

Neurological Manifestations of Dengue Fever

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Abstract

Background: Dengue is a common endemic infection in India. Neurological complications involving various parts of the neuro-axis have been reported. We report neurological complications amongst dengue patients admitted to a tertiary hospital in Western India. **Materials and Methods:** Patients admitted in a tertiary hospital in Western India with dengue infection and having neurological symptoms were included in this study. Their history, physical examination, laboratory investigations and imaging studies were obtained from the inpatient records and analysed. **Results:** Between January 2014 to December 2019, a total of 5821 patients were diagnosed with dengue. Of these, 154 (2.64%) had neurological manifestations. Encephalopathy in a setting of multisystem involvement was seen in 31.2% patients, encephalitis with focal features, abnormal imaging and/or abnormal cerebrospinal fluid (CSF) examination was seen in 15.6%, syncope in 27.3% and acute symptomatic seizure in 11.0%. Less common presentations were intracranial haemorrhage (4.5%), Guillain-Barre syndrome (GBS) (3.2%), optic neuritis (1.9%), myositis (1.3%), hypokalemic paralysis (1.3%), ischemic stroke (0.6%), posterior reversible encephalopathy syndrome (PRES) (0.6%), myoclonus (0.6%) and brachial plexopathy (0.6%). **Conclusions:** In this study of patients admitted with dengue, neurological complications due to dengue were seen in 2.64%. Encephalopathy, encephalitis and syncope were the commonest manifestations, followed by acute symptomatic seizures, intracranial haemorrhage and GBS. The entire neuroaxis can be involved in dengue infection. To the best of our knowledge, this is the largest reported study of neurological complications of dengue.

Keywords: Dengue, neurological manifestations.

INTRODUCTION

Dengue is a mosquito-borne, single positive-stranded ribonucleic acid (RNA) virus of the family Flaviviridae; genus Flavivirus. The vector is *Aedes aegypti* mosquito. It is a common endemic viral infection in India. Heavy rainfall, poor sanitation, stagnated water and poor mosquito control are factors that have led to dengue being a major public health burden in India. In 2010, India accounted for 34 of 96 million dengue cases in the world.^[1] The sero-prevalence of dengue infection in patients presenting with fever was 21.65% in a study from Pune city.^[2]

The typical presenting symptoms are fever, body ache, bone pain, muscle pain and generalized weakness. World Health Organization (WHO) has classified cases of dengue infection as dengue without warning signs, dengue with warning signs, and severe dengue.^[3] The revised classification also includes severe organ manifestations such as liver failure, heart involvement, or central nervous system (CNS) involvement.

In the 1970s, neurological manifestations were thought to be uncommon in dengue and the virus was believed to be non-neurotropic. Subsequently neuro-invasion was demonstrated by presence of dengue virus in cerebrospinal fluid (CSF) by polymerase chain reaction (PCR).^[4] Dengue virus has 4 serotypes: DENV1, DENV2, DENV3 and DENV4. Out of these, DENV2 and DENV3 have been associated with neurological manifestations.^[5]

Neurological complications involving central as well as peripheral nervous system have been reported with different

studies in India as well as worldwide^[4,6-11] with incidence of neurological manifestations varying between 2.63-40%. We report neurological manifestations from our cohort of hospital inpatients.

METHODOLOGY

This is a retrospective single centre study conducted in a multispecialty tertiary care private hospital in Western India between January 2014 to December 2019 over a 6-year period. The hospital is an 800-bedded hospital that caters to 400,000 outpatients per year and 68,000 inpatients per year. It serves as referral centre for Western and Southern Maharashtra.

Data for all patients admitted with dengue fever was collected from the electronic medical record database of hospital. Those patients having neurological involvement secondary

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to dengue were included in this study. Patients seen in out-patient department or with pre-existing neurological problems were excluded. Isolated headache not accompanied by other neurological symptoms or signs was not included in the neurological manifestations. Demographic details, neurological manifestations, systemic manifestations, laboratory results, imaging findings and outcomes were reviewed for each patient. The study was approved by the institute's ethics committee.

A diagnosis of dengue was made if the clinical syndrome was consistent with dengue and patient had either dengue non-structural protein 1 (NS1) antigen positive, or dengue immunoglobulin M (IgM) and/or immunoglobulin G (IgG) positive. Dengue NS1 antigen was analysed by the Qanticard kit method using fluorescence immune chromatography. Dengue IgM and IgG were analysed using IgM capture enzyme-linked immunoassay (ELISA) using the PanBio kit.

Dengue was classified as dengue without warning signs (lives in or travels to dengue endemic areas; fever with 2 of the following: nausea or vomiting, rash, ache and pains, tourniquet test positive, leukopenia, any warning signs), with warning signs (abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy or restlessness, liver enlargement >2 cm, laboratory increase in haematocrit concurrent with rapid decrease in platelet count) and severe dengue (severe plasma leakage leading to shock, fluid accumulation with respiratory distress; severe bleeding; severe organ involvement: liver transaminases >1000, CNS impaired consciousness, heart and other organs). Renal involvement was considered to be present in an adult if the serum creatinine was >1.4 mg/dl or in patients requiring dialysis for acute renal injury. Hepatic involvement was defined as elevation of transaminases greater than two times upper limit of normal. Haematological involvement was defined as clinical bleeding manifestations, platelets <1,50,000 and/or deranged prothrombin time (PT) or activated partial thromboplastin time (APTT).

