Original Article

Internal Medicine Section

Changing Clinical Profile of Dengue Fever Epidemic in North Kerala- A Retrospective Study

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ABSTRACT

Introduction: Dengue fever is one of the most common vector-borne infections worldwide and is now endemic in Kerala. Knowledge about changing clinical presentation of dengue fever is important for timely diagnosis and appropriate management.

Aim: To document changing trends in clinical presentation and course of illness among patients admitted with dengue fever in Kerala, India.

Materials and Methods: This hospital-based, retrospective, observational study was conducted at Government Medical College and Hospital, Kannur, Kerala, India, from September 2021 to June 2022. The patients with dengue fever, presented in seasonal epidemic of the year 2019 was compared to similar patients presented during the year 2014. Data regarding clinical presentation, duration of hospital stay, complications and haematological parameters of the study population was collected using prevalidated questionnaire. Descriptive data were expressed in frequency, percentage, mean and standard deviation. Continuous and discrete variables were compared by Welch's t-test, whereas categorical variables were compared using Pearson's Chi-square test.

Results: Out of the total 184 patients studied, 91 were from 2014 and 93 from 2019. The major presenting complaints were fever, body aches, headache, nausea and vomiting, arthralgia, and retroorbital pain incidence of which were similar in both the study years. Patients admitted in 2019 have shorter duration of fever (5.78 vs 6.79 days), earlier onset of severe thrombocytopaenia (6.62 vs 7.27 days) and delayed onset of complications (5.56 vs 3.6 days) compared to those admitted in 2014. They also had higher incidence of thrombocytopaenia (70.97% vs 54.94%) and complications (49.46% vs 14.29%) during the course of their illness.

Conclusion: The study indicates towards a significant shift in clinical presentation of dengue fever in Kerala which may influence the admission and monitoring protocol of dengue fever patients in the years to come.

Keywords: Complications, Hepatic dysfunction, Retroorbital pain, Significant shift, Thrombocytopaenia

INTRODUCTION

Dengue fever is an arboviral infection caused by Dengue Virus (DENV) which has become an endemic infection throughout Kerala with yearly monsoon and post monsoon outbreaks [1]. It is transmitted commonly by female *Aedes aegypti* mosquitoes but may also be transmitted by other mosquito species like *Aedes albopictus*. Patients classically presents with high grade fever, headache, retroorbital pain, muscle and joint pains, nausea, vomiting, and skin rash lasting for 2-7 days. 24-48 hours following this is usually the critical stage during which various complications including organ involvement sets in. This is the time period where a section of patient may manifest features of severe dengue including Dengue Haemorrhagic Fever (DHF), Dengue Shock Syndrome (DSS) and extended dengue syndrome [2,3].

Dengue fever incidences in various part of India have shown considerable seasonal variation. Previous studies had shown that both rainfall and favourable ambient temperature during the monsoon and postmonsoon periods increase the possibility of transmission of dengue virus during the period [1,4]. Recent observations have also suggested that there has been a notable change in the clinical presentation of dengue fever in various parts of Indian subcontinent [5,6]. In the present study institution, significant changes in the clinical presentation of dengue fever has been observed over the last few years, especially during the epidemics of 2018-2019. Such changes may lead to changes in the admission pattern of dengue fever patients to the hospital and may lead to an extended hospital stay for the illness. With a shift in the clinical profile and more patients presenting with severe dengue fever, an early identification and timely intervention is the key to better clinical outcome. The study aimed to document any changing trend in clinical presentation and course of illness among patients admitted with dengue fever in Kerala between the years 2014 and 2019.

MATERIALS AND METHODS

This hospital-based retrospective observational study was conducted at Government Medical College and Hospital, Kannur, Kerala, India, from September 2021 to June 2022. It was done on data collected from dengue fever patients admitted in the Medical Wards and Intensive Care Unit during the seasonal epidemics between the months of May and October in the years 2014 and 2019. Year 2019 was the year the study was formulated which had an increased number of dengue patients in the state of Kerala and a clinical observation of change in presentation was observed. Year 2014 was taken arbitrarily as a year, 5 years before the reference year (there was delay in completion of the data collection due to the intervening pandemic).

