Journal of Clinical Virology 72 (2015) 146–151

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Central nervous system and muscle involvement in dengue patients: A study from a tertiary care center

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ARTICLE INFO

Article history:
Received 24 June 2015
Received in revised form 26 August 2015
Accepted 31 August 2015

Keywords:
Dengue
Myopathy
Encephalopathy
Encephalitis
Transverse myelitis
Serotype
Outcome

ABSTRACT

Background: Neurological involvement in dengue virus (DENV) infection is being increasingly reported. There is paucity of studies evaluating the relative frequency of central nervous system (CNS) and muscle involvement in dengue.
Objectives: To evaluate the frequency and prognosis of neurological and muscle involvement in dengue, and correlate these with dengue subtypes.
Study design: Consecutive dengue patients were included, and their clinical features, laboratory investigations and cerebrospinal fluid (CSF) findings were recorded. Cranial MRI was done in unconscious patients and electromyography and nerve conduction study in patients with flaccid weakness. Patients were categorized into encephalopathy, encephalitis, immune mediated and dengue associated muscle dysfunction (DAMD). Outcome at 1 month and its predictors were evaluated.
Results: 116 patients aged 5–70 years were included; 82 had dengue fever (DF), 18 had dengue hemorrhagic fever (DHF), and 16 had dengue shock syndrome (DSS). Neurological manifestations were present in 92 (79%); encephalopathy in 17 (15%), encephalitis in 22 (19%), transverse myelitis in 1 (1%) and DAMD in 52 (45%) patients. Central nervous system (CNS) involvement was commoner in DHF/DSS compared to DF (44% vs 26%). 10 patients with CNS involvement died versus 1 with DAMD. The patients in the CNS group had more frequent hypotension, renal dysfunction and respiratory failure compared to the DAMD group, and had worse outcome. DENV2 and DENV3 were the commonest serotypes, but serotypes did not differ between CNS and DAMD groups.
Conclusions: DAMD is commoner than CNS involvement in dengue. CNS involvement however, is associated with more serious illness and predicts poorer outcome.

1. Background

Dengue is a mosquito borne disease with widespread impact causing 100 million symptomatic cases and 25,000 deaths annually. The clinical spectrum of dengue ranges from asymptomatic infection and mild nonspecific fever to classic dengue fever (DF) and severe dengue which includes dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [1]. The dengue virus (DENV) is an RNA flavivirus with 4 closely related serotypes (DENV1–4). Infection by DENV confers lifelong immunity against the same serotype, but offers only partial and transient (2–3 months) cross-protection against other serotypes. Secondary heterotypic DENV infection carries an increased risk of severe dengue [2]. India is endemic for both DF and severe dengue as transmission is sustained during the inter-epidemic period in large areas [3].

Neurological manifestations of DENV infection include encephalopathy, encephalitis, immune mediated neurological syndromes and muscle involvement [4]. Recently, the WHO has included central nervous system (CNS) involvement in the criteria for defining severe dengue infection [1]. CNS involvement in dengue is attributed to shock, hypoxia, hyponatremia, liver or kidney failure or intracranial bleeding [5,6]. We have previously reported the spectrum of dengue infection in 17 patients; with

Abbreviations: CSF, cerebrospinal fluid; DAMD, dengue associated muscle dysfunction; DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; DENV2, dengue serotype 2; DENV3, dengue serotype 3; RNA, ribonucleic acid; DENV, dengue virus; PNS, peripheral nervous system; GCS, Glasgow Coma Scale; MRC, Medical Research Council; mRS, modified Rankin Scale; PT, prothombin time; APTT, thromboplastin time; CK, creatine kinase; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; IgM, immunoglobulin M; IgG, immunoglobulin G.

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http://dx.doi.org/10.1016/j.jcv.2015.08.021
1386-6532/

encephalitis at one end and muscle dysfunction at the other, with overlapping features in between [5,7]. Most studies on neurological involvement in dengue have focused on encephalitis [8,9], encephalopathy [6], transverse myelitis [10], acute disseminated encephalomyelitis [11] and optic neuritis [12]. Peripheral nervous system (PNS) manifestations of dengue include peripheral neuropathy, Guillain-Barre syndrome [13], myositis [14] and transient muscle dysfunction [15]. It is not clear whether CNS involvement in dengue is a function of dengue severity or dengue serotype.

2. Objectives

The present study has been undertaken to evaluate the clinical spectrum of neurological involvement in dengue infection, the predictors of outcome and the relative frequency of central and peripheral nervous system involvement in dengue, and correlate these with dengue subtypes, dengue serotypes and laboratory findings.

