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Central nervous system involvement in dengue: A tertiary care centre study

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ABSTRACT

Background: Recent studies have shown dengue viral infection causing encephalopathy, with high morbidity and mortality. Patients with dengue encephalopathy usually present with altered sensorium, elevated lab parameters, and high antibody titers at the time of admission.
Objectives: The objective of this study was to study the clinical presentation, lab parameters and diagnostic features, and management and outcome of patients with dengue encephalopathy in Hadoti region in the period of August to November, 2017.
Methodology: The study was conducted in the Government Medical College Hospital, Kota and in other multispecialty hospitals in Kota. Study population comprised 60 patients presenting with febrile illness and thrombocytopenia, serologically proved to be having dengue fever. Among these 60 patients, 30 patients had encephalopathy and the remaining 30 had no signs and symptoms of encephalopathy.
Results: Among 30 patients with encephalopathy and positive serology, fever and altered sensorium were the most common symptoms. Out of 30 patients with encephalopathy, 16 patients had convulsions, 14 had respiratory distress, 17 had shock, and 3 had hemiplegia. Two patients also had visual blurring and dysarthria. Mean duration between appearance of fever and altered sensorium was 4.6 (±2.1) days. Most of the patients with encephalopathy had deranged hepatic, renal, and coagulation parameters. Nine patients with encephalopathy died.
Conclusions: Increased incidence of dengue encephalopathy in the recent years, in the absence of single sensitive test and with variable cerebrospinal fluid and magnetic resonance imaging brain features and associated high morbidity and mortality, poses a huge problem for clinicians. This study may be helpful in focusing on early diagnosis and aggressive initial management that can influence the final outcome.

1. Introduction

RNA virus of family Flaviviridae that spreads by *Aedes* mosquitoes is responsible for dengue fever.[1] Approximately 2.5 billion people are at risk primarily in the densely populated areas of tropical and subtropical countries, with an estimated infection load of 50 million worldwide annually. According to the World Health Organization (WHO), India is considered to be in endemicity category A, in which dengue is a major public health problem. Presentations in symptomatic patients include undifferentiated viral fever, dengue fever, and dengue hemorrhagic fever. Expanded dengue spectrum includes unusual manifestations such as neurological, hepatic, renal, and other isolated organ involvement.

Common clinical features are fever, arthralgia, headache, petechial spots, rashes, and hemorrhagic manifestations. Dengue virus is considered a nonneurotropic virus.[1] However, an increasing number of studies and case reports of central nervous involvement (CNS) involvement are being reported.[2–5] The CNS manifestations can be attributed to three factors: (a) neurotropic effect, (b) secondary to systemic manifestation, and (c) postinfectious sequelae including immune-mediated reactions.[5,6] Numerous neurological manifestations, such as encephalopathy, encephalitis, Guillain–Barre syndrome, transverse myelitis, acute disseminated encephalomyelitis, and myositis, are reported. These neurological complications are rare, and its pathogenesis is controversial. Few theories state that dengue neurological manifestation is secondary to systemic manifestation (encephalopathy), but recent evidence is in favor of dengue neurotropism because dengue virus[7] and dengue IgM antibodies have been discovered in the cerebrospinal fluid

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(CSF) of patients with encephalopathy which suggests that dengue virus is capable of CNS infection. Dengue fever associated with encephalitis has high morbidity and mortality, and only few studies or case series have been published regarding dengue encephalitis.[8] This study may be useful in early detection of patients with dengue encephalopathy (which might be encephalitis) using clinical features and laboratory parameters in resource-limited countries that have a maximum number of dengue cases, so that early diagnosis of dengue encephalopathy and timely supportive therapy can reduce or avoid morbidity and mortality. We present a total of 30 cases of dengue encephalopathy.

2. Material and methods

This epidemiological prospective study was conducted at the Government Medical College Hospital, Kota and in other multispecialty hospitals in Kota.

This study included a total of 60 patients serologically proved to be having dengue fever, among which 30 patients had encephalopathy (or encephalitis) who presented with altered sensorium, seizures, or any other neurological symptoms. The remaining 30 patients who had dengue fever without encephalopathy served as control.

