

Neurological Complications of Dengue Fever - A Study from a Tertiary Care Hospital of Eastern India

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Abstract: Dengue virus Dengue is a mosquito-borne disease caused by single positive-stranded RNA virus of family Flaviviridae of genus Flavivirus. Epidemiologically its predominantly prevalent in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas. Neurological complications are widely variable There are several types of neurological complications observed in dengue fever. This is a retrospective study showing various neurological complications in dengue fever in last 2 years. Patients with positive dengue serology (IgM Ab) with neurological manifestations were selected. They were subjected to routine laboratory investigations like CBC, PSC, Hematocrit, serum creatine kinase, Biochemical investigations, CT scan brain, MRI Brain, CSF Study, coagulation profile, EEG, Nerve conduction study. 22 patients were found to have some neurological complications, out of which 18 were male, 4 female. Out of 22 patients 13 patients presented with encephalopathy, 2 patients with intracerebral hemorrhage, 2 patients with Bell's palsy, 1 patient with cerebellitis, 1 patient with meningoencephalitis, 1 patient with AIDP, 1 patient with acute disseminated encephalomyelitis and 1 patient presented with compressive myelopathy secondary to epidural hemorrhage. Encephalopathy was found to be the most common neurological complication.

Keywords: Dengue fever, Neurological complications, Epidural hemorrhage.

INTRODUCTION

Dengue is a mosquito-borne viral disease that has rapidly spread in all regions of WHO in recent years. Dengue virus is transmitted by female mosquitoes mainly of the species *Aedes aegypti* and, to a lesser extent, *Ae. albopictus*.

The global incidence of dengue has grown dramatically in recent decades. About half of the world's population is now at risk. Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas [1]. One recent estimate indicates 390 million dengue infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease) [2]. In 2015, Delhi, India, recorded its worst outbreak since 2006 with over 15000 cases. There are 4 distinct, but closely related, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4) [3]. The clinical presentation of dengue range from mild clinical febrile illness to severe life-threatening situations like dengue hemorrhagic fever and dengue shock syndrome. Dengue can manifest with a wide range of neurological features, which have been noted--depending on the clinical setting--in 0.5-21% of patients with dengue admitted to hospital. Furthermore, dengue was identified in 4-47% of admissions with

encephalitis-like illness in endemic areas. Neurological complications can be categorized into dengue encephalopathy (eg, caused by hepatic failure or metabolic disorders), encephalitis (caused by direct virus invasion), neuromuscular complications (eg, Guillain-Barré syndrome or transient muscle dysfunctions), and neuro-ophthalmic involvement [4].

MATERIALS AND METHODS

This is a retrospective study done in a tertiary care hospital in eastern India i.e SCB Medical College and Hospital, Cuttack. All the patients with dengue fever presenting with neurological manifestations, admitted in the Department of Medicine from July 2015 to September 2017, were included in this study. This study was approved by the institutional ethical committee. The dengue fever was diagnosed by positive serum IgM antibody to dengue fever done by the enzyme-linked immunosorbent assay (ELISA) method using an IgM ELISA Kit. A detailed history, clinical

evaluation, and detailed neurological examination were performed in all patients. The muscle power was noted according to the Medical Research Council grading. Thorough general examination and other system examinations were done. The routine laboratory investigations including complete blood count, hematocrit, blood sugar, liver function test, renal function test, creatine kinase, prothrombin time, activated partial thromboplastin time and electrolytes and HIV antibody were performed in each patient. Nerve conduction studies, electromyography, electroencephalography, neuroimaging studies including magnetic resonance imaging of the brain and spine were performed in selected patients. The cerebrospinal fluid analysis including IgM antibody for dengue fever, polymerase chain reaction study for Japanese encephalitis virus, herpes simplex virus, Epstein Barr virus, Cytomegalovirus, varicella zoster and *Mycobacterium tuberculosis* were performed in the cerebrospinal fluid in patients suffering from encephalopathy/encephalitis /cerebellitis. The antinuclear antibody, rheumatoid factor, and antiphospholipid antibodies were also carried out in some cases to exclude autoimmune diseases. The

outcome was defined as the condition during discharge or follow up at 1 month.

