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Dengue infection: neurological manifestations and cerebrospinal fluid (CSF) analysis

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Abstract

Neurological manifestation is considered a rare complication of dengue infection. Neurological and cerebrospinal fluid (CSF) findings of 13 patients with dengue infection were studied. Seven patients had encephalitis, two had myelitis and four showed Guillain-Barré syndrome (GBS). No alteration in CSF was found from 57% of those with encephalitis. Patients with GBS and myelitis showed a CSF–blood barrier dysfunction. The differences in the CSF may be related to the location of the lesion and multiple mechanisms of the disease in the nervous system.

Keywords: Dengue infection; Neurological manifestations; CSF; Viral encephalitis; Myelitis and Guillain-Barré syndrome

1. Introduction

Dengue infection is one of the most common arboviruses in the world, recognized in more than 100 countries. It was estimated that a total of 50–100 million cases of dengue fever and about 250,000–500,000 cases of dengue hemorrhagic fever occur each year [1]. Dengue infection is caused by four different virus serotypes and is transmitted by the mosquito *Aedes aegypti*. It causes either a nonsymptomatic infection or two different clinical pictures: the dengue fever (DF) and/or dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). The former is characterized by an acute febrile illness, with headache, maculopapular rash, orbital and joint pains, thrombocytopenia and leucopenia that occur after 2–7 days of incubation [2]. The main symptoms characteristic of DHF/DSS include acute fever, hemorrhagic manifestations, thrombocytopenia, hemoconcentration and a tendency to develop shock.

In recent years, unusual manifestations of dengue infection, including neurological syndromes, have been described [3]. Sanguansermsri et al. first reported this association in 1976. Since then, encephalopathy, myelitis, GBS and cranial nerve palsies have been recognized as clinical manifestations of dengue infection [4].

We report an evaluation of 13 IgM seropositive patients for dengue who showed neurological manifestations in the course of the infection. CSF samples were analyzed in all cases. Clinical and laboratory findings were assessed to give distinct profiles. In addition, we report a case of a 71-year-old man exhibiting myelitis associated with dengue infection and intrathecal synthesis of IgG antibodies.

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2. Subjects and methods

2.1. Subjects

The current study involved 13 patients with clinical diagnosis and who were IgM seropositive for dengue infection, according to guidelines published by the World Health Organization [5]. All patients presented neurological symptoms and had their CSF and blood collected at the same time, from January to May of 2002. The samples were analyzed in a reference CSF laboratory (Neurolife Laboratory) located in Rio de Janeiro City.

The retrospective data that were collected included age, sex, time of neurological symptoms after the onset of the fever period (acute infection) and the neurological manifestations. Only two patients had a history of previous dengue infection (cases 3 and 7). Encephalitis was characterized by the presence of low level of consciousness, focal neurological signs (nystagmus, aphasia, pyramidal or cerebellar syndrome), and focal and generalized seizures. In all patients with encephalitis, cranial computed tomography (CT) was performed. Magnetic resonance image (MRI) of the spinal cord was also done in one patient with encephalitis and in those with myelitis. GBS patients were defined as having acute rising paraparesis and a demyelinating polyneuropathy on the electromyography [6]. The study protocol was approved by the Brazilian Committee Board.

2.2. Laboratory assays

Total and differential cytology counts, determination of protein and glucose levels and enzyme-linked immunosorbent assay (ELISA) for detection of IgM (Bio-Manguinhos, Rio de Janeiro, Brazil) dengue antibodies were performed in CSF samples from all 13 patients. We diluted the CSF sample (1:2) and the serum (1:100) according to the manufacturer's recommendation. CSF samples were also tested for syphilis, HTLV-I, herpes simplex, cytomegalovirus and HIV1/2 infections.

The albumin and IgG concentrations were determined in serum and CSF by immunoprecipitation nephelometry in

Table 1
Neurological characteristics of dengue patients

Cases	Diagnosis	Sex	Age (years)	Latency time	Dengue symptoms	Neurological characteristics	Sequelae
1	Encephalitis	F	56	7 days	Fever, vomits, cutaneous rash	Somnolence, aphasia, evolving to seizures, tetrapareses, bilateral spasms	Spasms
2	Encephalitis	F	55	12 days	Fever, headache, cutaneous rash, nausea	Confusion, psychomotor agitation, fogertfulness, generalized tonic–clonic seizure	No sequelae
3	Encephalitis	F	30	14 days	Vomit, cutaneous rash, myalgia, headache. Second infection: same symptoms but more intense. Two dengue infections (interval of 23 days between them)	Confusion, sphincteric incontinence, tetrapareses, ataxia, mioclonus, aphasia, coma	Brain death
4	Encephalitis	F	56	7 days	Fever, myalgias	Pulsatile and holocrania headache, confusion	No sequelae
5	Encephalitis	F	31	7 days	Fever, vomits	Confusion	No information
6	Encephalitis	F	11	10 days	Fever, cutaneous rash, headache	Ataxia, dysarthria, headache tetrapareses	No sequelae
7	Meningo encephalitis	M	60	4 days	Myalgias, fever dengue encephalitis 7 years ago	Confusion, aphasia, ataxia, meningeal irritation, seizures	No sequelae
8	GBS	M	79	14 days	Fever, myalgias	Parapareses and lumbar pain	No information
9	GBS	F	40	22 days	Fever, vomits	Ascending parapareses, paresthesias, facial diplegia	No information
10	GBS	F	52	17 days	Myalgias, fever, cutaneous rash	Ascending parapareses evolving to tetrapareses	No sequelae
11	GBS	F	51	30 days	Fever, cutaneous rash	Ascending parapareses evolving to tetrapareses, facial diplegia	No information
12	Myelitis	M	71	7 days	Nauseas, fever, dizziness	Abrupt onset of parapareses evolving to paraplegia, sensitive level (T6) and sphincteric retention	Sequelae: parapareses
13	Myelitis	F	40	14 days	Fever, myalgias	Parapareses, sphincteric retention	Sequelae: sphincteric retention