Dengue encephalitis - clinical spectrum and outcome

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Abstract

Background: Dengue viral infection is common worldwide caused by dengue virus. Recent studies have shown dengue viral infection causing encephalitis with high morbidity and mortality. The Dengue encephalitis patients usually present with altered sensorium, elevated lab parameters and high antibody titres at the time of admission.

Aims: To compare initial lab parameters, clinical spectrum and outcome in patients of dengue fever with or without encephalitis.

Settings and design: The study was done in a multi-speciality teaching hospital. Forty nine patients were included in the study with febrile illness and thrombocytopenia, proved to be having Dengue fever.

Material and Methods: A prospective study was conducted on 49 patients with febrile illness and thrombocytopenia proved to be having Dengue fever during a period of 6 months were included. Initial lab parameters, clinical spectrum and outcome were compared in patients with or without encephalitis.

Statistical analysis used: The database of all parameters were analysed using "STATA SOFTWARE VERSION10.0".

Results: 49 cases of proven dengue fever were included in the study. Among these patients 25 patients had no encephalitis and 24 patients had encephalitis. Most common clinical features in patients without encephalitis were fever with chills and rigors and in patients with encephalitis were fever with altered sensorium (P-value < 0.05). Among total 49 patients, 24 patients had encephalitis. There were no statistical difference among factors like age, sex, PCV, Platelet count, PT, and INR in these two groups (with or without encephalitis) at admission. The APTT, serum Ig-M antibodies, Ig-G antibodies, SGOT and SGPT were significantly high in encephalitis group (P-value < 0.05). All 25 dengue patients without encephalitis recovered completely without any complication. Among 24 dengue patients with encephalitis, 22 patients recovered completely (independent for activities of daily living), and 2 patients died (due to severe sepsis with MODS).

Conclusions: Increased incidence of dengue fever with encephalitis in the recent years, in the absence of single sensitive test for detecting dengue encephalitis, variable CSF and MRI Brain features, and associated high morbidity and mortality, this study may be helpful in focussing on early diagnosis and aggressive initial management which can influence final outcome.

Keywords: Dengue fever, encephalitis, aedes aegypti, thrombocytopenia

Introduction

Dengue viral infection is common worldwide, caused by dengue virus a member of flavivirus group in the family flaviviridae, a single stranded enveloped RNA virus. Four out of every 10 people in the world are at risk of dengue viral infection [1]. Dengue fever has varying clinical presentation ranging from asymptomatic infection to life threatening hemorrhagic fever and dengue shock syndrome [2]. Common clinical features are fever, arthralgia, headache, petechial spots, rashes and hemorrhagic manifestations. The association of dengue infection with unusual neurological manifestation was first reported by Sanguansermsri et al [3]. Complications of dengue fever are common and usually related to renal and hepatic dysfunction [4]. Numerous neurological manifestations are reported like encephalopathy, encephalitis, Guillaine-Barre syndrome, transverse myelitis, acute disseminated

encephalomyelitis, and myositis. These neurological complications are rare and its pathogenesis is controversial, few theories states dengue neurological manifestation is secondary to systemic manifestation (Encephalopathy), but recent evidence is in favour of dengue neurotropism, because dengue virus [5] and dengue IgM antibodies has been discovered in CSF of encephalopathy patients which suggests that dengue virus is capable of central nervous system infection.

Dengue fever associated with encephalitis has high morbidity and mortality and only few studies or case series has been published regarding dengue encephalitis [6]. This study may be useful in early detection of dengue fever patients with encephalitis using clinical features and laboratory parameters in resource limited countries which are having maximum number of dengue cases, so that early diagnosis of dengue encephalitis and timely

Table 1. Clinical features among patients with or without encephalitis at admission.

