



CENTRAL NERVOUS SYSTEM MANIFESTATIONS AND ITS OUTCOME IN DENGUE FEVER AFFECTED CHILDREN

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ABSTRACT Dengue infections is one of the most important arboviral infections of humans and is one of the most important tropical infectious disease of the world. The occurrence of neurological manifestations in dengue infection have been recognized for long. In previous reports of neurologic involvement in dengue infections, the observed “encephalopathy” was thought to be due to prolong shock, along with fluid extravasation, cerebral edema, hyponatremia and liver failure. Recently however, direct neurotropic potential of the virus has been recognized. In India too, neurological complications of dengue have been recognized. Hence the following study was conducted to find out the incidence of CNS manifestation in children with dengue, spectrum of neurological manifestations and presence of dengue specific IgM antibodies in the CSF. **Method :** A prospective study was conducted at Upgraded Department Of Paediatrics , Patna Medical College & Hospital ,Patna From January 2016 To August 2017. 104 children's presenting to department of Paediatrics, Patna Medical College & Hospital, Patna, aged between 6 months to 16 years, both in outdoor and indoor, during study period, were screened for features suggestive of probable dengue based on WHO definition (2009). **Results:** Out of these 3610 patients, 104 patients were found positive for dengue fever either by NS1 antigen/IgM antibody/ IgM & IgG antibody. These dengue positive 104 cases were further evaluated for clinical manifestations and immediate outcome based upon CNS involvement. **Conclusions :** dengue fever encompasses an expanding clinical spectrum, not just restricted to WHO specified criteria for making a diagnosis of other than DHF or DSS. It frequently involves encephalitis probably due to a direct neurotropic effect of dengue virus.

KEYWORDS : Dengue fever, encephalitis, encephalopathy, CNS manifestation of dengue.

INTRODUCTION:

Dengue is most rapidly spreading mosquito borne viral disease of 21st century in the world. Dengue fever is an arthropod borne viral fever. It is acquiring epidemic proportion in this part of the world . In the last 50 yrs, incidence has been increased 30 fold with significant outbreaks occurring in five of six WHO region , with increasing geographic expansion to new countries and, in the present decade, from urban to rural setting. One recent according to WHO (2013) estimate indicates that 390 million dengue infections occur every year (95% credible interval 284-528 million), of which 9 million (67-136 million) manifest clinically (with any severity of disease). Another (2012) study, of the prevalence of dengue , estimates that 3.9 billion people in 128 countries are at risk of infection with dengue viruses.[1]

Current estimates report that, at least 112 countries are endemic for dengue and about 40% of world populations(2.5-3 billion people)are at risk in tropics and sub tropics. In its most severe form, it manifests itself clinically as dengue hemorrhagic fever and dengue shock syndrome. Recent observations indicate that clinical profile of dengue is changing and neurological manifestations are reported frequently. The exact incidence of various neurological complications is uncertain. The reported incidence of encephalopathy and encephalitis, the most common neurological manifestations of dengue, have been found to vary between 0.5 -6.2%. 2,3 DHF with a case fatality in asian countries of 0.5%-3.5%. 90% of DHF subjects are less than 15 years of age. [2]

From the pathogenesis point of view, neurological manifestations of dengue can be grouped into three categories Related encephalitis, encephalopathy, acute disseminated encephalomyelitis, myelitis, Guillain-Barre syndrome, optic neuritis.[3-4]

An array of neurological manifestation have been reported with dengue infection: most outstanding among them are convulsion, unconsciousness, myositis, spasticity and paresis. Current report proposes that the DEN2 and DEN3 has strong neurotropism and is capable of causing encephalitis owing to direct viral invasion of brain. The reported incidence of encephalopathy and encephelitis, vary between 0.5-6.2% [5,6].

Using more sensitive techniques, it has been possible to demonstrate the invasion in the CNS by the virus. By detection of dengue specific IgM antibodies and isolation of dengue virus from CSF. The gold standard for diagnosis of dengue encephelitis is isolation of virus in CSF/CNS.

AIMS AND OBJECTIVES:

The Present Study have following aims and objective.

1. To know incidence of dengue viral infection in children.
2. To study the Spectrum of neurological manifestations of dengue viral infection in children.
3. To determine Immediate outcome of dengue viral infection in children with CNS manifestations.

