Original article:

A comparative study of clinical features and severity of Dengue outbreaks between two successive years in a tertiary care hospital in Kolkata: Are we facing a bigger challenge?

[1]DR RIMI SOM SENGUPTA, [2]DR UPAL SENGUPTA*, [3]DR ANIRBAN GHOSH, [4]DR ANIRBAN SARKAR, [5]PROF DR TAPAS KUMAR MONDAL

[1]MBBS, MD (INTERNAL MEDICINE): Assistant Professor Department of Internal medicine. ESIC PGIMSR and Medical College, Joka , Kolkata

[2]MBBS, MD (INTERNAL MEDICINE),DM (NEPHROLOGY): Consultant nephrologist and transplant physician Fortis Hospital Kolkata & Assistant Professor of Nephrology KPC Medical College Kolkata

[3]MBBS, MD (INTERNAL MEDICINE): Assistant Professor Department of Internal medicine. ESIC PGIMSR and Medical College, Joka , Kolkata

[4]MBBS, MD (INTERNAL MEDICINE): Assistant Professor Department of Internal medicine. ESIC PGIMSR and Medical College, Joka , Kolkata

[5]MBBS , MD (INTERNAL MEDICINE), Professor & Head of the Department , Medicine, ESIC PGIMSR and Medical College, Joka , Kolkata

Corresponding author *

Abstract:

Dengue is one of the most prevalent arboviral infection worldwide. As per WHO it is the most rapidly spreading arboviral infection. India is experiencing consecutive dengue outbreaks and some places are becoming endemic. In this study, we present comparative clinical data of dengue outbreaks in two consecutive years 2015 and 2016 from a tertiary care teaching hospital in Kolkata. Although fever and constitutional symptoms were the two most common presenting features, abdominal pain was the most common symptom that was also associated with disease severity. Taken together, abdominal pain, vomiting and altered sensorium (dengue encephalopathy) has got a significant correlation predicating dengue hemorrhagic fever. Major bleeding was significantly more common in 2016 and melena was the most common type of major bleeding in both the years.

Elevation of liver enzymes, thrombocytopenia and leucopenia were the three most common laboratory manifestations. Although secondary cases (IgG positive) were significantly more common in 2016, there was no difference in IgG positivity between severe and less severe cases in these two years. Although the mortality in these two years is only one, the outbreak in 2016 was considerably more severe as compared to 2015(23.8% of Dengue Shock Syndrome versus 6.3%). This is probably the first study in India where the conventional WHO classification (Dengue, Dengue Haemorrhagic Fever and Dengue Shock Syndrome) as well as the 2009 modification (Dengue with or without warning signs and severe dengue) has been used together for comparing the severity.

Introduction:

Dengue is one of the most common arboviral disease in the world and by far the fastest spreading mosquito born disease of the world[1]. The name dengue originated from the Swahili word for "bonebreakingfever" or the word for "the walk of a dandie" in Spanish [2]. Benjamin Rush first identified and named the disease in 1779.The first recognised epidemic occurred almost simultaneously in Asia,Africa and North America in the 1780s.[3] The first evidence of occurrence of DF in the country was reported during 1956from Vellore district in

Tamil Nadu.Kolkata was the first place to have a dengue haemorrhagic fever (DHF) epidemic in 1963.[4]

Dengue virus, asingle stranded RNA virus of the family Flaviviridae is the most common cause of arboviral infection worldwide.Dengue viruses have 4 serotypes DEN 1-4.Humans are by far the major reservoir of the disease.Dengue can be transmitted from person to person by the bite of the Aedes mosquito.[5]

Dengue can present with a wide range of manifestations starting from asymptomatic infection,undifferentiated febrile illness,different bleeding manifestation to shock and multiorgan failure.Case fatality rate in dengue is variably reported from 1 to 3 %.[1]Dengue has been a major public health problem.At present, around 40% world's population is at risk and 50-100 million cases occur worldwide every year.[1]Largest incidences of dengue are seen in five countries of south east Asia i.e. Indonesia, Myanmar, Sri Lanka, Thailand and Timor-Leste. In Africa dengue seems to be a lesser menace as compared to HIV and malaria but it seems this is predominantly due to under-reporting. In North America and Europe dengue is mainly due to importation from endemic countries.[1]

