Syndromic Approach to Diagnosis of Viral Thrombocytopenic Fever

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ABSTRACT

Introduction: Acute febrile illness with thrombocytopenia is quite common in the tropics. Most of them have a benign course with nonspecific symptoms. Dengue polymerase chain reaction (PCR) and viral cultures are expensive, time consuming and not feasible in all cases, especially in resource limited settings. Hence, in this study we have compared the clinical diagnosis of dengue illness according to CDC 2009 guidelines syndromic approach along with serological tests used routinely in the diagnosis of dengue.

Materials and methods: A total of 100 patients, admitted to our hospital during June 2015 to August 2015, with history of fever (>98.8 F), body ache and thrombocytopenia (platelets<1.5 lakhs/cumm), were enrolled in the study. A careful history was taken followed by relevant systematic examinations. The patients who were tested positive for malarial parasite, chikungunya, leptospira or hanta virus, were excluded. After excluding other causes of fever and thrombocytopenia, 83 patients were classified according to CDC 2009 definition of dengue.

Results: We found that NS-1 and IgM were positive in 40% and 6.8% of the cases respectively in patients having dengue without warning signs in whom the mean duration of illness was 3 days. The same tests were found positive in 35.5 % and 38.4% respectively in the category of patients who had warning signs where mean duration of illness was 6.5 days.

Conclusion: We concluded that the milder varieties of dengue illness should be managed according to CDC 2009 guidelines with a syndromic approach, after ruling out diseases with specific treatments such as malarial, leptospiral and ricketsial infections.

Keywords: Dengue, NS-1, polymerase chain reaction, CDC

INTRODUCTION

Acute febrile illness is extremely common in the tropics. The causes can range from treatable serious illnesses like falciparum malaria and leptospirosis to benign illnesses like non hemorrhagic dengue fever. Dengue is the most prevalent mosquito-borne viral disease; it is estimated that over 390 million dengue virus infections occur annually throughout-the world.[1] Symptomatic dengue virus infection can present with a wide range of clinical manifestations ranging from fever to life-threatening shock syndrome or multiple organ dysfunction.[2] Since there is no specific antiviral treatment available, timely and early diagnosis plays an important role in patient management and implementation of control measures.[3] There are several reasons why early and accurate diagnosis of dengue is important. First, it can help in patient management by directing clinical attention to the appearance of major warning signs of severe or even life threatening complications. Second, an accurate dengue diagnosis prevents unnecessary and expensive antibiotic usage. Third, prompt diagnosis of index cases can facilitate mosquito control measures in the community, so as to reduce further transmission. Lastly, the expanded use of accurate dengue diagnostics provides important data on the epidemiology and health burden of dengue in the community; and in doing so, it helps inform and guide public health policies, especially when dengue vaccines and anti-virals are under development.[4] In 2009, Centre of Disease Control had given its definitions for clinical diagnosis of dengue fever and the illness is clinically stratified as Dengue without warning signs, Dengue with warning signs and Severe Dengue.

Dengue without warning signs

Fever and any two of the following - Nausea, vomiting, Rash, Aches and pains, Leukopenia, Positive tourniquet test.

Dengue with warning signs

Dengue as defined above with any of the these - abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation (ascites, pleural effusion), mucosal bleeding, lethargy, restlessness, liver enlargement >2 cm; Laboratory: increase in HCT concurrent with rapid decrease in platelet count.

Severe Dengue

Dengue with at least one of the following criteria:

- Severe Plasma Leakage leading to:
  - Shock (DSS)
  - Fluid accumulation with respiratory distress
- Severe Bleeding as evaluated by clinician

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- Severe organ involvement
  – Liver: AST or ALT ≥ 1000
  – CNS: impaired consciousness
  – Failure of heart and other organs

The diagnostic approach to Dengue can be syndromic or very specific.The interpretation of dengue diagnostic tests, adapted from Dengue and Control (DENCO) study, is as follows:

Highly suggestive
One of the following
1. IgM + in a single serum sample
2. IgG + in a single serum sample with a HI titre of 1280 or greater.

Confirmed
One of the following – 1) PCR+ 2)Virus culture+ 3) IgM sero-conversion in paired sera 4) IgG sero-conversion in paired sera or four-fold IgG titer increase in paired sera.
The utility of antigen detection tests such as NS1 antigen in diagnosis of dengue infection is not yet determined.

AIM AND OBJECTIVES

Aims and objectives of the study was to evaluate the diagnostic utility of syndromic approach in the management of milder forms of dengue fever, as defined by CDC 2009.

MATERIAL AND METHOD

A total of 100 patients, admitted to our hospital during June 2015 to August 2015, with history of fever (>98.8 F), body ache and thrombocytopenia (platelets <1.5 lakhs/cumm), were enrolled in the study. A careful history was taken followed by relevant systematic examinations. History of an intake of alternative forms of medicine such as papaya leaf extracts, which is very popular in this area, was also taken. However the exact amount of the extract and its concentration could not be quantified. The following investigations were done: Complete blood count, dengue serology (NS1 antigen, IgM and IgG antibodies), malarial parasite, malarial antigen test, IgM leptospira, IgM chikungunya; hanta virus serology in some cases when suspected; and serum procalcitonin when sepsis was suspected. The patients who were tested positive for malarial parasite, chikungunya, leptospira or hanta virus,were excluded. Patients suspected to be having haematological disorders were excluded from the study. After excluding other causes of fever and thrombocytopenia, 83 patients were classified according to CDC 2009 definition of dengue. They were divided into two groups – Group 1 included patients without warning signs and Group 2 included patients with the warning signs. Patients with severe dengue (CDC 2009) were excluded from the study. The clinical symptoms, signs and the laboratory parameters were studied in each group. We compared the syndromic approach based clinical diagnosis with the dengue serological tests, there by inferring the usefulness of these tests in the diagnosis of early dengue.

