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Original Article

Presence of Warning Signs in Dengue Fever as the predictors of Progression to Severe Disease

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Abstract

Objective: To assess the prevalence of different Warning Signs, hematological and biochemical abnormalities in patients hospitalized with dengue fever and to assess the Presence of Warning Signs in Dengue Fever as the predictors of Progression to Severe Disease.

Methods: The study included those patients who had clinical evidence of the presence of some of the warning signs of dengue fever during primary evaluation either in the Emergency of Outpatient departments. The confirmation of diagnosis was based upon further clinical and serological evaluation (NS1Ag, IgM and IgG antibody titers). A study Performa was used to document the history and warning signs of dengue fever. All patients had complete hematological and relevant biochemical profiles during hospital stay. The prevalence of different warning signs was documented and their association with deterioration into severe disease was assessed.

Results: A total of 100 patients who had the confirmed diagnosis of dengue fever were included in the study. The fever, associated with chills and rigors was the most common symptom and mode of presentation. There was clinical evidence of dehydration in 30% and capillary refill was decreased in 70% of patients. The history of abdominal pain and vomiting was present in 31% and 19% of patients respectively. There was subjective feelings of weakness and lethargy in 35%, while 2% patients had a positive torniquet test. The clinical evidence of mucosal and gross bleeding was present in 8% of cases and 2% had capillary leakage and developed ascites and pleural effusions. The correlation of the presence of warning signs leading to severe disease was statistically not significant in the study.

Conclusion: Severe Dengue fever developed in 8% of cases, but the correlation of the presence of warning signs and deterioration to severe disease was statistically not significant in the study.

Keywords: Dengue Fever, Severe dengue fever, Dengue hemorrhagic fever

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Introduction

The dengue fever is now the emerging health problem in the tropical and sub-tropical regions. It is a vector borne disease, transmitted by Aedes Aegypti and albo-pictus mosquitoes. The causative agent is a single stranded RNA Virus from the Flaviviridae family. This virus has four distinct serotypes designated as DENV-1, DENV-2, DENV-3 and DENV-4. The immunity is life long but specific to a particular serotype. In the presence of this immunity, patients are at high risk of developing the severe form of dengue fever if there is another infection by a different serotype. In recent years the incidence of dengue fever has increased (100-400 million annual infections) and it has globally emerged as the 2nd most common cause of acute febrile illness after malaria. This risk has now extended to the half of the world population. There are 129 countries at high risk and fertile environmental condition for dengue fever.[1] The disease is endemic in South East Asia and 70% of global disease burden is in this region.[2]

The first case of Dengue Fever from Sub-Continent was reported from Madras in 1780. The first epidemic from this region in 1963-64, with virologically confirmed cases of Dengue fever was in Calcutta.[3] The cases of Dengue fever from areas now comprising Pakistan were reported from Karachi in 1941.The first major outbreak of public significance was in Lahore in 2014. Now the dengue fever is endemic in Pakistan and there

are several areas in all four provinces, Azad Kashmir and Northern areas with active viral transmission. There is escalation in the number of cases during the rainy seasons and early fall from these areas. According to WHO, there were 48,906 new cases in 2021 with 183 deaths directly attributed to Dengue fever in Pakistan.

The first ever outbreak of dengue fever in the State of Azad Jammu & Kashmir was in the capital city of Muzaffarabad in 2016. After three years there was a second outbreak of dengue fever in October-November 2019. A total number of 1057 patients had the confirmed diagnosis of dengue fever and 274 patients were admitted for indoor treatment. The third outbreak was from September to December 2021. A separate dengue management facility for indoor management of severe illness was established in the hospital and this study was conducted in AIMS during the 3rd epidemic of dengue fever.

In 1997, The World Health Organization (WHO) classified symptoms of DF in following three categories:

1- Dengue fever
2- Dengue hemorrhagic fever and
3- Dengue shock syndrome

In 2009, the World Health Organization updated the classification of dengue as:[4]

A- Dengue Fever without warning signs
B- Dengue Fever with warning signs and
C- Severe Dengue Fever

The sub-classification of Dengue Fever with or without warning signs is clinically relevant to triage the patients for hospitalization. The presence of warning signs has been thought to be the predictor of severe dengue fever. This classification was criticized due to lack of clarity and overlapping features of different clinical categories. In the present study, only those patients were admitted who had one or more warning signs during initial evaluation in Emergency or out-patient Departments.

