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Research Article

NEUROLOGICAL COMPLICATIONS OF DENGUE, A STUDY AT A TERIARY CARE CENTRE IN WESTERN U.P.

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A B S T R A C T

Objective: This study aimed to evaluate the clinical spectrum of neurologic complications and their outcome in patients of dengue virus infection (DENV).

Introduction: Dengue, an acute viral disease transmitted by Aedes mosquito's .It is highly endemic in many tropical and subtropical areas of the world. Neurological complications of dengue infection have been observed more frequently in the recent past and some studies highlighted varied neurological complications arising in the due course of dengue illness. In this retrospective study, we report various neurological complications observed in patients of dengue fever.

Materials and Methods: The patients presenting with neurological complications with positive serology (IgM antibody) for dengue infection were consecutively recruited from the Department of Medicine. These patients were subjected to a detailed clinical evaluation, laboratory assessment including blood count, hematocrit, coagulation parameters, biochemical assays, serology for dengue fever, enzyme-linked immunosorbent assay for human immunodeficiency virus and other relevant investigations.

Results: 22 patients with neurological complications associated with confirmed dengue infection were observed during the study period. Of the 22 patients, eleven patients had encephalopathy, four had encephalitis, three patients were consistent with the diagnosis of intra cranial hemorrhage, one had hypokalemic paralysis associated with dengue fever, one had ischemic stroke, 1 had G.B.S. and one had optic neuritis.

Conclusion: Dengue fever was associated with widespread neurological complications.

INTRODUCTION

Dengue is one of the most common arboviral infections globally. DENV are single- stranded RNA viruses, belonging to the Flaviviridae family, genus Flavivirus. The RNA genome comprises of seven non-structural protein genes (NS) and three structural protein genes known as core, membrane, and envelope, respectively. DENV is composed of four antigentically definite serotypes called DENV-1, DENV-2, DENV-3, DENV-4. The classical demonstration of dengue involves fever along with a frontal predominant headache, retro-orbital pain, rash, hemorrhagic manifestations, severe myalgias, and arthralgias. It also has the potential to permeate neural tissues.[1]

Neurological manifestations have also been postulated to be secondary to autoimmune reactions and metabolic alterations. The neurological manifestations can be widely divided into three groups which involve the manifestations regarding direct neuroinvasion consisting of encephalitis, meningitis, myelitis. Manifestations occurring due to systemic complications of dengue infection involve encephalopathy, stroke, and hypokalemic paralysis. Ultimately, manifestations connected to post-infectious immunological complications, like encephalomyelitis, acute disseminated encephalomyelitis, neuromyelitis optica, optic neuritis, myelitis, Guillain–Barre syndrome (GBS), Miller-Fisher syndrome, long thoracic neuropathy, and oculomotor palsy.[1,2]

Among the central nervous system involvement, encephalopathy and encephalitis are the most general. Dengue encephalopathy is commonly secondary to systemic manifestations of dengue- shock, metabolic abnormalities secondary to renal and hepatic dysfunction.[3]

Neurological manifestation of dengue

Dengue encephalopathyis a clinical syndrome of reduced level of consciousness. It is perhaps the most usually reported neurological disturbance connected with DENV infection. Dengue encephalopathy may occur as outcome of systemic infection and can be brought about by anoxia, cerebral edema, metabolic disturbances (like hyponatremia), prolonged shock, systemic hemorrhage, acute liver or renal failure, release of toxic substances. Dengue encephalitis is because of the Neurotropism and CNS invasion in DENV infection.

