

**INSIGHTS INTO A FEVER OUTBREAK AT A RURAL TERTIARY CARE CENTRE- A
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ABSTRACT

Importance: Dengue outbreaks occur in an unprecedented manner and cause a huge burden on health resources. Mortality is high among vulnerable population. **Aim:** To investigate the cause and clinical manifestations of a sudden upsurge of fever patients admitted to Govt Villupuram Medical college. **Design:** This is a prospective observational study of acute fever patients who got from September to November 2017. **Setting and Participants:** The study was conducted at Government Villupuram Medical College and Hospital, Southern India. All patients with more than 16 years of age, hospitalized with fever of < 7 days duration [oral temperature of 101°F at least once during admission]. **Results:** A total of 240 patients were included in the study. The male to female ratio was approximately 2:1 [male 65% (n=156), female 35% (n=84)]. The distribution of acute fever was Dengue 153, Enteric fever 9, Malaria 2, Scrub Typhus 2, other fevers [liver abscess, pneumonia, etc] 4 and undiagnosed 70 [Figure 3]. Symptom analysis into the illness revealed that only 3 were significantly associated with confirmed Dengue. These were giddiness 168 (p<0.001), bleeding manifestations 133 (p<0.001) and pruritis 57 (p<0.01). The dominant physical examination findings which had a predictive value for Dengue were orthostatic hypotension 187 (p<0.01), clinical shock 199 (p<0.001) and bleeding manifestations 133 (p<0.001). However Tourniquet test was positive only in 73 (30.4%) of patients. Cumulatively their positive predictive value was >90%. The important laboratory findings associated with Dengue were thrombocytopenia, leucopenia and raised hematocrit [p<0.01]. **Conclusion:** In the recent Dengue outbreak in Villupuram District many insights were drawn as regards the predictive capacity of clinical signs and symptoms for dengue. The information gained could be used in the early diagnosis and triage of patients in resource poor settings.

KEYWORDS: Dengue outbreak, Clinical features, Acute fever.**INTRODUCTION**

Dengue has been maligning human communities from time immemorial. Two and a half billion people reside in dengue-endemic regions^[1] worldwide and roughly 400 million infections occurring per year.^[2] In India Dengue records year round transmission as well as episodic epidemics.^[3] The dynamics of an outbreak is a complex interplay between a conducive environment, a formidable vector and vulnerable population.

In the monsoon months of 2017, Kerala and Tamil Nadu states experienced an unprecedented epidemic of Dengue which left the health care sector badly shaken. We the Infectious Diseases management team of Govt Villupuram Medical College derived much knowledge and experience in dealing with such an outbreak. We aimed to investigate the clinical profile of the fever patients admitted to our institute and find out their predictive accuracy.

AIM

To investigate the cause and clinical manifestations of a sudden upsurge of fever patients admitted to Govt Villupuram Medical college.

MATERIALS AND METHODS

Study type: A prospective observational study was planned to identify the clinical picture of acute fever patients who got admitted during the study period. A draft of the study protocol was drawn and put up for Ethical Committee approval.

Study Centre: Department of Internal Medicine, Govt Villupuram Medical College.

Study duration: Between 1st September and 30th November 2017.

Study Population: All patients with more than 16 years of age, hospitalized with fever of < 7 days duration [oral temperature of 101°F at least once during admission]

The inclusion and exclusion criteria were as per Figure 1. The diagnostic criteria was defined for acute fever [Figure 2.] and patients were selected based on this.

METHODOLOGY

Upon admission they were interviewed by any member study team and eligibility ascertained. Thereafter, those who consented were included into the study. The participants were subjected to detailed history taking and a thorough physical examination. The findings were documented on the case proforma designed for the study. The workup of the patients were as per the study protocol [Figure 2]. The patients were followed up by daily examination by members of the study team and findings recorded. The treatment was as per the institutional protocol. They were retained till 2 days after clinical defervescence or 7 days post a confirmed diagnosis, whichever was later. Upon discharge, selected patients [whose diagnoses were unclear] were asked to return after 4 weeks for convalescent serology. The data were periodically reviewed by the study team.