Present study was undertaken to assess the prevalence of different Warning Signs, hematological and biochemical abnormalities in patients hospitalized with dengue fever and to assess the Presence of Warning Signs as the predictors of Progression to Severe Disease in Dengue Fever.

The inclusion criteria 1 and 2 were prerequisite for admission in the presence of warning features. The clinical evaluation included a detailed History and physical examination of all patients. These findings were documented on Performa designed for this study. The laboratory investigations included complete Blood counts, Serology for dengue virus (NS1Ag, IgM and IgG antibody titers) and biochemical profile (BSR, Serum Electrolyte, Liver function tests, Blood urea and creatinine. The further evaluation and other tests were according to the clinical condition of the patients.

Methods: *Inclusion Criteria and Exclusion Criteria*

Inclusion Criteria	Exclusion Criteria
1. Acute febrile illness/clinically compatible with the diagnosis of DF.	1. Acute febrile illness with plausible alternate diagnosis other than DF
Duration of fever less than one week	Documented fever for a period of more than 7-days
2. Confirmed diagnosis of DF with viral Serology (NS1 Antigen, IgM and IgG anti-dengue virus antibodies)	2. No serological evidence of dengue fever (Negative: NS1 Ag, IgM or IgG antibodies)
3-Presence of one or more warning signs (abdominal pain associated with tenderness, vomiting, Clinical evidence of mucosal bleeding, lethargy and restlessness, presence of ascites or pleural effusion) and significant thrombocytopenia.	

Operational Definitions

1- Warning Signs of Dengue Fever: Persistent vomiting, dehydration, lethargy, decreased capillary refill, abdominal pain

2- Severe Dengue Fever: Presence of Plasma leakage, Overt hemorrhage or organ involvement, need for Blood transfusion, Need of ionotropic support, admission in ICU

a- Plasma leakage: Drop in hematocrit, pleural effusion or ascites

b- Hemorrhage: Mucosal (epistaxis, gingival bleeding, sub-conjuctival hemorrhages) or Overt Bleeding (hemoptysis, Gastrointestinal Bleeding, vaginal bleed, hematuria and Per Rectal Bleeding)

c- Organ involvement: Hepatitis, encephalitis or myocarditis

Results

Clinical features: 100 patients with confirmed diagnosis of dengue fever were included in the study. The most common presentation was sudden onset of high grade fever (100%), associated with chills and rigors. There was previous history of dengue fever in 13% of patients (table-1). There was clinical evidence of dehydration in 30% and capillary refill was decreased in 70% of patients. The history of abdominal pain and vomiting was present in 31% and 19% of patients respectively. There was subjective feelings of weakness

and lethargy in 35% patients (Table-1).

The clinical evidence of mucosal and gross bleeding was present in 8% of cases while only 2% had capillary leakage and developed ascites and pleural effusions. The torniquet test was positive in 2% of patients. When compared with Pearson's, there was no statistical significant correlation ($p > 0.62$) of warning signs leading to deterioration in severe disease in this study (Table-3)

Hematological and Biochemical parameters: There was leukopenia (WBC < 3000/cmm) in 31% of admitted patients. The significant thrombocytopenia with platelet counts less than 20,000/cmm in 6% of patients. 55% patients had a platelet count between 20,000 to 100,000/cmm and 39% had > 100,000/cmm. The mean hematocrit was 42.74% (std±22.12). The serum bilirubin was more than 1.1 mg/dl in 14% and ALT was more than 60 IU in 54% of patients. There was hyponatremia (Serum Sodium < 135 meq/L) in 6% of patients and mild hypokalemia (Serum potassium < 4.5 meq/L) was present in 17% of cases. The NS1 Antigen was positive in 77% of patients (Table-3).

