has increased throughout the 2000s with a consequent global increase in atypical clinical forms[3]. Several studies have described neurological symptoms among the unusual viral manifestations[4-7].

We previously reported clinical and laboratory findings related to dengue severity and outcome in adult patients recruited during the epidemic period of 2005 to 2006 in Central Brazil[8]. In the present study, we focused on neurological findings in this large cohort of patients with confirmed dengue infections.

This study reports findings from a series of cases with neurological manifestations of dengue out of 498 confirmed cases of laboratory dengue in the City of Goiânia in Midwestern region of Brazil, from January 2005 to July 2006. Patients were enrolled from the major referral center for dengue, the Hospital of Tropical Diseases, as well as from private hospitals and primary healthcare units. The follow-up duration for hospitalized patients was defined from the first medical visit to the discharge date. The follow up duration for outpatients was measured as the interval between the first and second blood collections during the convalescent phase (~15 days).

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We prospectively collected baseline demographic and clinical information from all patients using a standard study protocol. Data on age, sex, previous dengue episodes, and key clinical symptoms (hypotension, intense abdominal pain, and bleeding) were recorded. Clinical data and laboratory tests were recorded daily in patient files and reviewed by the clinical coordinator at the end of the follow-up. Dengue cases were confirmed by: a) isolation of dengue virus (DENV)[9] or detection of viral ribonucleic acid (RNA) by multiplex- or real-time polymerase chain reaction (qPCR)[10]; or b) immunoglobulin M (IgM) antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) of the first or second paired blood samples[11]. Confirmatory tests were performed at the State Central Laboratory and the University of São Paulo.

Patients with clinical symptoms compatible with a diagnosis of dengue and neurological manifestations were included in this study. Neurological manifestations were defined as the presence of one the following symptoms: paresthesia, paresis or plegia, encephalopathy (defined as altered level of consciousness, not attributable to hypotension or electrolyte disturbance), encephalitis, intracranial hypertension syndrome or meningoencephalitis, meningeal irritation, or seizure. Cerebrospinal fluid (CSF) was analyzed when the procedure was not contraindicated. IgM and molecular biology tests for dengue were performed on CSF collected from suspected cases. The brain tissue from patients who died was sent for immunohistochemistry and molecular biology analyses. Patients with a history of neurologic illness, use of illicit drugs, and pre-existing psychiatric illness were not included in the study.

Statistical analysis was performed using standard measures of central tendency; dispersion was applied to continuous variables and percentage distributions were calculated for categorical variables. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA).

Of 710 suspected cases of dengue, 498 (70.1%) were laboratory-confirmed. Of the 498 confirmed cases, 210 (42%) were compatible with dengue fever, 264 (53%) with dengue warning signs, and 24 (5%) with severe dengue. Neurological symptoms were present in 5.6% (28/498) of cases. Neurological manifestations included paresthesia (3.8%), encephalopathy (1%), seizures (0.8%), meningoencephalitis (0.4%), paresis (0.4%), and encephalitis (0.2%). Paresthesia, occurring in 12 (54.5%) patients, was the most frequent symptom among those patients with neurological symptoms of dengue. DENV-3 was the predominant serotype in the 28 neurological cases (5/28) and in the total 498 dengue cases (93%). Of the 28 neurological dengue cases, 20 (72%) were hospitalized. Most patients were female (22/498, 78.6%), and the average age was 34 years [standard deviation (SD) = 15.5], ranging from 14 to 71 years of age. The fever duration averaged 6.2 days (SD = 3.5), ranging from 1 to 16 days. The two patients who had 15 and 16 days of fever had negative cultures of blood and urine, and serologies for herpes, toxoplasmosis, cytomegalovirus, Epstein Barr, HIV, and viral hepatitis.