Data Analysis: Two-sided *P* values were calculated using the chi-square test or Fisher's exact test for (qualitative) dichotomous and ordinal variables. Continuous (quantitative) variables were compared using a two-sided Wilcoxon rank sum test and the unpaired student's *t*-test. Statistical software SPSS version 2.0 was used.

Ethical considerations: The study was approved by the Institutional Review Board of the Government Villupuram Medical College and Hospital, Villupuram. All patients in the study gave written informed consent.

RESULTS

A total of 240 patients were included in the study. The male to female ratio was approximately 2:1 [male 65% (n=156), female 35% (n=84)]. The mean age of the study population was 29.12 \pm 9.4 [Mean \pm SD]. The mean fever duration was 3.2 \pm 1.5 days. Precisely 70.8% had a confirmed diagnosis and 93.5% of cases were cured. The mean time to defervescence was 2.4 \pm 1.1 days and mean hospital stay was 4.5 \pm 1.8 days. The distribution of acute fever was Dengue 153, Enteric fever 9, Malaria 2, Scrub Typhus 2, other fevers [liver abscess, pneumonia, etc] 4 and undiagnosed 70 [Figure 3]. The clinical presentation showed that the majority reported headache 212, followed by nausea/vomit 201 and myalgia 186. Late symptom analysis into the illness on days 2 to 4 had a significant number of patients reporting giddiness 168 and bleeding manifestations 133. [Table 1].

The dominant physical examination findings were orthostatic hypotension 187, clinical shock 199 and bleeding manifestations 133. However Tourniquet test was positive only in 73 (30.4%) of patients. Among the clinical signs bleeding manifestations ($p < 0.001$), clinical shock ($p < 0.001$), orthostatic hypotension ($p < 0.01$) and Tourniquet sign ($p < 0.01$) were significantly associated with Dengue. Cumulatively their positive predictive value was $> 90\%$. The important laboratory findings included mean Hemoglobin [12.8 \pm 4.1 gm%], Total count [4200 \pm 1300/cu mm] and thrombocytopenia [1.12 \pm 0.7 lakhs/cu mm]. The association of thrombocytopenia, leucopenia and raised hematocrit with confirmed Dengue was statistically significant [$p < 0.01$]. Other important laboratory findings included AST/ALT elevations in 51% and acute kidney injury [serum creatinine > 1.5 mg%] in 4.7% of cases [Table 1].

Inclusion Criteria
All patients with age > 16 , admitted with fever of < 7 days duration, who recorded an oral temperature of 101°F at least once during hospital stay.
Exclusion Criteria
Immunocompromised patients, multiple comorbid illnesses [CKD, Diabetes, Heart failure, etc] and Hematological malignancies.
Patient Workup.
Detailed History, Blood investigations [Complete blood counts, Basic blood biochemistry, Liver function tests], Urine basic examination and Chest X-ray.

Figure 1: Patient selection criteria and workup plan.

Diagnosis	Case definition.
Dengue suspect.	All acute fever patients as per NVBDCP guidelines.
Dengue confirmed case	IgM ELISA Positive for dengue antibody.
Malaria .	Peripheral smear study positive of malarial parasite.
Typhoid fever.	Blood culture positive or Widal positive in 1:320 dilution or 4 fold rise in titre of antibody at 4 weeks.
Scrub typhus.	IgM antibody positive with Eschar or response to Doxycycline.
Alternate diagnosis	Pulmonary TB, Liver abscess, Urinary Tract Infection, Pneumonia, etc.
Undiagnosed Cases	Confirmed diagnosis could not be reached despite systematic work up.

Figure 2: Case definitions for acute fevers.

