International Journal of Contemporary Pediatrics
Shokeen P et al. Int J Contemp Pediatr. 2018 May;5(3):983-987
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20181526

Original Research Article

Neurological complications in Dengue fever

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Received: 08 February 2018
Accepted: 07 March 2018

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ABSTRACT

Background: Neurological involvement in dengue was previously observed as an encephalopathy mainly due to prolonged shock, hyponatremia and liver failure. Recently, direct neurotropic potential of the virus has been recognized. This study was performed to record the neurological complications in children with dengue infection.
Methods: A prospective, cross-sectional study was conducted in 315 consecutive pediatric cases of dengue fever to record the neurological complications and perform detailed clinical evaluation and laboratory assessment. These patients were admitted in the pediatric ward or ICU of the Department of Pediatrics of a tertiary care teaching hospital located 50 km from Jaipur city amidst rural surroundings from 1st January 2016 till 31st October 2017. Appropriate statistical analysis was carried out using SPSS software version 22.0.
Results: The neurological complications due to dengue fever was observed in 30 cases (9.5%). The most common symptoms were headache (73.3%, n = 22), altered sensorium (73.3%, n = 22), seizure (73.3%, n = 22), besides fever (100%, n = 30) and vomiting (56.6%, n = 17). The common signs were exaggerated DTR (73.3 %, n = 22), papilloedema (20%, n = 6) and muscle tenderness (13.3%, n = 4) besides hepatomegaly (100%, n = 30), and facial puffiness (66.6%, n = 20). The most commonly observed neurological complications were encephalopathy (53.3%, n = 16), encephalitis (n = 7, 23.3%), myositis (13.3%, n = 4), acute disseminated encephalomyelitis (3.3%, n = 1), hemiplegia with facial palsy (3.3%, n = 1) and intracranial hemorrhage (3.3%, n = 1). Mortality was observed in 3 cases (10%).
Conclusions: Neurological complications of dengue in children are relatively uncommon. However, awareness is required for prevention, early recognition, and timely therapeutic intervention to prevent further complications and mortality.

Keywords: Children, Dengue, Neurological, Rural

INTRODUCTION

Dengue fever is the most rapidly spreading mosquito-transmitted arboviral infection in tropical and subtropical countries. Around 3.9 billion people live in 128 dengue endemic countries and cases have increased from 2.2 million in 2010 to 3.2 million in 2015.[1] Dengue infection is caused by any of the four antigenically related distinct serotypes. The clinical presentation of dengue infection ranges from mild undifferentiated febrile illness to life-threatening situations like dengue with warning signs and severe dengue. Observations indicate that clinical profile of dengue is changing, and neurological manifestations are being reported frequently. Encephalopathy and encephalitis, varying between 0.5-6.2%, are the most common neurological manifestations of dengue.[2]

Keeping in view the significant morbidity and mortality associated with dengue infection and also the fact that there is a paucity of studies conducted in rural areas of

our country, this study was designed to record the neurological manifestations due to dengue fever in children admitted in a medical college hospital situated in a rural area.

METHODS

A prospective, cross-sectional study was conducted in 315 consecutive cases of dengue fever admitted in the Pediatric Ward of the Department of Pediatrics of a tertiary care teaching hospital located 50 km from Jaipur city amidst rural surroundings from 1st January 2016 till 31st October 2017. Convenience sampling technique was adopted owing to epidemic nature of disease and time constraints.

Children of age group 1-18 years with signs and symptoms suggestive of dengue fever and with positive serological tests: NS1 antigen, IgG and IgM antibodies specific for dengue were included in this study. Children with negative serological tests for dengue and refusal from parents were excluded.

