International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

Dengue Encephalitis: An Atypical Manifestation of Dengue Fever in Children

Gitali Kakoti[1*], Prafulla Dutta[2*], Bishnu Ram Das[3**]

[1]Former Women Scientist-A, DST & PhD Scholar, [2]Scientist 'G' & I/c Director, [3]Prof & Head,
[*]Regional Medical Research Centre, ICMR, Northeast Region, Post Box no. 105, Dibrugarh, Assam, India.
[**]Department of Community Medicine, Jorhat Medical College, Jorhat-785001, Assam, India.

Corresponding Author: Bishnu Ram Das

Received: 21/02/2016 *Revised: 11/03/2016* *Accepted: 14/03/2016*

ABSTRACT

Background: Recent studies have shown dengue viral infection causing encephalitis with high morbidity and mortality. However, there is little clinical documented evidence of Dengue fever with encephalitis in children in Assam. India

Aims: An attempt was made to determine the clinical spectrum and outcome in pediatric patients of dengue fever with encephalitis.

Materials and Methods: The study was done in a multi-specialty teaching hospital on 513 Acute Encephalitis Syndrome (AES) children with febrile illness.

Results: A total 513 AES patients were enrolled from 2011-2013. Of which 55.4% were male and age group mostly affected were 5-12 years (51.1%). Among the AES cases, 15 were found to be positive for Dengue IgM antibody. The age group mainly affected (73.3%) was 5-12 years. Majority of them were Male (60%) and from rural area (93.3%).

Most common clinical features in DEN patients with encephalitis were fever (100%), seizure (86.7%), altered sensorium (66.7%), vomiting (40%) and headache (33.3%). Around 20% of them had Glasgow Comma Scale (GCS) within 3 to 8. Signs of meningeal irritation were present in 3.6% cases and 20% cases were suffered from Diarrhea.

Outcome at discharge of DEN patients showed 66.7% were recovered completely, 13.3% had neurological sequelae and 20% were died in hospital.

Conclusion: Dengue encephalitis an atypical manifestation of Dengue fever causing menace to the children population which seeks attention for early diagnosis and prompt management through disease surveillance .

Key words: Dengue Fever, Dengue Encephalitis, AES.

INTRODUCTION

Encephalitis is an acute clinical syndrome of the central nervous system (CNS), often associated with fatal outcome and severe permanent damage including cognitive and behavioural impairment, affective disorders and epileptic seizures. To date, the infection of the CNS is considered to be the major cause of encephalitis and more than 100 different pathogens have been recognized as causative agents.

India is endemic for important mosquito-borne viral diseases, viz. Dengue hemorrhagic fever (DHF), Japanese encephalitis (JE) and West Nile virus (WNV). [1]

Dengue, which is the fastest re-emerging arboviral disease in the world, imposes a heavy economic and health

burden on countries, families and individual patients. [2,3] Over the past two decades there has been dramatic global increase in Dengue fever (DF), Dengue haemorrhagic fever (DHF), and Dengue shock syndrome (DSS) and their epidemics. [2,3] In India, there is increased proportion of Dengue cases with severe disease. In recent years there have been an increasing number of reports of DF or DHF with unusual manifestations. Atypical central nervous system manifestations, including convulsions, spasticity, altered consciousness and transient paresis, have been observed. Lately there have been report of neurological complications of dengue virus infection and include encephalitis, myelitis, Guillain-Barre (GB) syndrome and myositis. [4-6] There is insufficiency of data looking at the atypical manifestation of Dengue fever in children. From a perspective of disease surveillance and control, it is important to differentiate Dengue encephalitis from other causes of AES, in part because there is no antiviral drug. Initial clinical manifestation of dengue encephalitis and a complete medical assessment are important for early diagnosis and prompt supportive therapy. In view of the above an attempt was made to achieve a better understanding of clinical presentations and outcome of dengue fever with encephalitis in AES children.

MATERIALS AND METHODS

Study Site

Assam Medical College & Hospital is a tertiary level multi-specialty teaching hospital providing health care services mostly to the districts of upper Assam. People residing in neighbouring state like Arunachal Pradesh and Nagaland also benefit health care services from this medical college hospital. Most of the patients referred to this apex level institute are from periphery for better supportive care and treatment.

Case Enrollment and Sample Collection

The case enrollment and sample collection was carried out for 3-years from January, 2011 to December, 2013. All the hospitalized AES cases up to 12 years of age in pediatric ward of Assam Medical College hospital (AMCH) were included as study participants.

