Prospective Study on Changing Clinical Spectrum of Dengue Infection in Pediatric Population in the 2016 Epidemic from a Tertiary Care Teaching Hospital in Eastern India

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Abstract: *Introduction: In India, outbreaks of dengue infections are occuring in almost every year and have become a major heath concern since the last two decades. Many parts of India, including the eastern regions, are now endemic for the dengue infection with increased recognition of atypical neurological manifestations apart from the classical clinical features. Methods: This prospective study was conducted in the department of Pediatrics in a tertiary care teaching hospital in eastern India from July 2016 to November 2016 to determine the changing trends of the clinical features in the dengue patients of this region in the recent years among pediatric populations. All the serologicaly confirmed dengue patients admitted during this period satisfying the inclusion criteria were enrolled in the study population and classified as per new WHO-2009 classification into: dengue fever without warning signs (DF), dengue fever with warning signs (DFWS) and severe dengue (SD). Detailed history, clinical & laboratory parameters were recorded and analysed for all children. Results: Out of the total of 110 cases, 16 cases (14.55%) were DF, 80 cases (72.73%) were DFWS and 14 cases (12.73%) were SD. The commonest age group affected (63.64 %) was between 4-<10 years. The male: female ratio of cases was 1.68:1. Besides classical clinical manifestations, we observed CNS involvement in nine cases (8.18%). Among them, five patients had dengue encephalitis, two patients had dengue encephalopathy, one patient had hypokalemic paralysis and one patient had Guillain-Barré syndrome. All the patients were treated as per standard guidelines. Outcome was good except two cases who succumb inspite of our best effort.*
Keywords : *Dengue outbreak, neurological manifestations, encephalitis, encephalopathy Guillain-Barre syndrome, hypokalemic paralysis.*

I. Introduction

Dengue viral infection has emerged as a serious public health disease affecting almost half of the world's population. [1] In India frequent outbreaks of dengue have been reported from time to time across the country both from urban and rural areas. Dengue infection is caused by any of the four dengue virus serotypes and presents with varied clinical features ranging from fever, headache, myalgia, arthralgia, rash, bleeding from different sites, retro-orbital pain to severe fatal neurologic manifestations presenting amongst all segments of society.[2-15]

The present prospective study, which was done during dengue outbreak from the department of Pediatrics at a tertiary care teaching hospital in Kolkata, West Bengal in 2016, outlined the increased manifestation of atypical features with special emphasis on neurological manifestations thus indicating a paradigm shift in clinical features of this disease as compared to previous studies. [3-15]

II. Materials and Methods

This prospective study was conducted at Pediatrics Department, NRS Medical College and Hospital, Kolkata, a tertiary care-teaching institute in the state of West Bengal from the month of July to November 2016. Due permission was taken from ethical committee of the Institute. All children, between the age group of 0-12 years who were presenting with an acute febrile illness of 2–7 days' duration, with two or more of the following: headache, myalgia, arthralgia, rash, retro-orbital pain, haemorrhagic manifestations were considered as suspected dengue fever and were admitted in our department. After taking detailed history and clinical examinations, blood samples were send for complete blood count (CBC) and serology for dengue infection. Amongst all the suspected cases, only those who had a positive serological test for dengue IgM antibodies (IgM capture ELISA test) were included in the study population. However even amongst the serologically positive cases, the children who had co-infection with other diseases like chikungunya, enteric fever, malaria,

leptospirosis were excluded from the study population to avoid confusion arising due to confounding clinical features. Necessary consent was taken from the respective legal guardian of all the patients. Repeated clinical and laboratory evaluation like haematocrit, platelet count, liver function test (LFT) including serum albumin level, etc were performed at regular interval. Prothrombin time (PT), activated partial thromboplastin time (aPTT) abdominal USG, chest x-ray, lumbar puncture and magnetic resonance imaging (MRI) were performed according to the evolving and changing clinical scenario. However, frequent and repeated serological test (ELISA) could not be performed due to cost constraints.