Dengue encephalopathy was defined as dengue fever with reduced consciousness secondary to shock, metabolic abnormality, hypotension, hepatic failure or renal failure with normal CSF finding. Dengue encephalitis was defined as dengue fever with acute signs of cerebral involvement in absence of any metabolic abnormality, or any other explanation for reduced consciousness with any one of the following: CSF pleocytosis (CSF corrected white blood cell count >5 cells/mm³), focal neurological signs, seizures other than simple febrile seizures, abnormal imaging consistent with encephalitis, presence of dengue IgM antibodies in CSF or CSF positive for dengue PCR.^[12]

Acute symptomatic seizure was defined as seizure in a patient with dengue fever with altered sensorium during post-ictal phase lasting for a maximum duration of 48 hours. Syncope was defined as transient loss of consciousness with immediate post-event recovery without tonic-clonic movements.

Optic neuritis was defined as impairment of visual acuity and colour vision due to inflammation of optic disc in the setting of dengue infection.^[13] Guillain-Barre syndrome (GBS) was defined as acute, severe polyradiculoneuropathy in the setting of dengue fever.^[14] Posterior reversible encephalopathy syndrome (PRES) was defined as acute onset neurological deficit with characteristic bilateral symmetrical white matter hyperintensities on magnetic resonance imaging (MRI) in the setting of dengue.^[15] Brachial plexopathy was defined as acute onset proximal weakness of upper limb preceded by pain in the shoulder in the setting of dengue.^[16] Hypokalemic paralysis was defined as acute pure motor paralysis in the setting of dengue with concomitant hypokalemia.^[17] Myositis was defined as inflammation of the muscle associated with pain, tenderness, swelling and/or weakness.^[18]

RESULTS

Between January 2014 to December 2019, a total of 5,821 patients with laboratory confirmed dengue infection were admitted in the hospital. Of these 5,821 patients, 154 (2.64%) had neurological manifestations. Year-wise numbers of patients with neurological manifestations are shown in Figure 1a. Month-wise distribution of total dengue cases and cases with neurological manifestations are shown in Figure 1b and 1c.

Ninety-five patients (61.7%) were male and 59 (38.3%) were females. Thirty-two patients were children (20.8%). Table 1 shows demographic characteristics, and systemic features of these patients and Table 2 shows the neurological manifestations. Thirteen (8.4%) patients had neurological manifestations without any systemic complications of dengue (seizures 4, syncope 4, GBS 2, encephalopathy 1, encephalitis 1, myoclonus 1).

Encephalopathy

Forty-eight patients (31.2%) presented with dengue encephalopathy. All patients presented with reduced level of consciousness ranging from drowsiness with frank coma while 16 (33%) patients had seizures. Forty-seven (97.9%) patients had associated systemic manifestations. These included haematological in 44 (91.7%), renal in 18 (37.5%), hepatic in 31 (64.6%), hyponatremia in 29 (60.4%), shock in 15 (31.3%)

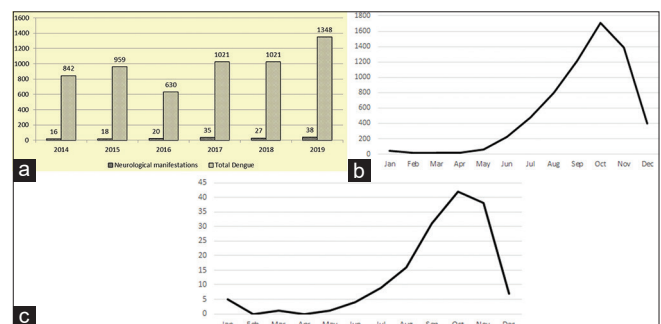


Figure 1: a. Year wise distribution of total Dengue cases and Dengue with neurological manifestations b. Monthly distribution of total dengue cases c. Monthly distribution of cases of dengue with neurological complications

Table 1: Demographic and Systemic Features of Patient with Dengue Fever and Neurological Manifestations (n=154)

	Number (SD range)	Percentage
Demographic features		
Age (years)	35.92 +/- 22.6 (0-89)	
Sex		
Male	95	61.7
Female	59	38.3
Systemic manifestations		
Shock	30	19.5
Renal involvement	26	16.9
Hepatic involvement	72	46.8
Haematological involvement	137	89
Hyponatremia	68	44.2
Hypoxia	44	28.6
Dengue serology		
Dengue NS1 antigen	111	72.8
Dengue IgM	67	43.5
Dengue IgG	28	18.2
Mean platelet count	77,792 +/-70,142 (3000-340000)	
Thrombocytopenia (<150,000)	137	89
Platelet count		
<20,000	33	21.4
20,000-50,000	37	24
50,000-1,00,000	41	26.6
>1,00,000	43	27.9
Dengue classification		
Dengue without warning signs	24	15.6
Dengue with warning signs	45	29.2
Severe dengue	85	55.2
Mean duration of hospitalization (days)	7.81 +/- 10.04 (1-83)	
Outcome		
Survived	135	87.7
Died	19	12.3

