Abstract

In order to detect the range of neurological manifestations, patients with dengue virus infection admitted to neurology service were subjected to detailed clinical evaluation, i.e. blood counts, serum chemistry, electrolytes, creatine kinase (CK), magnetic resonance imaging (MRI), nerve conduction study (NCS) and electromyography (EMG).

Out of 24 patients with dengue virus infection aged 5–65 years, six had dengue shock syndrome (DSS) and 5 had dengue haemorrhagic fever (DHF). A total of 16 patients had encephalopathy (encephalomyelopathy 1) and 8 had pure motor quadriparesis. In the encephalopathy group, 6 had secondary causes; intracranial haemorrhage was present in 2, renal failure in 1 and hepatic failure in 3 patients. Cerebrospinal fluid (CSF) pleocytosis was present in 10 patients. The pure motor quadriparesis group had normal NCS, myopathic EMG and raised serum CK suggesting myositis. All the patients in the myopathy group improved, but in the encephalopathy group, 3 died, 2 had poor recovery, 3 partial and 8 had complete recovery.

It can be concluded that neurological manifestations of dengue may have two polar forms – encephalopathy and myositis with varying degrees of overlap.

Keywords: Dengue, encephalitis, encephalopathy, myositis, quadriparesis, MRI outcome.

Introduction

Dengue virus belongs to the family Flaviviridae, which also includes yellow fever, Japanese encephalitis (JE) and West Nile encephalitis viruses. The yellow fever infection presents with liver dysfunction and JE with encephalomyelitis. The dengue virus infection may manifest with both hepatic and neurological involvement; the latter is attributed to metabolic alterations, hypotension and haemorrhagic manifestations. Lately, there have been reports of neurological complications of dengue virus infection and include encephalitis, myelitis, Guillain Barre (GB) syndrome and myositis.[1,2,3,4] Dengue virus is generally considered a non-neurotropic. Neuroinvasion, however, has been reported in five fatal cases of dengue encephalopathy in whom dengue virus antigen was detected in the brain by immunohistochemistry.[5] In patients with dengue encephalitis, CSF pleocytosis and positive IgM and PCR (polymerase chain reaction) tests have also been reported, suggesting neuroinvasion.[1,3] In this communication, we report various neurological manifestations of dengue virus infection in consecutive patients and associated confounding variables, which may have prognostic significance.
Materials and methods

During 2003–2006 we managed 24 patients with dengue virus infection who presented with fever and various neurological manifestations. The diagnosis of dengue was based on positive serum IgM antibody against dengue virus assayed by IgM capture enzyme-linked immunosorbent assay (ELISA) using dengue virus IgM ELISA kit (Novatec, Germany). The patients were subjected to detailed medical history and physical examination. Their age, area of residence, symptoms of fever, headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, seizures and neurological deficits were noted. Consciousness was assessed by Glasgow Coma Scale (GCS) and mental status by mini mental state examination (MMSE). Cranial nerve palsy was noted and limb weakness was assessed by the Medical Research Council (MRC) scale. Muscle tone, reflex and sensations were also recorded. Systemic manifestations such as jaundice, lymphadenopathy, cardiac, respiratory and gastrointestinal abnormalities were recorded. The laboratory test included haemoglobin, blood counts, haematocrit, blood sugar, blood urea nitrogen, serum bilirubin, creatinine, transaminases, electrolyte, creatine kinase (CK), prothrombin time and activated partial thromboplastin time. Electrocardiogram, radiograph of chest, cranial computed tomography (CT) scan or magnetic resonance imaging (MRI) were carried out. Cerebrospinal fluid (CSF) and electromyography (EMG) examinations were carried out after ensuring normal bleeding and coagulation time. CSF was examined for protein, sugar and cells. CSF smear and culture were also done for fungus and bacteria. Electromyogram and nerve conduction study (NCS) were carried out as indicated. The patients were conservatively managed as per the World Health Organization (WHO) guideline. Those with respiratory failure were intubated and given artificial ventilation. In patients with haemorrhagic complications, platelet and fresh frozen plasma were administered. The outcome was defined at the end of one month into death, complete (independent for activities of daily living), partial (dependent for activities of daily living) and poor (bedridden) status.

Analysis

The neurological syndromes of dengue virus infection were categorized and correlated with various clinical and laboratory parameters employing Chi square, Fisher’s exact and independent t-test using SPSS 10 version software.

Results

There were 24 patients with dengue virus infection with neurological manifestations. Their age ranged between 5 and 65 (mean 30.5) years; 6 were females and 4 below 13 years of age. The majority of the patients were from urban and only 4 from rural areas of Uttar Pradesh, India. Six patients had dengue shock syndrome (DSS), 5 dengue haemorrhagic fever (DHF) and remaining 13 patients had dengue fever (DF).

