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Clinico-Radiological Profile and Outcome of Dengue Patients with Neurological Manifestations- A Cross-Sectional Study

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ABSTRACT

Introduction: *Dengue fever is an endemic infection in India and is a major public health problem. The expanded dengue syndrome incorporates rare and unusual manifestations affecting other organ systems like the CNS, respiratory, hepatic and gastrointestinal systems. The neurological complications of dengue fever can be broadly classified as Dengue viral encephalitis, Dengue viral encephalopathy, immune mediated syndrome which includes acutedisseminated encephalomyelitis, and dengue associated stroke.*

Aim*: To evaluate the clinico- radiological profile and outcome of serologically confirmed dengue patients having varied manifestations of central nervous system involvement.*

Materials and methods: *This descriptive cross-sectional study was done at the Department of Paediatrics, and Department of Neurology, Sree Balaji Medical College & Hospital, Chennai from January 2021 to January 2022. The total 562 children of dengue fever were studied within the study duration and out of these 11 children with neurological complications were subjected to a detailed clinical evaluation, laboratory assessment, CSF study, EEG and neuroimaging. The summary of the statistical analysis is presented as frequencies and percentages.*

Results: *During the study period out of the total of 562 children with dengue 11 (1.9%) had neurological manifestations.The mean age of the children with neurological complications was 6.8 +/- 3.88 years. The male: female ratio was 1.75:1. Most common neurological manifestation was acute encephalitic syndrome (AES) seen in 7 patients (63.6%) out of the 11 children. MRI done for severe headache following second week of fever showed severe manifestations like thalamus infarct, and cerebral hemorrhage with mass effect. Headache following first week of fever showed mild manifestations like ADEM, and double doughnut sign in MRI.*

Conclusion *In the present study, the prevalence of neurological symptoms among childrenwith dengue fever were found as 1.9%. It was also observed that new onset headache occurring in the second week following dengue fever is a warning sign for severe CNS disease.*

Keywords: *Encephalitis, central nervous system, Encephalomyelitis, stroke*

INTRODUCTION

Dengue fever is an endemic infection in India and is a major public health problem.[1] Dengue is a vector borne viral disease caused by dengue virus serotypes, DENV 1- 4. It is anacute viral disease, transmitted by Aedes aegypti mosquito and has a variable clinical spectrum ranging from asymptomatic infection, dengue

fever, to life-threatening sever dengue fever with warning signs [2] The World Health Organisation (WHO) revised guidelines in 2011 included the expanded dengue syndrome. This incorporates rare and unusual manifestations of dengue fever affecting other organ systems like the CNS, respiratory, hepatic and gastrointestinal systems. [3]

Although dengue is classically considered a non-neurotropic virus, there is increasing evidence for dengue viral neurotropism. Neurological manifestations were first reportedduring 1976 as atypical features of dengue infection.

CNS involvement occurs in about 0.5%–20% of the cases. [4,5] CNS involvement can occur in all types of dengue – dengue fever, Dengue Hemorrhagic Fever (DHF) and Dengue shock syndrome (DSS). The CNS manifestations of dengue infection includes neurotropism causing encephalitis, meningitis and myelitis. It includes systemic complications resulting in encephalopathy and stroke. It can be post infectious (immune mediated) causing Guillain Barre Syndrome, viral mononeuritis, plexitis, acute disseminated encephalomyelitis (ADEM), neuro-ophthalmic disorders. [6- 8]

There is paucity of studies evaluating the relative frequency of central nervous system (CNS)manifestations in dengue, specifically in pediatric population of TamilNadu. Hence, present study was planned to evaluate the clinico-radiological profile and outcome of serologically confirmed dengue patients having varied manifestations of central nervous system (CNS) involvement.

MATERIALS AND METHODS:

This descriptive cross-sectional study was done in the Department of Paediatrics and Department of Neurology Sree Balaji Medical College and Hospital, Chennai from January2021 January 2022. The study was carried out after IEC approval [Ref. No.002/SBMC/IHEC/2018/1163]. The written informed consent from the parents of the childrenwas obtained for inclusion in the study.

Inclusion Criteria: All the children, aged between 1 month to 14 years, who presented with confirmed diagnosis of dengue within the study period, were included. Dengue fever was confirmed when the child had clinical features of dengue fever with one of the following namely demonstration of dengue virus antigen, NS1 by ELISA method or demonstration ofIgM antibodies against dengue virus by ELISA. [2]

Exclusion Criteria: Patients with history of any neurological or developmental disorders inthe past, and those who were sero-positive for other infections and patients not admitted as in-patient, were excluded from the study.