NS1 - Non-Structural Protein 1, IgM - Immunoglobulin M, IgG - Immunoglobulin G

Table 2: Neurological Manifestations in Patients with Dengue Fever (n=154)

	Number	Percentage
CNS		
Encephalopathy	48	31.2
Encephalitis	24	15.6
Acute symptomatic seizures	17	11.0
Syncope	42	27.3
Intracranial haemorrhage	7	4.5
Ischemic stroke	1	0.6
Optic neuritis	3	1.9
PRES	1	0.6
Myoclonus	1	0.6
PNS		
GBS	5	3.2
Brachial plexopathy	1	0.6
Hypokalemic paralysis	2	1.3
Myositis	2	1.3

CNS - Central Nervous System, PRES - Posterior Reversible Encephalopathy Syndrome, PNS - Peripheral Nervous System, GBS - Guillain-Barre syndrome

and hypoxia in 26 (54.2%). CSF analysis was performed in 9 patients. Mean CSF protein was 54.1 mg% and median CSF cell count was 5 cell/ml. Neuroimaging was performed in 26 patients; 12 had computerised tomography (CT) and 14 had MRI. The imaging findings were: 16 normal, 4 cerebral oedema, 4 cerebral atrophy, 2 old lacunar infarcts. Electroencephalogram (EEG) was done in 4 patients; two were normal, 1 each showed generalized slowing and electrocerebral silence. Out of these 48 patients, dengue serology showed dengue NS1 positive in 32 patients, IgM positive in 24 patients and IgG positive in 10 patients. Among patients with encephalopathy, 33 survived while 15 died.

Encephalitis

Total of 24 (15.6%) patients presented with dengue encephalitis [Table 3]. Twenty-two (91.7%) patients presented with fever. The other manifestations included seizures in 14 (58.3%), status epilepticus in 4 (16.6%), reduced level of consciousness in 14 (58.3%), focal neurological features in 6 (25%) and nuchal rigidity in 5 (20.8%). Associated systemic manifestations were seen in

Table 3: Encephalitis in Patients with Dengue Fever (n=24)

	Number (SD range)	Percentage
Demographic features		
Age (years)	32.96 +/-17.3 (0-71)	
Male	14	58.3
Female	10	42.7
Neurological features		
Seizures	14	58.3
Status epilepticus	4	16.6
Reduced level of consciousness	14	58.3
Focal deficits	6	25
Nuchal rigidity	5	20.8
Systemic manifestations		
Fever	22	91.7
Shock	5	20.8
Renal involvement	2	8.3
Hepatic involvement	16	66.7
Haematological involvement	22	91.7
Hyponatremia	7	29.1
Hypoxia	10	41.6
None	2	8.3
CSF		
Proteins	186.5 +/- 249 (29-968)	
Cells	117.8 +/-237 (2-676)	
Imaging features		
Normal	3	12.5
Splenic hyperintensity	3	12.5
Bilateral thalamic hyperintensities	6	25
Bilateral basal ganglion hyperintensities	1	4.2
Cortical-subcortical involvement	6	25
Meningeal enhancement and cerebral oedema	5	20.8
Dengue serology		
Dengue NS1 antigen	13	54.2
Dengue IgM	14	58.3
Dengue IgG	6	25
Outcome		
Survived	22	91.7
Died	2	8.3

PCR - Polymerase Chain Reaction, NS1 - Non-Structural Protein 1, IgM - Immunoglobulin M, IgG - Immunoglobulin G

22 (91.7%). Dengue serology showed NS1 positive in 13, IgM positive in 14 and IgG positive in 6 patients. Among patients with encephalitis 22 (91.7%) survived and 2 (8.3%) died.

CSF analysis was performed in 13 patients. Mean CSF protein was 186.5 mg% and mean CSF cells were 117.8/ml with lymphocytic pleocytosis. IgM antibody was checked in one patient which was positive and PCR was performed in 7; of which 1 was positive. EEG was performed in 5 patients. Two were normal, 1 each showed right occipital spikes, generalized slowing and periodic lateralizing epileptiform discharges.

Four patients had evidence of concomitant meningoencephalitis due to other organisms. Two had positive Weil Felix test, suggestive of scrub typhus. One patient had IgM antibodies

against Japanese encephalitis virus (JEV) in serum and dengue IgM antibodies in serum as well as CSF. One patient had tubercular meningitis with tuberculoma. All 4 patients had positive dengue serology.