Dengue has been endemic in 16 statesof India including West Bengal, from the beginning.It has spread to other states subsequently(3,4).There is been large outbreaks of dengue in 2003 and again in 2005-2008 involving northern, southern as well as eastern India. All the serotypes are prevalent in India. Epidemiologically, dengue has now become endemic in most parts of India, places with highest case burden like Delhi and Kolkata being hyperendemic. A recent study done at the University of Oxford estimated that, India contributes to the largest case burden (> 35%) of dengue in the world with 33 million apparent and another 100 million asymptomatic infections occurring annually.[4]We have undertaken a single centre observational study in a tertiary care hospital in Kolkata during the recent dengue outbreak in Kolkata fortwo consecutive years:2015 and 2016.

OBJECTIVE OF THE STUDY:

- To identify serologically proven dengue cases
- To study the epidemiological and clinical profile of the serologically proven dengue cases
- To compare different clinical parameters between cases of 2015 and that of 2016

MATERIALS AND METHODS:

All consecutive dengue cases from in-patient as well as reporting in outpatient in the department of General Medicine was included in the study.

Diagnosis of dengue infection-blood samples were sent on or after 5th day of fever and was analysed by micro capture dengue IgM enzyme-linked immunosorbentassay for dengue-specific IgM antibodies and indirect ELISA for IGG antibodies.

PanbioDengue IgM Capture ELISA and Panbio Dengue IgG Indirect ELISA kits were used and manufacturer's instructions were followed while performing the tests.

Following laboratory tests were performed in all patients:

1.Complete hemogram including hematocrit value,platelet count

2.Sodium,potassium,urea,creatinine

3.Liver function test

4. Chest x ray

5.Ultrasound whole abdomen

Along with

6.Special tests like arterial blood gas analysis,2D Echocardiography, neuroimaging,CSF analysis as and when required

Inclusion criteria:

1. Age group-15 years and above

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2. Patients tested positive for IGM ELISA for dengue during a specific time period

Exclusion criteria:

1. Patient age < 15 years
2. Laboratory evidence of presence of any other infection

All patients satisfying above criteria between the time period of August to November of 2015 and the corresponding months of 2016 were included in the study.A predesigned questionnaire was used for systematic data collection. For statistical analysis SPSS 23 was used.All the data were mainly entered into binomial format and cross tabulation with Chi-square testing was used to see difference between various parameters between cases of 2015 and that of 2016.ANNOVA testing was used to test variance and correlation was assessed by Pearson's rank log coefficient.

RESULTS:

Demographic characteristics:

A total of 80 and 122 cases were included in the study respectively from 2015 and 2016 databases.

Out of total 80 patients in 2015,there were 45 males and 35 female patients with a male female ratio of 1.28. In 2016, however the respective numbers were 70 and 52 the ratio being 1.34.

The mean age at presentation was 36.9(SD ±12.8) in 2015 and 35.6(SD±11.8)in 2016.Oldest patient included in the study was an 82 years old male. Maximum number of patients were in the age group between 30 to 45 years (52.5% and 50% respectively in 2015 and 2016). Approximately 4% of the patients in each group were more than sixty years old. Maximum number (>60%) of cases were reported in the months of September-October in both the years. This is similar to the temporal trend found in Delhi in the study byNishat Hussain Ahmed.[6] Majority of the patients were from urban background of greater Kolkata.

Clinical characteristics:

Fever was the most common mode of clinical presentation and was present in all the cases. The average duration of the fever was 5 days in both the years. Constitutional symptoms were present in more than 75% patients in both the groups among which myalgia was by far the commonest.

The second most common presentation in both the years were gastrointestinal disturbances. Pain abdomen and vomiting was present more commonly than loose stool(see table 1).Approximately 3 to 4 % of patients in both the years complained of persistent vomiting which is one of the warning signs of more severe disease in the suggested WHO modification to the older case classification.[1]

Overt jaundice was rarely seen. Significantly, around 29% in 2015 and 17% in 2016 patients complained of cough with mucoid expectoration.Haemoptysis however was present only in 2.5% cases in both the groups.