The diagnosis of dengue fever was based on clinical features (fever, headache, body ache, altered sensorium, hemorrhagic manifestation, jaundice, and shock) and positive serum NS1 Ag or IgM/IgG antibodies. It was carried out initially by Dengue DAY 1 rapid diagnostic test (J. Mitra & Co. Pvt. Ltd.) and confirmed by MAC-ELISA NIV (National Institute of Virology) test. The diagnosis of encephalopathy was based on clinical features (low Glasgow coma scale [GCS], altered sensorium, headache, seizures, or any other neurological deficits), magnetic resonance imaging (MRI) brain findings (hyperintense areas), and CSF study (cell count, protein, and sugar).

The detailed medical history, age, area of residence, and clinical features were noted. Consciousness was assessed by the GCS. Systemic manifestations such as lymphadenopathy; hepatosplenomegaly; jaundice; and cardiac, renal, and respiratory findings were also recorded.

The laboratory tests included complete blood examination (hemoglobin, hematocrit, white blood cell count, and platelet count, blood sugar, blood urea, serum creatinine, bilirubin, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), prothrombin time, international normalised ratio (INR), and serum dengue antibodies). Electrocardiogram and chest X-ray (posteroanterior (PA) view) were carried out in all patients, and computed tomography scan and/or MRI brain and cerebrospinal fluid analysis (analyzed for protein, sugar, and cells) were carried out in as much patients of encephalopathy group as possible.

To rule out other concurrent causes of such presentation, tests for malaria by peripheral blood film (thick and thin both) as well as card test named ErbaQik one step malaria Ag Pf/Pv (HRPII/pLDH), chickungunya IgM by BIOCREDIT Chikungunya IgM immunochrmatographic test, and scrub typhus IgG/IgM/IgA antibodies by BIO LINE SD (Standard Diagnostics) immunochromatographic method were also conducted. Only isolated patients with dengue were included in the study.

2.1. Exclusion criteria

1. Patients with previous liver or kidney failure and recent cerebral events (stroke and meningoencephalitis), malaria, and hepatitis.
2. Patients with concurrent infection of malaria, chikungunya, or scrub typhus.

Indication for admission (cases): In encephalopathy group, patients with a history of fever with any neurological event (seizures, altered sensorium, or focal neurological deficit) and positive dengue serology.

3. Results

Among 30 patients with proven dengue fever with altered sensorium, seizures, or any other neurological symptoms suggestive of encephalopathy/encephalitis, 22 patients were male and 8 were female. All patients presented with fever with or without chills. Headache, vomiting, and pain in the abdomen were also prominent features. Detailed symptomatic profile of the encephalopathy group and controls is given in Table 1.

Most common clinical features in patients with encephalopathy were fever with altered sensorium. Clinical features such as seizures, shock, generalized weakness, and shortness of breath were significant (Table 1).

All 30 patients had altered sensorium, among which 19 patients required intubation and ventilator support, 2 patients required bilavel positive airway pressure (BIPAP) support, and 9 patients were maintained on oxygen supply using a face mask.

3.1. Neurological examination

All patients with encephalopathy presented with altered sensorium, 11 patients had exaggerated deep tendon reflexes (DTRs), 12 patients had extensor plantar reflex, and the remaining patients had normal DTR and plantar reflex.

Hepatic dysfunction was found in most patients as deranged transaminases or bilirubin levels. Fourteen patients (46%) also had renal impairment as deranged urea/creatinine or decreased urine output (Table 2). All patients had thrombocytopenia of varying degrees. Detailed laboratory results are analyzed in Table 2.

All 30 patients with encephalopathy had severely deranged liver enzymes (SGOT and SGPT), coagulopathy (raised prothrombin time (PT) and INR), severe thrombocytopenia, and positive serology (NS1/IgM/IgG). Six patients were positive for both IgG and IgM antibodies, 16 patients were positive for NS1 and IgM, and 8 were positive for NS1, IgM, and IgG.

Three patients required continuous renal replacement therapy (CRRT) for acute kidney injury for a short period. Sixteen patients had generalized seizures, and 14 patients had respiratory distress out of which two patients had acute respiratory distress syndrome

Table 1
Comparative clinical profile of patients who had dengue fever with or without encephalopathy.

Clinical symptoms	Patients with encephalopathy, N = 30	Patients without encephalopathy, N = 30	P value (unpaired student's *t*-test)
Fever	*30*	30	
Headache	19	14	0.18
Vomiting	10	11	0.80
Pain in the abdomen	10	8	0.55
Rash	7	9	0.73
Altered sensorium	30	0	**0.001**
Shock	17	1	**0.03**
Seizure	*16*	0	**0.001**
Hemiplegia	3	0	0.07
Respiratory distress	14	1	**0.001**
Visual blurring and dysarthria	2	0	0.15
GCS	6 ± 2/15	14–15/15	**0.02**

GCS, Glasgow Coma Scale.
P value <0.05 is significant.