For investigating AES cases, WHO case definition was adopted. Clinically a case of AES is defined as fever or recent history of fever with change in mental status (including confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures). Other early clinical findings could include an increase in irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness. Details of patient's information, travel history, immunization history, clinical findings and status at the time of discharge were recorded on WHO standardized form.

Children meeting the clinical diagnosis of AES and willing to give consent for lumber puncture or for collection of blood samples were included. Routinely, lumber puncture was performed and blood samples were taken by the attending pediatricians as a part of clinical care. A part of CSF (1ml) and blood (2 ml) samples were collected in sterile condition separately. The samples were then transferred under cold chain to Regional Medical Research Centre Laboratory, ICMR, Dibrugarh. Blood samples were kept at 4°C overnight and sera were separated. Both serum and CSF were then stored at -80°C for further analysis. Reports of CSF samples analyzed for physical, chemical, and cytological examination and other laboratory investigations done at the time of admission were recorded from the bed head tickets of the patient. The study was approved by the Institutional Ethics Committee (Human) of Regional Medical Research Centre (ICMR), NER, Dibrugarh.

Serology

Among the enrolled 513 AES participants we could collect at least one CSF or Serum sample from 482(94%) patients at the time of admission. All the serum samples obtained from AES patients

were tested for the presence of Dengue viral nonstructural 1 (NS1) antigen by using Platelia Dengue NS1 kits (Bio-Rad, USA) and DENV- specific IgM antibodies using MAC ELISA kits obtained from National Institute of Virology (NIV), Pune, India. DEN IgM positive samples were further tested for the presence of IgM antibody against other flaviviruses *viz*. Japanese encephalitis (MAC ELISA kit, NIV, Pune) and West Nile (MAC ELISA kit, PanBio, Australia) prevalent in this region. All tests were performed according to manufacturer's instruction.

Statistical analysis

A χ^2 or Fisher's exact test was used to analyze categorical variables. *P* values of less than 0.05 were considered to indicate as statistical significance. All statistical analyses were performed with the use of Statistical Package for Social Sciences (SPSS) software, IBM SPSS - version 20.

RESULTS

Demographic profile of AES patients and distribution of study participants

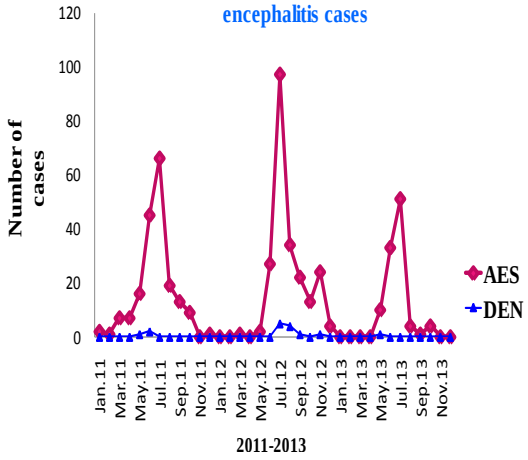
Over a period of three years from 2011 to 2013, a total of 513 AES patients admitted in pediatric ward of Assam Medical College & Hospital, Dibrugarh, Assam were enrolled as study participants. Of these total participants, 186(36.2%) were admitted in 2011, 224(43.6%) in 2012 and 103(20%) in 2013. Among them, 494 were from Assam, 16 were from Arunalchal Pradesh and 3 were from Nagaland. Maximum no of AES patients of Assam were from Dibrugarh district 217(43.9%) followed by Tinsukia 107(21.7%), Sivasagar 100(20.2%), Dhemaji 39(7.9%), Golaghat 17 (3.4%) and from Jorhat 14 (2.8%).Children from rural area were predominantly affected 487(94.9%) and majority of them belonged to low socioeconomic group.

Of the total AES patients, 284(55.4%) were male and age group mostly affected were 5-12 years (51.1%).

Monthly admission pattern of AES patients

Admission pattern of AES patients demonstrated that maximum numbers of patients were hospitalized in rainy season starting from the month of May to October with a clear peak in July in study years (Figure 1).

Figure 1: Monthly incidence of AES/DEN encephalitis cases



Outcome of AES cases

At the time of discharge of the total 513 AES cases, 281(55%) were found to recover completely while 34(6.6%) patients developed some short of neurological disability and 139(27%) patients were died in hospital.