Data collection was started after obtaining the approval from Institutional Ethical Committee (IEC No.09/2019/GMCK dt 12.07.2019). A convenient sampling method was used, where, all patients admitted with dengue fever during the study period were taken.

Inclusion criteria: All consecutive patients admitted with typical symptoms suggestive of dengue fever who had confirmed seropositivity (NS1 antigen or IgM Dengue antibody) above the age group of 18 years during the study periods were enrolled for the study.

Exclusion criteria: Any patient having evidence of co-infection from other endemic diseases were excluded from the study.

Data were collected from case records of the selected patients from both 2014 and 2019 using a prevalidated questionnaire. Clinical presentation, haematological investigations including serial platelet

counts, haemoglobin level, biochemical investigations including renal and hepatic function, course of illness during the hospital stay, and details about complication arisen during the illness were noted down.

STATISTICAL ANALYSIS

Data were tabulated in Microsoft excel sheet and was analysed using the software R' for statistical computing (Version-RStudio2021.09.1+372,PBS). Descriptive data were expressed in frequency, percentage, mean and standard deviation. Continuous and discrete variables were compared by Welch's t-test, whereas categorical variables were compared using Pearson's Chi-square test. Kaplan-Meier curve and log rank score test were used for time to event analysis of various clinical and investigative parameters. Logistic regression analysis was carried out to determine the independent parameters that have role in predicting the incidence of complication during the illness.

RESULTS

The data was collected from the hospital records of 184 patients with confirmed dengue fever. Total 91 patients were enrolled from the year 2014, and 93 in the year 2019. There were 60 (32.61%) females and 124 (67.39%) males. Mean age was 40.73±17.44 years. Apart from fever, major symptoms reported by the patients included body ache, headache, nausea and vomiting, arthralgia, retro-orbital pain, cough, loose stools, and rash. On comparison, the patients admitted in the two study years had a similar incidence of various symptoms at presentation, except, nausea and vomiting which was seen significantly higher in patients admitted in the year 2019 [Table/Fig-1].

Presenting symptoms	Year 2014 (n,%)	Year 2019 (n,%)	p-value
Fever	91 (100%)	93 (100%)	1.00
Body ache	48 (52.75%)	55 (59.14%)	0.38
Headache	41 (45.05%)	51 (54.84%)	0.18
Nausea and vomiting	45 (49.45%)	23 (24.73%)	<0.01
Arthralgia	14 (15.38%)	16 (17.20%)	0.74
Retro-orbital pain	8 (8.79%)	13 (13.97%)	0.27
Cough	10 (10.99%)	9 (9.68%)	0.77
Rash	10 (10.99%)	5 (5.38%)	0.16
Loose stools	7 (7.69%)	8 (8.60%)	0.82
Bleeding manifestation	7 (7.69%)	6 (6.45%)	0.74
Tiredness	6 (6.59%)	4 (4.30%)	0.49
Abdominal pain	6 (6.59%)	3 (3.22%)	0.29
Chills and rigor	1 (1.09%)	3 (3.22%)	0.32
Dysuria	2 (2.19%)	2 (2.15%)	0.98
Chest pain	1 (1.09%)	2 (2.15%)	0.57
Anorexia	0 (0%)	2 (2.15%)	0.16
Others	2 (2.19%)	5 (5.38%)	0.26

[Table/Fig-1]: Presenting symptoms.
p-value <0.05 was considered as statistically significant

Patients from the two study years had similar co-morbidities with no statistically significant difference between them. About 65.21% of patients did not report any significant previous medical illness. Among the rest of the patients, common pre-existing illnesses reported were hypertension, type 2 diabetes mellitus, dyslipidaemia and coronary artery disease [Table/Fig-2].