Imaging was done in all patients (22 MRI, 1 CT and 1 head ultrasound). Three patients (12.5%) had normal imaging findings. Three (12.5%) had hyperintensities in splenium of corpus callosum with diffusion restriction [Figure 2a]. Six patients (25%) had bilateral thalamic hyperintensities with variable haemorrhagic component and simultaneous involvement of pons, cerebellum and subcortical areas [Figure 2b]. One patient had bilateral basal ganglion and subcortical hyperintensities who had concomitant antibodies against JEV. Six patients (25%) had cortical-subcortical involvement [Figure 3a]. Five patients (20.8%) had leptomeningeal enhancement with cerebral oedema including

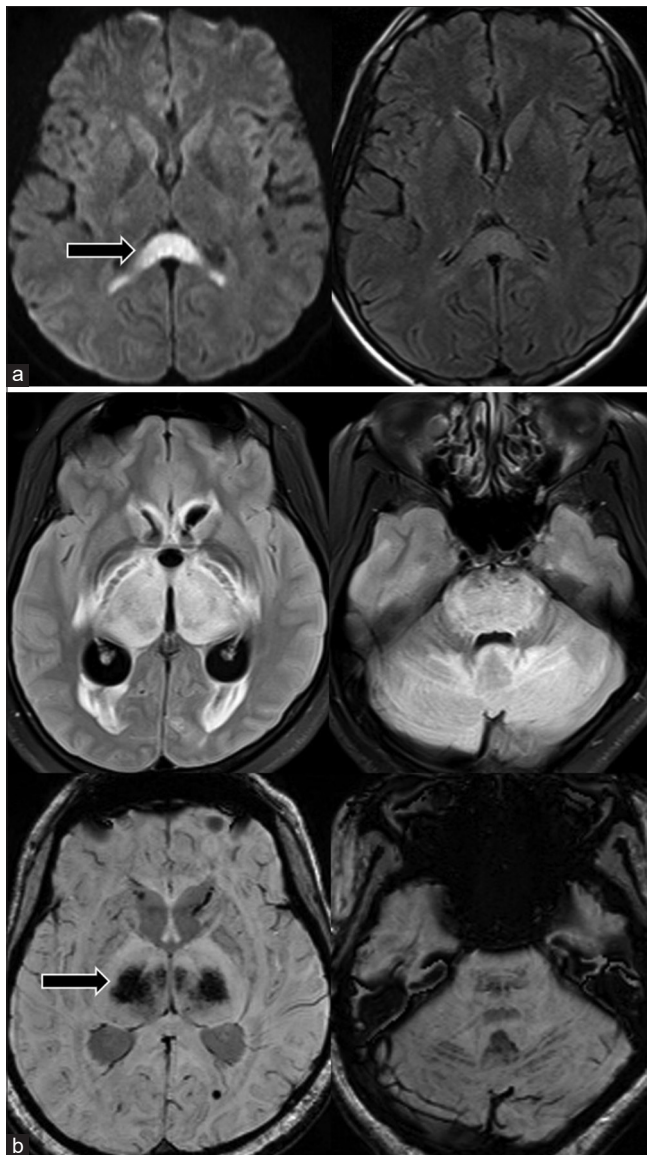


Figure 2: a- DWI and FLAIR axial images of a patient showing DWI restriction and hyperintensity in FLAIR sequences in the splenium of corpus callosum- boomerang sign. b- FLAIR and SWI axial MRI sequences of a patient with dengue encephalitis showing bilateral thalamic, cerebellar and pontine hyperintensities with severe oedema. Thalamic lesions show large central areas of hemorrhage

one who also had additional multiple ring-enhancing lesions suggestive of tuberculoma.

Acute symptomatic seizures

Seventeen (11.0%) patients presented with dengue fever and seizures. In all these patients, imaging and CSF were normal and none of them had any metabolic impairment. Of 17 patients, 13 (76.5%) were children while 4 were adults. The types of seizures were tonic-clonic in 15, focal seizures in 1 and jitteriness in 1 patient. Status epilepticus was seen in one patient. EEG was performed in 4 which showed right hemispheric epileptic discharges in 1 and normal EEG in 3.