Overall bleeding manifestations were significantly more commonly seen in 2016 (39.3% versus 20% $p < 0.05$). This difference was mainly contributed by presence of more patients with melena in 2016(15.6% versus 5%, $p< 0.05$).About 15% of the patients had bleeding from more than one site compared to only 4% in 2015 ($p<0.05$).Significantly more patients required platelet transfusions in the year 2016($p=0.03$). Rash of various types was another major clinical sign that we have seen in our patients. Again in 2016 more number of patients were found to have rash as compared to .

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Table 1: Clinical Characteristics of Dengue patients in 2015 & 2016

Clinical feature	2015	2016	P value
myalgia	68(85%)	65(53.3%)	<.05
arthralgia	40(50%)	50(41%)	>.05
headache	41(51.2%)	60(49.2%)	>.05
Back pain	46(57.5%)	30(24.6%)	<.05
GI feature overall	43(53.8%)	67(54.9%)	>.05
Pain abdomen	29(36.3%)	34(28.5%)	>.05
Vomiting	28(35%)	45(36.9%)	>.05
Loose stool	12(15%)	17(13.9%)	>0.5
cough	23(28.7%)	21(17.2%)	<.05
rash	17(21.3%)	40(32.8%)	.05
hepatomegaly	15(18.8%)	22(18%)	.05
splenomegaly	9(11.3%)	13(10.3%)	>.05
Bleeding	16(20%)	28(39.3%)	<.05
ascites	21(26.3%)	27(22.1%)	>.05
pleural effusion	19(23.8%)	8(14.8%)	>.05
Gall bladder wall oedema	12(15%)	17(14%)	>.05
Encephalopathy	6(7.5%)	11(9%)	<.05

2015(32.8% versus 21.3%, p = 0.05).Diffuse flushing and pinpoint eruption on the neck ,chest, back and lower extremity were the predominant clinical forms of rash seen.

Laboratory Characteristics:

Elevation of transaminases was by far the most common laboratory parameter seen in both the years (62% and 64.8% respectively in 2015 and 2016) followed by thrombocytopenia and leucopoenia (see table 2).A big study conducted in Rio de Janeiro in 2002 by Souza LJ et al reported almost similar incidence of Transaminitis.[7]Severe Transaminitis (more than 1000IU/L)one of the severity defining criteria[1] was present in 2 patients(2.5%)in 2015 and 5 patients(4.1%)in 2016.One young patientwith severe tranaminitis had hepatic encephalopathy and improved subsequently. Another young female patient had DSS with ARDS and succumbed to her illness in ICU.Although there was no difference in these parameters between the study groups in two years.Severe thrombocytopenia(less than 50,000/µl), which is again a part of parameters defining worsening disease condition, however, was more common in 2016(21.3% versus 36.1%, p < 0.05). Hyponatremia was present in half of the patients in 2015 which was significantly more than that of 2016(p< 0.05).

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Table 2: Laboratory parameters in Dengue patients in 2015 & 2016

LABORATORY PARAMETERS	2015	2016	P value
Leucopenia	36(45%)	65(53.3%)	>.05
Thrombocytopenia	58(72.5%)	84(69.8%)	>.05
Severe thrombocytopenia	17(21.3%)	44(36.1%)	<.05
Haematocrit increase of 20%	15(18.5%)	35(28.7%)	>.05
Transaminitis	49(62%)	79(64.8%)	>.05
Hyponatremia	40(50%)	40(32.85)	<.05
Hypoalbuminemia	21(26.3%)	29(23.8%)	>.05

Disease severity assessment:

Conventionally, dengue used to be classified as dengue fever and with increasing presence of complicating factors, dengue haemorrhagic fever (DHF I,II,III and IV). Dengue haemorrhagic Fever III and IV is also known as dengue shock syndrome (DSS). As per this classification, 2016 had significantly more number of DSS cases. Cases in the DHF II category was also almost significantly more in 2016 (p=0.09).

