A study of dengue encephalitis with laboratory and clinical parameters in Tertiary Center of North India

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ABSTRACT

Introduction: With expanding clinical spectrum of dengue fever, encephalitis has been documented with increasing frequency. The aim of this study was to investigate the incidence, predictors and prognostic factors of dengue encephalitis (DE) in the setting of dengue viruses (DENV) infection. Materials and Methods: A hospital-based prospective cohort study was carried out, which included laboratory confirmed dengue positive cases. All dengue cases were categorized into nonencephalitis or encephalitis group. We estimated DE incidence and analyzed clinical, laboratory and neuroimaging data on admission, discharge and follow-up for 3 months to assess its predictors and prognostic factors. Results: Out of the enrolled 540 confirmed dengue cases, 27 patients had DE, representing 5% incidence. Two third of the DE patients were 20 years of age or younger, with male preponderance (81.5%). Fever, headache, and altered sensorium were present in >90% on admission. Significant predictors of encephalitis were mean body temperature during fever \( P < 0.001 \), headache \( P = 0.015 \), secondary dengue \( P = 0.005 \), dengue hemorrhagic fever \( P < 0.001 \), elevated hematocrit \( P < 0.001 \), liver function test derangement \( P < 0.05 \), and low platelet count \( P = 0.006 \). Poor outcome factors for DE patients were prolonged duration of fever \( P < 0.001 \), seizure \( P = 0.002 \), and cerebrospinal fluid (CSF) DENV positivity \( P = 0.049 \). One third patients died and the remainder of them recovered. An increasingly higher incidence rate with high mortality of DE is reported. Conclusion: Clinical and laboratory parameter along with DENV positivity in CSF can predict and prognosticate dengue encephalitis.

Keywords: Cerebrospinal fluid, dengue fever, dengue virus, encephalitis, flaviviridae

Introduction

Dengue infection is the most important tropical viral disease in the world today. According to the World Health Organization, 50 million symptomatic dengue infections occur annually representing a huge public health problem mainly in Southeast Asia and Western Pacific regions. D Dengue virus (DENV) are single-stranded RNA arboviruses with four serological types (DENV 1–4) and belong to the Flaviviridae family. Clinical symptoms of dengue infection vary, ranging from simple myalgia, arthralgia, headache, dengue fever (DF), dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) to neurological dengue manifesting as encephalopathy, encephalitis, encephalomyelitis, myelitis, brachial neuritis, Guillain Barre syndrome, hypokalemic paralysis, viral myositis and rare opsoclonus-myoclonus syndrome. Dengue infection with acute encephalopathy was first reported by Sanguansermsri et al., in 1976 since that time, there have been reports from several Southeast Asian countries. Although basic pathophysiology of central nervous system involvement in dengue infection remains...
unclear, the encephalopathy in the reported cases have been attributed to cerebral edema, anoxia, hemorrhage, hypotension, hepatic failure, and release of toxic substances. Various animal and clinical studies have suggested a neurotropic potential of DENV leading to encephalitis. Detection of virus antigen in brain autopsy samples, dengue-specific immunoglobulin M antibody (IgM Ab) and positive reverse transcriptase PCR (RT-PCR) in cerebrospinal fluid (CSF) support the hypothesis of neuro-invasion during acute dengue infection. Patients as well as Clinician both face difficulties due to overlapping symptoms between dengue fever and COVID-19. Misdiagnosis of COVID-19 as dengue has been reported even after use of rapid dengue tests. The consequences of COVID-19 and dengue misdiagnosis are relevant, and may include ineffective patient management, possibly leading to preventable patient death, as well as unsuccessful prevention strategies, including rapid patient isolation (in the case of COVID-19) and vector control (in the case of dengue fever). So Diagnostic (clinical, hematological and biochemical) accuracy should be there before any treatment and management. Due to lack of aforementioned literature for early confirmatory clinical and laboratory diagnosis for DENV, we have planned this study. The objective of this study was to investigate the incidence, predicting and prognostic factors of dengue encephalitis (DE) in the background of DENV infection.