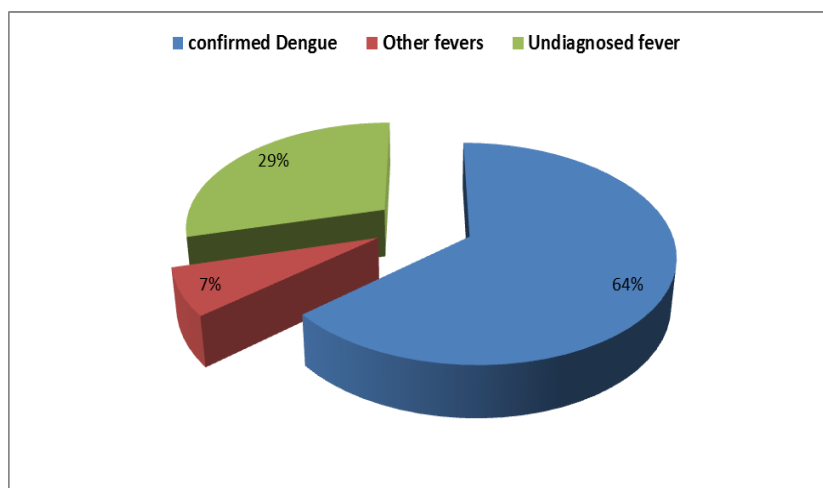


Figure 3: Distribution of Acute fever cases between Sep 2017 to Nov 2017.

Table 1: Clinical features of acute fever cases and association with Dengue.

S. No.	Variable	Numbers (n=240)	Associated with confirmed Dengue cases	Associated with other fevers.	Significance
1.	Headache	212	93.5%	79.3%	
2.	Nausea/vomit	201	85.6%	80.5%	
3	Myalgia	186	78.4%	75.9%	
4	Giddiness	168	84.9%	43.7%	P<0.001
5	Bleeding manifestations	133	65.4%	37.9%	P<0.001
6	Rash	83	39.9%	25.3%	
7	Cough	63	27.5%	24.1%	
8	Diarrhoea	61	25.5%	25.3%	
9	Abdominal pain	57	24.8%	21.8%	
10	Pruritis	57	33.3%	6.9%	P<0.01
11	Arthralgia	42	20.3%	12.6%	
12	Altered mentation	9	2.6%	5.7%	
Clinical signs					
13.	Clinical shock	199	96.7%	58.6%	P<0.001
14	Orthostatic hypotension	187	84.9%	65.5%	P<0.01
15	Bleeding manifestations	133	65.4%	37.9%	P<0.001
16	Torniquet sign	73	38.6%	16.1%	P<0.01
17	Hepatosplenomegaly	32	3.2%	31%	
18	Anemia	29	5.2%	24.1%	
19	Coated tongue	17	7.1%	6.9%	
20	Arthritis	17	8.5%	12.6%	
Laboratory data - Mean(SD)					
21.	Haemoglobin	12.8(4.1)			
22.	Platelet count	1.12(0.9)			
23.	Thrombocytopenia		86.9%	62.1%	P<0.01
24.	Hematocrit	42(7)	92.2%	62.1%	P<0.01
25.	Total count	4200(1300)			
26.	Leucopenia		84.9%	60.9%	P<0.01
25	Bilirubin	1.41(0.7)	7.2%	18.4%	
26.	AST	71(41.8)	13.7%	13.8%	
27	ALT	69(35.7)	14.4%	17.2%	

DISCUSSION

Dengue is a mosquito borne flavivirus found in tropical and sub-tropical regions of the world, mostly in urban and semi-urban settings spread by *Aedes* mosquitoes. Dengue has seen a 30-fold upsurge worldwide between 1960 and 2010, due to increased population growth rate,

global warming, unplanned urbanization, inefficient mosquito control, frequent air travel, and lack of health care facilities.^[4,5] Two and a half billion people reside in dengue-endemic regions^[1] and roughly 400 million infections occurring per year, with a mortality rate surpassing 5–20% in some areas.^[6]