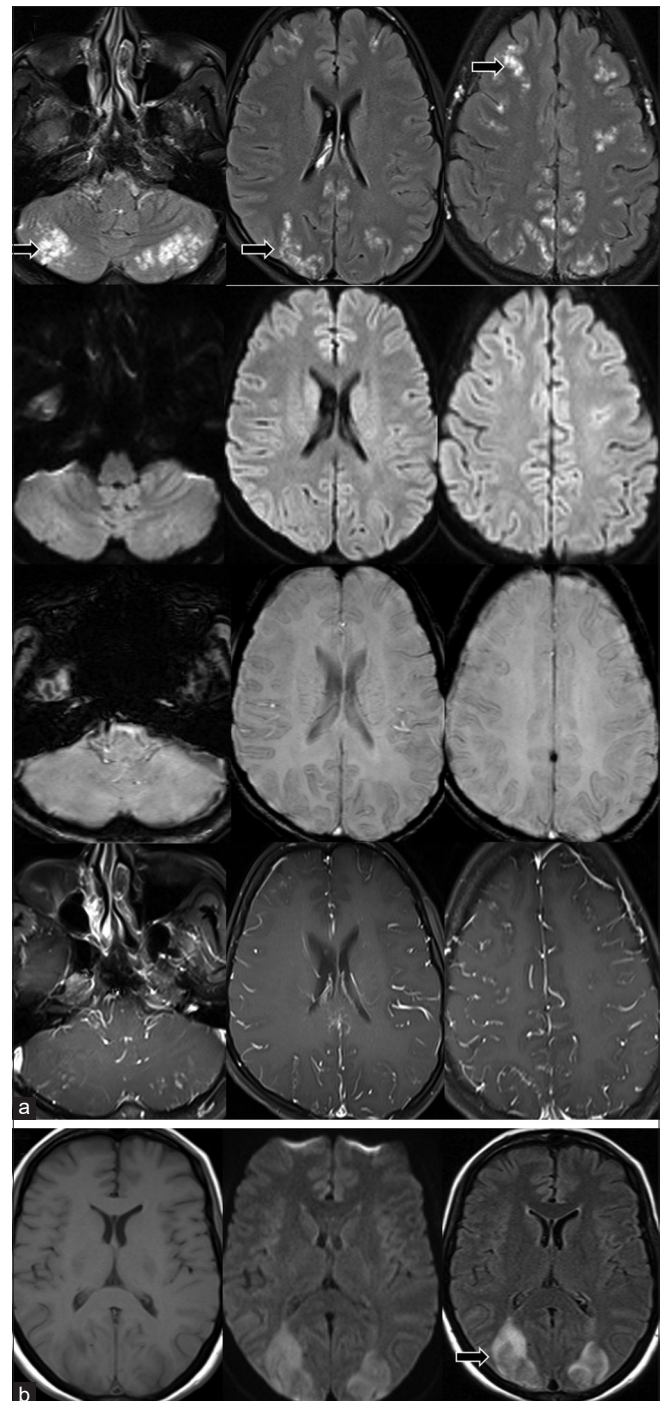


Figure 3: a - FLAIR, DWI, SWI and T1W contrast axial MRI brain sequences of a patient with dengue encephalitis revealing multiple ill-defined lesions in bilateral fronto-temporo-parieto-occipital and cerebellar regions predominantly along the sulcal spaces. Some of these lesions show contrast enhancement. This pattern of parenchymal involvement showed neither diffusion restriction nor hemorrhages within the lesions. b - T1W, DWI and FLAIR axial images of a patient showing oedema and hyperintensities in the posterior region suggestive of PRES

Myoclonus

A 38-year-old lady presented with febrile illness followed by myoclonus and ataxia. She did not have opsoclonus. Her

dengue IgM was positive. Her syndrome was self-limiting and started improving within 10 days.

PRES

A 42-years old hypertensive lady was admitted with dengue fever. Four days later she developed 2 tonic-clonic seizures and her MRI was suggestive of PRES [Figure 3b]. She did not have raised blood pressure, renal failure or history of consumption of drugs known to cause PRES. CSF was not done due to thrombocytopenia. Patient did not get further seizure and at one year after diagnosis of PRES, the patient remained seizure free.

Syncope

Forty-two patients (27.3%) presented with syncope and their subsequent evaluation revealed diagnosis of dengue fever. Six patients had >1 episode of syncope. None had syncopal episodes in past. Hypotension was recorded in 5 patients in-hospital.

Ischemic stroke

A 54-year male presented with fever for 6 days followed by vomiting, dysarthria and right sided ataxia. His MRI brain showed right midbrain infarct and normal angiogram. His dengue NS1, IgM and IgG were positive.

Intracranial haemorrhage

Seven patients presented with dengue and intracranial haemorrhage. Four had sub-arachnoid haemorrhage (SAH), 2 sub-dural haemorrhage (SDH) and one had parenchymal haemorrhage. Two SAH and one SDH were following fall secondary to syncope. All patients had thrombocytopenia with mean platelet count of 37,571/ml. They presented within 2 to 14 days of onset of fever. One patient was a known case of aplastic anaemia who presented with dengue fever. One patient with left cerebral SDH with midline shift required craniotomy with evacuation of SDH who later succumbed. Another patient with intra-parenchymal haemorrhage had Intra-ventricular extension and multi-organ dysfunction died later. Rest of the patients were treated conservatively and improved.

Optic neuritis

Three patients presented with optic neuritis. One patient had left eye optic neuritis 6 months ago who presented with right eye

blurring of vision with worsening after 5 days of fever. MRI showed features of left optic neuritis and multiple demyelinating plaques in cervical and dorsal cord. CSF oligoclonal bands were negative, and bilateral visual evoked potentials were prolonged. This patient probably suffered from multiple sclerosis with worsening of optic neuritis secondary to dengue fever which improved with intravenous steroids. Other 2 patients presented with acute onset unilateral blurring of vision occurring 2 and 5 days after onset of fever. MRI brain was normal. CSF analysis was not performed. VEP was prolonged in one patient and normal in the other. Both patients were treated with intravenous methylprednisolone and improved.