Subjects and Methods

A hospital-based prospective cohort study, conducted in a tertiary care referral center of north India. The Institutional Ethics Committee approved (4082/R-col B Ref no- 60th. ECM II-B/ P13) the study and informed consent was obtained from patients or parents or legal guardians. The patients irrespective of age and gender who were presented in indoor or outpatient departments of neurology, medicine and pediatrics with febrile illness suspecting DF, fulfilling the diagnostic criteria of DF according to WHO guidelines and confirmed by laboratory results were included. Patients of DE were defined as those who had altered sensorium to the level of mental confusion, stupor, semicoma, or coma, with or without other neurological features including convulsions, spasticity, and focal neurological signs and tested positive for dengue in CSF or serum. We excluded patients having encephalitic illness due to malarial, bacterial, fungal, and other viral infections and encephalopathy caused by systemic complication of dengue.

During the study period all patients underwent clinical evaluation regardless of encephalitis manifestation. Demographic data included age, and sex. Clinical data included degree (body temperature ≥99.5°F) and duration of fever, presence of headache, myalgia, arthralgia, rash, hemorrhagic manifestations, tourniquet test as per WHO guidelines, time of onset and type of encephalitis signs-symptoms were also recorded. Consciousness was assessed by Glasgow Coma Scale (GCS) score.

Laboratory and radiological assessments

Para clinical tests included complete blood count; glucose, electrolytes, serum urea, creatinine, bilirubin, transaminases, albumin, and peripheral blood smear for malarial parasites were done in all the cases. Prothrombin time activated partial thromboplastin time, chest radiograph, electrocardiogram ultrasound abdomen, arterial blood gas analysis were done according to clinical condition in selected cases. We categorized dengue patients as nonencephalitis (Group A) and encephalitis (Group B).

A lumbar puncture was carried out in encephalitis group and CSF was examined for cell, protein, and sugar. CSF Gram and acid fast bacilli staining as well as India ink staining were also done to exclude common bacterial or fungal infection. Positive IgM Ab ELISA (enzyme link immunosorbent assay) or four-fold rise in IgG antibody titer or nonstructural protein antigen (NS1 Ag) positivity or detection of dengue RNA by real-time PCR assay in CSF/serum was considered for definitive diagnosis of DE. We excluded other viral infection by testing CSF and serum for HIV1 and 2, HTLV-I, Herpes simplex, Enterotox, Coxackie, Epstein bar, Japanese encephalitis, measles, mumps, Varicella zoster and cytomegalovirus. Cranial magnetic resonance imaging or contrast computed tomography scan was carried out in 26 patients, remaining one patient was not transportable.

Treatment

There is no specific treatment for dengue infection. All patients were monitored and managed with intravenous fluids, blood products according to standard WHO guidelines.

Follow-up

All cases were followed until total recovery and for a minimum of 3 months after hospital discharge. The neurological status was evaluated using modified Rankin Scale (mRS) in encephalitis group. The outcome was defined as good (mRS scores ≤3) and poor (mRS score >3 or death).

Statistical analysis

For data analysis we used Statistical Package for Social Sciences, version 16 for Windows (SPSS, Chicago II, USA). We recorded discrete data as frequency and percentage (%) and symmetrical distributed continuous data as mean ± standard deviation (SD). To evaluate the predictors of encephalitis, we used univariate and multivariate analysis. For nonparametric data, we used univariate analysis with Chi-square test and student “t” test for parametric data. We ascertained relative risks with 95% confidence interval (95% CI). We used binary logistic regression for multivariate analysis to assess the impact of individual predictors of encephalitis and to reduce the effect of confounders. P value < 0.05 was considered statistically significant.

Results

A total of 546 laboratory confirmed dengue infection patients were included in the study. Six patients were excluded due to loss in follow-up.
Baseline characteristics
In 540 enrolled dengue patients male to female ratio was approximately 2:1. Mean age was 37.94 ± 22.027, the youngest one was 1 year old and the oldest one was 84 years. Only 8 (1.5%) patients had history of previous dengue infection [Table 1].