Headache was present in 16 patients, vomiting in 15, hepatomegaly in 6, splenomegaly in 1, pleural effusion in 2 and ascites in 1 patient. Jaundice was present in 2 and renal failure requiring dialysis in 1 patient. Respiratory failure requiring artificial ventilation was present in 2 patients.

The neurological manifestations could be categorized into encephalopathy, encephalo-myelopathy and flaccid quadriparesis.
**Encephalopathy**

There were 16 patients with encephalopathy and one of them also had associated myelopathy. Their GCS ranged between 3 and 14 (mean 9.6). Five patients had delirium and psychosis and 6 quadripareisis. Seizures were present in 5 patients; generalized tonic clonic in 4 and partial motor in 1 patient. The underlying hypoxic metabolic factor was present in 6 patients, which included hypotension in 6, renal failure in 1 and hyper-bilirubinemia in 3. Two of these patients, however, had CSF pleocytosis. In the remaining 10 patients, there was no significant hypoxia or metabolic abnormality and CSF showed pleocytosis in 8, suggesting encephalitis.

The CT scan was carried out in 2 patients and MRI in 11 patients. The CT scan revealed extradural, subarachnoid and cerebellar haematoma in 1 and intra-ventricular haemorrhage in another (Figure). The MRI revealed thalamic, basal ganglia and brainstem involvement in 1 patient and only thalamic hyperintensity in T2 in another. These 2 patients had JE co-infection confirmed by CSF IgM capture ELISA against JE virus.

Three patients died; the cause of death was renal failure, intracranial haematoma and cardiac in one patient each. At one month follow-up, 2 patients had poor, 3 partial and 8 complete recovery. In the patients with partial recovery, 2 had JE coinfection and 1 had associated myelopathy.

**Pure motor flaccid quadripareisis**

This group comprised of 8 patients whose age ranged between 9–42 (mean 28.1) years and 1 each was a child and a female. All the patients belonged to urban areas and were admitted within 7 days of onset of illness. Headache and vomiting were reported by 5 patients. Purpura or ecchymosis was present in 5 patients; 3 of them also had gastrointestinal haemorrhage. None of these patients had hypotension. Muscle weakness was pronounced (MRC grade ≤3) in 4 and mild (MRC grade 4) in 4 patients. Hypotonia was present in 5 and tendon reflexes were reduced in 4 patients. Nerve conduction studies were normal in all patients and EMG was consistent with myopathy in 2 patients. CSF was done in 5 patients and revealed mild protein rise in 2, but none had pleocytosis. Thrombocytopenia (<100 000/mm³) was present in all. Hyperbilirubinemia was present in 1 (2.9 mg/dl) and raised transaminase in 7 patients. CK was also elevated in 7 patients. All these patients had complete recovery by 2 weeks.

The demographic, clinical and laboratory variables in encephalopathy and pure...
Neurological Manifestations of Dengue

Table: Comparison of demographic, clinical and laboratory findings of dengue virus infection with encephalopathy and myositis

<table>
<thead>
<tr>
<th></th>
<th>Encephalopathy (n=16)</th>
<th>Myositis (n=8)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.7 ± 18.9</td>
<td>28.1 ± 11.7</td>
<td>0.63</td>
</tr>
<tr>
<td>Females</td>
<td>5</td>
<td>1</td>
<td>0.62</td>
</tr>
<tr>
<td>Rural</td>
<td>4</td>
<td>0</td>
<td>0.26</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>5</td>
<td>1.00</td>
</tr>
<tr>
<td>Behavioural abnormality</td>
<td>6</td>
<td>0</td>
<td>0.07</td>
</tr>
<tr>
<td>Seizure</td>
<td>5</td>
<td>0</td>
<td>0.20</td>
</tr>
<tr>
<td>GCS score</td>
<td>9.6 ± 4.2</td>
<td>15 ± 0.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Focal weakness</td>
<td>6</td>
<td>8</td>
<td>0.006</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpura</td>
<td>3</td>
<td>5</td>
<td>0.06</td>
</tr>
<tr>
<td>GI, Epistaxis</td>
<td>6</td>
<td>3</td>
<td>1.00</td>
</tr>
<tr>
<td>Shock</td>
<td>6</td>
<td>0</td>
<td>0.07</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. Bilirubin</td>
<td>3.67 ± 6.07</td>
<td>0.82 ± 0.87</td>
<td>0.08</td>
</tr>
<tr>
<td>serum glutamic pyruvic transaminase (SGPT)</td>
<td>305.40 ± 628.25</td>
<td>262.00 ± 299.50</td>
<td>0.82</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>423.17 ± 417.80</td>
<td>765.14 ± 120.80</td>
<td>0.42</td>
</tr>
<tr>
<td>S. creatinine</td>
<td>1.44 ± 1.08</td>
<td>1.19 ± 0.35</td>
<td>0.40</td>
</tr>
<tr>
<td>Platelet count</td>
<td>1.37 ± 1.24</td>
<td>0.57 ± 0.43</td>
<td>0.03</td>
</tr>
<tr>
<td>CSF pleocytosis</td>
<td>38.13 ± 87.70</td>
<td>2.00 ± 2.74</td>
<td>0.13</td>
</tr>
<tr>
<td>CT</td>
<td>2 (ICH, IVH)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>2 (thal 2, BG 2, BS 1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Outcome (Death/poor/partial/complete)</td>
<td>3/2/3/8</td>
<td>0/0/0/8</td>
<td>0.05</td>
</tr>
</tbody>
</table>