Incidence of thrombocytopaenia in patients admitted in 2014 was markedly less compared to those patients in 2019 (54.94% vs 70.97%;p-value=0.024). Whereas, even though haemoconcentration was seen more in 2014 compared to 2019 the difference was not statistically significant (9.89% vs 7.52%; p-value=0.569). Further analysis showed that there was no statistically significant difference

Past illness	Year 2014 (n,%)	Year 2014 (n,%)	p-value
Hypertension	11 (12.09%)	11 (11.83%)	0.96
Diabetes mellitus	11 (12.09%)	10 (10.75%)	0.78
Dyslipidaemia	4 (4.39%)	2 (2.15%)	0.39
Coronary artery disease	4 (4.39%)	2 (2.15%)	0.39
Chronic kidney disease	1 (1.09%)	1 (1.07%)	0.99
Chronic liver disease	3 (3.29%)	1 (1.07%)	0.3
COPD*	3 (3.29%)	1 (1.07%)	0.3
Others	24 (26.37%)	15 (16.13%)	0.09
None	56 (61.54%)	64 (68.82%)	0.3

[Table/Fig-2]: Prevalence of past medical illness in year 2014 (n=91) and year 2019 (n=93).
*COPD: Chronic obstructive pulmonary disease; p-value <0.05 was considered as statistically significant

between the duration of thrombocytopaenia or the lowest platelet level attained, signifying the severity of thrombocytopaenia during the course of illness between the two study years. But there was statistically significant differences in time taken to reach the minimum platelet count during the course of illness (mean: 7.27 vs 6.62 days, p-value=0.026) [Table/Fig-3] and the duration of hospital stay (mean: 5.47 vs 4.65 days, p-value=0.004) [Table/Fig-4] in the years 2014 and 2019, respectively. No significant differences were noted between biochemical parameters including the hepatic and renal function between the patients of two study years. Mortality rates between the two study years also showed no statistically significant difference (p-value=0.72).
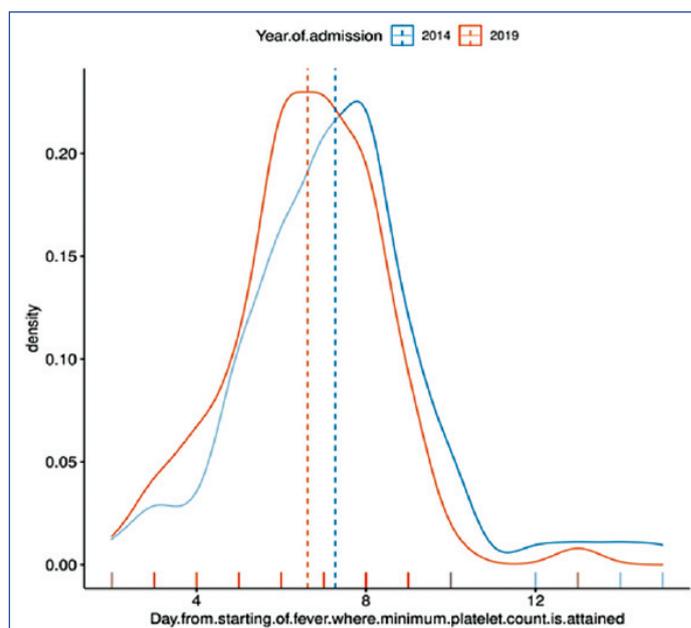
[Table/Fig-3]: Comparing days of illness by which minimum platelet count was attained between the study years.