Variable	Encephalitis		p-value
	No (n=25)	Yes (n=24)	
Age	43.8 Years	39.88 years	0.56
Sex	Males-17, Females-8.	Males-14, Females-10.	0.76
Fever	25	24	0.792
Headache	12	20	0.430
Chills and rigor	16	18	0.747
Altered sensorium	2	24	0.004
GCS	(14-15 / 15) 25	(7-8 / 15) 24	0.03
Seizures	NONE	14	0.006
Shock	4	14	0.04
Cough	4	9	0.659
Shortness of breath	1	9	0.04
Generalised weakness	4	14	0.04
Bleeding (Purpura/ GI bleed/Epistaxis)	12	24	0.004

Table 2. Initial lab parameters among patients with or without encephalitis at admission.

Variable	Encephalitis		p-value
	No (n=25)	Yes (n=24)	
HB%	11.03	11.66	0.48
PCV	33.78	32.60	0.63
Platelets	53,826	45,400	0.126
PT	15.52 (13.2)	17.925 (13.2)	0.27
INR	1.55	1.69	0.68
APTT	30.95 (27.8)	55.02	0.008
Serum Ig-M Antibodies	10.4	45.6	0.004
Serum Ig-G Antibodies	16.85	39.89	0.006
S. Creatinine	0.99	1.82	0.132
S.Bilirubin	1.125	2.21	0.15
SGOT	54.8	205	0.002
SGPT	57.55	324	0.001
LDH	483	5289	0.0001
S.Lactate	16.2	43.7	0.004

supportive therapy can reduce or avoid morbidity and mortality. We present a total of 49 cases of dengue fever with or without encephalitis.

Material and methods

49 patients aged between 19-65 years with febrile illness and thrombocytopenia, who were admitted in acute medical care unit, Yashoda Super-speciality Hospital

Somajiguda, Hyderabad, between May 2012 to October 2012 were included in the study.

The diagnosis of dengue fever was based on clinical features, (fever, headache or bodyache, altered sensorium in case of encephalitis or encephalopathy, hemorrhagic manifestation, jaundice, and shock) and positive serum IgM / IgG antibodies.

The encephalitis group were based on clinical features (Low GCS, altered sensorium, headache, and seizures), MRI brain findings (Hyperintense areas), EEG or CSF study (IgM and IgG antibodies, Cell count, protein and sugar) suggestive of encephalitis. These tests were not done in group of dengue fever without encephalitis (without altered sensorium) or normal GCS (due to financial constraints).

Exclusion criteria were patients with previous liver or kidney failure and recent cerebral events (stroke, meningo-encephalitis), malaria, and hepatitis were excluded.

The detailed medical history, age, area of residence, and clinical features were noted. Consciousness was assessed by Glasgow coma scale (GCS), Systemic manifestations such as lymphadenopathy, hepato-splenomegaly, jaundice, Cardiac, Renal and Respiratory findings were also recorded.

The laboratory tests included complete blood examination (hemoglobin, hematocrit, blood counts, platelet counts), blood sugar, blood urea, serum creatinine, bilirubin, SGOT, SGPT, prothrombin time, INR, activated partial thromboplastin time, S.lactate, LDH, Procalcitonin, C-Reactive Protein and Dengue serum antibodies. Electrocardiogram, 2D-Echo, Chest X-ray(PA view) done in all patients, and CT scan and/ or MRI brain, Cerebrospinal fluid analysis (analyzed for protein, sugar, cells, fungal and bacterial smear and culture) and Electroencephalogram were carried out in patients with altered sensorium.

Patients were conservatively managed as per WHO guidelines. Outcome was defined at 1month into complete (independent for activities of daily living), partial (dependent for activities of daily living) and poor (bed ridden) [7].

Results

49 cases of proven dengue fever were included in the study. Among these patients 25 patients had no encephalitis and 24 patients had encephalitis.

The clinical features between patients of two groups at admission are shown in **Table 1**. Most common clinical features in patients without encephalitis were fever with chills and rigors and in patients with encephalitis were fever with altered sensorium. Clinical features like altered sensorium, seizures, shock, generalised weakness and shortness of breath were significant in encephalitis group (P-value < 0.05).