GBS

Five patients presented with acute severe neuropathy suggestive of GBS with dengue fever [Table 4]. All patients had quadriparesis, 3 had respiratory muscle involvement, 3 had bulbar involvement, 1 had bifacial weakness and 2 had extra-ocular muscle involvement. Nerve conduction studies showed axonal pattern in 3 and demyelinating in 2. CSF showed raised proteins and pleocytosis in 3, albumino-cytological disassociation in 1 and no abnormality in 1. They were treated with intravenous immunoglobulin in 3 and plasma exchange in 2. One patient died, 3 showed partial recovery and 1 showed good recovery.

Brachial plexopathy

A 24-year-old male presented with dengue fever and weakness of right arm involving deltoid and spinati muscles with absent reflexes in right upper limb and sensory loss over right lateral arm. Dengue NS1 antigen was positive. Ultrasound of the right shoulder was normal. Electrophysiological evaluation was not done. He improved with conservative management.

Hypokalemic paralysis

Two patients presented with hypokalemic paralysis associated with dengue fever. Both were adult males who presented with fever and pure motor flaccid quadriparesis with hyporeflexia. Neither patient had any past history of similar weakness. Their serum potassium was 1.4 and 2.4 meq/dl respectively. Both patients improved with potassium supplementation. Relevant investigations for other causes of hypokalemia were normal in both.

Table 4: GBS with Dengue Fever

Age/ Sex	Symptoms onset after fever	Symptoms	NCS	CSF	Treatment	Outcome
55/M	6 days	Quadriplegia, dysphagia, respiratory muscle involvement, ophthalmoplegia	Axonal	P 330, cells 10	IVIg	Death
31/M	4 days	Quadriplegia, dysphagia, respiratory muscle involvement, ophthalmoplegia, bifacial weakness	Axonal	P 200, cells 30	IVIg	Partial recovery
59/F	9 days	Quadriparesis	Demyelinating	P 960, cells 36	PLEx	Partial recovery
43/F	2 days	Quadriparesis, bifacial weakness	Demyelinating	P 114, cells 5	IVIg	Good recovery
55/F	3 days	Quadriparesis, dysphagia, respiratory muscle involvement	Axonal	P 20, cells 3	PLEx	Partial recovery

NCS - Nerve Conduction Studies, CSF - Cerebrospinal Fluid, M - Male, F - Female, P - Proteins, IVIg - Intravenous Immunoglobulin, PLEx - Plasma Exchange

Myositis

Two patients presented with dengue and myositis. Both presented with 4 and 5 days of fever, weakness in limbs, myalgia and elevated serum creatinine phosphokinase. One patient recovered with symptomatic treatment while the other was treated with steroids. Neither showed any signs of rhabdomyolysis. Electromyography and muscle biopsy were deferred in view of thrombocytopenia in both.

Discussion

The prevalence of neurological manifestations in dengue is variable depending on where the study was conducted, whether children or adults were included and which neurological manifestations were studied.^[6-11] Most of these studies are single centre and retrospective except a few.^[10] In our study, 2.64% of patients admitted with dengue developed neurological manifestations. We did not include patients who were managed on outpatient basis; hence the true prevalence of neurological manifestations will be lesser.

The neurological manifestations of dengue can be divided into 3 categories:

1. Direct neurotropism- encephalitis, meningitis, myelitis and myositis;
2. Systemic complications-encephalopathy, stroke and hypokalemic paralysis;
3. Post-infectious/immune mediated- acute disseminated encephalomyelitis (ADEM), GBS and optic neuritis.^[5]

Headache is very common in patients of dengue fever, seen in >97% patients in a study.^[19] It is usually not included in the list of neurological manifestations in reported studies.

Some patients may get acute neurological problems like stroke or acute demyelinating event with dengue. The relation between dengue and neurological episode is difficult to establish and dengue may be a co-incidental or precipitating factor in these.^[3]

Encephalopathy

Encephalopathy is the most common neurological manifestation of dengue.^[5] In Thailand, Pancharoen *et al.*,^[6] reported encephalopathy in half of all children with neurological manifestations due to dengue. In various studies from India, encephalopathy was reported in 19.4% of patients with neurological manifestations by Koshy *et al.*,^[7] 22% by Sahu *et al.*,^[10] and 67% by Misra *et al.* The incidence of encephalopathy varies amongst different studies depending on type of population studied (adult vs children). The difference between encephalopathy and encephalitis is not clearly defined in all studies. In our series, encephalopathy was the most common neurological manifestation seen in 31.2% with mortality of 31.25%.

The pathophysiology of dengue encephalopathy is multifactorial and is due to cerebral oedema, hypoxia, haemorrhage and associated systemic dysfunction like shock, hyponatremia, liver and kidney failure.^[3,5]

Encephalitis

Acute encephalitic syndrome is an illness with altered mentation, fever, seizures and focal deficits usually occurring with viral illness. The causative virus may not be found in all cases; hence the terminology encephalitic syndrome is used. Certain viruses like herpes simplex virus (HSV) and JEV are well known causes of viral encephalitis. Dengue is an uncommon cause of encephalitic syndrome. There are several proposed definitions of dengue encephalitis.^[3,12] Earlier definition was dependent on CSF findings of pleocytosis and serology.^[3] The definition used by us is all inclusive and takes into consideration clinical, CSF, radiological and serological features. In cases of dengue, many times performing CSF is not possible due to thrombocytopenia and facilities to perform CSF antibody or PCR testing may not be available at all centres. In these cases, imaging findings may be useful in diagnosing dengue encephalitis. Since the term encephalitis has been used in different contexts in various studies, the prevalence of dengue encephalitis differs in various series.^[3] In our study, 24 patients (15.6%) had dengue encephalitis.