As per the World Health Organization (WHO) 2009 criteria, the cases were finally categorized as following. (A) Dengue fever without warning signs (DF) : Lived in/travel to dengue endemic area, presenting with Fever and 2 of the following criteria: i) Nausea, vomiting, ii) Rash, iii) Aches and pain, iv) Tourniquet test positive, v) Leucopenia, vi) Laboratory confirmed dengue; (B) Dengue fever with warning signs (DFWS) : The Warning signs included were: (i) Abdominal pain or tenderness. (ii) Persistent vomiting. (iii) Clinical fluid accumulation. (iv) Mucosal bleed. (v) Lethargy. (vi) Restlessness. (vii) Liver enlargement >2cm. (viii) Laboratory: Increase in haematocrit concurrent with rapid decrease in platelet count; (C) Severe dengue (SD) : Criteria for inclusion were: i) Severe plasma leakage leading to: a) Shock. b) Fluid accumulation with respiratory distress. ii) Severe bleeding as evaluated by clinician. iii) Severe organ involvement: a) Liver: AST or ALT>=1000. b) CNS: Impaired consciousness. c) Heart and other organs.[16] All cases were managed as per WHO standard guideline. Outcome was evaluated by parameters like duration of hospital stay, complications noted in dengue cases and number of deaths. All categorical variables like clinical characteristics and biochemical tests were expressed as numbers and percentages and continuous variables like age were expressed as mean ± standard deviation (SD).

III. Results

In our prospective study, although 359 patients were admitted in our department with the clinical diagnosis of suspected dengue, only 127 cases were found to be serologically positive. Out of these 127 cases, 17 cases turned out to be positive for chikungunya, enteric fever, malaria, leptospirosis and hence were excluded from the study population keeping the remaining 110 cases for the final study population. In our study out of total 110 cases 69 (62.73%) were males and the remaining 41 (37.27 %) were females, with a male to female ratio of 1.68:1 (Fig 1 and Table 1). Distribution of cases according to different age group showed maximum incidence of the disease (n=70; 63.64%) in the age group of 4-<10 years; with mean age of affection being 6.93 years with standard deviation of 2.92 (Table: 1). The outbreak of dengue started from July 2016 and continued till the end of November 2016. The maximum incidence of cases was observed in the month of September (Fig 2). Out of total 110 cases, 61 (55.45%) were came from Kolkata and suburban areas and the remaining 49 (44.55%) from villages. Categorizing cases as per WHO revised clinical criteria, DF, DFWS and SD were diagnosed in 16 (14.55%), 80(72.73%), and 14(12.73%) cases respectively in this study (Table 2).

Fever was present ubiquitously amongst all categories of patient (100%). Mild to moderate degree of fever was observed in a majority of patients, but it had no specific pattern. The duration of fever of less than 7 days was found in 71 cases (64.55%), while it was of more than 7 days in remaining 39 cases (35.45%). Prolonged duration of fever was particularly observed in SD cases. The other main complaints besides fever were vomiting (75.45%), arthralgia & or myalgia (66.55%), pain in upper abdomen (59.09%), and headache (41.82%) (Table 3 and Fig 3). Maculo-papular erythematous rash and positive tourniquet test were found to be present in 78 (70.91%) and 49 (44.55%) cases respectively. Although petechiae was present in 39 (35.45%) cases, only 10 (9.10%) cases showed a tendency for spontaneous bleeding. The gastrointestinal tract was the most common site for the bleeding in six patients, followed by epistaxis (3 cases) and episodes of haemoptysis (2 cases). Among these 10 cases who had presented with bleeding tendencies, 3 interesting cases showed normal platelet counts and prothrombin time. Hepatomegaly (>2cm) was observed in 57 (51.82%) cases. A significant number of case of diarrhea (n=10; 9.10%) was found in our study.