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Immune-mediated neurological syndromes have been recorded after DENV infection. They involve mononeuropathies, GBS, brachial neuritis, transverse myelitis, ADEM, acute cerebellitis, opsoclonus-myoclonus, and Parkinsonism. Mononeuropathies comprise involvement of cranial nerves after dengue fever has been reported. Optic neuritis, oculomotor nerve palsy, isolated sixth nerve palsy, isolated Bell's palsy, long thoracic neuropathy, and isolated phrenic nerve palsy. Polyradiculoneuritis and GBS manifests as acute and progressive weakness acting on distal-to-proximal muscles in both upper and lower limbs. Albuminocytological dissociation with raised protein levels and absence of pleocytosis are observed in the CSF.Acute transverse myelitis after DENV infection can happen during either the parainfectious or the postinfectious phases of dengue. Acute paraparesis and also paraplegia, neurogenic pain, sensory symptoms, and neurogenic bladder are observed.[4]

Acute disseminated encephalomyelitis is an immune-mediated syndrome that may happen during the convalescence stage after DENV infection and dengue hemorrhagic fever. Neurological symptoms involve seizures, altered sensorium, and focal neurological deficiency. Cerebellitis and other autoimmune syndromes comprise of dysarthria, horizontal nystagmus, bilateral dysmetria, dysdiadochokinesia, incoordination and broad-based ataxic gait.

Neuromuscular complications can be because of hypokalemia, myositis, and GBS.Dengue transient muscle dysfunction is generally self-limiting and may range from mild myalgia to severe myositis and even rhabdomyolysis. A variable degree of transient myalgia continuing for a few days, muscle tenderness upon stretching, proximal muscle weakness, hypotonia, and raised muscle enzymes can be observed.Dengue-associated hypokalemic paralysisis demonstrated as acute weakness and quadriparesis. Motor weakness, hypotonia, hyporeflexia, flexor plantar reflexes, and indemnity of sensory function.

Dengue connected with stroke can involve both ischemic and hemorrhagic strokes, though the latter is much more usual. Clinical presentation involves fever, moderate to severe headache, vomiting, acute hemiparesis, and loss of consciousness connected with intracranial bleeding. Neuro-ophthalmic difficulty of DENV infection comprises of dengue maculopathy, retinal hemorrhages, optic disc swelling, and optic neuropathy.

METHODOLOGY

It is a retrospective single centre study carried out in a multispecialty tertiary care hospital in India between September 2020 to December 2021 over a 16 month span. Details for all patients admitted with dengue fever were collected from the electronic medical record database of hospital. Those patients who had neurological association secondary to dengue were involved in this study. Patients observed in out-patient department or with pre-existing neurological manifestations were eliminated. Demographic data, neurological manifestations, systemic manifestations, laboratory findings, imaging findings and outcomes were evaluated for every patient. A diagnosis of dengue was built if the clinical syndrome was compatible with dengue and patient either had dengue non-structural protein 1 (NS1) antigen positive, or dengue immunoglobulin M (IgM) and/or immunoglobulin G (IgG) positive.

Dengue was grouped as dengue without warning signs (lives in/or travels to dengue endemic areas; fever with two of the following: nausea or vomiting, rash, ache and pains, tourniquet test positive, leucopenia), with warning signs (abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy or restlessness, liver enlargement >2 cm, laboratory raise in hematocrit concurrent with sudden decline in platelet number) and severe dengue (severe plasma leakage causing shock, fluid collection along with respiratory distress; intense bleeding; severe organ involvement: liver transaminases >1000, CNS impaired consciousness, heart and other organs). Renal association was observed to be existing in an adult if the serum creatinine was >1.4 mg/dl or in patients needing dialysis for acute renal injury. Hepatic involvement was explained as elevation of transaminases more than two times the upper limit of normal. Hematological association was explained as clinical bleeding manifestations, platelets <1,50,000 and/or deranged prothrombin time (PT) or activated partial thromboplastin time (aPTT).

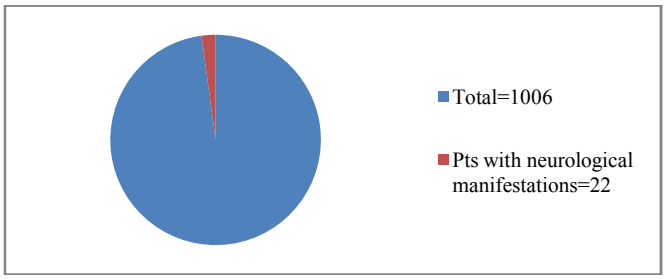
Dengue encephalopathy was explained as dengue fever with decreased consciousness secondary to shock, metabolic derangement, hypotension, hepatic failure or renal failure with normal CSF finding. Dengue encephalitis was explained as dengue fever with severe signs of cerebral involvement in absence of any metabolic abnormality, or any other clarification for reduced consciousness with any one of the following: CSF pleocytosis (CSF corrected white blood cell count >5 cells/mm^3), focal neurological signs, seizures other than febrile seizures, unusual imaging consistent with encephalitis, existence of dengue IgM antibodies in CSF or CSF positive for dengue PCR.[5]