Dengue Baseline characteristics

Out of 482 AES cases 191children found to be infected with flavivirus. Among the flavivirus infections 15 were detected as Dengue IgM positive during the study period (Table 1). However, none were positive by NS1 Ag-ELISA kit. The age groups mainly affected (73.3%) were 5-12 years. Majority of the patients were Male 9(60%) and from rural area 14(93.3%). The district wise distribution of all the DEN patients showed that maximum patients were from Sivasagar district 6(40%) while 4 (26.7 %) each from Dibrugarh and Tinsukia district. Only one case was from Mon district of neighboring state Nagaland.

Clinical profile of DEN cases

Most common presenting symptoms (Table 2) were fever 100%, Seizure 86.7%, altered sensorium (66.7%), vomiting (40%) and headache (33.3%). Around 20% of

DEN patients had Glasgow Comma Scale (GCS) within 3 to 8. Signs of meningeal irritation were present in 3.6% cases and 20% cases were suffered from Diarrhea.

Table 1: Demographic characteristics of Dengue cases

Characteristics	Year wise DEN IgM positive cases			Total
Age in years, no (%)	**2011 n =3**	**2012 n = 11**	**2013 n = 1**	**n = 15**
<1	0(0)	0(0)	0(0)	0(0)
1 to 5	1(33.3)	3(27.3)	0(0)	4 (26.7)
5 to 12	2(66.7)	8(72.7)	1(100)	11(73.3)
Sex, no (%)				
Male	1(33.3)	7(63.6)	1(100)	9(60)
Female	2(66.7)	4(36.5)	0(0)	6(40)
Settings, no (%)				
Urban	1(33.3)	0(0)	0(0)	1(6.7)
Rural	2(66.7)	11(100)	1(100)	14(93.3)

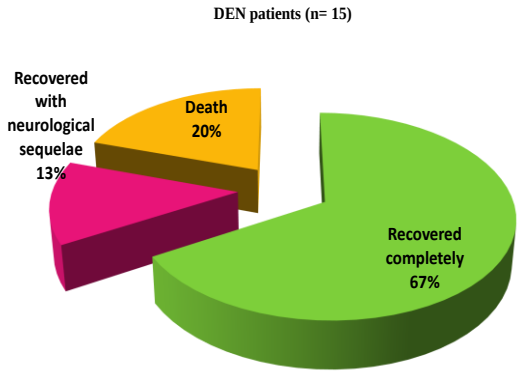
Table 2: Clinical Profile of children with Dengue (n=15)

Features	Number	%
Fever	15	100
Altered Sensorium	10	66.7
Headache	5	33.3
Irritable	2	13.3
Vomiting	6	40
Abnormal behavior	0	0
Diarrhoea	3	20
Seizure	13	86.7
Glasgow Coma Scale (GCS) ≤ 8	3	20
Signs of meningeal irritation	8	3.6

Outcome of DEN Patients

Outcome at discharge of DEN patients showed that 66.7% were recovered completely while 13.3% cases had neurological sequelae. 20% patients were died in the hospital (Figure 2). The mortality rate was more in patients with GCS between 3 to 8 (25.6 %). However, it was statistically insignificant.

Figure 2: Out come of DEN patients at the time of discharge



DISCUSSION

The present study demonstrates that AES is a significant public health problem in this part of country. We confirmed DEN encephalitis as one of the important cause of AES in reference to flavivirus infection next to Japanese encephalitis. [7] Of the total AES patients of flavivirus infection 7.9% were laboratory confirmed Dengue. Earlier studies also confirmed that other agents that have been caused to AES in India include dengue virus besides other etiologies. [8-10]

In our study, majority of the AES children were male and age group mainly affected was 5 to 12 years. Study conducted by Kumar *et al.*, 2006; Bandyopadhyay *et al.*, 2013, Avabratha *et al.*, 2012 also observed similar findings. [11-13] This may be explained that among the AES patients, flavivirus infections like DEN, JE are more common. Children in 5-12 years age group are actively mobile and they love to play outside which make them more prone to get mosquito bite. Moreover, in low socioeconomic status, male children are helping hands for their parents in cultivating seasons. As such male children are more exposed to the exophilic mosquito bites which are highly abundant outside the houses. [7]