MATERIAL AND METHODS:

A prospective study was conducted at Upgraded Department Of Pediatrics , Patna Medical College & Hospital ,Patna From January 2016 To August 2017. 104 childrens presenting to department of Pediatrics, Patna Medical College & Hospital, Patna, aged between 6 months to 16 years, both in outdoor and indoor, during study period, were screened for features suggestive of probable dengue based on WHO definition (2009). Features included fever and 2 of the following Nausea , vomiting , Rash , Aches and pains , Torniquet test Positive, Leukopenia ,Any warning sign . Patients fulfilling the WHO criteria for probable dengue were tested for seropositivity for dengue either by NS1 antigen/IgM antibody/IgM & IgG antibody. Patient found to be seropositive for dengue were included.

Inclusion Criteria-

1. All children with dengue fever- seropositive for either NS 1 antigen/ IgM antibody/ IgM & IgG antibody.
2. Age between 6month –16 yrs.

Exclusion Criteria :

1. Children with dengue like illness but negative for dengue Serology(NS1 antigen/ IgM antibody /IgG antibody).
2. Patient's relatives not giving consents.
3. Patients with previous CNS manifestations.

RESULTS :

During study period total of 9610 patients (outdoor-4510 and indoor-5100) presented to Department of pediatrics, PMCH, Patna. Out of these 3610 patients were found to fulfill the WHO criteria (2009) for probable dengue. These 3610 patients was then subjected to either by NS1 antigen/IgM antibody/IgM & IgG antibody. Out of these 3610 patients, 104 patients were found positive for dengue fever either by NS1 antigen/IgM antibody/ IgM & IgG antibody. These dengue positive 104 cases were further evaluated for clinical manifestations and immediate outcome based upon CNS involvement. These are the following results of our study.

Table 1.
INCIDENCE OF NEUROLOGICAL MANIFESTATIONS

	Dengue fever (DF)	DF with CNS involvement
No of cases	104	40

Table 2.
SIGN AND SYMPTOMS IN CHILDREN WITH NEUROLOGICAL MANIFESTATIONS

Symptoms	Cases(n=40)	Percentage
Fever	40	100%
Headache	22	55%
Vomiting	25	62.5%
Seizure	31	77.5%
Altered sensorium	34	85%
Abdominal pain	7	17.5%
Arthralgia	3	7.5%
Malena	1	2.5%
Lymphadenopathy	24	60%
Rash	10	25%
Puffiness	15	37.5%
Petechiae	15	37.5%
Hepatomegaly	26	65%
Spleenomegaly	15	37.5%
Papilloedema	13	32.5%
CN palsy	13	32.5%
Meningeal sign	33	82.5%

Table 3.
CSF ANALYSIS

CSF	Protein(mg/dl)	Glucose(mg/dl)
Average	84.6	47.67
Range	28-178	4-86
SD	45.56	19.95

Table 4.
CSF IgM Positivity

CSF IgM	DF With CNS Involvement (n=40)
CSF IgM Positive	14 (35%)

DISCUSSION

Dengue infections is one of the most important arboviral infections of humans and is one of the most important tropical infectious disease in the world. The occurrence of neurological manifestations in dengue infection have been recognized for long.[7] In previous reports of neurologic involvement in dengue infections, the observed "encephalopathy" was thought to be due to prolong shock, along with fluid extravasation, cerebral edema, hyponatremia and liver failure.[8] Recently however, direct neurotropic potential of the virus has been recognized.[9] In India too, neurological complications of dengue have been reported.