RESULTS

We observed 22 patients with dengue infection presenting with various neurological complications who were admitted to our institution in the last 2 years. A total number of admissions were about 1000. Neurological complications were found in 2.2% cases. The age of patients ranged from 15 to 60 years. Mean age of presentation 32.6 yrs. eighteen patients (81.8%) were male and four (18.2%) were female. The demographic and clinical profile of these patients is described in Table 1. Thrombocytopenia was found in 11 (50%) patients. Four patients had AKI. Two patients had jaundiced. Four patients' died. So the mortality was 18.2%. The neurological complications found can be divided into those affecting central nervous system like encephalopathy, meningoencephalitis, cerebellitis, ICH. Diseases affecting both brain and spinal cord like ADEM. Only spinal cord involvement in spinal epidural hemorrhage. AIDP and Bell's palsy affects the peripheral nerves.

Table-1: Clinical profile of study group

| | age | sex | Prior fever | Type of dengue fever | Total platelet count | Neurologic manifestation | Outcome |
|----|-------|-----|-------------|----------------------|----------------------|--------------------------|----------|
| 1 | 16 YR | F | YES | DF | 1.8 LACS | AIDP | IMPROVED |
| 2 | 35 YR | F | YES | DSS | 1.2 LACS | Meningoencephalitis | EXPIRED |
| 3 | 22 YR | F | YES | DF | 86,000 | CEREBELLITIS | IMPROVED |
| 4 | 28 YR | F | YES | DF | 2.1 LACS | ENCEPHALOPATHY | IMPROVED |
| 5 | 14 YR | M | YES | DSS | 60,000 | ENCEPHALOPATHY | IMPROVED |
| 6 | 60 YR | M | YES | DF | 80,000 | BELL'S PALSYP | IMPROVED |
| 7 | 44 YR | M | YES | DF | 1.2 LAKH | ADEM | IMPROVED |
| 8 | 48 YR | M | YES | DHF | 20,000 | ICH | EXPIRED |
| 9 | 29 YR | M | NO | DHF | 64000 | COMPRESSIVE MYELOPATHY | IMPROVED |
| 10 | 24 YR | M | YES | DF | 2.4 LAKHS | ENCEPHALOPATHY | IMPROVED |
| 11 | 21 YR | M | YES | DHF | 30,000 | ENCEPHALOPATHY | IMPROVED |
| 12 | 25 YR | M | YES | DF | 1.1 LAKHS | ENCEPHALOPATHY | IMPROVED |
| 13 | 32 YR | M | YES | DSS | 1.2 LAKHS | ENCEPHALOPATHY | IMPROVED |
| 14 | 36 YR | M | YES | DSS | 80,000 | ENCEPHALOPATHY | IMPROVED |
| 15 | 31 YR | M | YES | DF | 1.2 LAKHS | BELL'S PALSYP | IMPROVED |
| 16 | 37 YR | M | YES | DF | 70,000 | ENCEPHALOPATHY | IMPROVED |
| 17 | 36 YR | M | YES | DF | 1.1 LAKHS | ENCEPHALOPATHY | IMPROVED |
| 18 | 39 YR | M | YES | DSS | 1.0 LAKH | ENCEPHALOPATHY | EXPIRED |
| 19 | 35 YR | M | YES | DF | 40,000 | ENCEPHALOPATHY | IMPROVED |
| 20 | 38 YR | M | YES | DF | 1.2 LAKHS | ENCEPHALOPATHY | IMPROVED |
| 21 | 32 YR | M | YES | DF | 80,000 | ENCEPHALOPATHY | IMPROVED |
| 22 | 35 YR | M | YES | DHF | 30000 | ICH | EXPIRED |

DF-Dengue fever, DSS-Dengue shock syndrome, DHF- dengue hemorrhagic fever, M-male, F-female

Encephalopathy and meningoencephalitis were found in 14 patients and all patients presented with fever, altered sensorium and generalized tonic-clonic convulsion with serum IgM antibody for dengue positive. Among them, one patient presented with a

fever headache altered sensorium and meningeal signs, that patient later developed ARDS and expired. ICT test for malaria was negative in all cases. CT scan brain was normal in all cases. EEG study showed diffuse slow waves in eight patients and was normal in rest. CSF

study was normal except one patient had CSF dengue Ig M antibody positive. Six patients had thrombocytopenia. Four patients of DSS presented with encephalopathy one DSS patient presented with meningoencephalitis.