Among the 5 patients with encephalopathy, 2 had symptoms that included mental confusion, liver failure, and cerebrospinal fluid (CNS) bleeding; magnetic resonance imaging (MRI) examination showed a laminar subdural hematoma in the left cerebral hemisphere, and CSF analysis were normal. One patient with neuropsychiatric symptoms was also observed, characterized by behavioral disorder during the acute phase of the disease. Results of CSF analysis were normal and CSF PCR was negative for dengue. The single case of encephalitis occurred in a 71-year-old male patient, who developed mental confusion, fever, and paresis of the left lower limb after 15 days of clinical symptoms consistent with classic dengue fever; MAC-ELISA of blood samples was positive for dengue, but CSF samples tested by IgM and PCR were negative for the virus. The findings from computed tomography (CT) without contrast were normal; electroneuromyography showed amended, continuous, severe, and focal right frontotemporal cortical-subcortical dysfunction.

Neurological cases were detected in 43% of severe dengue cases, and 36% of cases of dengue with warning signs. **Table 1** shows the distribution of patients diagnosed with dengue by sex, age, fever duration, classification of cases according to the World Health Organization (WHO) classification 2009, neurological manifestations, results of serological and virological tests, and clinical outcomes.

The mortality rate in patients with neurological symptoms was 7% (2/28). One female patient was 15 years old and had meningoencephalitis; CSF analysis showed 76 leukocytes/ μL, 80% mononuclear cells, 64mg/dL glucose, and 127mg/dL total protein. CT scans revealed sulci effacement and signs of intracranial hypertension. MAC-ELISA and PCR analysis of brain tissues showed positive results for dengue virus serotype 3 (DENV-3). The other patient who died was a 41-year-old woman; on the tenth day, she was admitted to the hospital with tonic-clonic seizures and acute liver failure. PCR tests of blood and viscera samples were positive for the DENV-3. CSF analysis was contraindicated owing to thrombocytopenia.

To conclude, we detected neurological dengue in 5.6% of cases among patients recruited from the major referral hospital unit for dengue, general hospitals, and basic health units. In this study, most patients had mild neurological manifestations; 67.9% of cases presented with paresthesias. Data from the Brazilian information system described in Rondônia, a state in the Northern region of Brazil, an outbreak of dengue with neurological symptoms in 2005; their 28 cases, the most frequent manifestation was difficulty to walk, followed by paresthesia[12]. This symptom was the most relevant among our cases. Other studies do not describe paresthesia as a neurological manifestation,[13] perhaps because it is a symptom and not a disease entity. Nonetheless, paresthesia is a classic symptom of neuropathy[14]. In this study, we did not describe the paresthesias as neuropathy because they were not confirmed by detailed neurological examination or electromyography.

Few studies in the literature have claimed a relationship between viral serotype and neurological complications, probably because many of these manifestations occur late, and the relatively short viremia makes it difficult to recover viral type from patient samples. DENV-3 is globally associated with neurovirulence, and has been cited as a probable predictor of severe clinical manifestations[10].

In our study, we did not observe patients with Guillain-Barré syndrome, although there have been several reports in Brazil and others regions[15]. This can be explained by the short time for patient follow-ups in this study, which likely reduced the detection of post-neurological viral cases, such as Guillain-Barré syndrome and acute disseminated encephalomyelitis. Others authors have described cases of Guillain-Barré in patients with a history of dengue, confirming the relationship of this endemic disease in our country, with potentially severe cases[13]. The limitations of this study include a lack of routine ancillary tests, such as cranial CT, MRI, and electroneuromyography, at most of the hospitals in this study. This study was part of a cohort of dengue cases, and the neurological symptoms could have recorded more information, such as duration of neurological symptoms, the Glasgow scale for assessment of impairment of conscious level in response to defined stimuli, and results of clinical neurological examinations, and could have included longer follow-ups to detect cases with late manifestations.

Excluding the two deaths in the study, no patient remained with sequelae, even in the other severe cases that included encephalopathy and meningoencephalitis. Previous studies have reported variable fatality rates. A cohort in Vietnam reported no fatalities[4], while a study in Jamaica reported a 3.7% mortality rate[15]. Carod-Artal et al. suggest that the severity of encephalopathy depends on its causative factors, including the main causes such as liver failure, electrolyte imbalance, and shock[6].