The clinical features of dengue encephalopathy and encephalitis are indistinguishable. These include reduced level of consciousness and seizures. Presence of CSF pleocytosis, abnormal imaging consistent with encephalitis, presence of dengue antibodies in CSF or detection of PCR in CSF would favour encephalitis. Encephalopathy would occur in the setting of metabolic or organ dysfunction. In some patients with encephalopathy without significant metabolic or organ dysfunction, without CSF pleocytosis and normal imaging, the differentiation is even harder. CSF antibodies, PCR or autopsy may help to differentiate these 2 syndromes. Dengue PCR in CSF was performed in only 7 out of 24 patients due to logistic issues, out of which it was positive in one case. It is possible that some of our patients with encephalopathy might actually had direct involvement of brain by dengue virus but we may have misclassified them as encephalopathy while they may have had encephalitis because we did not do CSF PCR in every patient.

Unlike more classic neurotropic viruses like HSV where the imaging abnormalities are clearly defined, imaging abnormalities of dengue encephalitis are many and vary in reported series. It is partly due to different definitions of dengue encephalitis. Recently Vyas *et al.*,^[20] had defined patterns of dengue encephalitis on imaging. Of the 24 patients in our series, 3 had normal MRIs. Three patients had hyperintense lesions in the splenium of corpus callosum with diffusion restriction. This pattern has been previously described with dengue by Mathew *et al.*,^[21] as well as other infections including influenza, rotavirus, mumps, legionella, mycoplasma. It has been described with various names like dot sign, boomerang sign, mild encephalitis/encephalopathy with reversible splenial lesion, transient splenial hyperintensity. The causative factors for this lesion are intra-myelin oedema and myelinolysis and it is usually reversible.

Six patients in our study presented with lesions involving bilateral thalami, pons and cerebellum with varying degrees of haemorrhage. This pattern has been described previously with dengue by Kamble *et al.*,^[22] and also with influenza, JEV, coronavirus and in children as acute necrotizing encephalopathy.

There were 6 patients who had hyperintense lesions involving cortical and subcortical areas either unilaterally or bilaterally in multiple areas, not in a specific location. Five patients had meningeal enhancement with cerebral oedema on imaging. These features have been described in dengue, but are not specific for the same.

Amongst the 24 patients of dengue encephalitis, we were able to see following imaging patterns:

1. Normal,
2. Splenial hyperintensity,
3. Bithalamic/pontine/cerebellar involvement,
4. Cortical/subcortical involvement,
5. Meningo-encephalitic pattern.

There were 4 patients in our study with dual infections. Two patients had evidence of scrub typhus infection with dengue. Since both these infections occur in similar regions in tropics, co-infection has been described.^[23] One encephalitic patient had evidence of dual JEV and dengue infection with positive serology of both viruses. His MRI showed predominant basal ganglionic involvement. Dual infection of JEV and dengue has been described earlier.^[24] One patient had dengue fever with meningo-encephalitic syndrome and radiological evidence of multiple tuberculomas. In high endemic area, co-infections pose diagnostic and therapeutic challenges.

Acute symptomatic seizures

Seizures can occur in dengue as part of encephalopathy, encephalitis or as isolated seizure episodes not associated with prolonged alteration of sensorium. Reported incidence of seizures from different series varies between 43-70%.^[6,8] Most of these studies have reported seizures as a symptom including in patients with encephalopathy and encephalitis. Children tend to get more frequent seizures, and if the study has larger proportion of children included, then the incidence of seizure is higher. In our series amongst patient with acute symptomatic seizures 76% were children.

Myoclonus

Various post-infectious manifestations are described with dengue fever including GBS, ADEM and opsoclonus myoclonus syndrome.^[25] One patient in our study had self-limiting illness of myoclonus and ataxia without opsoclonus. We did not have any other patient with ADEM.

PRES

PRES is usually seen with elevated blood pressure and diagnosed by characteristic radiographic findings of bilateral white matter changes more common posteriorly. It has also been previously described with infections including dengue by Mai *et al.*,^[15] Capillary endothelial dysfunction in dengue

leads to loss of cerebral auto-regulation and vasogenic oedema. In our study, one patient with dengue had developed PRES. In absence of accelerated hypertension or drugs precipitating PRES; dengue infection was the only causative factor.

Syncope

Hypotension and shock secondary to capillary leak syndrome is hallmark of dengue fever. Syncope can occur in dengue secondary to hypotension, high-grade fever or myocarditis. Syncope was a common finding seen in 27.3% patients in our series.