ICH=intracranial haemorrhage, IVH= intraventricular haemorrhage, BG=basal ganglia, BS=brain stem.

Quadriaparesis groups are shown in the Table. A few representative cases are presented to highlight the spectrum of neurological manifestations of dengue virus infection.

Case reports

Case 1

A 48-year-old bank manager presented with 3 days’ history of continuous fever reaching up to 38.5 °C, headache and vomiting. On the 2nd day of illness he felt giddy and lapsed into deep coma over 3–4 hours. He also had haematemesis. On examination he was deeply comatose and had bilateral haemiplegia and decerebration. His pulse was 120/min, systolic blood pressure 70 mm and diastolic BP was not recordable. Haematocrit was 43%, platelet count 32 000/mm³, APTT 56.8 sec, PT 19 sec, serum creatinine 1.9 mg/dl, bilirubin 1.8 mg/dl, transaminase 270 U/L and CK 270 U/L. His CT scan revealed extradural haematoma with
fluid level and frontal and cerebellar haematoma. His serum IgM ELISA for dengue virus was positive. The patient was treated with IV fluid and antiedema measures. He was put on artificial ventilation but died on day 5 of illness. This patient highlights dengue-associated thrombocytopenia and coagulopathy resulting in fatal intracranial haemorrhage.

Case 2

A 30-year-old housewife presented with history of fever, headache and vomiting for 10 day. Three days later she became drowsy and developed retention of urine and paraparesis. On examination, her pulse was 54/min, blood pressure 104/76 mmHg, temperature 38 °C and she had ecchymotic patches on her limbs and trunk. Her lower limb power was grade III, with hypotonia and areflexia. Blood counts, serum chemistry and CSF were normal. The MRI revealed T2 hyperintensity in dorsal spinal cord and brainstem. Her serum IgM ELISA was positive for dengue. She was given supportive treatment and by 1 month her mentation became normal but paraparesis and retention of urine persisted. This patient highlights a rare association of dengue encephalopathy with myelopathy.

Case 3

A 56-year-old scientist presented with 8 days’ history of fever, headache and vomiting and developed altered sensorium for 2 days. On examination he was febrile and had hypotension (BP 90/60 mmHg). He was drowsy (GCS score 13) and there was no focal weakness. Tendon reflexes and sensations were normal. He developed oliguria. His haemoglobin was 15 gm/dl, haematocrit 55%, platelet count 16 000/mm³, activated partial thromboplastin time (APTT) 21 sec, prothrombin time (PT) 28 sec, serum creatinine 5.2 mg/dl, bilirubin 7 mg/dl, transaminase 115 U/L and CK 3260 U/L. His IgM ELISA for dengue was positive. He received IV fluids, platelet infusion and was subjected to haemodialysis. He died at 1 month due to multi-organ failure. This dengue patient illustrates renal impairment, liver dysfunction and thrombocytopenia contributing to encephalopathy. His elevated CK suggests possible myositis.

Case 4

A 42-year-old male presented with fever and headache for 4 days and quadriparetesis for 2 days with myalgia. His blood pressure was 110/90 mmHg, pulse 86/min and had 3 cm hepatomegaly. He was conscious and oriented. There was grade II flaccid quadriparetesis with hyporeflexia and sensations were normal. His platelet count was 20 000/mm³, CK 3050 U/L, bilirubin 2.9 mg/dl, transaminase 202 U/L, and remaining haematology and chemistry were normal. IgM ELISA was positive for dengue. CSF revealed 5 lymphocytes/mm³ and 40 mg% protein. He was treated conservatively and improved completely by 15th day of illness. This case illustrates occurrence of myositis in dengue.