Figure:1 Old WHO classification of symptomatic dengue infection

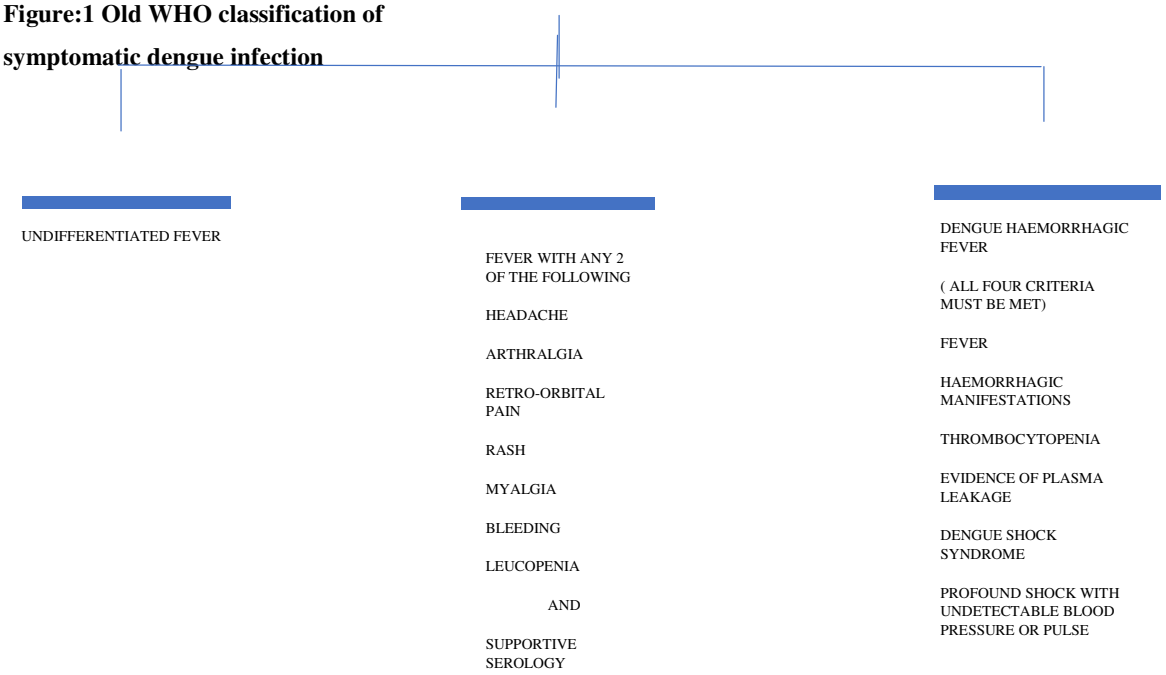


Figure 2) Symptomatic Dengue infection (WHO 2009)

