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## Acute encephalitis syndrome in denue

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### Abstract

**Background:** Encephalitis and encephalopathy both has been incriminated as cause of Acute Encephalitis Syndrome (AES) in Dengue. But incriminating either has never been easy.

**Objective:** To observe the incidence, cause and outcome of AES in Dengue patients.

**Methods:** Laboratory proved Dengue patients admitted to a Tertiary care hospital were observed for development and consequences of AES.

**Results:** Out of 2660 admitted Dengue cases 32 developed AES. All had warning signs and comorbid conditions. IgM antibody for Dengue was detected in 2 samples of CSF. Four patients expired and 2 had cognitive impairment at the end of one month.

**Conclusion:** Neurotropism of Dengue could be established in small proportion of cases.

**Keywords:** AES, dengue, encephalitis, Encephalopathy

### Introduction

As per the World Health Organization (WHO), Acute Encephalitis Syndrome (AES) is defined as, "Acute onset of fever and change in mental status which includes symptoms such as confusion, disorientation, coma, inability to talk and/or new onset of seizure (excluding simple febrile seizure) in a person of any age at anytime of the year <sup>[1]</sup>.

Dengue is growing faster than any other vector borne disease. It has increased by 30 times over last 5 decades <sup>[2]</sup>. As most the infections are asymptomatic or mildly symptomatic and the patients manage themselves at home, true incidence is difficult to know. Around 3.9 billion people are at the risk of infection. Though Dengue is prevalent in 129 countries, 70% of the disease burden is borne by Asian countries <sup>[3]</sup>.

Dengue has 4 serotypes. Infection with one confers long-term immunity to that serotype only. Infection with another serotype causes secondary Dengue which is more severe than the primary attack. With increased number of cases each year, there is more chance of secondary Dengue. Similarly with rise in number of cases and increased awareness, more and more atypical manifestations of Dengue are reported <sup>[4]</sup>

Neurological manifestations including encephalopathy have been described in Dengue. Dengue was believed to cause encephalopathy by metabolic abnormality, haemodynamic alteration or intracerebral haemorrhage. But neurotropism of the virus has been proposed as Dengue virus and anti-dengue IgM antibody has been demonstrated in cerebrospinal fluid (CSF) <sup>[5-9]</sup>.

Various other neurological manifestations have been described. They include Guillain – Barre Syndrome, Acute disseminated encephalomyelitis, Acute transverse myelitis, muscle weakness, parasthesia, cerebellar symptoms, Miller –Fisher Syndrome etc. <sup>[5]</sup>.

Our Medical College is in an endemic area of Dengue. During epidemics 20000 to 25000 dengue cases attend OPD in some years out of which 5000 to 6000 cases are admitted. This study was done to observe Acute Encephalitis Syndrome in Dengue.

### Material and Methods

The study was done at a teaching hospital of the eastern India between July 2018 to December 2018. Permission was taken from the Institutional Ethics Committee vide IEC/IRB No.468/16.9.2017. This is an observational perspective study.

During the study period, patients of acute febrile illness attending Medicine outdoor were investigated for etiological causes including Dengue.

If the duration of fever was less than 5 days, Nonstructural Antigen 1(NS<sub>1</sub>Ag) by ELISA based method was looked for. IgM antibody for dengue was tested by ELISA if duration of fever was more than 5 days.

History was taken and physical examination was done with particular attention to past history of another attack of Dengue, warning signs and symptoms of Dengue (i.e. persistent vomiting, pain and tenderness in abdomen, patient feeling restlessness, lethargy or general weakness, fluid collection in pleural cavity or abdomen, hepatomegaly, haemoconcentration as evidenced by rise in haematocrit by 20% or more) and presence of comorbid conditions (i.e. extremes of age, diabetes mellitus, hypertension, ischemic heart disease, gestational state, haemoglobinopathies, patients with compromised immunity, patients on immunosuppressive drugs – steroids - anticoagulants or NSAIDS).

Hospitalised patients with acute encephalitis syndrome (AES) were included in the study. AES was considered when the patient had change in mental status which includes symptoms such as confusion, disorientation, coma, inability to talk and/or new onset seizure (excluding febrile convulsion). [WHO 2008]

Patients with past history of psychiatric illness, recent stroke, liver or kidney disease prior to onset of Dengue, patients detected positive for Malaria, Leptospira or Scrub typhus were excluded from the study.

Laboratory proved Dengue patients having comorbid condition or warning signs/symptoms or major organ involvement like that of brain, liver, kidney, heart or lungs were institutionalized as per the guidelines by National Vector Borne Disease Control Programme (NVBDCP) [10].