Monthly admission rate of AES children were recorded more from May to October with a peak in July. These findings are comparable with the findings of previous studies that suggest a climate dependent transmission cycle. [14-17] The hot and humid time of the year is characterized by water-logging, filling up of the perennial rivers, paddy fields, increased agricultural activity in the rural areas and more water collection in artificial containers in nearby houses. These conditions are attributable to enhance vector densities (e.g. via increased mosquito breeding) and increased man mosquito contact leading proportionately

increased hospitalization of AES cases (Borah *et al.,* 2012). [18]

Outcome of AES cases at the time of discharge showed that 6.6% patient developed neurological disability while 27% died in hospital. Mortality among children with viral encephalitis is extraordinarily high in South and South-east Asia ranging from 17 to 50%. [19-21] This high mortality may be due to late reporting of cases or due to lack of availability standard neuro-intensive care facilities. Moreover, in rural area initially people prefer to visit a traditional faith healer than attending recognized health care facility. This may be due to poor road communication, lack of transport facilities and more specifically prevailing ignorance among the rural under privileged masses.

The total numbers of dengue cases were 15 and all were positive for Dengue virus specific IgM antibody with MAC ELISA. The mean age of all dengue cases was 6.8±3 years. We did not find any significant difference between male and female ratio. However, disease was more severe in male. The sex ratio of the patients was rather equal in most studies (Witayathawornwong, 2006). [22] All the Dengue cases were found in rainy season from May to September except one case in November, 2012. Similar findings were also observed by Witayathawornwong in Thailand. This may be due to increase of Aedes mosquito density in container habitats after rain posing risk of DENV transmission.

Our study demonstrated that Dengue encephalitis were prevalent in the rural area. This may be due to the rapid growth of industries and building activities, improvement of transport facilities such as railway and roads, increased movement of people from urban to rural areas, and environmental changes that all may have favoured the spread of dengue in rural as well as urban areas. Other studies also observed the same. [23]

Clinical characteristics of dengue positive patients indicated that dengue fever was severe with significant involvement of CNS. Similarly, in earlier studies it was recorded that Dengue infection can cause neurological manifestation ranging from nonspecific symptoms to encephalitis. [24,25] Predominant clinical features noted in the current study in order of frequency were fever 100%, Seizure 86.7%, altered sensorium (66.7%), vomiting (40 %) and headache (33.3%). Around 20% of DEN patients had GCS within 3 to 8 and 20% cases were found to suffer from Diarrhoea. Our findings were consistent with other studies. [26-28]

Among the other clinical findings rash was present in one patient. In another patient who had thrombocytopania developed neurological sequelae at the time of discharge. Kishore *et al.,* 2006 also observed similar findings. Fatal disease occurred in 20 % cases and 13.3% children developed neurological sequelae. This may be explained that enhanced mortality and neurological disability in our study may be due to dengue encephalopathy in contrast to low mortality in dengue fever. [29]

CONCLUSION

The present study reveals that Dengue virus infection in children is a significant public health problem in this part of the country with climate dependent transmission cycle. Our findings confirm that Dengue encephalitis is prevalent in pediatric age group and responsible for creating the pool of differently able children with increased fatal outcome. This public health menace is a growing challenge to health officials and policymakers.

ACKNOWLEDGEMENT

G. Kakoti acknowledges Department of Science and Technology, Government of India for providing Women Scientist-A fellowship to carry out the study and Director, National Institute of Virology (NIV), Pune, India for supplying the JE/Dengue IgM ELISA kits at no cost. G. Kakoti also acknowledges Regional Medical Research Centre (ICMR), Dibrugarh for giving the infrastructure facility to carry out the lab work. Authors would like to thank the

entire staff of pediatric department, AMCH, Dibrugarh for their assistance during data and sample collection from study subjects. It is gracefully acknowledged the pediatric participants and their guardians for giving unconditional consent to participate in this scientific research venture in spite of their adverse torment event of life. Thanks are due to Lab members of Entomology & Filariasis section for their help during sample processing and Dr. Hiranya Saikia, Senior Lecturer of Statistics at Department of Community Medicine, AMC, Dibrugarh for his support in analysis of data.

Conflict of Interests: The authors declare that they have no conflict of interests.

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How to cite this article: Kakoti G, Dutta P, Das BR. Dengue encephalitis: an atypical manifestation of dengue fever in children. Int J Health Sci Res. 2016; 6(4):1-7.

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