A detailed clinical evaluation including history taking, clinical examination and relevant laboratory tests-complete blood counts including hematocrit, blood sugar, liver function tests, renal function tests, prothrombin time, activated partial thromboplastin time, electrolytes, ECG, chest radiography and ultrasonography of abdomen was performed in all patients. NS1antigen, IgG and IgM antibodies specific for dengue were qualitatively detected by commercially available kits based on rapid solid phase immunochromatography. All study subjects were categorized according to the 2009 WHO classification for dengue fever as:

- Dengue without warning signs
- Dengue with warning signs
- Severe dengue[3]

All neurological signs and symptoms as observed in the study subjects at the time of admission or during hospitalization were recorded in a pre-tested proforma. Magnetic resonance imaging or computerized tomography of the brain and spinal cord along with a detailed cerebrospinal fluid analysis was performed in patients suffering from encephalopathy/encephalitis/ Acute disseminated encephalomyelitis. S. CPK levels, electromyography (EMG), muscle biopsy, EEG, nerve conduction velocity (NCV) and fundus examination were performed as required. For the purpose of this study, the following diagnostic criteria were considered besides a corroborating systemic examination supporting dengue infection and detection of NS1, IgG and IgM antibody for dengue in serum sample.

Dengue encephalitis

- Reduced consciousness confirmed by evaluating modified Glasgow Coma scale and not explained by acute liver failure, shock, electrolyte disturbance, intracranial haemorrhage.
- Presence of associated features like seizures, vomiting, focal neurological deficits

Dengue encephalopathy

- Reduced consciousness confirmed by evaluating modified Glasgow Coma scale and associated with prolonged shock/acute liver or renal failure/electrolyte disturbances like hyponatremia, metabolic acidosis/intracranial haemorrhage.

Dengue myositis

- Varying degree of myalgia associated with muscle tenderness on stretching, proximal muscle weakness, hypotonia
- Presence of elevated creatine phosphokinase levels.

Acute disseminated encephalomyelitis

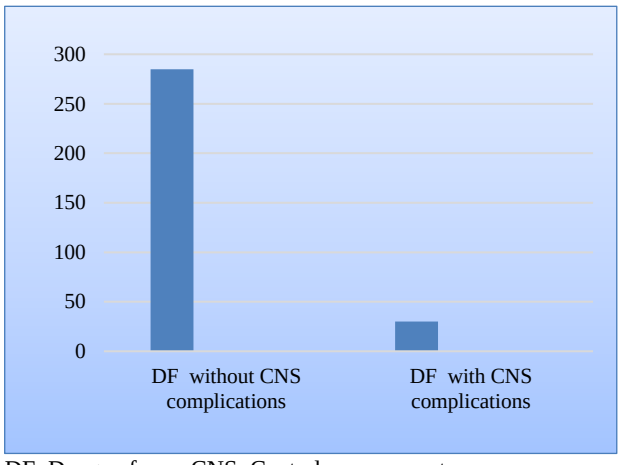
- Appearance of fever, seizures and altered sensorium during convalescent phase of dengue infection.
- Presence of white matter lesions on T2-weighted images in the centrum semiovale, corona radiate, corpus callosum and thalamus.

All study subjects were treated as per standard recommendations[3].

Appropriate statistical analysis was carried out using SPSS software version 22.0 The permission to perform this study was provided by the Ethics Committee of this Institution.

RESULTS

Of the 315 study subjects with dengue fever, 30 children (9.5%) had neurological complications (Figure 1).



DF: Dengue fever; CNS: Central nervous system

Figure 1: Number of dengue fever patients with / without neurological complications.

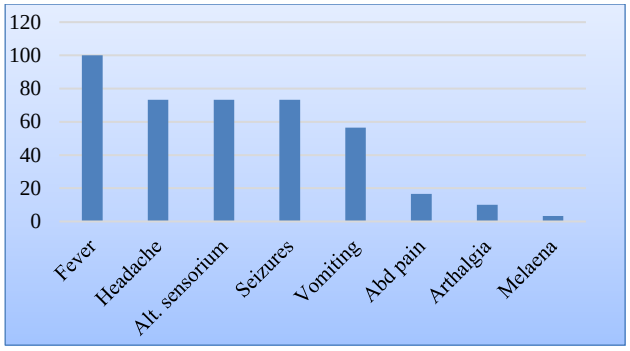


Figure 2: Common symptoms in study subjects with neurological complications.