Laboratory investigations included complete blood count (CBC), blood sugar, blood urea, serum creatine, serum sodium (Na) and potassium (k), Liver Function Test (LFT), Prothrombin time (PT), Activated Partial Thromboplastin Time (APTT), Internationalised Normal Ratio (INR), X – ray Chest(PA) view and ultrasonogram of abdomen-pelvis. Patients with AES were subjected to MRI of brain and lumbar puncture. CSF was sent for cytological – biochemical examination and test for NS<sub>1</sub>Ag/IgM antibody for Dengue by ELISA. Other investigations were decided on case to case basis.

The patients were managed as per the WHO/NVBDCP protocol. They were followed up for one month either physically or by telephone. At the end of one month, the recovery was defined as complete (independent for activities of daily living), partial (dependant for activities of daily living), or poor (bed ridden) [11].

## Results

Out of 15385 patients of acute febrile illness attending medicine OPD of this tertiary care teaching hospital, 3157 patients tested positive for Dengue. Hospitalisation was required in 2660 cases. Age group of 15 to 50 years contributed 84% of hospitalized patients and males dominated over female (Table 1).

Thirty two of the hospitalized patients had mild Dengue fever who could have been managed at home. They were admitted as they came from distant places. More than half of the patients (i.e.N= 2552; 57.2%) had either warning sign /

symptom or comorbid illness which place them at moderate risk and they required hospitalization. Seventy six (2.89%) patients presented with severe Dengue. Thirty two patients had manifestations of AES. All of the patients presenting with AES had both warning signs and comorbid conditions (Table-2).

As far as severity is concerned, one third (i.e. 32.93%; N= 876) did not have any complication. As many as 208 (7.8%) patients had dengue haemorrhagic fever (DHF) and 128 (4.8%) had dengue shock syndrome (DSS).Expanded dengue syndrome (EDS) characterised by involvement of major organs in the form of CNS, Renal, Hepatic, Respiratory or Cardiac system was seen in 1448 (54.43%) cases. Liver affection contributed maximum numbers in this category and in all cases rise in SGOT was significantly more than the level of SGPT. Rest 876 (32.93%) cases were without any complication (Table -3). As per the definition, all 32 cases of AES came under EDS category. Eleven patients of DSS (8.6%) and 6 patients of DHF (2.9%) presented with AES.

Laboratory parameters of hepatic involvement was seen in 1299 patients, renal failure in 224 cases, hyponatremia in 76 cases (Table 4).But the rise was modest in most of the cases and it is difficult to tell how much it contributed to encephalopathy. Some cases had elevation of transaminase enzymes more than thousand without rise in serum bilirubin level. Also there was shock in 128 cases.

MRI was done in 32 cases of AES. Eighteen of them reveal no abnormality and 8 had generalized edema. Rest six had localized edema but there was no predilection for any particular site.

Lumbar puncture could be done only in 14 patients because of poor general condition and bleeding tendency. Five of them had raised protein with cellular pleocytosis. Two of these 5 had IgM antibody against dengue. Another 2 CSF samples had only cellular pleocytosis and there was no marker for Dengue.

The patients were managed in the line of Dengue as per the WHO/NVBDCP protocol. But considering the possibility of other viral infection due to absence of Dengue marker in CSF, antiviral Acyclovir injection was added for the sake of benefit of doubt. Moreover as ours is an endemic zone of malaria and the parasite is often not detectable, anti-malarial was added in some cases as per the existing clinical practice. Most of the AES patients had multi-organ dysfunction and 4 of them died during their hospital stay.

During one month follow up, one patient presented with transverse myelitis and 2 developed Guillain-Barre Syndrome. At the end of one month all of these 3 patients had motor weakness. Another 2 had cognitive impairment. Others recovered completely.

**Table 1:** Demographic profile of admitted Dengue patients

Age group in years	Male	Female	Total
15-30	504	232	736
31-40	443	309	752
41-50	478	273	751
51-60	224	103	327
61-70	49	28	77
>70	14	03	17
Total	1712	948	2660

**Table 2:** Relationship between the category of patients and AES

Category	No of patients	% of patients	No of AES patients	% of the category
Mild dengue fever	32	1.2	0	0
Dengue with warning signs	1146	43	32	2.8
Dengue with comorbidity	1406	52.9	32	2.3
Severe dengue	76	2.89	32	42
Total	2660			

**Table 3:** Relationship between severity of Dengue and AES

Severity	No of patients	% of patients	No of AES patients	% of the Category
Dengue fever	876	32.93	0	0
DHF	208	7.8	6	2.9
DSS	128	4.8	11	8.6
EDS	1448	54.43	32	2.2
Total	2660			

DHF-Dengue haemorrhagic fever DSS-Dengue shock syndrome  
EDS-Expanded dengue syndrome

