ORIGINAL RESEARCH PAPER

Neurology

A NEUROLOGICAL MANIFESTATIONS OF DENGUE INFECTION: A PROSPECTIVE CLINICAL EXPLORATORY STUDY

KEY WORDS: Dengue, neurological, encephalopathy

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ABSTRACT

Dengue is an important vector-borne tropical illness with prominent neurological involvement. The aim of this study is to evaluate the incidence, clinical and neuroimaging characteristics of neurological spectrum in dengue. A hospital-based prospective study was carried out in a tertiary-care hospital from December 2021 to August 2023, which included laboratory confirmed dengue positive cases with neurological involvement. We estimated DE incidence and analyzed clinical, laboratory and neuroimaging data. Out of 238 dengue patients, 24 patients were finally enrolled with a mean age of 26.14±10.97 years and a male preponderance (58.33 %). The clinical spectrum included 7 cases of encephalopathy (29.17 %), 5 encephalitis (20.83 %), 4 myelitis (16.67 %), 3 stroke (12.5 %), two Guillain-Barre syndrome(GBS) and Bell's palsy each (8.33 %) and one acute disseminated encephalomyelitis and hypokalemic paralysis each (4.17 %) with mortality in 1 patient (4.17%). Abnormal neuroimaging occurred in 14 cases (58.33 %) with double-doughnut sign (5 cases) and longitudinally extensive transverse myelitis (3 cases). In this study, neurological complications due to dengue were seen in 10.08%. Encephalopathy, encephalitis and myelitis were the commonest manifestations, followed by stroke and GBS. The entire neuro-axis can be affected by dengue infection.

INTRODUCTION

Dengue is a mosquito-borne viral infection with multi-systemic manifestation affecting tropical countries globally. The Global Burden of Disease study1 estimated that dengue accounted for 1.14 million (0.73 million–1.98 million) disability-adjusted life-years in 2013, with the southeast Asia region contributing 52% of the disease burden.[1] Nervous system involvement is an important aspect of dengue infection with a plethora of neurological disorders.[2] Neurological manifestation in dengue infection can be central and peripheral, which is explained by three distinct mechanisms, (i) direct invasion of the central nervous system, leading to encephalitis, meningitis, and myelitis; (2) systemic complications resulting in encephalopathy and stroke; and (3) immune-mediated inflammatory reaction (para or post-infectious) such as acute disseminated encephalomyelitis, Guillain-Barré syndrome, Bell's palsy and optic neuritis.[3] In addition, dengue fever can be complicated by stroke, thrombocytopenia and immune-mediated vasculitis.[4] In this study, we tried to explore the neurological entities observed in dengue viral infection with their prognosis.

MATERIAL AND METHOD

- It was an observational study done in a tertiary-care hospital in northern India (Figure-1). This institute is situated in the eastern part of Uttar Pradesh which is an endemic region for dengue viral infection. The ethical approval was obtained from the Institutional Ethics Committee of the university. The written informed consent was taken from all the cases and controls. Patients were enrolled from December 2021 to August 2023 and followed-up at 2 month from discharge.
- Patients with confirmed dengue infection who attended the out-patient department, in-patient department and emergency ward were enrolled. Further screening was done, and patients with neurological involvement based on clinical and/or laboratorical features were included in the study. We excluded co-existent infections, and known pre-existing disorders including diabetes mellitus, hypertension, systemic lupus erythematosus, thyroid disorder, kidney disease and liver disease.
- The diagnosis of dengue fever was made according to presence of fever with reactive immunoglobulin M (IgM) dengue antibody, non-structural protein 1 (NS1) antigen or positive dengue polymerase chain reaction (PCR) on serum or cerebrospinal fluid.
- In all patients, we analyzed the detailed history and performed complete neurological examination. The patients/attendants were asked about the duration of fever, mental status, presence of headache/ seizures/ diplopia/ visual difficulty, limb weakness, extra-pyramidal symptoms, bladder/bowel symptoms and focal neurological deficits. Baseline Glasgow coma scale (GCS) score and vitals were recorded at the time of enrolment. Entire neurological assessment including other system evaluation was recorded.
- We did blood investigations, including complete blood count, liver and renal function test, thyroid function test, blood glucose, and electrolytes (sodium, potassium, calcium and magnesium). The human immunodeficiency virus ELISA was done in all patients. Serum NS1 and IgM dengue were assessed to confirm the dengue infection.
- CSF analysis was done for protein, total leukocyte and differential leukocyte counts, sugar with simultaneous measurement of plasma sugar. CSF IgM ELISA was performed with the National Institute of Virology Dengue MAC ELISA kit (Version No.1.4), Pune, India. All CSF samples were also tested by ELISA, for Japanese Encephalitis (JE) and herpes simplex virus to rule out co-infections
- Computed tomography (CT) and/or magnetic resonance imaging (MRI) was done according to the clinical status of the patient. CT images were looked for any hypodense or hyperdense areas while MRI of the brain with contrast was especially evaluated for any area of hyperintensity on fluid-attenuated inversion recovery (FLAIR) and T2-weighted images, restriction on diffusion weighted imaging, presence of contrast enhancement, and blooming on gradient recalled echo (GRE) sequences. MRI of spine was performed to look for T2 hyper-intense cord signal or contrast enhancement for myelitis when indicated.
- Nerve conduction study was performed for median, ulnar, tibial and common peroneal nerves for motor study, and median, ulnar and sural nerves for sensory study whenever required.