Incidence and clinical characteristics of encephalitis
Out of 540 enrolled cases, 513 cases had no encephalitis features (Group A) and remaining 27 patients including 5 females and 22 males, developed features of encephalitis representing the 5% incidence of encephalitis with dengue infection (Group B). Total 99 patients of both groups had DHF. Majority of patients in group B (63%) were ≤20 years of age (mean age was 19.13 ± 17.030, P < 0.001) [Table 1]. All patients were in altered sensorium at admission except two whose alteration of sensorium developed on day 2 of admission at our institute but had history of seizure episode before admission. Other 14 experienced generalized convulsions during hospital course. Their median Glasgow coma scale (GCS) score was 8.0 (range 3–14).

Neuroimaging and cerebrospinal findings
In Group B, five magnetic resonance imaging scans and 21 contrast computed tomography of cranium were performed, the clinical condition of the remaining one patient did not allow for transportation. Sixteen patients (59.25%) had abnormal neuroimaging. Cerebral edema was present in 12 patients (44.4%) and remaining 4 patients had edema with scattered focal lesions [Figure 1].

Lumbar puncture was performed in all 27 patients of Group B. Mean protein was slightly raised and mean glucose was normal. CSF lymphocytic pleocytosis was found in 23 (85%) patients. Dengue was confirmed in 17 CSF samples (3 NS1 Ag and 14 IgM Ab). Remaining 10 CSF negative samples were confirmed in serum (3 NS1 Ag and 7 IgM Ab).

Predictors of encephalitis
Younger age patients (P < 0.001) and male gender (P = 0.043) were more affected in Group B. Mean temperature of fever was higher in Group B than in Group A (P < 0.001). Interestingly overall frequency of secondary dengue infection was low but more common (P = 0.005) along with DHF (P < 0.001) in group B. Headache occurred more frequently in Group B (P = 0.015). Myalgia and arthralgia was found more frequently in Group A (P < 0.001). Nausea, vomiting, and abdominal pain showed no statistical difference in frequency but diarrhoea was more common in Group A (P = 0.007) [Table 1].

Mean platelet count was low (P = 0.006) and mean hematocrit was higher (P < 0.001) in Group B. Mean serum aspartate transaminase (AST), alanine transaminase (ALT), and bilirubin level were elevated in Group B [(P = 0.002), (P = 0.005), (P = 0.004)], respectively [Table 1].

There was no significant difference in mean systolic and diastolic blood pressure, total leukocyte count, serum creatinine, serum sodium and potassium level between both the groups (P > 0.05) [Table 1].

Independent predictors of encephalitis
To evaluate independent impact of predictors, data subjected for multivariate analysis and we found that higher mean body

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**Table 1: Comparison of demographic, clinical and laboratory parameters for Group A (nonencephalitis) to Group B (encephalitis)**

| Variables | Group A (n=513) (%) | Group B (n=27) (%) | P |
|-----------|---------------------|--------------------|---|
| Age (mean) | 38.77±21.7          | 19.13±17.03        | <0.001* |
| Sex (male) | 319 (62.2)          | 22 (81.5)          | 0.043*  |
| Fever     | 474 (92.4)          | 27 (100)           | 0.137   |
| MBT       | 99.66±0.9           | 102.71±1.37        | <0.001* |
| DHF       | 84 (16.4)           | 15 (55.6)          | <0.001* |
| Secondary dengue | 5 (1)           | 3 (11.1)           | 0.005*  |
| Nausea - Vomiting | 335 (65.3)       | 15 (55.6)          | 0.301   |
| Headache  | 341 (66.5)          | 24 (88.9)          | 0.015*  |
| Diarrhea  | 188 (36.6)          | 3 (11.1)           | 0.007*  |
| Abdominal pain | 153 (29.8)       | 5 (18.5)           | 0.208   |
| Myalgia   | 400 (78)            | 6 (22.2)           | <0.001* |
| Arthralgia| 281 (54.8)          | 5 (18.5)           | <0.001* |
| SBP (mm Hg) | 116.49±8.59       | 115.7±11.96        | 0.650   |
| DBP (mm Hg) | 77.80±6.43        | 76.22±7.3          | 0.217   |
| TLC (per mm3) | 7348±1493         | 8519±3303          | 0.078   |
| Hematocrit (%) | 27.33±3.875     | 34.59±2.981        | <0.001* |
| Platelet (10³/mm³) | 1.616±0.40       | 1.180±0.75         | 0.006*  |
| Serum sodium | 141.98±5.8       | 140.33±4.2         | 0.059   |
| Serum potassium | 3.642±0.37       | 3.67±0.3           | 0.649   |
| AST (IU/L) | 39.43±8             | 68.26±44.5         | 0.002*  |
| ALT (IU/L) | 37.61±7.13          | 61.85±40.49        | 0.005*  |
| Total bilirubin (mg/dl) | 0.956±0.185 | 1.348±0.65        | 0.004*  |
| Serum creatinine (mg/dl) | 1.447±0.479 | 1.437±0.391    | 0.914   |