Table 2
Comparative laboratory parameters of patients who had dengue fever with or without encephalopathy.

Laboratory parameter	With encephalopathy	Without encephalopathy	P value (<0.05-significant)
Total leucocyte count (TLC)	7850 ± 2878	6550 ± 2770	0.07
Mean platelet on admission	92000 ± 23000	102000 ± 25000	0.11
Mean minimum platelet	19000 ± 12000	17000 ± 10000	0.48
Hematocrit	37.25 ± 5.72	39.2 ± 6.1	0.20
Bilirubin	2.56 ± 1.76	1.2 ± 0.6	**0.0002**
SGOT	2004 ± 1359	254 ± 130	**0.0001**
SGPT	1304 ± 981	196 ± 94	**0.0001**
Urea	62.26 ± 50.9	34.1 ± 9.8	**0.004**
Creatinine	1.64 ± 1.37	0.9 ± 0.5	**0.007**

Bold p values are statistically significant.

(ARDS) and one patient had hemoptysis. Seven patients (23%) had hyponatremia and required intravenous sodium.

3.2. CSF study

CSF examination showed high protein and normal cell counts in 10 patients and normal protein and normal cell count in 14 patients (CSF examination was not performed in 7 patients). CSF polymerase chain reaction (PCR) to identify the presence of dengue virus was not performed because of poor availability of resources.

3.3. MRI brain study

MRI brain was performed in 23 patients, out of which

1. 4 patients had diffuse cerebral edema
2. Hyperintensities in temporal lobes/thalamus or pons were seen in 10 patients, among which 6 patients had hyperintensities in the thalamus, 3 patients in temporal lobes, and 1 patient had diffuse cerebral atrophy and multiple small infarct. MRI features in dengue encephalopathy are nonspecific, and these findings can be similar as in Japanese encephalitis, herpes encephalitis, chikungunya encephalitis.
3. 7 patients' MRI was normal
4. 1 patient's MRI showed left basal ganglia bleed, and 1 had only sinusitis. Platelet count is low of varying degree in almost all patients in study population. Patient who had basal ganglia bleed had platelet count of 21000. There was no any other cause of bleeding in this patient as he had no HTN or any other bleeding diathesis.

Among 30 patients with dengue encephalopathy, 20 patients recovered completely at the end of 1 month (independent for activities of daily living) and 9 patients died (due to severe sepsis with multiorgan dysfunction syndrome [MODS]).

Table 3
Comparative study between patients with dengue encephalopathy who improved and died.

Parameters	Improved patients (n = 20)	Died patients (n = 9)
Seizures	9 (45%)	8 (89%)
Respiratory distress	10 (50%)	4 (45%)
Mean bilirubin	2.6	2.75
Mean urea	61.65	71.2
Mean creatinine	1.5	2.13
Time between fever and altered sensorium	4 to 6–7 days (mean, 4.85)	4 to 6–7 days (mean, 4.11)

Comparative study of patients who survived and died on the basis of various parameters is given in Table 3.

Among all patients, 24 patients were given mannitol/dexamethasone and 16 patients also received inj. acyclovir.

Inj. acyclovir was found to be beneficial in patients with dengue encephalopathy, most probably due to cross-reactivity with viral antigens; however, exact reason is not known. Sixteen patients were given acyclovir, of which 12 patients' condition improved and 4 (25%) died, whereas among 14 patients who were not given acyclovir, 5 (35%) patients died.

4. Discussion

Dengue is endemic to more than 100 countries, and approximately 2.5 billion people are at risk. It is estimated that 50–100 million infections and 25,000 fatalities occur worldwide every year. The WHO surveillance shows that global incidence is increasing.[8] The primary vector is the mosquito *Aedes aegypti*. Dengue fever has varying clinical presentation, ranging from asymptomatic infection to life-threatening hemorrhagic fever and dengue shock syndrome. Complications of dengue fever are common and usually related to renal and hepatic dysfunction. In our study, almost all patients had severely deranged liver enzymes (SGOT and SGPT), coagulopathy (raised PT and INR), severe thrombocytopenia, and positive serology (NS1, IgM, and IgG) (Table 2). Patients were managed conservatively as per WHO guidelines. In the patients with hemorrhagic diathesis, platelet concentrate and/or fresh frozen plasma were administered as indicated. Among all patients, those with low GCS were intubated to protect the airway and most were extubated after 5–7 days. Nine patients who were on prolonged ventilation died later due to refractory septic shock and MODS due to secondary bacterial sepsis. CRRT was given for three patients with acute kidney injury having oliguria/anuria, pulmonary edema, hyperkalemia, and severe metabolic acidosis.