Table 1: *Presenting clinical features in patients*

Clinical features	Present	Absent
Previous history of dengue fever	13	87
Dehydration	30	70
Capillary Refill	70 (Decreased)	30 (normal)
Lethargy	35	65
Abdominal pain	31	69
Vomiting	19	81
Pleural effusion	2	98
Ascites	2	98
Mucosal bleeding	8	92
Gross bleeding	8	92
Tourniquet test	2	98

Table 2: *Correlation*

Correlations			
		Presence of warning features	Severe disease
Presence of warning features	Pearson Correlation	1	.053
	Sig. (2-tailed)		.602
Severe disease	Pearson Correlation	.053	1
	Sig. (2-tailed)	.602	

Table 3: *Hematological and Biochemical parameters*

Hematological and Biochemical values	(%Percent patients)
White Blood Count	
3000-5000/cMM	69
< 3000/cmm	31
Platelets	
< 20,000	6
20,000-100,000	55
>100,000- 150,000	39
Liver Function Tests	
ALT (IU/L)	
< 35	8
35-60	38
>60	54
S/Bilirubin (mg/dl)	
<1.1	86
>1.1	14
NS1 Antigen	
Positive	77
Dengue Serology	
(IgM or IgG)	23
Serum Electrolytes	
Serum Na^+ (mEq/L)	
<135	6
135-144	88
>144	6
Serum K^+ (mEq/L)	
<3.5	0
3.5-4.5	83
>4.5	17

Discussion

The number of infections with Dengue Virus has been increasing during the last twenty years. There has been 8-fold escalation in cases of dengue fever reported to WHO during the last 2 decades. The majority of these cases are in tropics and sub-tropical regions with 70% disease burden in Asia. After malaria, dengue fever is the second most common underlying etiology of acute febrile illness in this region. There is overlap of symptoms with other viral illnesses and in the ongoing pandemic of covid-19 awareness of clinical manifestations of dengue fever is imperative to clinically differentiate and categories the severity of illness. There are wide variations in the severity of disease and wide spectrum of clinical presentations in Dengue Fever[5,6]. The majority of cases are either asymptomatic or have only mild symptoms. While at the other end of the spectrum patients may end up with capillary leakage and dengue shock syndrome (DSS). The 2009 sub-classification of Dengue fever by WHO as dengue fever without warning signs, dengue fever with warning signs and sever dengue fever lacks clarity and there is significant mixing of

and overlaps in otherwise distinct clinical sub-types. It neither predicts the outcome of disease in each category nor it predicts the deterioration from one mild category of the disease to the severe one. The present study supported these observations as no correlation was found in the presence of warning signs and deterioration into severe disease.

In the present study, the common warning features in patients were the presence of dehydration (30%), lethargy (35%), abdominal pain (31%), and vomiting (19%). The correlation of the presence of these symptoms and deterioration in severe disease was not statistically significant. The other studies from the dengue fever endemic regions have reported life threatening complications in the absence of any of these symptoms. The WHO is now reevaluating the case definitions of dengue fever and dengue hemorrhagic fever. In the present study none of these patients progressed to dengue shock syndrome in spite of the presence of these warning features. There is already criticism of the present WHO classification of DF and skepticism for overlapping of symptoms while assigning the different categories. Similarly, the presence of the warning symptoms as predictor of severe dengue fever has been clearly denied in the present study and these findings are also supported by several other studies. Hence, the clinical utility of "warning signs" becomes questionable if they are not a definite predictor of progression to severe disease.

Hemorrhagic manifestations in the form of mucosal and gross bleeding were observed in 8% of patients. 2% of the hospitalized patients developed capillary leakage and developed pleural effusions and ascites. The torniquet test was positive in only 2% of patients. The 3/4th of patients with mucosal bleeds had negative torniquet test. Though a useful clinical tool, it was of limited clinical utility in this study. Only 6% patients had thrombocytopenia with platelet counts of less than 20,000/cmm. There was only one patient who had severe hemorrhagic complications and developed epistaxis, per rectal and vaginal bleeding with platelets counts dropping to 6,000/cmm and hematocrit dropped to 12%. The patient was managed in high dependency area and recovered in one week. However, there was no other incident of severe bleeding, shock or need of intensive care treatment in the participants of this study. In another study from Pakistan epistaxis, bruises, hematuria and gingival bleeding were the common hemorrhagic manifestations[7]. These findings were similar to the findings in our study.