STATISTICAL ANALYSIS

Continuous variables were summarized employing mean and standard deviation and categorical variables were presented using frequencies and percentages. Chi square test was used to compare differences in proportions for categorical variables. *P* value less than 0.05 was considered as statistically significant. Data was entered and analysed using SPSS software (Version 20).

RESULTS

83 patients admitted to the medical wards were enrolled according to CDC 2009 definition of Dengue. Table-1 summarizes the clinical features of the patients at presentation.
Among the 70 patients who presented with vomiting prior to hospitalization, 60 (90%) patients gave history of consuming papaya leaf extract.
Patients were divided into two groups – Dengue fever without warning signs (Group-1) and dengue fever with warning signs (Group-2).
44 patients had Dengue fever without warning signs (Group 1) and 39 patients had dengue with warning signs (Group 2). The mean duration of illness in the first group was 3.2 days, and 6.5 days in second group. (Table-2). The mean platelet count at admission was 80,000 in group 1 and 45,000 in group 2. Mean packed cell volume (PCV) in group 1 was 40 % and that in group 2 was 48%. In the first group, 18 patients (40%) had NS-1 positive status and 3 patients (6.8%) tested IgM-positive for dengue. The remaining 19 patients (43.18%) were NS-1, IgM and IgG negative. In the second group, 14 patients (35.5%) tested positive for NS-1 antigen and 15 patients (38.4%) tested positive for IgM Dengue. 3 patients tested positive for IgG. 10 patients (25.6%) did not test positive for NS-1 or IgM.
We also compared the clinical profile between the patients who were seropositive and seronegative for dengue.(Table-3)

DISCUSSION

In this study we observed that dengue NS-1 was tested positive in 40% of the cases and IgM tested positive in 6.8% of the cases of early dengue (mean duration of illness 3.5 days).

Symptoms	Number of patients
Fever	80 (96.38%)
Arthralgia	75 (90.36%)
Headache	63 (75.9%)
Vomiting	70 (90%)
Pain abdomen	35 (42.16%)
Bleeding manifestations	06 (7.22%)
Diarrhoea	10 (12%)
Lab parameter	MEAN
Leucocyte count	3500/MM^3
Lowest platelet count	22,000/MM^3
Hematocrit	48

Table-1: Clinical features of the patients at presentation

	Mean duration of illness (days)	NS-1 positive	IgM positive
Dengue fever without warning signs	3.20	18 (40%)	3 (6.8%)
Dengue fever with warning signs	6.50	14 (35.5%)	15 (38.4%)

Table-2 Mean duration of illness and dengue NS-1 and IgM positivity

Clinical parameter	Dengue seropositive (N=53)	Dengue seronegative (N=30)	*P* value
Vomiting	42 (79%)	28 (93%)	0.12
Pain abdomen	20 (38%)	15 (50%)	0.11
Headache	34 (64%)	29 (97%)	0.091
Hypotension	2 (4%)	3 (10%)	0.21
Bleeding manifestation	4 (7.5%)	2 (6.7%)	0.35
Lowest platelet count	18000/mm^3	21000/mm^3	0.98
Hematocrit	48	46	0.76

Table-3: Comparison of clinical profile between dengue seropositive and seronegative groups

43% of patients did not test positive with both the tests in the early phases of dengue. In the second group, the mean duration of illness was 6.5 days. NS-1 tested positive in 35.5% of cases and IgM tested positive in 38.4% of cases.

52.2% of patients after 3 days of fever and 26% of patients at the end of 6 days of fever, tested negative for the commonly used serological tests such as NS1 antigen, IgM and IgG antibodies. When the clinical features, duration of hospital stay, the lowest platelet count and hematocrit values were compared between the seropositive and seronegative groups, no significant difference was found. The supportive treatment as well as the complications were similar in the two groups. The specificity and sensitivity of the serological tests do not seem to be uniform across various studies. According to the study conducted by Wang et al (2010) in South Korea, NS-1 was tested positive in 64% of patients with acute infection.[8] In another study by Kassim et al (2011) in Malaysia, 32.2% of their patients tested positive for NS-1 antigen while, 40.9% were positive for IgM.[9] Therefore, based on the results of these serological tests, patients should not be missed in the setting of dengue epidemics in resource limited areas. Chatterji et al (2011) suggested that WHO 1997 definition can be used to exclude dengue and NS-1 strip test can be used to confirm dengue.[10] In our study, we also observed that there was no statistical significance in the presentation and clinical profile of the patients between seropositive and seronegative group. The syndromic approach incorporating the clinical definitions as per CDC should be used even if the serological results are negative after excluding common causes of fever in the region.

CONCLUSION

The clinical diagnosis based on syndromic approach is more appropriate in milder forms of thrombocytopenic fevers rather than trying to establish an exact guideline based diagnosis in appropriate geographical location and season (after rainfall) in the setting of primary care after ruling out diseases like malaria, leptospirosis and rickettsial infections. The unusually high prevalence of vomiting persisting for 2-3 days is probably related to the consumption of herbal treatments like papaya leaf extracts in the local population.

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