Ascites was detected clinically 13.64% (n=15) while 10.91% (n=12), had pleural effusion while some of them had both. The total number of patients with radiological evidence of effusions either pleural or peritoneal or both were 47(42.73%). Evidences of shock was found in 5 (4.55%). Apart from the classical profile, we observed nine patients (8.18%) who had developed various neurological complications of dengue fever in our study (Table 3 and Fig 3). Among them, five patients had dengue encephalitis, two patients had dengue encephalopathy, one patient had hypokalemic paralysis and one patient had Guillain-Barré syndrome (Table 4). Amongst the laboratory findings, haemoconcentration (PCV > 45%) and thrombocytopenia (platelet count of <1,00,000/cmm) was found in 29 (26.36%) and 81 (73.64%) cases respectively whereas 45 (40.91%) cases had elevated liver enzymes. Mean duration of fever, bleeding manifestations, evidence of shock and serous effusion all were significantly associated with severe disease. All the cases were managed as per the standard WHO guideline and the overall recovery rate in our study was good but unfortunately two patients expired due to multiorgan failure and refractory shock.
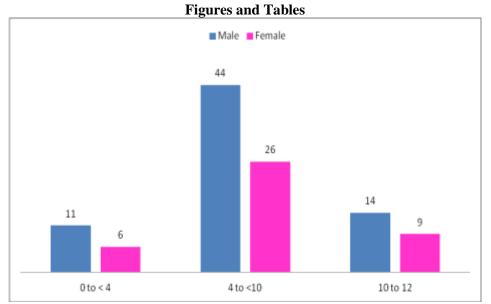
Figures and Tables

Fig 1: Distribution of patients according to age and sex

Table 1: Age & Sex Wise Distribution of Cases

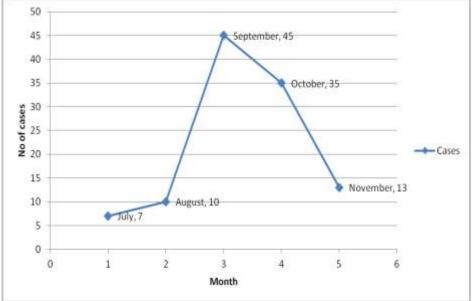| Age (years)	Male	Percentage	Female	Percentage	Total	Percentage
0 to < 4	11	10.00%	6	5.45%	17	15.45%
4 to <10	44	40.00%	26	23.64%	70	63.64%
10 to 12	14	12.73%	9	8.18%	23	20.91%
Total	69	62.73%	41	37.27%	110	100.00%

Fig 2: Month wise distribution of serologically positive cases

Table 2: Distribution of Different Categories of Dengue Cases According to Age Group

Category of Dengue	Age Group (years)						Total	Percentage
	0 to < 4		4 to <10		10 to 12			
	Cases	Percentage	Cases	Percentage	Cases	Percentage		
DF	3	2.73%	11	10.00%	2	1.82%	16	14.55%
DFWS	14	12.73%	53	48.18%	13	11.82%	80	72.73%
SD	0	0.00%	6	5.45%	8	7.27%	14	12.73%
Total	17	15.45%	70	63.64%	23	20.91%	110	100.00%