**Table 4:** Contributory factors for AES in Dengue

Factor	No of patients
Hepatic involvement	1299
Renal failure	224
Hyponatremia	76
Shock	128

**Discussion**

Acute Encephalitis Syndrome in dengue is well known. But there has been debate whether this is due to neurotropism of the Dengue virus or as a result of metabolic consequences of Dengue infection or other factors related to it. Hepatic dysfunction, renal failure, shock leading to cerebral hypo perfusion, capillary leak syndrome in Dengue resulting in cerebral edema, deranged electrolytes, intracerebral haemorrhage – are all seen in Dengue. Altered alertness or seizure can occur as a consequence of any of these factors. But Dengue virus and antidengue IgM antibody has been detected in brain and CSF in some studies which points towards neurotropism of the virus [5-9].

In our study 32 patients had AES out of 2660 admitted cases (1.2%) and 3157 Dengue patients attending OPD (1%). Since most of the Dengue infections are asymptomatic or mildly symptomatic who manage themselves with home remedies, the true number of mild infections and the percentage of AES being related to it – is difficult to ascertain. Moreover the study centre is a Tertiary Care Hospital which receives more percentages of severe patients. Reported proportion of neurological manifestations vary from study to study – 0.5% by Cam *et al.* [6], 5.6% by Tassara *et al.* [12], 6.2% by Hendarto *et al.* [13]. As per the study by Kankirawatana *et al* in aThai Hospital, 18% of children admitted as suspected encephalitis had Dengue infection [7].

All patients of AES in our series had comorbid conditions and warning signs. All of them also belonged to severe category. By definition they belonged to Expanded Dengue Syndrome (EDS) category. It is important to note that 1448 patients of EDS had different vital organ involvement either alone or in different combinations. But only 32 manifested with AES. In most of the cases biochemical abnormality as a consequence of major organ dysfunction was only modest. It is also not possible to draw a cut off mark for parameters above which they are responsible for encephalopathy. At the same time, the speculated neurotropism of Dengue becomes

a difficult postulation in absence of Dengue virus or it's antibody in the brain or CSF.

In our study, patient's condition permitted lumbar puncture in 14 cases only. Five cases had raised protein in CSF with cellular pleocytosis and 2 of them had IgM antibody for Dengue. So proof of encephalitis and that too of Dengue etiology was possible in less number of cases. While one depends upon NS<sub>1</sub>Ag or IgM antibody, another problem remains. There is cross reactivity amongst Flavivirus and many of them are known to cause AES. This is especially true for Japanese Encephalitis in Asia and West Nile virus in the West [14, 15].

MRI of the brain was done in all 32 cases of AES. Usually generalized edema is seen in cases of metabolic abnormality or toxicity where as localized edema is suggestive of encephalitis. Different viruses have predilection for different areas of brain. Herpes virus invades temporal and frontal area. Rabies virus has predilection for hippocampus. Japanese Encephalitis produces abnormality in thalamus, basal ganglia, brain stem and cerebellum [15].

In our study, MRI of brain was normal in 18 out of 32 cases. In 8 cases there was generalized edema. Localised edema was present in 6 cases but there was no preference for any site. In Misra's series of 11 cases, MRI was done on 9. There was abnormality in only one patient who had hyperintense areas in Globus Pallidus [16]. In Cam's study, 18 patients had MRI of brain. Four had encephalitis like focal changes [6]. Other authors have described focal changes in hippocampus [17], temporal lobe [18, 19], pons [19] and spinal cord [19, 20]. So to summarize, though there are areas of focal lesions suggesting encephalitis, there is no particular area to get involved in Dengue.

After discharge and during one month of follow up period, 2 patients developed Guillain-Barre Syndrome and one had Acute Transverse myelitis. But it is difficult to prove causal association of Dengue with these disorders. However immune mediated syndromes have been described by others like acute disseminated encephalomyelitis, acute transvers myelitis and Guillain –Barre Syndrome [21].

Outcome of Dengue encephalitis has been different in various studies. Kularatne *et al*, 2008(n=6), Solomon *et al*, 2006 (n=9), Kankirawatana *et al*, 2000 (n=8) had complete recovery in all cases [15]. In Misra's series 3 patients died out of 11 [16]. Tassara reported death of 2 patients out of 28 [12].

In our study 4 patients died. At the end of one month follow up, 3 patients had residual weakness and two patients had cognitive impairment.

**Conclusion**

AES is an established manifestation in Dengue. Neurotropism is postulated but viral antigen or antibody is detectable in few samples of CSF. Similarly though there is multiple organ involvement, biochemical abnormalities are often modest. It is difficult to draw a cut-off mark for a parameter above which it can be attributed as the cause of

encephalopathy. At times antiviral or antimalarial drugs were added for benefit of doubt.

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