*P value is significant
temperature during fever and elevated hematocrit were related independently with encephalitis.

**Clinical outcome**

In Group A, 5 of 513 patients (2 female and 3 male) presented with DSS, died. Nine patients (33.33%), all male in group B died. We also analyzed mRS disability scores in encephalitis group at the time of discharge and at 3-month follow-up. In this group, at the time of discharge 5 (18.52%) patients had mRS scores ≤3, and 22 (81.48%) cases had mRS scores between 4 and 5. By 3-months, remaining all 18 patients recovered (mRS ≤3). All deceased patients had seizure (P = 0.002) with prolonged mean duration of fever (P < 0.001). Although mortality was higher in younger age (mean age of deceased patients were 11.1 ± 12.180), but not significant. In deceased patients dengue positivity was more common in CSF ([8/9], (P = 0.049)) [Table 2]. Complete recovery of all neurologic symptoms was observed within a maximum of 14 days in survivors.

There was no significant difference in mean systolic and diastolic blood pressure, serum creatinine, liver function test (LFT), sodium and potassium level between survivor and nonsurvivor (P > 0.05). CSF cytology, biochemistry, and neuroimaging abnormality were also not significant between both groups [Table 2].

**Discussion**

DENV belongs to the Flaviviridae family in which Japanese encephalitis, St. Louis encephalitis virus, tick-borne encephalitis virus, West Nile encephalitis virus and yellow fever have well known neurotropism. Earlier central nervous system involvement in dengue infection was thought to be secondary to prolonged DHF with fluid extravasation, cerebral edema, hyponatremia and liver failure, renal failure, or both, known as dengue encephalopathy as opposed to direct involvement of the brain by the dengue virus referred as encephalitis. Animal studies in mice provided a virus-induced, cytokine-mediated breakdown of the blood–brain barrier and a study from Thailand of acute encephalitis, without systemic complications with positive laboratory evidence of dengue in CSF concluded that dengue virus can actively produce acute central nervous system manifestation.[1-13] In few other studies, incidence of encephalitis ranging from 0.5% to 6.2% have been reported.[15,16,14] In present 2 year study, 5.0% of patients with dengue infection developed encephalitis. It is higher than previously reported observations of 2.8%[15] and 0.5%[16] but lower than 12.9% reported frequency from Brazil.[13]

Overall males were more infected with dengue virus (M: F: 2:1) and frequency of encephalitis was more common in male (P = 0.043). All except two had fever with decreased sensorium on day 2 or day 3 of fever, rest developed drowsiness on next day of admission. A study from Malaysia also observed similar result that all the affected patients were male and feature of encephalitis on early period of fever.[18] It is tough to explain this preponderance. Higher frequency of secondary dengue and DHF was observed in patients with encephalitis. Vascular permeability with plasma leakage in dengue is usually described after the third day of illness. In our study, patients admitted were usually on their fourth to fifth day of fever, by which time hemoconcentration had already developed.