These cases were initially categorized as severe dengue (n = 25, 83.3%), dengue with warning signs (n = 4, 13.3%) and dengue without warning sign (n = 1, 3.3%).

The mean age of these patients was 9.6 years and M:F ratio was 2:1. Adolescents in the age group 12-18 years constituted 56.6% (n = 17) of the patients in which dengue fever had associated CNS presentation. The most common symptoms (Figure 2) were fever (100%, = 30) followed by headache (73.3%, n = 22), altered sensorium (73.3%, n = 22), seizure (73.3%, n = 22), vomiting (56.6%, n = 17), abdominal pain (16.67%, n = 5), arthralgia (10%, n = 3) and malena (3.3%, n = 1).

The most common signs (Figure 3) were hepatomegaly (100%, n = 30), exaggerated deep tendon reflexes (73.3%, n = 22), puffiness (66.6%, n = 20), petechiae (36.67%, n = 11), lymphadenopathy (23.3%, n = 7), papilloedema (20%, n = 6), rash (20%, n = 6), splenomegaly (16.6%, n = 5), muscle tenderness (13.3%, n = 4), absent deep tendon reflexes (6.6%, n = 2) and cranial nerve palsy (3.3%, n = 1).

Table 1: Neurological complications and mortality in study subjects (n = 30).

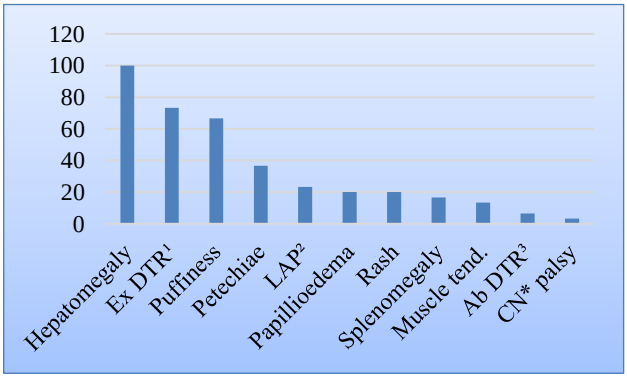
Neurological manifestations	No. of cases n=30 (%)	CT / MRI Brain findings	No. of deaths
Encephalopathy	16 (53.3)	Normal (n=12, 75%) Extensive involvement of b/l cerebellar region, brainstem and thalami with peculiar rim enhancement (n = 4, 25%)	01
Encephalitis	07 (23.3)	Normal (n = 4, 57.2%) Cerebral edema (n = 3, 42.8%)	00
Myositis	04 (13.3)	Normal	00
Acute disseminated encephalomyelitis	01 (3.3)	Hyperintense white matter lesions on T2-weighted images in centrum semiovale, corona radiata and corpus callosum	01
Hemiplegia with facial nerve palsy	01 (3.3)	Hypodensity (ischemic infarct) in right parietal lobe in cranial CT scan	00
Intracranial haemorrhage	01 (3.3)	Hyperdensity in frontal lobe in cranial CT scan	01

Table 2: Association of platelet counts in dengue fever with/without neurological complications.

Platelets (per cu.mm)	DF with CNS complications (n=30)	DF without CNS complications (n = 285)
< 30,000	9 (30%)	05 (1.7%)
30,000-50,000	16 (53.3%)	53 (18.5%)
50,000-100,000	4 (13.3%)	156 (54.7%)
>100,000 -1,50,000	1 (3.3%)	71 (24.9%)

The neurological complications and CT/MRI Brain findings as observed in the study subjects are shown in Table 1. CPK levels were elevated in all cases of myositis (Range: 1500-30,000 IU/L, Mean±SD: 16,500±447 IU/L). EMG findings in these patients were suggestive of early recruitment of motor action potentials with normal morphology and no spontaneous activity. Nerve conduction velocities were normal in these patients.

Thrombocytopenia was more common in children with CNS involvement (Table 2).