One patient presented with fever, headache myalgia for 2-3 days followed by unsteadiness of gait with swaying towards the right. On examination cerebellar signs were present. MRI Brain was normal. CSF study showed mild exocytosis with normal protein and all the viral markers in CSF including Varicella was negative.

Two patients developed left LMN type facial weakness (Bell's palsy) three days after fever. Other neurological examinations were normal.

One patient presented with fever, myalgia for 5 days, then fever subsided and he developed reflexes quadriparesis without bladder bowel and sensory involvement. Serum potassium level was normal. Nerve conduction study showed demyelinating and axonal polyradiculoneuropathy. CSF study showed albuminocytological evaluation. So a diagnosis of GB syndrome was made and the patient was treated with iv immunoglobulin for 5 days. The patient improved thereafter.

One patient presented with fever, headache, and altered sensorium for 3 days and the sensorium improved thereafter. When he became conscious he found that he was unable to move her both lower limbs. His lower limb muscle power was 2/5, upper limb power was 5/5. Deep tendon reflexes were normal in upper limb and brisk in the lower limb. Plantar was extensor bilaterally. All modalities of sensation were intact. Fundus examination was normal. MRI brain revealed large fluffy cotton wool like lesions in right temporoparietal area. MRI Spine was normal. CSF

study showed a cell count of two with protein 50mg/dl (slightly raised). A diagnosis of ADEM was made and the patient was treated with IV Methylprednisolone 1 gram daily for 5 days followed by a short course of tapering oral steroids. The patient improved dramatically.

Two patients developed intracerebral hemorrhage. It was associated with DHF and very low platelet count. There was also subconjunctival hemorrhage, hematuria, bleeding from the oral cavity. The outcome was very bad and both the patients expired.

One patient presented with fever, myalgia, and rash. Fever subsided after 7 days, and then he developed back pain followed by sudden onset quadriparesis with retention of urine. His higher mental function and cranial nerve testing were normal. Muscle power in the upper limb was 2/5 and in lower limb 1/5. Deep tendon reflexes were brisk in both upper limb and lower limb. Plantar was bilaterally extensor. All modalities of sensation diminished below C5. Abdominal and cremasteric reflexes were absent. MRI Cervical spine showed T1 iso to hyperintense and T2 hyperintense collection in anterior epidural space extending from C2 to C5 representing anterior epidural hemorrhage. The patient's platelet count was 64,000/cmm. The hemorrhage occurred secondary to thrombocytopenia. He underwent decompressive laminectomy in a private hospital. After 1 month of surgery his power in upper limb was 3/5 and in lower limb was 2/5.

In our study, 4 patients out of 22 (18.2%) patients died during hospitalization. Among them, two patients presented with DHF and intracerebral hemorrhage and another two patients presented with DSS and encephalitis.