The first DHF outbreak occurred in Calcutta (Kolkata, West Bengal) in 1963 with 30% of cases showing haemorrhagic manifestations.^[7,14] Ever since dengue has been prevailing by year round transmission as also periodic outbreaks in the subcontinent. According to the Directorate of National Vector Borne Disease Control Programme (NVBDCP), till July 30, 2016, the total dengue cases in the country were 16,870 while for the same period in 2017 they numbered 28,702. Epidemiologists believe that a major epidemic occurs when the prevalent viral serotype is replaced by a new one to which the population are non immune.^[8,9,10,15] All 4 serotypes[DENV 1-4] are circulating in India. A recently published article has unveiled a new serotype (DENV-5), to be added to the existing ones whose epidemiologic importance is as yet undetermined.^[5]

Between September and November 2017 there was an unusual upsurge of patients admitted for acute fever at Govt Villupuram Medical College and Hospital. This unexpected event triggered knee jerk responses from the treating team and administrative staff. However the situation was brought under control quickly with the establishment of an acute fever management ward and reallocation of resources to tackle the crisis. We, the Infectious Disease Management team of Villupuram Medical College found the right opportunity to derive insights into such an uncommon scenario.

A wide array of clinical manifestations were observed [Table 1], however only three symptoms had significant association with confirmed Dengue. Bleeding manifestations like epistaxis, melena, gum bleeds, venipuncture site ecchymoses and pallatal petechiae were the prime predictors of confirmed cases. Bleeding manifestations occurred in 65.4% of dengue cases, but only in 37.9% of other febrile patients. The positive predictive value of mucosal bleed was 85%. Thoughless significant, giddiness and pruritis also were statistically more common in Dengue patients. Unlike other reports which claim that skin rash is strongly associated with dengue,^[11] our study showed that only 39.9% of confirmed cases had a rash. The vast majority of other symptoms like headache, myalgia, abdominal pain, etc had no significant association with dengue.

Among the clinical signs, orthostatic hypotension ($p < 0.01$), Tourniquet sign ($p < 0.01$), bleeding manifestations ($p < 0.001$) and clinical shock ($p < 0.001$) were significantly associated with Dengue, with a cumulative positive predictive value of $> 90\%$. These manifestations were highly unlikely in other causes of acute fever. Previous research studies showed that high fever with positive Tourniquet test, leukopenia ($WBC \leq 5,000$ cells/mm³) had a positive predictive value 70–83% (marked by a morbilliform rash and hemorrhagic tendencies).^[12,13] However, in our study, Tourniquet test was positive only in 38.6% of confirmed dengue patients. The probable reason for this phenomenon could

be the dark complexion of our population which hinders the accurate identification of petechiae.

Much of the laboratory features have already been highlighted in our national guidelines. In coincidence with that, our data revealed that thrombocytopenia[86.9%], elevated hematocrit[92.2%] and leucopenia[84.9%] had significant predictive capacity for dengue[$> 80\%$]. Furthermore, elevation of serum bilirubin was documented in a significant number of patients with alternate diagnosis for fever. Interestingly serum bilirubin rise had a strong negative predictive value for dengue[70%].

LIMITATIONS

This is a hospital based study, wherein admitted patients with dengue were studied meticulously. However the sample size was only 240 which is fraction of the cases in the community. Furthermore, only sick and incapacitated patients were admitted to the hospital, whereas the huge bulk of dengue cases pass off as mild self limiting fever. Hence extrapolation of the results of this study into the general population would not be appropriate. Our study could be utilized to reliably predict dengue among in patients with acute febrile illness.

CONCLUSION

Dengue outbreaks have done havoc to our healthcare machinery earlier and will continue to do so in years to come. In the recent outbreak in Villupuram District, an effort was put up to study the clinical profile of dengue patients admitted to a tertiary care hospital. Many insights were drawn as regards the predictive capacity of clinical signs and symptoms for dengue. The inference gathered highlighted the importance of appreciation of clinical features of dengue and their variability among ethnic populations. Such information could be used in the early diagnosis and triage of patients in resource poor settings.

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