The significant leukopenia (WBC count less than 3000/cmm) was present in 31% of patients. The virus induced inhibition or destruction of the progenitor cell is the postulated mechanism of leukopenia in dengue fever. A study by Hari Kishan found leukopenia in 44% of patients[8], Ahmed et al, observed in 43%[9], and Dhooria et al in 26% of cases[10]. The results of these studies were similar to the findings of our study.

There was slight derangement of liver functions in the majority of patients. ALT was more than 60 IU in 54% of patients while it was 35-60 IU in 38% of patients. Only 8% of patients had normal reference levels of ALT in the participants of this study. The derangements in serum bilirubin levels were subtle. 86% patients had normal levels of Bilirubin (< 1.1 mg/dl) and only 14% had levels above 1.1 mg/dl. A study by Swamy found raised ALT in 78.6% of patients in dengue fever with warning signs[11]. The involvement of liver and deranged Liver Functions in dengue fever has been described in many observational studies since 1967[12]. There is wide spectrum of liver involvement in dengue fever, ranging from mild elevations of transaminases to severe hepatocyte injury resulting in jaundice and raised levels of bilirubin[13,14]. There is evidence of direct viral hepatotoxicity and role of deranged host immune response against the virus resulting in hepatic injury[15]. Despite deranged liver functions in majority of patients, there was no case of acute liver failure or fulminant hepatitis in this study.

Abdominal pain and vomiting were relatively common presentations (31% and 19% respectively). The differential diagnosis included other causes of acute abdominal pain (appendicitis, hepatitis, acalculus cholecystitis, pancreatitis and peptic ulcer). There are case reports of rectus sheath hematoma as the underlying etiology of abdominal pain in dengue fever[16].

In severe dengue fever there is endothelial dysfunction leading to increased vascular permeability and leakage of fluid into the pleural and peritoneal cavities. There is role of cytokines such as TNF-α and DENV-NS1 antigens in the pathogenesis of increased capillary permeability[17]. The clinical evidence of capillary leakage was present in 2% of patients. There are wide differences in the reported frequency of capillary leakage in different studies. A systemic review reported capillary leakage in 36.8 % of hospitalized patients[18].

The clinical diagnosis of dengue fever was confirmed with NS1 Structural antigen or by IgM and IgG anti-dengue virus antibodies[19]. The NS1 antigen was positive in 77 % of patients while 23% patient had either IgM or IgG anti-dengue antibodies present in their blood.

The Malaria and acute upper respiratory tract infections were the most common clinical mimics. The other important differential diagnosis in this region was the enteric fever. However, the list of possible differentials also included acute viral hepatitis and gastrointestinal infections[20,21]. The distinct clinical features supporting the diagnosis of DF were the skin rash, facial flushing,

conjunctival injection, myalgias, backache, retro-orbital pain accompanied with cytopenia. There are number of clinical features of Chikungunya fever and Zika virus infections similar to dengue fever[22]. There are reports of Chikungunya fever from the Southern regions of Pakistan it should be considered in the differential diagnosis of dengue fever in those areas.

The sub-classification of dengue fever in different categories would be more relevant and clinically useful if it helps in the prediction of deterioration from one subclass to the other. Similarly predicting the probability of mortality in sub-classes. This sub-classification needs review to be more objective for example by assigning scores to different parameters and total scores for each sub-class.

Conclusion

Dengue fever (along with malaria) is now the leading cause of acute febrile illness around the globe. Only 8% patients with warning signs deteriorated into severe dengue fever. This study adds to the existing doubts for the efficacy and clinical utility of warning signs as the predictor of deterioration to severe dengue fever. The term "warning signs" may contribute towards undue anxiety of patients and concerns in treating medical staff.

Recommendations

The dengue fever is the problem of the developing world and clinicians don't have resources to conduct and then publish their research in high impact medical journals. It is recommended to have a collaborative research from South East Asia, especially from countries with high prevalence of dengue fever to classify the disease and to assign a scoring system to help the subclassification and predicting the outcomes of disease based upon the scoring system. A Large, preferably multicenter trials from different regional countries of the South-East Asia for future research to evaluate the significance of "warning signs" and to update the clinically relevant sub-classification of dengue fever. It is also recommended to discontinue the use of this term "warning signs" till more clarity.

Conflict of Interest *None*

Funding Source *None*

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