The initial lab parameters between patients of two groups at admission are shown in **Table 2**. Among total 49 patients, 24 patients had encephalitis. There were no statistical difference among factors like Hb%, PCV, Platelet count, PT, and INR in these two groups (with or without encephalitis) at admission. The APTT, serum Ig-M antibodies, Ig-G antibodies, SGOT and SGPT were significantly high in encephalitis group

(P-value < 0.05).

Among encephalitis patient group all 24 patients had altered sensorium (GCS: 7-8/15) requiring intubation and mechanical ventilator support during their stay in the hospital. All 24 encephalitis patients had severely deranged liver enzymes (SGOT, SGPT), coagulopathy (Raised PT, INR, APTT), severe thrombocytopenia and high antibody titres (Ig-M and Ig-G), 7 patients required CRRT for Acute Kidney Injury for short period of time, 14 patients had generalized seizures, 3 patients had ARDS. 16 patients showed features of encephalopathy on EEG. CSF study showed high protein and normal cell counts among 15 patients and normal protein among remaining patients, In our study CSF IgM / IgG done only in 7 patients with encephalitis and IgM was positive in only 1 patient (CSF study was not done in non encephalitis patients and remaining encephalitis patients). MRI Brain study showed Bilateral hyperintensities in temporal lobes in 9 patients, thalamus in 3 patients, pons in 1 patient, and remaining patients had normal MRI findings.

All 25 dengue patients without encephalitis recovered completely without any complications during the course of stay. Among 24 dengue patients with encephalitis, 22 patients recovered completely at the end of 1 month (independent for activities of daily living), and 2 patients died (due to severe sepsis with MODS).

Discussion

Dengue viral infection is common worldwide, caused by dengue virus a member of flavivirus group in the family flaviviridae, a single stranded enveloped RNA virus. Dengue is endemic to over 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. World health organization (WHO) surveillance shows that global incidence is increasing [8]. The primary vector is the mosquito *Aedes Aegypti*, found in abundance from latitudes 35 degree North to 35 degree South.

Dengue fever has varying clinical presentation ranging from asymptomatic infection to life threatening hemorrhagic fever and dengue shock syndrome. Common clinical features are fever, arthralgia, headache, petechial spots, rashes and hemorrhagic manifestations. The association of dengue infection with unusual neurological manifestation was first reported by Sanguanserm Sri et al.

Complications of dengue fever are common and usually related to renal and hepatic dysfunction. In our study all 25 patients without encephalitis had mild hepatic or renal dysfunction, where as all 24 encephalitis patients had severely deranged liver enzymes (SGOT, SGPT), coagulopathy (Raised PT, INR, APTT), severe thrombocytopenia and high antibody titres (Ig-M and Ig-G).

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. All patients with low GCS (n=24)

were intubated to protect the airway and majority of them extubated after 5-7 days. Tracheostomy was done in four patients among them 2 patients were de-cannulated and other 2 patients were on prolonged ventilation who died later due to refractory septic shock and MODS due to secondary bacterial sepsis (Procalcitonin and CRP were high in these two patients). CRRT done for patients with AKI (Acute kidney injury) having oliguria/anuria, Pulmonary edema, Hyperkalemia and severe metabolic acidosis.

Numerous neurological manifestations are reported like encephalopathy, encephalitis, Guillaine-Barre syndrome [9], transverse myelitis, acute disseminated encephalomyelitis [10], and myositis [11]. These neurological complications are rare and its pathogenesis is controversial, few theories states dengue neurological manifestation is secondary to systemic manifestation (Encephalopathy), but recent evidence is in favour of dengue neurotropism, because dengue virus [12] and dengue IgM antibodies [13] has been discovered in CSF of encephalopathy patients which suggests that dengue virus is capable of central nervous system infection.