TABLE 1

Neurological manifestations of dengue in a case series of patients recruited in Central Brazil, 2005-2006.

Patient/ number	Sex	Age (years)	Fever/ days	2009 WHO classification	Neurological/ manifestation	MAC-ELISA	Virus isolation	Molecular test	Outcome
1	F	52	4	Dengue	Paresthesia/hands	Pos	Neg	DENV-3	Cured
2	F	3	5	Dengue	Paresthesia/face	Pos	Neg	---	Cured
3	F	35	6	DWS	Paresthesia/UL+LL	Pos	Neg	---	Cured
4	M	36	3	Severe	Paresthesia/hands	Pos	DENV-3	DENV-3	Cured
5	F	17	5	DWS	Paresthesia/lips	Pos	Neg	---	Cured
6	F	56	8	Severe	Encephalo	Pos	Neg	---	Cured
7	F	24	5	Severe	Paresthesia/UL+LL	Undeter.	DENV-3	DENV-3	Cured
8	F	20	6	DWS	Paresthesia/LL	Pos	Neg	---	Cured
9	F	31	9	DWS	Paresthesia/LL	Pos	Neg	---	Cured
10	F	36	7	DWS	Paresthesia/hands	Pos	Neg	---	Cured
11	F	29	7	Dengue	Paresthesia/hands	Pos	Neg	---	Cured
12	F	47	6	Dengue	Paresthesia/hands	Pos	Neg	---	Cured
13	F	41	10	Severe	Encephalo /Seizures	Pos	Neg	DENV-3	Death
14	F	45	6	Dengue	Paresthesia/LL	Pos	Neg	---	Cured
15	F	25	7	Severe	Paresthesia/LL	Pos	Neg	---	Cured
16	F	17	8	Severe	Meningoenceph	Pos	Neg	---	Cured
17	F	19	1	DWS	Paresthesia/feet	Pos	Neg	---	Cured
18	F	54	7	Dengue	Paresthesia+Paresis	Pos	Neg	---	Cured
19	F	27	6	DWS	Paresthesia	Pos	Neg	---	Cured
20	F	34	7	DWS	Paresthesia/LL	Pos	Neg	---	Cured
21	M	68	10	Severe	Encephalo	Pos	Neg	---	Cured
22	F	39	3	DWS	Paresthesia/UL+LL	Pos	Neg	---	Cured
23	M	14	5	Severe	Encephalo	Pos	Neg	---	Cured
24	M	71	15	Severe	Encephalitis/Paresis	Pos	Neg	---	Cured
25	F	38	7	DWS	Paresthesia/hands	Pos	Neg	---	Cured
26	F	15	16	Severe	Meningoenceph	Pos	Neg	DENV-3	Death
27	M	24	1	Severe	Encephalo/Seizures	Pos	Neg	---	Cured
28	F	18	3	Severe	Seizures	Pos	Neg	---	Cured

WHO: World Health Organization; **MAC-ELISA:** immunoglobulin M (IgM) antibody-capture enzyme-linked immunosorbent assay; **F:** female; **M:** male; **DENV:** dengue virus; **DWS:** dengue warning sign;; **LL:** lower limbs; **UL:** upper limbs;**:**; **Severe:** severe dengue; **Encephalo:** encephalopathy; **Meningoenceph:** meningoencephalitis.; **Pos**: positive; **Neg**: negative

In endemic regions, dengue should be considered as a diagnosis in all cases with neurological manifestations in the course of acute febrile illnesses.

Ethical considerations

The study protocol was approved by the Ethics Committee in Human and Animal Medical Research/HC/UFG, number 001/02. Signed informed consent was obtained from all participants or their legal guardians.

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Conflicts of interest

The authors declare that have no conflicts of interest.

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