Clinically, high mean body temperature along with laboratory parameters, such as increased mean hematocrit, were independent predictors of encephalitis in this study. Earlier studies found increased serum transaminase levels in severe dengue infection.[17] We therefore hypothesize that rapid development of hemoconcentration with raised liver enzyme levels in high temperature is predictive of DE.

There is an “integral hypothesis” for the pathogenesis of DHF that secondary infections (epidemiological factor), increase virulence of virus strains (viral factor), and host susceptibility are responsible for development of DHF. Secondary dengue infection during repeated outbreaks enhances the virulence, possibly due to antibody dependent enhancement which leads to the early pathophysiological changes predicting severity of dengue infection.[19] In most of the patients cerebral edema was observed in neuroimaging and in four patient’s edema with scattered focal lesions involving the basal ganglia, hippocampus, thalamus, or internal capsule. Similar neuroimaging features were also described in previous studies.[6,20,21] As IgM Ab cannot cross the blood–brain barrier, detection of dengue IgM in the CSF of
encephalitic patient suggests DE.[2,20] We identified either IgM Ab or NS1 Ag positivity in CSF of patients with encephalitis, strongly supporting direct neuro-invasion by DENV. Lymphocytic pleocytosis, mild elevated CSF proteins and normal glucose were also consistent with a viral etiology.

Mortality rates reported in neurological dengue and severe dengue infection range from 5% to 8.35%.[5,23,24] Higher mortality (32%) in DE and encephalomyelitis has been reported in a study from Pakistan.[19] We also observed higher mortality (33.33%) in patients with DE. In our study, all deceased patients of DE were young age male, having prolonged duration of fever with seizure. Earlier study from south India also noted that most neurological events were not related to the decrease perfusion (shock) of patients studied and were found to be the commonest cause of death in complicated dengue infection.[23] Higher mortality rate in DENV-positive CSF in our study also indicate the increased risk for development of severe dengue infection. Higher relative risk for death in DENV-positive CSF patients compared to those who recovered was also found in a Brazilian study.[23] Dengue encephalopathy, though a rare diagnosis, should be considered a differential in cases of fever with altered sensorium, especially at the times of a dengue epidemic.[24] Infection may be asymptomatic or present with a broad range of clinical manifestations including a mild febrile illness to a life-threatening shock syndrome. Numerous viral, host, and vector factors are thought to impact risk of infection, disease, and disease severity.[27]

Limitations of our study include the hospital-based enrollment of patients, asymptomatic or mild DF usually not reported to this tertiary center and possibly missed out. In different studies the incidence of DE and mortality rate in patients with dengue infection also vary with severity of specific dengue strain, but incidence is rising, probably due to the neuro-invasive properties of the virus and increased index of suspicion about encephalitis in patients presenting with neurological manifestations in dengue endemic countries. Further strain-specific population-based epidemiological studies are required to ascertain the true incidence, to elucidate the underlying pathophysiology, predictors and poor prognostic factors of DE.

Clinical determinants, such as headache, high mean temperature of fever and DHF along with laboratory parameters, such as low platelet count, elevated hematocrit and deranged LFT in male patients with background of previous dengue, when observed during early stages of infection are predictors of encephalitis. Seizure, prolonged duration of fever and DENV-CSF positivity are poor prognostic factors. Recovered patients do well without any sequelae.

Given the likelihood of encephalitis, early in the course of symptomatic dengue infection, primary physicians should remain vigilant with high index of suspicion, looking for early features of encephalitis and poor prognostic feature in the outpatient as well as inpatient department to ensure appropriate early clinical management for better outcome.

Clinicians must be mindful of unusual features and early diagnosis of DENV, so that they can suspect dengue early, especially during ongoing COVID-19 pandemic. Physician/clinician must have a strong clinical suspension, early diagnosis with supportive management. It can reduce the risk of morbidity and mortality. Our observation should be expanded and replicated by others and used by primary care physician regarding identification of sign and symptoms of neurological involvement. Early detection of poor prognosis factors (clinical, hematological and biochemical) in Dengue infection can expedite appropriate and early diagnosis of DE. This could further help them for best management or referral to higher center for better outcome.

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Conflicts of interest
There are no conflicts of interest.

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