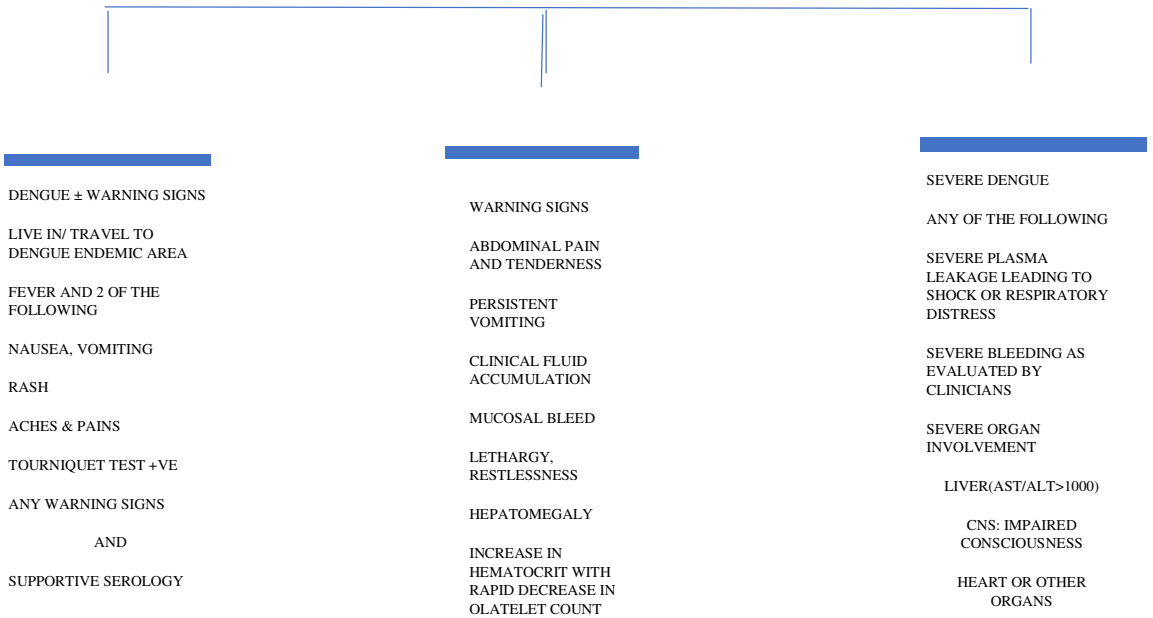
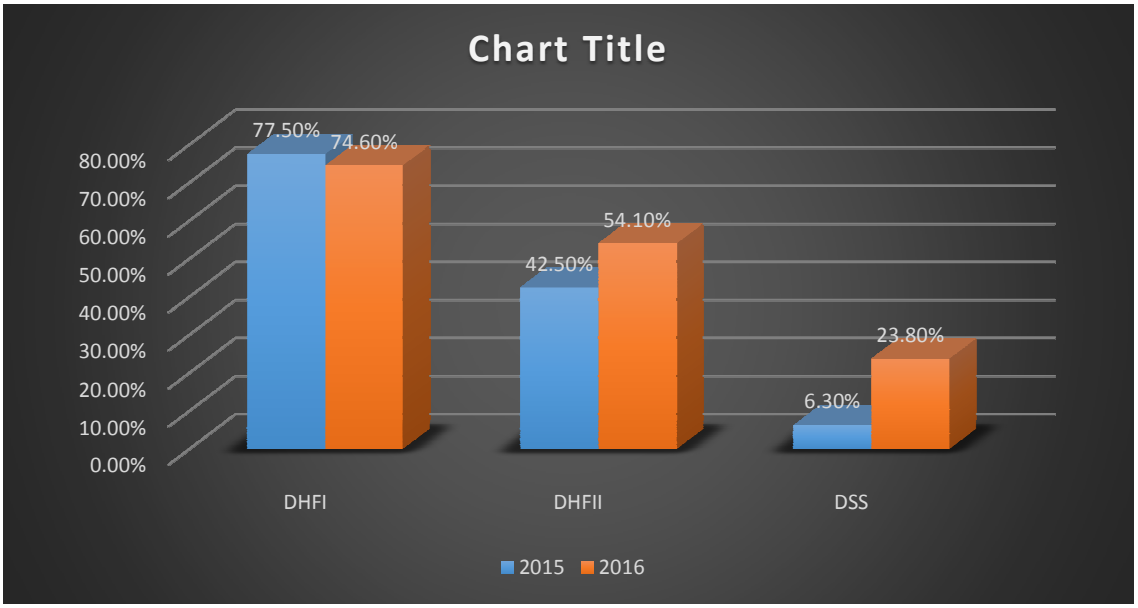
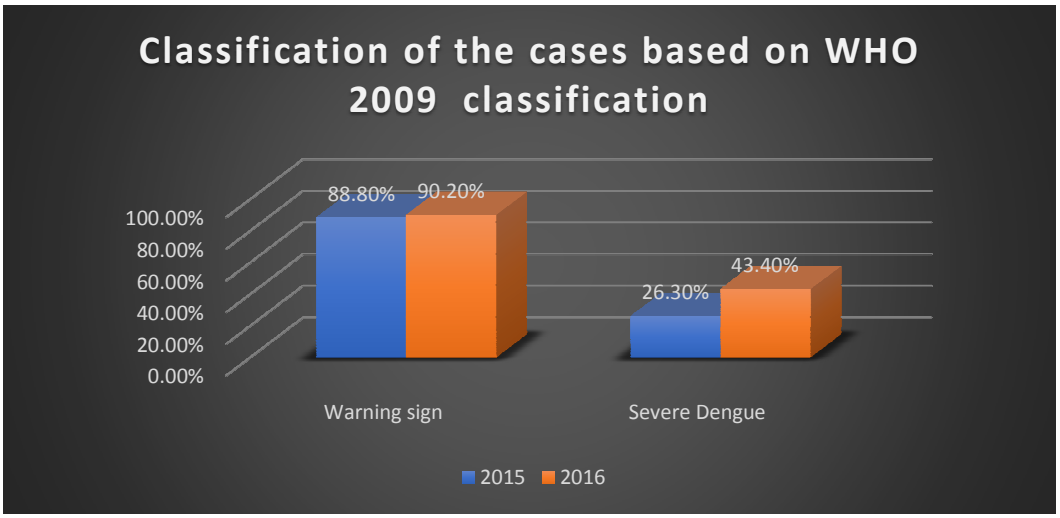