- The patients were managed conservatively with intravenous fluids, nasogastric tube feeding, antibiotics (if required), antipyretics, blood product as per WHO guidelines and as per disease-specificity {anti-seizure medication for seizure, decongestants (mannitol, glycerol, and acetazolamide) for cerebral edema, intravenous methyl prednisolone (for myelitis/ optic neuritis) and intravenous immunoglobulin (for Guillain-Barre syndrome)}.[5]
- The data was analyzed using Microsoft Excel 2007. (Microsoft, Seattle, WA, USA) and IBM SPSS was used for statistical analysis (20.0 version).All categorical variables were expressed as percentages, and continuous variables were expressed as mean ±standard deviation. Odds ratios and 95% confidence intervals were calculated as applicable. The p-value of less than 0.05 was considered to be statistically significant.

RESULT

A total of two hundred and thirty-eight patients with dengue infection were screened during the period of enrolment. Among this, 33 patients showed neurological manifestations and were included. After excluding 9 cases (4 hypertensive, 3 diabetic, 1 co-existent viral encephalitis and 1 kidney disease), a total of 24 cases were finally evaluated in this study and observed for 2 months in follow-up.

3.1 Demographic, Clinical and Laboratory Parameters

The baseline demographic, clinical and laboratory features of cases are shown in Table-1. Among the 24 patients, the mean age observed was 26.14±10.97 with male preponderance (58.33 %). The neuro-clinical spectrum included 7 cases of encephalopathy (29.17 %), 5 cases of encephalitis (20.83 %), 4 myelitis (16.67 %), 3 stroke (12.5 %), two cases of Guillain-Barre syndrome and Bell's palsy each (8.33 %) and one each for acute disseminated encephalomyelitis and hypokalemic paralysis (4.17 %) [Figure-1]. Hemogram showed a mean hemoglobin level of 11.58±3.72 g/dL, leucocyte count of 3744.14±2685.62 cells/mm^3, platelet count of 1.35±0.64 10^3 cells/mm^3. Serological study showed transaminitis in 10 cases (41.67 %), acute kidney injury in 2 cases (8.33 %) with hyponatremia in 4 cases (16.67 %), hypokalemia in 4 cases (16.67 %). Cerebrospinal fluid study was abnormal in 12 cases with a mean cell count of 24.71±18.74 cells/ mm^3, mean protein of 67.19±50.78 mg/dL and mean glucose of 83.79±13.41 mg/dL. Abnormal neuroimaging was observed in 14 cases (58.33 %) with subtyping showing predominant double-doughnut sign (5 cases) and longitudinally extensive transverse myelitis (3 cases) in MRI scanning. [Table-2] Mortality was observed in 1 case (4.17 %) who was suffering from dengue encephalitis during hospital stay.

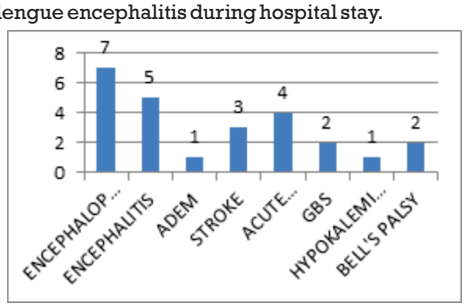

Figure 1: Spectrum Of Neurological Manifestation In Dengue Infection.

Table – 1 Clinico-laboratory Characteristics Of Dengue Infection With Neurological Involvement (n=24)

Parameters	n(%)
Number of patients with neurological involvement	24(10.08)
Age (mean)	26.14±10.97
Sex (male)	14(58.33)
Duration of illness (mean days)	14.14±10.97
Diagnosis	
1. Encephalopathy	7(29.17)
2. Encephalitis	5(20.83)
3. Acute disseminated encephalomyelitis	1(4.17)
4. Stroke	3(12.5)
5. Acute myelitis	4(16.67)
6. Guillain-Barre syndrome	2(8.33)
7. Hypokalemic periodic paralysis	1(4.17)
8. Bell's palsy	2(8.33)
9. Optic neuritis	0(0)
10. Myositis	0(0)
Blood Hemoglobin (g/dL)	11.58±3.72
Blood Leucocyte count (cells /mm3)	3744.14±2685.62
Leucocytopenia	13(54.17)
Serum Hematocrit (%)	33.81±2.62
Thrombocytopenia	19(79.17)
Blood Platelet count (103 cells/mm3)	1.35±0.64
Transaminitis	10 (41.67)
Serum AST (IU/L)	67.82±37.14
Serum ALT (IU/L)	74.73±29.37
Serum Bilirubin (mg/dL)	2.49±1.01
Acute kidney injury	2(8.33)
Serum Urea (mg/dL)	52.15±27.34
Serum Creatinine (mg/dL)	0.91±0.24
Hyponatremia	4(16.67)
Serum Sodium (mmol/L)	147.81±7.13
Hypokalemia	4(16.67)
Serum Potassium (mmol/L)	3.79±1.44
Calcium (mg/dL)	8.85±1.38
Abnormal CSF study	12(50.0)
CSF cells (cells /mm3)	24.71±18.74
CSF protein (mg/dL)	67.19±50.78
CSF glucose (mg/dL)	83.79±13.41
Abnormal neuroimaging	14(58.33)
Abnormal nerve conduction study	3(12.5)
Death	1(4.17)