Optic neuritis was explained as injury of visual acuity and color vision because of inflammation of optic disc in the setting of dengue infection. Guillain-Barre syndrome (GBS) was explained as acute, severe polyradiculoneuropathy in the setting of dengue fever. Posterior reversible encephalopathy syndrome (PRES) was explained as severe onset of neurological deficiency with distinct bilateral symmetrical white matter hyperintensities on magnetic resonance imaging (MRI) in the setting of dengue. Brachial plexopathy was explained as acute beginning of proximal weakness of upper limb preceded by pain in the shoulder in the setting of dengue.[6] Hypokalemic paralysis was explained as acute pure motor paralysis in the setting of dengue with consequent hypokalemia. Myositis was explained as inflammation of the muscle connected with pain, tenderness, swelling and/or weakness.[7,8]

Acute symptomatic seizure was explained as seizure in a patient with dengue fever along with changed sensorium during post-ictal phase continuing for a maximum span of 48 hours. Syncope was explained as transient loss of consciousness with sudden post-event recovery without tonic-clonic movements.[9]

RESULTS

A total of 1006 patients with laboratory confirmed dengue infection were admitted in the hospital. Out of the1006 patients admitted, 22 (2.1%) had neurological manifestations.



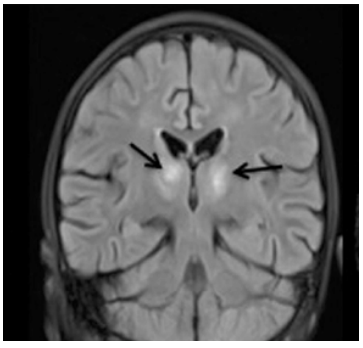
Dengue igM positivity was seen in majority of the cases. Majority of the patients had hematological involvement (72%) followed by hepatic involvement (59%) and shock (18%). This was associated with a reduced platelet count in most of the patients. Major number of the patients had a platelet count of <50000(73%) and had manifestations of severe dengue infection (72%). The mean span of hospitalization was 13 days and 86% were treated successfully. The total male patients were 9(41%) and female patients were 13 (59%) as depicted in table 1.

Table 1 Systemic Featurs of Patient With Dengue Fever And Neurological Manifestations (N=22)

Sex	Number	Percentage
Male	9	41%
Female	13	59%
Systemic manifestations		
Haematological involvement	16	72%
Hyponatremia	2	9%
Shock	4	18%
Renal involvement	4	18%
Hepatic involvement	13	59%
Dengue serology		
Dengue NS1 antigen	6	27%
Dengue IgM	13	59%
Dengue IgG	3	14%
Mean platelet count		
Platelet count		
<20,000	7	32%
20,000-50,000	9	41%
50,000-1,00,000	4	18%
>1,00,000	2	9%
Dengue classification		
Dengue without warning signs	3	14%
Dengue with warning signs	3	14%
Severe dengue	16	72%
Mean duration of hospitalization (days)	13	
Outcome		
Survived	19	86%
Died	3	9%

Central Nervous System Manifestations

In our study, 11(50%) patients had presented with encephalopathy. Neuroimaging of some patients' showed bilateral thalamic hyperintensities, cortical/ subcortical involvement, meningeal enhancement and cerebral oedema.