Figure 3: Severity of the cases as per traditional WHO criterion



The newer classification that was suggested by WHO in 2009 and still largely in validation stage, classifies dengue into with or without warning sign and severe dengue category.[1] It is been told to be more practical and clinically relevant as compared to the previous classification.[1,8] As per this classification criteria, 2016 observed significantly more number of severe dengue cases(26.3% versus 52.5%, $p< 0.05$).

Figure 4: Severity of the cases as per modified WHO criterion



Subgroup analysis:

Table 3: IgG POSITIVITY IN STUDY POPULATION

CASES	2015	2016	P value
ALL CASES	8(10.1%)	30(24.6%)	<.05
DHF(I+II)	8(12.7%)	21(21.2%)	>.05
DSS	1(20%)	10(34.5%)	>.05
SEVERE DENGUE	3(15%)	18(28%)	>.05

Incidence of secondary dengue caseswere significantly higher in 2016 than 2015. Analysis of different parameters across different age category revealed that dengue with warning symptoms were more common in patients between 30 and 45 years of age(95.1% versus 83.6%, $p < 0.05$), although this trend was not so apparent in severe dengue groups. Major bleeding was more common in 30-45 years group whereas patients who were more than 45 years old showed more tendency to present or develop neurological symptoms(22.9% versus 9.6%, P= 0.08).

Atypical feature:

Dengue can present with various atypical neurological features.Encephalopathy is one of the major neurological manifestations.[8,9]Eleven patients(9%) presented with encephalopathy in 2016 whereas only 6 patients (7.5%)had similar presentation in 2015 and this difference was statistically significant.We had performed neuroimaging and CSF analysis in majority of the patients with encephalopathic presentation due to dengue, and our observation was almost similar to another study conducted in north India by Verma et al.[10]The most consistent finding was normal CSF. Mild lymphocytic pleocytosis with normal protein and sugar levelwas present in 4 patients in 2016 and 2 patients in 2015.Cerebral oedema was the commonest neuroimaging finding on MRI brain. In 2015 we found one34 years male patient with isolated orbicularis oculi weakness.This patient presented with eye discomfort and watering.Ophthalmological evaluation revealed lagophthalmos and EMG study confirmed orbicularis oculi weakness.This peculiar presentation improved on follow up visits after discharge from hospital.This may be first reporting of isolated reversible orbicularis weakness in dengue patients.

Pancreatitis was one of the atypical gastrointestinal presentation of dengue. [11,12]We found two cases of pancreatitis in dengue patients in 2016.Both were young and without any previous comorbidity.Pain abdomen with elevation of liver enzymes along with elevation of serum amylase and lipase of more than 10 times normal was found. CT abdomen revealed evidence of interstitial pancreatitis and patient improved on conservative management.