Sample Size: During the study period a total of 562 children aged 1 month to 14 years admitted with the confirmed diagnosis of dengue fever, were included in the study.

Data Collection: Data was collected using a prestructured proforma which included proformaregarding the charecterics of dengue fever. Data regarding age, gender, mother's education, social economic status, area of residence, duration of fever, symptoms of dengue fever, and duration of hospitalisation was collected. All the patients were subjected to a detailed clinical examination, neurological examination and assessment for signs of shock was done periodically. Laboratory assessment including complete hemogram, coagulation profile, liver function test, serum electrolytes, and routine CSF (cerebrospinal fluid) study, EEG and neuroimaging (MRI) were done in all patients.

Statistical Analysis: The data entry and statistical analysis was done using the SPSS version 20. The summary of the statistical analysis is presented as frequencies and percentages.

RESULTS

A total of 562 children aged 1 month to 14 years admitted with dengue fever were included inthe study. Total 11(1.9 %) out of the 562 patients with dengue fever had neurological manifestations. Most common age group was <5 years. Out of the 11 children, 7 were boys and 4 were girls [Table/fig 1].

Table /Fig 1: Sociodemographic charecteristics of the study participants:

Age in years	**Total n (%)(n=562)**
< 5	214 (38%)
6 - 10	157 (28%)
11 - 14	191 (34%)
Gender	
Male	270 (48%)
Female	292 (52%)
Mother's education	
Illiterate	74 (13.1)
Primary school	138 (24.5)
Secondary school	190 (33.9)
College	160 (28.5)
Socio economic status (Modified BG Prasad classification2020)	
Class I (Rs.7533 & above)	30 (5.4)
Class II (Rs. 3766-7532)	147 (26.2)
Class III (Rs.2260-3765)	125 (22.3)
Class IV (Rs. 1130-2259)	143 (25.4)
Class V (Rs. 1129 and Below)	117 (20.7)
Area of Residence	
Urban	255 (45.4)
Rural	307 (54.6)
Duration of hospitalization (days)	
0-3	162 (28.8)
3-6	359 (63.9)
>6	41 (7.3)
Classification	
Dengue without warning signs	112 (20)
Dengue with warning signs	363 (64.6)
Severe dengue	87 (15.4)

Table/Fig 2. Neurological manifestation of Dengue fever

Acute encephalitic syndrome (AES)	7 (63.6%)
Cerebral hemorrhage	2 (18.2%)
Stroke	1(9.1%)
Acute disseminated encephalomyelitis (ADEM)	1(9.1%)
Total	11(100%)

Most common neurological manifestation was acute encephalitic syndrome (AES) seen in 7(63.6%) out of the 11 children. Out of the remaining four children, 2 (18.2%) children had cerebral hemorrhage, 1(9.1%) child had stroke and 1 (9.1%) child had ADEM [Table/fig 2].

Table/Fig 3. Association of headache with clinical features of CNS manifestations

Headache after fever	TotalN(%)	meurologicalmenifestation	N(%)
After 2weeks	3[27.3%]	Hemorrhage	2[18.2 %]
		stroke	1[9.1%]
After 1week	8[72.7]	Acute disseminated encephalomyelitis (ADEM)	1[9.1%]
		encephalitis	7[63.6%]

The clinical presentation among them varied from altered higher mental function, seiures, intense headache, weakness, rigidities / Parkinsonism like features.

All patients had history of headache one or two weeks after onset of fever. It was observed that children who had prolonged headache even in second week after fever, showed severe manifestations like hemorrhage and stroke in MRI while children with headache presentingone week after fever showed less severe manifestations like acute disseminated encephalomyelitis (ADEM), and double doughnut sign suggestive of encephalitis in MRI [Table/fig-3]

Table/Fig 4. Association of headache with MRI findings of CNS manifestations

parameter	MRI findings	
	Headache 1 weeks after fever (n=8)	Headache 2weeks after fever (n=3)
Thalamus infarct		1[9.1%]
Cerebral hemorrhage with mass effect		2[18.2 %]
ADEM	1[9.1%]	
Double doughnut sign	1[9.1%]	

CSF study was done in all patients. CSF examination showed lymphocytic pleocytosis in 3 patients. In other patients, the CSF examination was normal. EEG study was done in all the11 patients. EEG was abnormal in 5 patients: epileptic changes were seen in 1 patient and 4 patients showed diffuse slowing.