Neurological complications are rare, and their pathogenesis is controversial; few theories state that dengue neurological manifestation is secondary to systemic manifestation (encephalopathy), but recent evidence is in favor of dengue neurotropism because dengue virus[9] and dengue IgM antibodies[10] have been detected in the CSF of patients with encephalopathy, which suggests that dengue virus is capable of CNS infection.

In our study, the features of encephalitis (headache, altered sensorium, and seizures) in most patients were seen more commonly after 4–7 days of onset of fever (Table 3). Among the four dengue serotypes (DEN-1 to DEN-4), DEN-2 and DEN-3 have highest propensity to neurological complications.[11,12] However, test for dengue serotype was not conducted in this study because of nonavailability of this facility.

Cam BV et al.[9] have reported the encephalopathy incidence ranging from 0.5% to 6.2%. Kankirawatana et al.[10] found that 18% of children with suspected encephalitis in Thai hospitals were found to have dengue infection.

All the patients who died in the encephalopathy group (9 out of 30 patients) presented with low GCS, seizures, and headache. Hence, patients with dengue fever with predominance of these clinical features and severely deranged laboratory parameters are probably manifesting encephalopathy that has high morbidity and mortality, so early diagnosis and aggressive management should be given to prevent anticipated complications.

In case of dengue encephalitis, diagnosis can be made either by detection of virus in the CSF (viral culture/PCR) or immune response by the body (IgM antibodies in CSF). The gold standard method is viral culture that is difficult and time-consuming. Regarding CSF IgM and IgG antibodies, Puccioni-Sohler M et al.[13]

and Cristiane Nascimento Soares[14] have shown that these antibodies can be found in the CSF but their absence will not rule out encephalitis. In our study, CSF IgM and IgG were not examined because the sensitivity of this test was found to be very low and this test was thought to be a financial burden for those patients.

CSF study in the encephalopathy group showed high protein and normal cell counts among 10 patients and normal protein and normal cell count among 13 patients, but serum IgM and IgG were positive in all patients. These findings are similar to that of viral encephalitis.

Brain imaging: MRI is the modality of choice that shows the findings consistent with viral encephalitis including cerebral edema, white matter changes, necrosis, and brain atrophy. Encephalitis features in the brain (hyperintense areas) can be seen in globus pallidus, temporal lobes,[15,16] thalamus,[17] hippocampus,[18] pons, and spinal cord.[19] Among 30 patients with dengue encephalopathy, 20 patients recovered completely at the end of 1 month (independent for activities of daily living) and 9 patients died (due to severe sepsis with MODS). CSF culture or PCR for viral detection in the CSF was not carried out. But, all patients proved to be having dengue serum antibodies were managed conservatively according to WHO guidelines. More research is necessary for the changing trend of host immunological response and dengue viral characteristics as more patients with dengue viral infection in recent years are presenting with encephalopathy.

Acyclovir in dengue encephalopathy: There is no specific antiviral drug for dengue encephalopathy, but patients who presented initially in critically ill condition with encephalopathy signs and symptoms were given inj. acyclovir as empirical therapy for viral encephalitis.[8]

Also, research into the pathogenesis of dengue infection may yield new treatments, and current work has shown inhibition of dengue replication in cell culture by many promising antiviral agents, including ribavirin, Morpholino oligomers, Geneticin, and blockers of viral envelope proteins.[20]

In Hadoti region, mortality rate was high among patients with dengue encephalopathy as comparative to other studies, which may be due to more virulent strain of dengue virus or delayed reach of patients to the health-care center.

Study population was small because of exclusion of many patients due to concurrent other infections such as malaria, chikungunya, or scrub typhus; hence, a large population study is required.

5. Conclusion

There has been increased incidence of dengue encephalopathy in recent years, in the absence of single sensitive test for detecting dengue encephalitis and with variable CSF and MRI brain features and associated high morbidity and mortality. This study may be helpful in focusing on early diagnosis and aggressive initial management that can influence the final outcome.

Conflicts of interest

There is no actual or potential conflict of interest in relation to this article.

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