Table 3: Clinical features and laboratory investigations of study population

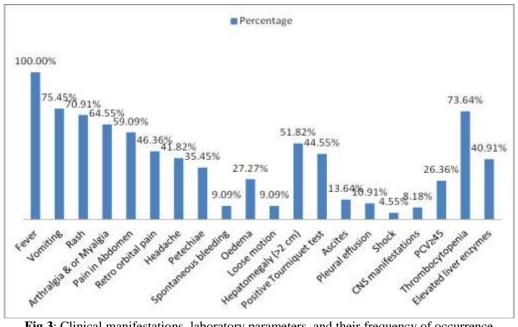| Clinical manifestations and Laboratory Investigations	DF (n=16)		DFWS (n=80)		SD (n=14)		Total (n=110)	
	Cases	Percentage	Cases	Percentage	Cases	Percentage	Cases	Percentage
Fever	16	100.00%	80	100.00%	14	100.00%	110	100.00%
Vomiting	11	68.75%	61	76.25%	11	78.57%	83	75.45%
Rash	11	68.75%	56	70.00%	11	78.57%	78	70.91%
Arthralgia & or Myalgia	12	75.00%	51	63.75%	8	57.14%	71	64.55%
Pain in Abdomen	3	18.75%	57	71.25%	5	35.71%	65	59.09%
Retro orbital pain	9	56.25%	37	46.25%	5	35.71%	51	46.36%
Headache	8	50.00%	34	42.50%	4	28.57%	46	41.82%
Petechiae	1	6.25%	33	41.25%	5	35.71%	39	35.45%
Spontaneous bleeding	0	0.00%	7	8.75%	3	21.43%	10	9.09%
Oedema	0	0.00%	25	31.25%	5	35.71%	30	27.27%
Loose motion	0	0.00%	9	11.25%	1	7.14%	10	9.09%
Hepatomegaly (>2 cm)	0	0.00%	55	68.75%	2	14.29%	57	51.82%
Positive Tourniquet test	7	43.75%	37	46.25%	5	35.71%	49	44.55%
Ascites	0	0.00%	11	13.75%	4	28.57%	15	13.64%
Pleural effusion	0	0.00%	8	10.00%	4	28.57%	12	10.91%
Shock	0	0.00%	2	2.50%	3	21.43%	5	4.55%
CNS manifestations	0	0.00%	0	0.00%	9	64.29%	9	8.18%
PCV≥45	3	18.75%	21	26.25%	5	35.71%	29	26.36%
Thrombocytopenia	7	43.75%	67	83.75%	7	50.00%	81	73.64%
Elevated liver enzymes	1	6.25%	38	47.50%	6	42.86%	45	40.91%

Fig 3: Clinical manifestations, laboratory parameters, and their frequency of occurrence

Table 4: Frequency of different neurological complications in the study group

Neurological complications	Number of patients
Encephalitis	5
Encephalopathy	2
Hypokalaemic paralysis	1
Guillain-Barré syndrome	1

IV. Discussion

Dengue has become a major public health hazard with outbreaks occurring regularly during monsoon season in various parts of India, especially in West Bengal. [9-14] Based on the WHO 2009 dengue guidelines, in our study, the total number of cases analyzed was 110, out of which 16 (14.55%) cases were categorized as Dengue fever without warning signs (DF), 80 (72.73%) cases were Dengue fever with warning signs (DFWS), and 14 (12.73%) cases were diagnosed as Severe disease (SD). Majority of the patients in our study got admitted in the hospital in the months of September and October than in August and November which was in accordance with various other studies. [9,17] These finding shows that preventive measures should be taken aggressively against dengue virus infection especially during the periods of water stagnation after the initial episodes of rainfall and towards the end of rainy season. Distinct male preponderance (1.68:1) was found in the present study as compared to other studies. [8,9,17,18,19] However, equitable sex distribution or female predominance was also reported from few recent studies. [11,12,13,20]

Maximum incidence of disease was found in the age group of 4-<10 years whereas incidence in the first four years of age was low in the present study as was reported in other studies. [9,20] Dengue is traditionally known to be an urban disease, but epidemics are extending geographically even into rural areas now-a-days as observed in the present study as well as in other studies also. [12,13,18]

Out of all the clinical manifestations, fever was the most common symptoms in almost every patient followed by vomiting (75.45%), rash (70.91%), arthralgia and or myalgia (66.55%), pain in the upper abdomen (59.09%), retro orbital pain (46.36%), and headache (41.82%). Our finding were consistent with other previous studies done in pediatric population. [9,12,17,18,20] Relative high incidence of headache with retro orbital pain, in few studies might be due to inclusion of adult in study population who can express such symptoms better than children do.[13,19] Besides vomiting, considerable number of case of diarrhea (n=10; 9.10%) was found in our study as compared to other studies [13,19,21]. Although a significant number of cases (n=81; 73.64%) had thrombocytopenia, 35.45% cases (n=39) had come with cutaneous bleeding in the form of petechiae and only ten (9.09%) had presented with spontaneous bleeding. Most interestingly out of ten cases, three had normal platelet counts and prothrombin time. Our observation is similar to the other studies. [9,19,21] This signifies the fact that factors other than thrombocytopenia like platelet dysfunction, consumption coagulopathy, and endothelial dysfunction might be the cause for bleeding in dengue patients. Gastrointestinal bleeding in the form of melaena was significantly associated with severe dengue cases, while epistaxis and hemoptysis were less common. In our study, tourniquet test was positive in 44.55% cases whereas it was found in varying percentage in different studies. [9,13,18,21]