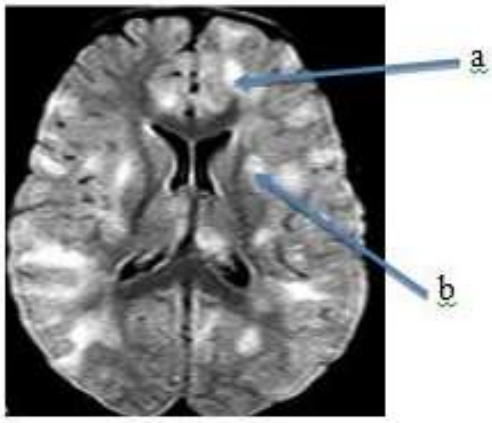
Imaging findings were normal in 4 and abnormal in 7. MRI done for severe headache following second week of fever showed severe manifestations like thalamus infarct, CT brain showing hemorrhage with mass effect was seen in 1 patient. Headache following first week of fever showed mild manifestations like ADEM, and double doughnut sign in MRI [Table/fig- 4].

Table/Fig 5: CNS Manifestations of Dengue fever

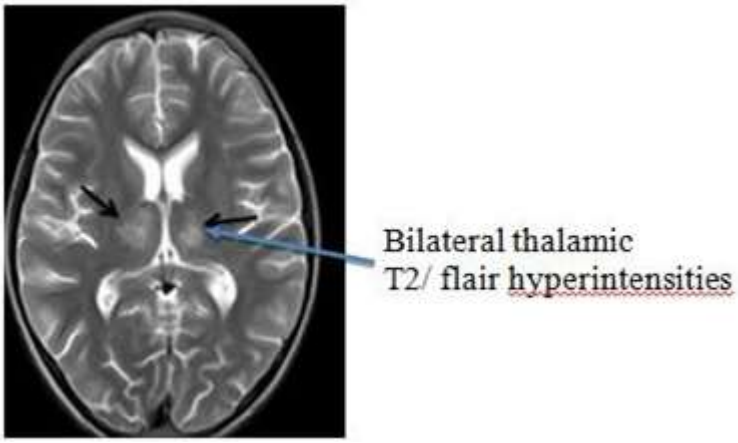
S. No	Author	Place & year of the study	Age years	Total no of samples	Number	CNS MANIFESTATIONS				
						Encephalopathy	Encephalitis	ICH	Motor weakness	Stroke	ADEM
1	**Present study**		1-14		11	-	7	2		1	1
2	Misra UK et.al.[8]	Lucknow2003-2005	5 to 56		17	11		-	6	-	-
3	Kulkarni R et.al.[9]	Western India 2014-19	0-89		154	48	24	7	-	1	-
4	Mathew T et.al.[12]	Banglore 2015	18		1	-	1	-	-	-	-
5	Solomon T et.al. [13]	Vietnam 1995	-		9	-	9	-	-	-	-
6	Neeraja et.al.[15]	Hyderabad 2011-13	18 to 80		13	-	13	-	-	-	-
7	Sil et.al.[17]	2017 Eastern India	1- 14		20	8	6	-	3	2	1
8	Kamath et.al.[18]	2020 Mangalore	6		1	-	-	-	-	-	1
9	Yoganathan et.al.[19]	2017 Vellore	2.4		1	1	-	-	-	-	-

ICH- intracranial hemorrhage

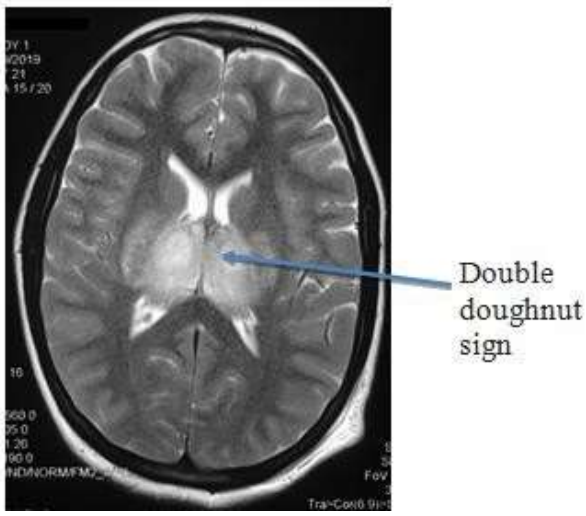
Table/Fig 6. ADEM: multiple T2 hyperintensities are seen in the basal ganglia (a)and white matter regions (b)



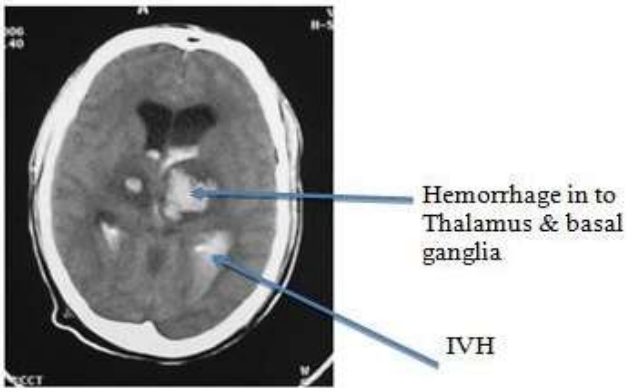
Table/Fig 7. Thalamic infarcts: bilateral thalami show T2/ flair hyper-intensities whichshowed diffusion restriction



Table/Fig 8: Double doughnut sign: Edematous and enlarged bilateral thalami



Table/Fig 9: CT-Hemorrhage



Following treatment was given to children with Neurological manifestations.