Axial T2-Weighted Showing A Hyperintense Signal In Bilateral Thalami

In our study 4(18%) patients had manifestations of encephalitis. Encephalopathy was seen in major number of patients (50%). Intracranial hemorrhage was observed in 3(13%) patients out of which 1 showed sub-arachnoid hemorrhage (SAH), 1 sub-dural hemorrhage (SDH) and 1 had parenchymal hemorrhage. Ischemic stroke was seen in one patient and optic neuritis was observed in one patient. In hospital hypotension was noted in 4(18%) patients. PRES and Myoclonus were not observed in any patients of our study group.

Peripheral Nervous System Manifestations

Hypokalemic paralysis was seen in 1(4%) patient who had fever and pure motor flaccid quadriparesis along with hyporeflexia. GBS was observed in 1(4%) patient who had quadriparesis, respiratory muscle involvement and bulbar association. NCV demonstrated axonal pattern. CSF presented elevated proteins and pleocytosis. Myositis and brachial plexopathy was not seen in any patients. The CNS/PNS manifestations have been depicted in table 2.

Table 2 Neurological manifestations in Patients with Dengue Fever (N=22)

Neurological Manifestations		
Central Nervous System		
Encephalopathy	11	50%
Encephalitis	4	18%
Intracranial hemorrhage	3	13%
Ischemic stroke	1	4%
Optic neuritis	1	4%
PRES	0	0%
Peripheral Nervous System		
Hypokalemic paralysis	1	4%
Myositis	0	0%
GBS	1	4%
Brachial plexopathy	0	0%

DISCUSSION

The neurological manifestations of dengue can be grouped into three classes which involve direct neurotropism; Systemic associated complications and Post -infectious/immune mediated. Encephalopathy is the most usual neurological manifestation as observed in our study. The pathophysiology of dengue encephalopathy is multifactorial and is possibly due to cerebral oedema, hypoxia, hemorrhage and associated systemic dysfunction such as shock, hyponatremia, liver and kidneyfailure. In Thailand, Pancharoen *et al*., recorded encephalopathy in half of the patients associated with neurological manifestations and in several other studies from India, encephalopathy was recorded in 19.4% of patients associated with neurological manifestations by Koshy *et al*., 22% by Sahu *et al*., and 67% by Misra *et al*. Severe encephalitis is an illness with altered mentation, fever, seizures and focal deficits generally occurring with viral illness.[10,4,8]

Neuroimaging of a few patients showed bilateral thalamic hyperintensities and other neurological signs as reported earlier with dengue by Kamble *et al* in his studies.[11]

Seizures can occur in dengue as part of encephalopathy, encephalitis or as isolated seizure episodes not connected with continued alteration of sensorium. PRES was not observed in any of our patients. It is generally observed along with

hypertension and diagnosed by radiographic findings of bilateral white matter changes more usual posteriorly. It was also observed earlier with infections involving dengue by Mai *et al*.[12]

Hypotension and shock occur secondary to capillary leak as was seen in our study. Verma *et al* had observed patients along with ischemic stroke which could perhaps be because of deranged hemostasis, hypotension. Intracranial hemorrhage could be because of thrombocytopenia and deranged bleeding parameters. In a study by Kumar *et al*. similar observation as that of our study was noted.[13]

Dengue antigens may copy antigens in peripheral nerves and cell mediated immunological response to viral antigens may select peripheral nerves in GBS associated with dengue infection. The severe neuropathies connected with viral infections can occur along with infection or after infection. These neuropathies presented with acute weakness, are axonal/demyelinating, demonstrate CSF pleocytosis and have poor reaction to therapy. GBS was observed in one of our patients, Patel *et al* had observed close results in studies done by them.[14]

The suggested mechanism in hypokalemic paralysis is transient renal tubular acidosis with raised urinary potassium wasting secondary to stress associated with raised catecholamines in dengue. Hypokalemic paralysis was seen in one of our patients and also observed in many other studies.[15]

CONCLUSION

We observed a variety of neurological problems, which included various areas of the nervous system as observed by other reports and case studies. The varied manifestations of dengue fever in the neuronal axis need to be further studied and followed up to find out long-term implications for management and prognosis. The present study describes different neurological manifestations of dengue in a large retrospective cohort. It is mandatory to recognize and manage neurological complications early to optimize neurological recovery.

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