Acalculous cholecystitis is another known atypical manifestation of dengue.[13,14]Patients had fever, pain abdomen, positive Murphys sign, elevated liver enzymes and gall bladder wall oedema (without gall stone on ultrasound imaging). By these diagnostic criteria our study showed 63.7% and 67.2% patients respectively had evidence of acalculous cholecystitis.A study by Sharma et all from PGI Chandigarh in 2006 reported 51.8% incidence ofacalculous cholecystitis in dengue patients.[13].

ARDS is one of the atypical respiratory presentation and severity defining criteria.We found one patients with ARDS in each year. The

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patient in 2016 succumbed to her illness in ICU.[15,16]

In our study, a total of four patients presented with myocarditis (three in 2015 and one in 2016). Clinically, they were one of the sickest with acute left ventricular failure, hypotension, suggestive ST-T changes in electrocardiogram and positive cardiac enzyme markers. Echocardiography showed global hypokinesia. All the patients recovered with conservative managements. In the largest series of dengue with cardiac dysfunction 6.7% showed echocardiographic evidence of cardiac dysfunction.[17]

DISCUSSION:

After 2015,India has again been badly hit by dengue outbreak in the very next year.

As per the National Vector Borne Disease Control Programme (NVBDCP), around 99913cases of dengue have been reported across the country in 2015 and 111880 cases have been reported till 30th December 2016.The corresponding figure in 2014 was 40571.The total number of reported cases from West Bengal was 8516 in 2015 and 17702 in 2016, which is the highest across India in 2016.[18]Dengue has been traditionally classified into 3 clinical classes -Dengue fever, dengue hemorrhagic fever (DHF),dengue shock syndrome (DSS)[1].According to recent recommendation of WHO in the year 2009,dengue has been classified clinically into dengue with and without warning signs and severe dengue[1].This classification can be used easily in practical clinical scenario and is potentially more useful for prognostication and triage based management.This classification system has been used recently in a number of publications(4).In our study we have followedboth the classifications.

Fever was the commonest presentation and present in 100% cases.Average duration of fever was approximately 5days in both the groups.

We got more number of dengue patients (n=122)in the year 2016 than in 2015(n=80)for the corresponding time frame.We had found a statistically significant higher number of patients with myalgia,backache in 2015. Overall these constitutional symptoms were the commonest presenting symptoms in both the years. This difference can possibly be attributed to a more early and conscious use of medicines like paracetamol by pre-referral doctors due to the consecutive nature of the dengue outbreaks in 2015 and 2016. We found statistically higher incidences of bleedingsincluding major bleeding in 2016 which was mainly contributed by significantly higher incidences of melena.Other than thrombocytopenia, factors which positively identified patients at risk of bleeding are pain abdomen, vomiting and shock. If we consider melena in particular, pain abdomen is the only clinical parameter which is almost significantly correlated; indicating gastric ulcers or erosions may be the underlyingetiology.

We found significantly higher incidences of encephalopathic presentation in 2016. Although encephalopathy was more commonly found in the age group of more than sixty years(p=0.08), that was not explained by hyponatremia (r= -0.035).We had performed neuroimaging and CSF analysis in majority of the patients with encephalopathic presentation due to dengue. The most common finding was mild lymphocytic pleocytosis with normal protein and sugar levels.Magnetic resonance imaging of brain in those patients mostly revealed cerebral edema. All these findings were consistent with Largest case series regarding neurological manifestations of dengue in our country.[10]

We found a higher incidence of DHF 1(76.95%),DHF 11(57.65%) than a large study published in Srilanka by G.N.Malavige et al in