Seven Children who had encephalitis were treated with supportive measures. Even though acyclovir was added in four of them, once the serological diagnosis was confirmed, it was stopped. One patient with ADEM was treated with IV immuno globulin 400 mg kg/day for five days and as improvement was delayed IV

Methyl prednisolone 30 mg/ kg/day for five days followed by oral prednisolone 1 mg/ kg/day for two more weeks was given. Child withintracerebral haemorrhage was given anti edema measures and the bleeding was managed conservatively. Period of hospitalisation varied between 14 to 40 days.

Out of the 11 children with neurological manifestations, 10 recovered completely and 1 childwho had stroke had residual weakness in the upper and lower limbs.

DISCUSSION

Neurological manifestations of dengue fever are rare and unusual. During the recent years, they are being increasingly reported in the literature. The neurological complications range from non-specific symptoms to acute encephalitis, cerebral hemorrhage, and rarely Guillain Barre Syndrome and acute disseminated encephalomyelitis. [8]

In the present study, 1.9% of the children who presented with dengue fever had neurologicalcomplications. This is in concurrence with the study conducted in Western India by Kulkarni et al. [9] They reported that 2.64% of the children with dengue fever had neurological complications. The study done in Lucknow by Sahu et al. [10] reported a higher incidence (9.26%) of neurological complications following dengue fever and they found a significant number of children had peripheral nervous system involvement also.

In the present study children between the ages of 4 to 14 years were the most commonly affected with neurological complications. Similar observations were made in the case series report done in Kolkata by Samanta et al. [11] They reported that CNS manifestations by thedengue virus is on the increase among the pediatric age group.

The neuroimaging findings for dengue encephalitis are non-specific.{12] In the present study, the most common presentation was acute encephalitis syndrome (AES) seen in (63.6%) 7 outof the 11 children. Similar observations were made by Solomon et al.[13] in the study conducted in Southern Vietnam. They recommended that all cases of encephalitis and encephalopathy should be investigated for dengue infection in the endemic areas even if they do not present with other symptoms of dengue fever. The study by Araujo et al. and Neeraja et al. [14,15] also found that acute encephalitis syndrome (AES) was the most common neurological manifestation and this is in concurrence with our findings. Vasanthapuram et al.

[16] noted that dengue accounted for 5% of the acute encephalitis syndrome and it was the third most common etiological agent causing AES following Japanese encephalitis and scrub typhus. Sil et al. [17] conducted a study in eastern India and found the encephalitis and encephalopathy were the most common neurological complications of dengue infection and this is in concurrence with the findings of our study.

Acute disseminated encephalomyelitis usually occurs following viral infection with measles, mumps and rubella infection, enterovirus, herpes virus, cytomegalovirus, and rarely dengue virus. Few cases have been reported in the literature about the association of ADEM with dengue fever. In the present study, 1 child presented with ADEM as a complication of denguefever. Similarly, Kamath et al. [18] reported one case of ADEM following dengue fever in a six year old child who recovered with IV steroids and supportive treatment.

Dengue infection associated with stroke is a very rare event in the paediatric population. Thismay occur due to ischaemia or haemorrhage. In the present study we had one child who presented with stroke. Yoganathan et al. [19] reported a case of stroke in a 29-month-old child with the encephalopathy manifesting with altered sensorium and seizures. The details of the CNS manifestations of dengue fever discussed in the above studies are shown in table 5.

LIMITATIONS

The limitation of this study is the small sample size, this being a single centrestudy. This can be overcome by conducting a multi-centre study.

CONCLUSION

In the present study, it was found that 1.9% of the children had neurological complications.The most common neurological manifestation was acute encephalitic syndrome. Hence, dengue should be considered as an etiological agent in all cases of acute encephalitic syndrome in children. In the present study, we also observed that new onset headache occurring in the second week following fever is a warning sign for severe CNS disease.

Prompt diagnosis along with early imaging helps in the effective management of thesechildren which can lead to a good outcome without neurological sequealue.

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