Note: n, number; %, percentage; CSF, cerebrospinal fluid; mm, millimeter; IU, international unit; L, litre; mg, milligram.

Table-2: Neuro-imaging Characteristics In Dengue Infection With Neurological Manifestations

Imaging pattern	Total number	Site(s)
1. Double doughnut sign	5	Bilateral Thalamus
2. ADEM	1	Parietal lobes (asymmetric), pons, cerebellum
3. Infarct	1	Middle cerebral artery territory
4. Hemorrhage	1	Sulcal bleed
5. CVT	1	Superior sagittal sinus
6. LETM	3	Cervico-dorsal spinal cord
7. SSTM	1	Cervical spinal cord
8. Non-specific	1	Basal ganglia hyper-intense signal changes (Acute renal injury)

Note: ADEM, acute disseminated encephalomyelitis; CVT, cerebral venous thrombosis; LETM, longitudinally extensive transverse myelitis; SSTM, short segment transverse myelitis.

DISCUSSION

In this study, we observed neurological involvement in 10.28% of patients with dengue infection. Multiple studies (mostly retrospective) have been performed globally till date to ascertain the pattern of neurological manifestations in

dengue infection with variable incidences. In the largest multi-centric retrospective study (n=5821) from India over 6 years period from India (Kulkarni et al.), neurological involvement was observed in 154 patients (2.64%) with male preponderance (61.7 %) and mean age of 35.92 +/- 22.6 years. [6] The presentation included encephalopathy (31.2%), encephalitis (15.6%), syncope (27.3%), acute symptomatic seizure (11.0%), intracranial haemorrhage (4.5%), Guillain-Barre syndrome (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%). Our study showed similar presentation to this retrospective study by Kulkarni et al.

In another retrospective study of 2 years duration by Verma et al., neurological manifestation was observed in 26 cases with a mean age of 29.08 years, male predilection in 18 patients (69.23%) with presentation including brachial neuritis (38.46%), encephalopathy (15.38%), Guillain Barre syndrome (11.54%), hypokalemic paralysis (11.54%), acute viral myositis (7.69%), opsoclonus-myoclonus syndrome (7.69%), and 1 patient each having myelitis and acute disseminated encephalomyelitis (3.85%).[7]

In a prospective study by Koshy et al. in India, neurological manifestations occurred in 21 out of 799 dengue patients (2.63%), with a male preponderance (90.47%) with a mean age of 33.7 ± 13.9 years with spectrum including hypokalaemia quadriparesis (33.33%), myositis (19.05%), encephalopathy (19.05%), Guillain–Barre syndrome (9.52%), acute disseminated encephalomyelitis (9.52%), lumbosacral plexopathy (4.76%) and intracranial haemorrhage (4.76%).[8] In another prospective study by sahu et al. in India, the incidence of neurological dengue was 9.26% with a mortality of 4.5%.[9] The neuroimaging pattern observed in this study was comparable to a retrospective study by Vyas et al. where they studied 36 cases to observe abnormal MRI in 25 cases (69.44%) in the form of encephalitic pattern (48%), encephalopathic (seizure related/metabolic) pattern (16%), ADEM (12%), and isolated micro- or macro-hemorrhages (24%). [10] In addition, there have been occurrence of bifacial weakness in dengue virus as reported by Patel et al. and Peter et al.[11,12] ; optic neuropathy by Sanjay et al.[13] ; phrenic nerve palsy [14] ; abducens nerve palsy [15] ; lateral rectus palsy[16] and long thoracic nerve palsy[17] . In a case series of 7 dengue patients with atypical neurological presentations, ocular flutter and intramedullary hemorrhage in conus medullaris and cauda equine were observed by Prabhat et al.[18] In another recent case series of 7 patients of dengue fever with neurological manifestations, a case of mononeuritis multiplex was observed with similar sporadic observations.[19,20,21]

CONCLUSIONS

Dengue is an established, yet an emerging tropical disease of protean neurological manifestations. The exact aetio-immunopathogenesis is not well explored. The expanding clinical spectrum of neurological dengue infection and its complications needs proper classification and therapeutic exploration. A greater awareness of dengue fever and its neurological impact can lead to better outcome

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