3. Study design

3.1. Patient selection and evaluation

Patients with DENV infection admitted between 2003 and 2014 to the neurology service of a tertiary care teaching institute in Northern India were retrospectively analyzed. The diagnosis of dengue virus infection was based on history of fever with positive NS1 antigen and/or IgM dengue antibody in the serum. A detailed history including fever, headache, skin rash, bleeding manifestations, altered sensorium, seizure and focal weakness was taken. The clinical examination included pulse, blood pressure, edema, conjunctival congestion, jaundice, petechiae, lymphadenopathy, hepatosplenomegaly, ascites, pleural effusion, and chest rales. Consciousness was assessed by the Glasgow Coma Scale (GCS). Muscle tone, power and tendon reflexes were noted. Co-ordination and sensations were tested in those who could cooperate.

3.2. Investigations

Hemoglobin, hematocrit, complete blood counts, prothrombin time (PT), activated partial thromboplastin time (APTT), blood sugars, electrolytes, blood urea nitrogen, serum creatinine, bilirubin, transaminases and creatine kinase (CK) were measured. All the patients underwent an electrocardiogram, chest radiograph, and abdominal ultrasonography.

Dengue IgM, IgG and NS1 antigen were tested in serum by ELISA {Panbio ELISA (Queensland, Australia), and Bio-red (Marnnes-la-Coquette, France)}. CSF IgM ELISA for Japanese encephalitis virus was tested, and serum IgM ELISA for leptospira and chikungunya was carried out. Enterovirus infection was ruled out by CSF PCR. Primary or DENV infection was diagnosed if IgM/IgG ratio was more than 1.32, and secondary if below 1.32 [16]. Dengue serotyping was done in few patients (Lanciotti et al. [17].

3.3. Dengue subtypes

Patients were classified on the basis of clinical features into dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

3.4. Neuroimaging

Cranial MRI was done in the patients with impaired consciousness, using 3-Tesla MRI (SIGNA GE Medical system, Wisconsin, USA). T_1, T_2, FLAIR and DWI sequences were obtained. The nature of signal alterations and their locations were noted. In critical patients however, only cranial CT scan was obtained.

3.5. Categorization of neurological findings

Based on neurological and laboratory findings patients were categorized as follows:

3.5.1. Dengue encephalitis

Dengue encephalitis was defined if there was altered sensorium (GCS score ≤ 14), focal signs or seizures, with CSF pleocytosis or DENV-RNA, IgM or NSI antigen in the CSF, in the absence of other neuro-invasive pathogens.

3.5.2. Dengue encephalopathy

Dengue encephalopathy was clinically similar to dengue encephalitis, except for a normal CSF study, and associated metabolic abnormalities (hyponatremia, acidosis, liver or kidney dysfunction), prolonged shock, disseminated intravascular coagulation or intracranial hemorrhage.

3.5.3. Immune-mediated neurological syndrome

This included immunologically mediated neurological dysfunction (acute disseminated encephalomyelitis, acute transverse myelitis, optic neuritis, Guillain-Barre syndrome or mononeuropathy) 2–4 weeks after documented dengue virus infection.

3.5.4. Dengue associated muscle dysfunction

Raised serum CK levels with or without muscle weakness was defined as dengue associated muscle dysfunction (DAMD).

3.6. Outcome

Death and its immediate cause during hospital stay were noted. In the others, outcome was recorded after 1 month, and categorized into good outcome (mRS 0–2) and poor outcome (mRS 3–6).

3.7. Statistical analysis

Patients were categorized into DENV infection with and without neurological manifestations, central and peripheral neurological involvement, and encephalitis and encephalopathy, and their clinical and laboratory characteristics were compared using the Fisher Exact test for categorical and independent '*t*' test for continuous variables. The frequencies of neurological manifestations in different clinical subtypes of dengue were compared using the Fisher Exact test, which was also used to compare the severity of disease in dengue serotypes, as well as primary versus secondary dengue infection. The predictors of death were evaluated using univariate followed by multivariate regression analysis, including variables with p value of <0.1. Two-tailed p values <0.05 were considered significant. All statistical analyses were done using SPSS version 16 software.

4. Results

There were 137 serologically confirmed dengue patients. Results of the present study are based on 116 patients, because 21 had serological co-infection (with Japanese encephalitis in 9, scrub typhus in 5, leptospira in 4 and chikungunya in 3 patients), and were excluded. Patients' ages ranged between 5 and 70 (median 32) years. 26 (22%) were females and 86 (74%) lived in cities. All patients had fever (99–103 °F). Headache was present in 92 (79%) patients, vomiting in 76 (66%), diarrhea in 10 (9%), abdominal pain in 34 (29%), myalgia in 86 (74%), joint pains in 8 (7%) and retro-orbital pain in 10 (9%) patients. Thirty nine (34%) patients had skin