In the present study 3610 cases was found to fulfill the WHO criteria (2009) for probable dengue and was included in the study. Out of 3610

cases 104 cases was positive for dengue virus specific either NS1 antigen/IgM antibody/IgM & IgG antibody. Hence the incidence of dengue viral infection in our hospital based study was 3%, which was very low as compared to other study. [10]

In study conducted by Sunil Kumar et al in Patna in 2015 out of 526 cases 84 cases (16%) has dengue positive by NS1 antigen, IgM antibody and IgG antibody. This study have higher incidence because the study was done in dengue epidemic period. [11]

In a study conducted by Nishant Hussain Ahmad et al in Delhi in 2014, out of 4370 cases 1700 cases (38.9%) has IgM positive. This study have higher incidence of dengue because of this study was done in dengue endemic region and dengue epidemic period. [12]

In the present study all the 104 cases studied were serum IgM positive for dengue infection. Out of these 104 cases, 40 children had symptoms and signs pertaining to CNS involvement. Hence the incidence of neurological involvement in our study was 38.5%, which we believe is very high as compared to other studies.[13]

The median age of presentation of children in our study is 6.9 yrs (0.6-16 yrs). Similar observation were made by others. The following table show age distribution observed in various other studies.

The incidence of male children that were affected is slightly more in our study, the ratio being 1.5:1. Similar observation were made by others also.[14]

Incidence of neurological involvement was more in the children who met the clinical features of WHO specified criteria of only dengue fever. Similar observation was made by Misra et al which suggest that neurological involvement may not be necessarily due to shock or bleeding. It may be due to direct neurotrophic effect of virus.

In present study fever (100%) is a predominant symptom followed by altered sensorium (85%), seizure (77.5%), vomiting (62.5%) and headache (55%).The following pattern of symptoms have been observed in other studies. [15]

In present study, however altered sensorium and convulsion were the most frequent presentation which was almost similar to the previous observation done by Solomon et al.

An interesting observation that we made in our cases were that the presence of papilloedema and meningeal sign which were significantly more being 32.5% and 82.5% respectively. The other comparable study in this aspect showed only 5% of children having papilloedema and 18% of children having meningeal signs.[16]

CSF pleocytosis is an indication of the inflammation of meninges and encephalon probably due to direct viral invasion. In our study CSF pleocytosis was seen in 82% of the cases. Among the other studies only Soares et al showed CSF pleocytosis to be around 80% and other 2 studies that were done by Misra et al showed to be around 50%.[17]

Though the gold standard of diagnosing viral encephalitis is isolation of virus either from neural tissue or CSF, however detection of viral specific IgM in the CSF is considered as an indication of viral replication in the CNS. In the present study CSF IgM was positive in 35% of the cases, which is little less when compared to the other studies. The reason for low percentage of positivity of IgM in CSF in our study, could be, because of we used CSF in 1:10 dilution as per the guidelines given by NIV Pune, the manufacturer of the kit.[18] In one study, done by Soares et al CSF 1:2 dilution was used, probably we could have got more positive test results if lesser dilution was used. CECT of brain were done in all cases with CNS involvement and it was normal in [19] cases. In 8 cases it showed cerebral edema. Misra et al conducted a study in Lucknow on 17 patients CT scan was carried out in 5 patients and it was normal in all.[20] Wasy et al conducted a study in Karachi Pakistan Jun 2008 on 225 patients, CT scan were done in 6 patients, 5 patients had abnormal finding out of them 3 patients showed cerebral edema.[20]

Results of our study almost match to previous study done by different author. In our study, the mortality rate was 7.5% and there was one morbidity which had left sided hemiplegia. All the other patients recovered without any neurological deficit. Mortality rate was higher

in the other studies as shown in the table. In the other two studies, morbidity was also noted.

CONCLUSION

Dengue is a rising public health issue in Patna and surrounding district in the state of Bihar in east India. Over the last few years, we have been observing varied clinical manifestations of dengue, which rather does not fulfill WHO criteria for making a diagnosis of severe dengue infections like DHF and DSS. A wide range of neurological manifestations were observed in our study. Altered sensorium, seizures, papilloedema, cranial nerve palsy, meningeal signs are among the common manifestations. Detection of dengue specific IgM in CSF using ELISA has high specificity and it is difficult to explain the presence of IgM antibody in the CSF other than by viral invasion across the blood brain barrier. In our study IgM in CSF was isolated in 14(35%) of cases, along with mean CSF protein of 84 mg/dl and with CSF mean cell count of 61 cells/cmm³ which suggest viral invasion into the CNS. In endemic area dengue encephalopathy should be considered in patients who present with the clinical features of encephalopathy, whether or not classical manifestation of dengue are present. Standard case definition for dengue, if adopted by encephalopathy WHO would help clarify the importance of dengue neurotropism world-wide.

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