[1]Exaggerated deep tendon reflexes; [2]Lymphadenopathy; [3]Absent deep tendon reflexes; *Cranial nerve

Figure 3: Common signs in study subjects with neurological complications.

CSF analysis was done in 26 cases who had neurological manifestations, protein was in range of 28-116 mg/dl with mean of 66.86 mg/dl, glucose was in range of 40-86 with mean of 63.2 mg/dl. Cell count was in range of 4-100 cells per cumm (Mean±SD, 52.4 ± 5.7 per cumm) in all 26 cases who had neurological manifestations. The mortality rate in our study was 10% (n=3) in 1 patient each with encepahalopathy, acute disseminated encephalomyelitis and intracranial haemorrhage (Table 1).

DISCUSSION

Dengue causes high morbidity and mortality in children living in the tropical and subtropical areas of the world.[4] The 2009 WHO Guidelines included involvement of CNS in definition of severe dengue but there are no standardized case definitions or diagnostic criteria for 'neuro-dengue' in these updated guidelines.[5]

Neurological manifestations were first reported in 1976 as atypical symptoms of dengue infection with incidence rates varying from 0.5 to 20% in heterogenous study groups covering both pediatric and adult patients.[6,5,7-10] In this study, the overall incidence was 9.5%.

The occurrence of neurological complications was observed to be significantly associated with cases of severe dengue (n = 25, 83.3%). According to the antibody-dependent enhancement hypothesis, non-neutralizing, cross-reacting antibodies from previous infection may bind to viral surface epitopes of a heterologous infecting serotype facilitating viral entry into Fc-receptor bearing phagocytes. This may further facilitate cell invasion, viremia, and multi-organ involvement including the nervous system.[5] In this study, out of 30 cases with neurological manifestations, 22 patients (73.3%) presented with secondary dengue and thus were predisposed to develop severe dengue. There are three ways by which neurological alterations occur in dengue infection:[7,11]

- Encephalopathy secondary to metabolic disturbances e.g. prolonged shock, hyponatremia, metabolic acidosis, acute liver or renal failure.
- Direct viral invasion resulting in encephalitis, meningitis, myositis and myelitis.
- Autoimmune reactions leading to acute disseminated encephalomyelitis occurring within a limited time (average: 5.6 days) after initial dengue infection.

In this study, encephalopathy was the commonest complication associated with shock and multi-organ failure in study subjects. This correlates with the observations of Oehler et al.[12] Initially, the dengue virus was considered as non-neurotropic. However, recent studies have demonstrated its invasiveness and ability to penetrate blood-brain barrier in experimental animal models especially in relation to serotype 2 and 3.[13-15] The reported incidence of encephalopathy and encephalitis, the most common neurological complications of dengue, has been found to vary from 0.5% to 6.2%.[2] In this study, it was 7.9%. In a prospective study of 175 hospitalized dengue patients in South India, dengue encephalitis was recorded in 7.4% cases.[16] In this study, 4 cases of myositis were observed presenting with muscle tenderness and mild non-progressive weakness which is similar to the observation of Ahmad R et al.[17]

In this study, the mortality rate was 10% and residual weakness was observed in one patient with hemiplegia and facial palsy. All the other patients recovered without any neurological deficit.

The strengths of this study were that it involved a significant number of patients considering the epidemic nature of the disease. However, owing to economic and resource constraints, ELISA technique could not be employed for dengue serology or for detecting dengue-specific IgM in CSF and also extensive investigations to rule out other possible viral etiology could not be carried out. A diagnosis of neurological manifestations secondary to dengue can be considered in presence of suggestive clinical features in dengue endemic regions.[5]

CONCLUSION

Neurological complications of dengue infection are widespread and may involve almost various parts of the nervous system through diverse mechanisms. The specific reason for presenting these observations is to develop awareness regarding the various common neurological complications of dengue in pediatric population especially in developing nations where there is limited access to diagnostic techniques.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Shokeen P, Yadav S, Verma CR, Masand R. Neurological complications in Dengue fever. Int J Contemp Pediatr 2018;5:983-7.