Logistic regression analysis was done to test whether clinical and haematological parameters of patients during the course of illness significantly predicted the incidence of complications that arose. It showed that among the various parameters, only the year of admission, duration of thrombocytopaenia and lowest platelet count attained had statistically significant role in predicting the incidence of complication during the course of illness. It was found that decrease of minimum attained platelet count by a value of 1000 will increase the odds of developing complication by 1.48% {95% CI (0.78,2.18)}. Also, increase in duration of thrombocytopaenia by one day will increase the odds of developing complication by {95%CI (22.20, 72.06)}.

A patient admitted in year 2019 had 5.87 times {95%CI (2.87,11.99)} higher odds of developing complication than a patient admitted in year
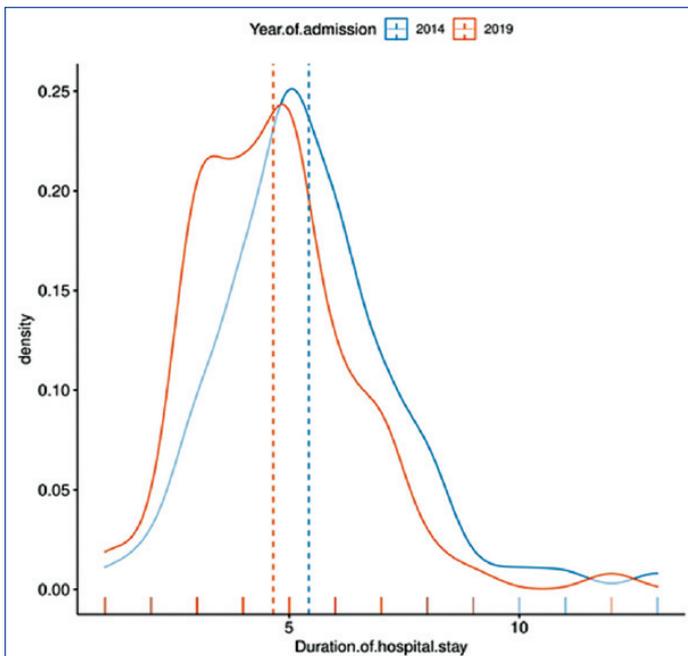
[Table/Fig-4]: Comparing duration of hospital stay between study years.

2014(exp(B) = 5.872615, Wald=4.859, p-value<0.001). Incidence of complications including organ involvement were considerably higher in the year 2019 compared to patients admitted in 2014 (49.46% vs 14.29%) (χ^2=26.127, p-value<0.001). Most common complications recorded include hepatic dysfunction (transaminase level >2 times the upper limit), bleeding manifestation, renal dysfunction, hypotension and cardiac dysfunction. There were also incidences of Acute Respiratory Distress Syndrome (ARDS) in 2014 whereas neurologic manifestations were more common in 2019 [Table/Fig-5].

Complications	Year 2014 (n,%)	Year 2019 (n,%)	p-value
Hepatic dysfunction	9 (9.89%)	35 (37.63%)	<0.01
Renal dysfunction	4 (4.39%)	6 (6.45%)	0.54
Hypotension	2 (2.20%)	6 (6.45%)	0.16
Haemorrhagic manifestation	2 (2.20%)	18 (19.35%)	<0.01
Cardiac dysfunction	2 (2.20%)	2 (2.15%)	0.98
Central nervous system manifestations	0	3 (3.22%)	0.08
Acute respiratory distress syndrome	2 (2.20%)	0	0.15
None	78 (85.71%)	47 (50.54%)	<0.01

[Table/Fig-5]: Complications arising during the course of illness.
p-value<0.05 was considered as statistically significant

Various clinical and haematological parameters like recovery from fever (temperature <99°F consistently for 2 days), onset of complications, recovery from thrombocytopaenia (<1 lakh/cmm), and haemoconcentration (>17gm/dL) were monitored during the course of hospital stay [Table/Fig-6].

| Parameters	Year 2014 Mean duration (days)	Year 2019 Mean duration (days)	p-value (log-rank test)
Length of fever	6.79	5.78	**<0.001**
Onset of complications	3.6	5.56	**0.03**
Duration of haemoconcentration	1.44	1.86	0.2
Duration of thrombocytopaenia	3.22	3.24	0.1
Onset of lowest platelet count	7.27	6.62	**0.0134**