Case 5

A 35-year-old male admitted with 5 days’ history of fever and bodyache. Three days later he developed quadriparetesis. On examination, his temperature was 38 °C, pulse 120/min, BP 90/60 mmHg and had 3 cm hepatomegaly. He had moderate quadriparetesis (grade III), hypotonia and hyporeflexia with normal sensations. On the second day of hospitalization he became drowsy and lapsed into coma on the third day and developed haematemesis, melaena, jaundice and hypotension. His platelet count was 14 000/
Neurological Manifestations of Dengue

mm$^3$, APTT 39 sec, PT 12.4 sec, bilirubin 8 mg/dl, transaminase 2472 U/L and CK 812 /L. His electroencephalography (EEG) showed delta slowing and CSF done on day 10 was normal. He was treated with IV fluid, platelet infusion, antibiotics and bowel wash. He started improving from the 5th day of illness and improved completely by day 15. This patient highlights overlap of myositis and encephalopathy with hepatic failure as a confounding factor.

Case 6

A 50-year-old man presented with 7 days’ history of high fever and behavioural abnormality. On day 3 of illness, he developed two episodes of generalized tonic clonic seizures. On examination, his pulse was 80/min, BP 170/80 mmHg and temperature 39 °C. He was drowsy (GCS score 13). There was no focal weakness; tendon reflexes were normal and plantar response flexor. His blood counts, serum chemistry and cranial MRI were normal. Cerebrospinal fluid analysis revealed 40 lymphocytes/mm$^3$, 49 mg/dl protein and 73 mg/dl sugar. Serum IgM ELISA was positive for dengue. He was given supportive treatment and phenytoin 300 mg daily. He improved completely by the third week. This patient illustrates encephalitic presentation of dengue infection.

Discussion

Our study reveals two polar forms of neurological syndrome of dengue virus infection – encephalopathy and myositis with variable degree of overlap. Encephalopathy in dengue can be attributed to metabolic alteration such as liver failure, electrolyte imbalance and renal impairment as well as hypotension. Bleeding and coagulation abnormalities in dengue haemorrhagic fever and dengue shock syndrome can also contribute to altered sensorium. In the encephalopathy group, associated metabolic and a hypoxic changes were noted in 6 (hypotension in 6, renal failure in 1 and liver failure in 3) and intracranial haemorrhage in 2 patients. In the remaining 8 patients no such factors could be detected. CSF examination in these patients revealed lymphocytic pleocytosis ranging for 10 to 950/mm$^3$ and CSF IgM ELISA was positive in 3 patients. There have been reports of encephalitis in dengue from Viet Nam in which encephalitis was present in 9, hepatic encephalopathy in 5 and other metabolic dysfunction in 4 patients. The basis of the diagnosis of encephalitis in these patients was CSF pleocytosis, positive ELISA and PCR in CSF. In a study on 27 DHF cases developing encephalopathy, 26 were comatose, 21 had convulsion and 1 haemiplegia. MRI was carried out in 18 patients and was abnormal in 12 patients. The MRI abnormalities included oedema and scattered focal lesions in 2, cerebral haemorrhage in 1 and cerebral oedema in 12 patients. In our study, CT scan or MRI revealed intracranial haemorrhage in 2 and thalamic and basal ganglia lesions in 2 patients who had JE coinfection. Therefore, our results suggest paucity of radiological change in dengue encephalopathy/encephalitis, which is in contrast to JE where thalamic, basal ganglia and brainstem abnormalities are common.

The flaccid motor weakness was noted in 8 patients. These patients resembled Guillain Barre syndrome; but normal sensations, cranial nerves and NCS, presence of reflexes in 4 patients and fever during the onset of weakness excluded the possibility of Guillain Barre syndrome. Elevated CK in all but one patient was suggestive of myositis. EMG in 2 cases was consistent with myopathy. In other patients the EMG was performed after 2 weeks, keeping the referral diagnosis of GB syndrome and
associated coagulopathy which might be responsible for normal EMG. In influenza myositis, EMG is reported to be abnormal in nearly half the patients.\(^\text{[10]}\) Diagnosis of dengue myositis in earlier studies was based on raised CK level\(^\text{[11]}\) and muscle biopsy.\(^\text{[4]}\) It seems that our patients though presented with 2 major syndromes – encephalopathy and pure motor weakness – but some patients with encephalopathy also had raised CK levels. This may suggest a continuum of neurological manifestations of dengue.

**Acknowledgement**

This work was supported by the Council of Science and Technology, Uttar Pradesh, India, project No. CST/SERPD/D-422.

**References**