Syncope is an important and common cause of episodic loss of consciousness, so they present to and are often investigated by neurologists. It is the first differential diagnosis of seizure. Additionally, there are multiple causes for syncope in dengue. In some patients, it was one of the presenting manifestations along with fever. Hence, we considered it necessary to document it in our study.

Ischemic stroke

Ischemic stroke is not common with dengue fever, but has been described by Verma *et al.*,^[26] Possible mechanisms of stroke include deranged haemostasis, severe volume depletion, hypotension, meningo-vasculitis and myocarditis. There was one patient of ischemic stroke in our series. We did not have any case of venous thrombosis with dengue.

Intracranial haemorrhage

Intracranial haemorrhage occurs in dengue secondary to thrombocytopenia and deranged bleeding parameters. In a study by Kumar *et al.*,^[27] 3 patients had parenchymal and 2 subdural haemorrhages. In our study 4 had SAH, 2 SDH and 1 parenchymal haemorrhage. Surgical intervention is usually challenging in view of concomitant thrombocytopenia and shock.

Optic neuritis

Dengue can cause a plethora of neuro-ophthalmological manifestations which occur in the convalescent phase of the disease suggesting an immunological basis. Dengue related optic neuropathy has variable visual outcomes.^[11,13] In our study, 3 patients presented with unilateral optic neuritis. One patient had previous demyelinating episodes and imaging finding suggestive of multiple sclerosis. This patient presented with a relapse of optic neuritis associated with dengue fever.

GBS

GBS is an acute neuropathy following antecedent infection due to different organisms. Peripheral nervous system involvement in the form of GBS has been reported in dengue patients.^[3,7,11,13,28] Sometimes the patient presents with GBS without typical symptoms to raise suspicion of dengue and this has been termed oligo-symptomatic dengue.^[28] It has been suggested that in endemic areas, all patients with GBS should undergo serological tests for dengue. Dengue antigens may mimic antigens in peripheral nerves and cell mediated immunological response to viral antigens may target peripheral nerves in dengue associated GBS.

The acute neuropathies associated with viral infections can occur with infection (para-infectious) or after infection (post-infectious). Para-infectious neuropathies may be due to direct consequence of infection, or due to unusual hyperimmune response.^[29] These neuropathies present with severe weakness, are axonal, show CSF pleocytosis and have poor response to therapy. Post-infectious neuropathies are typically demyelinating with albumino-cytological dissociation and better response to immunotherapy.

In our study, 5 patients had dengue associated GBS. Of these 3 patients had axonal neuropathy. These 3 patients had severe neuropathy with respiratory muscle involvement, 2 of these had ophthalmoplegia, which is not a common feature of GBS and 2 had CSF pleocytosis. Two patients had demyelinating neuropathy; one of which had albumino-cytological dissociation in CSF and the other showed CSF pleocytosis. One patient had bifacial weakness which has been described with dengue by Patel *et al.*^[30] Whether dengue GBS has two subgroups is a question that can be answered in larger studies.

Brachial plexopathy

Post dengue brachial plexopathy has been reported previously by Verma *et al.*^[16,25] The patients presented with pain, weakness and muscle atrophy 14 days after dengue fever. In our study, one patient had post dengue brachial plexopathy.

Hypokalemic paralysis

Hypokalemic paralysis has been described with dengue in various case reports and case series.^[7,10,17] The postulated mechanism is transient renal tubular acidosis with increased urinary potassium wasting secondary to stress related increase of catecholamines in dengue. Two patients had hypokalemic paralysis in this series.

Myositis

Dengue can cause myalgia, myositis and rhabdomyolysis. Dengue associated myositis has been reported earlier.^[9-11,18] Patients with dengue myositis have shorter duration of symptoms, fever, hyporeflexia, thrombocytopenia and leukopenia compared to other causes of acute myositis. In our study, 2 patients had dengue myositis.

The incidence and pattern of neurological complications may be different between primary care centres and tertiary care hospitals. A higher number of severe complications such as encephalopathy, encephalitis and GBS in our series may be due to a referral bias. This series presents all types of complications including those directly affected by the virus such as encephalitis, para-infectious neuropathy, immune mediated processes like GBS, optic neuritis and systemic manifestations in the form of encephalopathy, intracranial haemorrhage, PRES and syncope.

Being a retrospective study, all patients with dengue were not investigated to the same extent and data was not recorded prospectively in a standard proforma. This might have led to some missing or inadequate information such as dengue CSF PCR in those with encephalitis.

CONCLUSION

In this large study of dengue inpatients in Western India, we report a variety of neurological problems, involving different areas of the neuroaxis, a lot of them previously described in case reports and case series. In the 2009 WHO clinical case classification for dengue, CNS involvement is classified as severe dengue, a situation which needs meticulous intensive care management. Thus, it is imperative to identify and manage neurological complications early in order to optimize neurological recovery. Physicians caring for patients with dengue should be aware of these neurological manifestations of dengue. To the best of our knowledge, this is the largest reported study of neurological complications in dengue.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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