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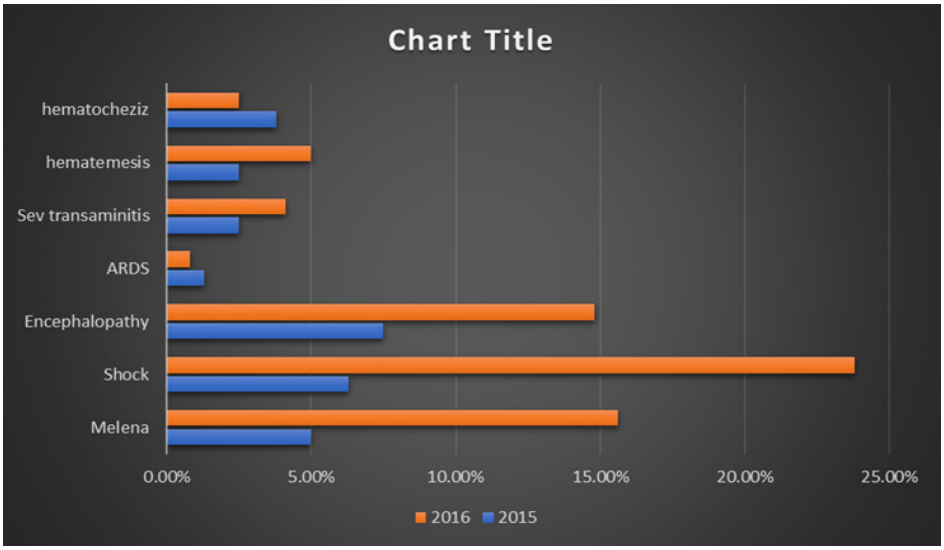
2006(44%,37.4%).[19]Although incidences of DSS was almost similar in incidence to that study in 2015(8.11%)that of 2016 was much higher (25.3%).Arecent study in published in 2016 conducted in Eastern India showed incidence of DSS to be 6%.The study period was from July 2014 to August 2015.It might me concluded that the outbreak in 2016 was much more severe in comparison to that of in 2015.[20]The higher incidence of secondary infection in 2016 may be one explanation for that .The higher incidence of secondary infection in 2016 outbreak may be due to cumulative exposure due to consecutive outbreaks.There are 4 serotypes of dengue virus DEN1-4.Infection against a particular serotype gives lifelong immunity to that specific serotype but only a transient protection to another serotype. This leads to increased severity of second infection as per the concept of immunological enhancement proposed by Halstead and later on shown by Vaughn et al.[20,21]

The most striking finding in our study was the increase in severity of dengue cases in 2016 outbreak. In most of the previous studies, the older WHO classification was used to categorize and assess clinical severity but we are the first in India to use both the criteria together in analysis.

Both severe dengue and DSS were significantly more common in 2016. However, we feel that as a marker of severity, severe dengue criteria is a more sensitive mean of identifying cases which will potentially need specialized medical care including critical care. Among the different components, circulatory failure and melena was the two most important contributing factors(see figure 3).the previous WHO classification has been criticized for being less practical to be applied in the clinical setting. The modified WHO classification, although does not include the laboratory parameters, did correlate well with thrombocytopenia (r=0.15, p = 0.026) severe thrombocytopenia(r=0.2, p=0.06) and significant haematocrit rise(r=0.1, p=0.09) in our study.We have also found that a composite index consisting of pain abdomen, vomiting and neurological manifestations mainly dengue encephalopathy, can identify a patient group who are much more likely to have dengue hemorrhagic fever.

Figure5: Contributions of different severity defining components



Mortality in our study patients was low. There was no mortality in 2015 and only one in 2016. This is at par with the low mortality rate in India and West Bengal (0.19% to 0.2%).

The limitation of our study was the absence of data on serotyping, which would have cast more light from epidemiological point of view. However, we have been able to give a detail clinical picture of the recent dengue epidemics in a place where the infection is gradually becoming endemic. The area of concern regarding the vast increase in severity of the dengue cases clearly shown in our study needs to be addressed in a large scale. We also conclude that the modified WHO classification criterion is far more clinical, easy to use but again has the capacity to correlate very well with the traditional laboratory parameters conventionally used to describe dengue case severity. In our opinion, the modified system of classification is to be used universally in the clinical scenario for triage of cases even in baseline healthcare settings for appropriate allocation of resources and prevent misutilization of available tertiary care set-ups.

Appendix:

Thrombocytopenia < 100000/µl

Severe thrombocytopenia < 50000/µl

Leucopenia< 4000/ µl

Transaminitis: ALT,AST > 40IU/L

Severe Transaminitis: AST,ALT > 1000IU/L

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