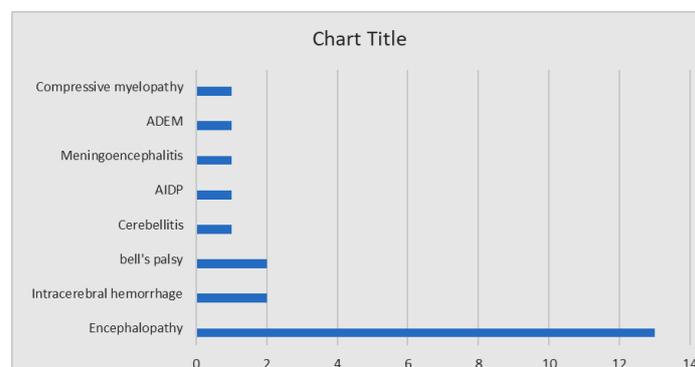


Fig-1: Frequency of different neurological complications among the study group

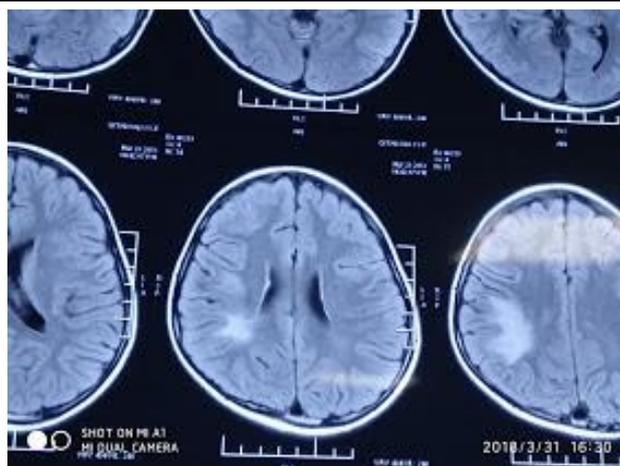


Fig-2: MRI brain showing large fluffy lesions in patient with ADEM

DISCUSSION

In our study, we have taken dengue patients presenting with various neurological complications. We found that males outnumbered females which are also seen demographically in other studies. We found the patients in the age range of 15-60 yrs (mean age-32.6 yrs). The mean age of presentation was 29.08 yrs in a study done by Mishra *et al.* Misra *et al.* included 17 patients with neurological complications in his prospective hospital-based study [7]. Verma *et al.* reported 26 patients with neurological complications of dengue fever⁸. From the literature, we didn't find the true incidence of neurological complications as all are mainly hospital-based studies but the number of patients with neurological complications is increasing over time. The increased vigilance of the healthcare personnel during dengue epidemic is responsible for early diagnosis of patients presenting with fever and acute neurological manifestations. Our study center was the nodal center for dengue during the epidemic, so a maximum number of patients with dengue with complications all over the state were referred to our institute. So it reflects the true incidence of our locality.

Wasay *et al.* reported six patients with neurological manifestations [9] and Solomon *et al.* mentioned nine patients with encephalitis associated with dengue fever [10]. Verma *et al.* reported 4 cases of encephalopathy. Misra *et al.* gave the description of 11 patients of encephalopathy with dengue infection. In our study, we found 14 cases of encephalopathy including one case of meningoencephalitis. Dengue encephalopathy could be caused by cerebral edema, cerebral hemorrhage, and hyponatremia, and hypoxia, renal and hepatic insult.

Among immune-mediated disorders, we found one case of GB Syndrome and one case of ADEM which was very less in comparison to other studies. Soares *et al.* discussed seven cases of Guillain Barre Syndrome associated with dengue-positive IgM antibody in serum [6]. Verma *et al.* found two cases of

GBS in their study. Verma *et al.* found one case of ADEM and one case of myelitis. We found two patients with Bell's palsy which is a very rare manifestation. On review of the literature, we found one case of isolated Bell's palsy with dengue fever has been reported from North India by Peter *et al.* [11].

Two patients presented with ICH. The mortality rate was very high and the two patients expired. Both the cases were associated with DHF and thrombocytopenia. One of the cases had also bleeding from other sites as a consequence of thrombocytopenia. Verma *et al.* didn't find any case of intracerebral hemorrhage. One case of cervical compressive myelopathy secondary to thrombocytopenia and spinal epidural hemorrhage was found which a very rare manifestation is also. Singh *et al.* reported one case of paraplegia due to spinal epidural hemorrhage in dengue [5].

In various other studies myositis, brachial neuritis, opsoclonus-myoclonus syndrome and hypokalemic palsy have been found in association with dengue fever. But in our study, we didn't find any such cases.

So we found encephalopathy as the most common neurologic manifestation of dengue which matches other literature also. We didn't find any association of total platelet count with neurological manifestations except intracerebral hemorrhage and spinal epidural hemorrhage.

CONCLUSION

Dengue can manifest with a wide range of neurological features. In endemic countries and after travel to these regions, dengue should be considered in patients presenting with fever and acute neurological manifestations. In our study, we found Bell's palsy, ICH and epidural hematoma of the spinal cord which are very rare manifestations. More studies are needed to

determine the actual incidence of neurological complications of dengue.

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