In our study the features of encephalitis (headache, altered sensorium, and seizures) in majority of patients were seen more commonly in secondary dengue infection and after 5-7 days of onset of fever. Among the four dengue serotypes (DEN-1 to DEN-4) DEN-2 and DEN-3 have highest propensity to neurological complications [14,15].

Our study had more number of Dengue encephalitis patients, probably due to tertiary hospital (Referral hospital) or may be due to antigenic variation of virus. Cam BV et al., and Hendarto SK et al., have reported the encephalopathy incidence ranging from 0.5% to 6.2%. Kankirawatana et al., found that 18% of children with suspected Encephalitis in Thai hospital were found to have dengue infection. Misra et al., described 11 encephalopathy patients with confirmed dengue infection, and they demonstrated lymphocytic pleocytosis in CSF.

The patients who died in encephalitis group (2 out of 24 patients), both of them presented with – low GCS, seizures, headache and upper GI bleed. Hence patients with dengue fever with predominance of these clinical features and severely deranged lab parameters are probably manifesting encephalitis which has high morbidity and mortality unless diagnosed early and treated accordingly.

The outcome in dengue encephalitis depends upon how early the diagnosis is made and managed aggressively in due course of time because we can anticipate the course of encephalitis and its complications. Misra et al., proposed that Encephalitis lies at the severe end of the spectrum of dengue infection, but others reported a more benign disease [16].

In case of dengue Encephalitis diagnosis can be made either by detection of virus in CSF (viral culture / PCR) or immune response by the body (Ig-M antibodies in CSF). The gold standard method is viral culture which is difficult and time consuming. Regarding CSF IgM and IgG antibodies,

Puccioni-Sohler M et al., [17] and Cristiane Nascimento Soares [18] have shown that these antibodies can be seen in CSF but the absence will not rule out encephalitis. In our study CSF IgM and IgG done only in 7 patients with encephalitis and IgM was positive in only 1 patient (CSF study was not done in remaining patients as the sensitivity of this test found to be very low and was thought to be financial burden for those patients). CSF study in encephalitis group showed high protein and normal cell counts among 15 patients and normal protein among remaining patients but serum IgM and IgG were positive in all patients.

Singh et al., [19], found specificity of PCR assay to be 100% and sensitivity of 70% when sample are taken in first 5 days of fever.

Brain imaging- MRI is the modality of choice which shows the findings consistent with viral encephalitis include cerebral edema, white matter changes, necrosis and brain atrophy. Encephalitis features in brain (Hyperintense areas) can be seen in global pallidus, temporal lobes [20,21], thalamus [22], hippocampus [23], pons, and spinal cord [24]. In our study, MRI Brain study showed Bilateral hyperintense areas in temporal lobes in 9 patients, thalamus in 3 patients, pons in 1 patient, and remaining patients had normal MRI findings (MRI Brain was not done in non encephalitis patients).

All 25 dengue patients without encephalitis recovered completely without any complications during the course of stay. Among 24 dengue patients with encephalitis, 22 patients recovered completely at the end of 1 month (independent for activities of daily living), and 2 patients died (due to severe sepsis with MODS).

The limitation of our study is that we could not do CSF study, and MRI imaging in proven dengue patients without encephalitis (as thought not essential). We could do only serum Ig-M and Ig-G antibodies. CSF culture or PCR for viral detection in CSF was not done. But all patients proved to be having dengue serum antibodies are 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 encephalitis.

Conclusion

Increased incidence of dengue fever with encephalitis in the recent years, in the absence of single sensitive test for detecting dengue encephalitis, variable CSF and MRI Brain features, and associated high morbidity and mortality, this study may be helpful in focussing on early diagnosis and aggressive initial management which can influence final outcome.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	RMS	MVP	MD	TA
Research concept and design	√	--	√	--
Collection and/or assembly of data	√	√	--	--
Data analysis and interpretation	√	--	√	--
Writing the article	√	√	--	--
Critical revision of the article	√	√	--	--
Final approval of article	√	--	√	--
Statistical analysis	√	√	--	√

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