[Table/Fig-6]: Clinical parameters monitored during the course of illness.
p-value <0.05 was considered as statistically significant

Time to event analysis, using Kaplan-Meier curve and log rank test, were conducted for the study variables. Patients admitted in 2019 showed earlier recovery from fever compared to those admitted in 2014 (p-value<0.001) [Table/Fig-7], and had a delayed onset of complications (p-value=0.03) [Table/Fig-8]. No significant difference was noted between the recovery time from thrombocytopaenia (p-value=0.1) or haemoconcentration (p-value=0.2) during the course of hospital stay on time to event analysis.
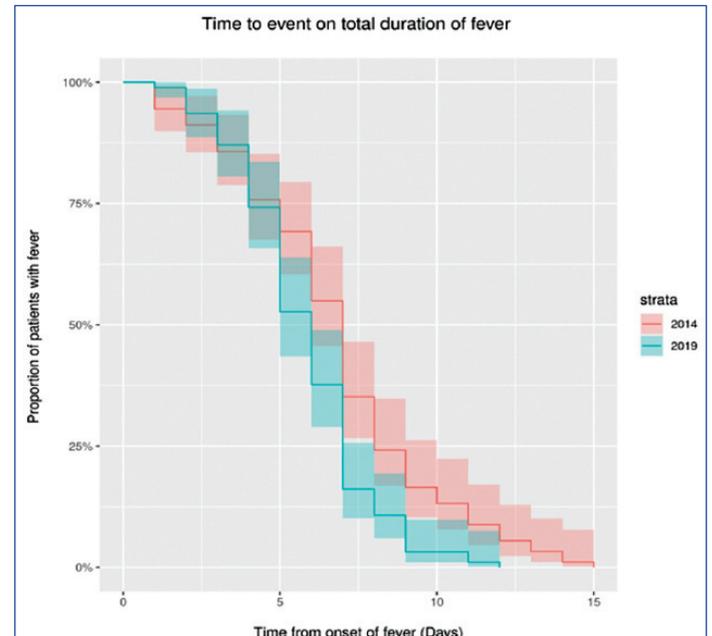
[Table/Fig-7]: Time to event on total duration of fever.
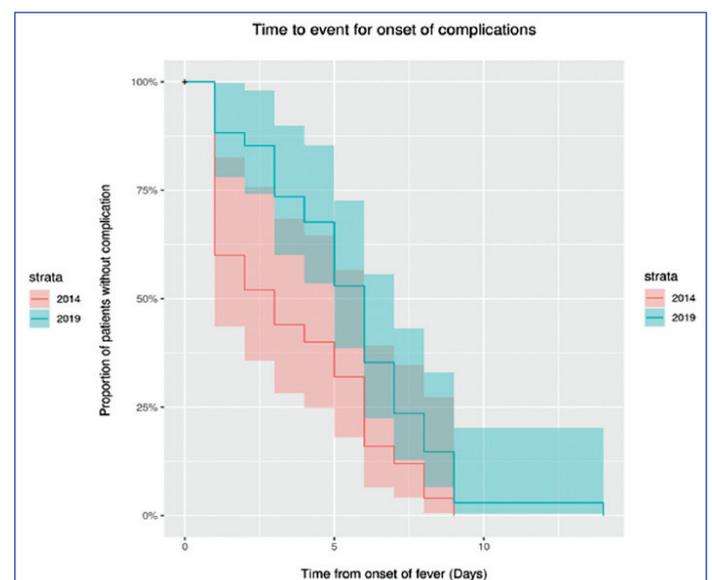
[Table/Fig-8]: Time to event for onset of complication.