Hepatomegaly (>2 cm) was present in 51.82% cases which was similar to the observation done by Kale AV et al. [18] Elevated level of transaminases, which was found in forty patients (40.91%), was usually mild to moderate in majority of cases (< 5-fold greater than the normal upper limit for aspartate amino transferase (AST) and alanine amino transferase (ALT) suggesting that liver involvement was mild-to moderate in dengue infection. In our study, radiological evidence of serositis in the form of ascites and pleural effusion from capillary leak was seen in 42.73% cases, which are comparable to the study done by Chatterjee et al.[13] Contrary to our findings, Jain P et al[19] found serositis in 16.67% subjects which was self-limiting and subsided within 2 - 3 weeks of recovery. Involvement of the central nervous system (CNS) in patients with acute dengue infection is being frequently reported in recent outbreaks with varying frequency ranging from 4% to 21.2%. [22,23] In our study, neurological involvement was seen in 9 (8.18%) patients in the form of dengue encephalitis (5), dengue encephalopathy (2), hypokalaemic paralysis (1), and Guillain-Barré syndrome (1). Although there are no standardized case definitions or diagnostic criteria for dengue encephalitis or encephalopathy, we have diagnosed those cases in our study based on their clinicopathological and radiological profiles. Other than few case reports, there are no such prospective studies from this part of the country in the previous literature on increasing incidence of such varied neurological manifestations among dengue cases in pediatric population. [14]

As of now, three pathogenic mechanisms are there to explain the different neurological complications associated with dengue infection. [24] Some workers suggest that neurological manifestations are secondary to metabolic or hematological derangement related with the disease process itself, where the cerebrospinal fluid (CSF) analyses, including measurements of protein, glucose, and cell count, are usually normal. [25] This can explain encephalopathy, stroke (both hemorrhagic and ischemic), hypokalemic paralysis, and papilledema in dengue infection. However, isolation of dengue virus antigen in brain specimens or dengue viral RNA in CSF samples of patients with neurological symptoms in some studies support the increasing trend of dengue neurotropism. [15,22,26,27] Encephalitis, meningitis, myositis, rhabdomyolysis, and myelitis in dengue can be due to this neurotrophic effect of this virus. Post infection neurological syndrome like ADEM, encephalomyelitis, myelitis, neuromyelitis optica, optic neuritis, Guillain–Barré syndrome, probable Miller–Fisher syndrome, mononeuropathies such as phrenic neuropathy, long thoracic neuropathy oculomotor palsy, isolated Bell's palsy, abducens nerve palsy, maculopathy, and fatigue syndrome are usually immune mediated. [28]

V.   Conclusion

The clinical profile of the dengue virus infection is changing in different epidemics, even in the same regions as well as with the period of time. In the present study, we observed varied neurological manifestations in nine pediatric cases of dengue infection. The increasing trend of such changing scenario has not being reported previously from the same region of our country which indicates the need for a continuous sero-epidemiological surveillance. The increasing evidence of neurotropism by dengue virus emphasizes that clinician must be aware of such association during dengue outbreak because early diagnosis and appropriate supportive care can reverse this potentially fatal disease. This study has few limitations, as the high prevalence of neurological manifestations, which has been noted in our study, may not represent the true prevalence of CNS involvement associated with dengue infection in pediatric population since we only have evaluated children admitted to a tertiary care teaching hospital where it is expected that patients have a severe condition. Henceforth it should be supported by a larger, detailed population based study.

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