DISCUSSION

In this study comparison of clinical profile, haematological, and biochemical parameters, the onset of various complications and duration of hospital stay between the dengue epidemics in the years 2014 and 2019 were done. It was found that most of the patients in both periods presented with similar symptoms of body ache, headache, nausea-vomiting and arthralgia. Similar studies from other parts of India also described these as major symptoms along with others like rash and abdominal pain [5,7]. In the current study, skin rash and abdominal pain were seen in less than 10% of patients. There was no significant difference in clinical symptoms in dengue fever between the years 2014 and 2019.

Thrombocytopaenia (<1,00,000/cmm) was more common during the course of illness in patients admitted in the year 2019 compared to those admitted in the year 2014. But the total duration and severity of thrombocytopenia was not significantly different between

the two study years. Kumar R et al., reported a similar incidence of thrombocytopaenia [6]. Compared to these results many of the other previous studies reported a higher incidence of thrombocytopaenia during the course of illness [5,7].

Incidence of haemoconcentration and its duration did not show any significant difference over the two study years. The incidence of complications was significantly higher in patients admitted in 2019 compared to those admitted in 2014 out of which hepatic dysfunction and haemorrhagic manifestation were the most frequent complications. Previous studies also shows that haemorrhagic manifestation, hepatic dysfunction and pleural effusion are the most common complication in dengue fever [8-10]. Mortality rates between the two study years were similar and showed no statistically significant difference in this study. In contrast a systematic analysis done by Zeng Z et al., studying global trends of dengue infection between 1990 to 2017, showed that age-adjusted death rates were gradually increasing worldwide, especially in Southeast Asian region [11]. Smaller sample size and shorter time interval between the study years in the current study might have resulted in its inability to detect this long-term trend of increasing mortality.

During the course of illness even though patients tend to become afebrile earlier if they contracted dengue in 2019 compared to 2014, onset of complications were significantly delayed in 2019. This was observed even when the lowest platelet count attained were comparatively earlier in 2019. This may indicate a significant shift in the clinical presentation of dengue fever especially a longer period of critical phase in illness emerging along with shorter febrile phase. Even though on logistic regression analysis it was evident that apart from the year of admission, duration of thrombocytopaenia and severity of thrombocytopaenia also had predictive value in the incidence of complication during the illness, these parameters did not differ over the two years and could not explain the documented change in incidence and pattern of complication in any way. No previous studies had compared the clinical presentation and complication of dengue fever with a previous reference year. The pattern emerged in this study may represent a more secular trend in shift of clinical profile of dengue fever in the subcontinent and need further detailed research. The underlying reason for this shift may be explained by the change in viral characteristics with respect to the climatic variations that various regions of the country is subjected to as evidenced by findings of Mutheneni SR et al.. [1]. Or it may also indicate the increased prevalence of newer serotypes (DENV4) in the region compared to those serotypes which were earlier more prevalent (DENV 1 and 2) as evidenced in a study from Southern Kerala [12].

This is one of the first study to directly compare the clinical manifestations, investigations and course of illness during the hospital stay between two years with a gap of 5 years. This may give us an empirical evidence to the gradual change in presentation of dengue fever in India, which has been reported by clinicians over the years.

Limitation(s)

The study could not investigate the reasons for the observed shift in clinical presentation between the years on real-time basis as it was a retrospective study. A more detailed research work in this regard should be done to include investigating the possible serotype variability.

CONCLUSION(S)

Since dengue fever is now an endemic disease with yearly seasonal outbreaks and is responsible for significant disease load in our part of the world, we should be aware of any significant change in clinical presentations of the disease so that monitoring of patients are better and unnecessary morbidity and mortality are avoided. Dengue fever epidemic of 2019 was characterised by a shorter duration of fever with increased incidence of complications compared to 2014. The onset of complication during the course of illness were found to be delayed. The study clearly showed a significant shift in course of illness of dengue fever and may indicate a long-term trend in changing clinical presentation in the region.

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