Original Article

Clinical Spectrum of Dengue Fever: A Single Center Study

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Abstract

Objectives: To assess the clinical features, diagnostic modalities and clinical outcomes in patients of dengue fever and dengue hemorrhagic fever to guide clinician for an early diagnosis and effective treatment.

Methods: A single-centered retrospective cross-sectional study which included 150 patient of confirmed dengue fever admitted at Northwest General Hospital, Peshawar, Pakistan in the year 2017.

Results: Our study showed that the incidence of dengue fever was more common in male patients. Blood counts show that thrombocytopenia and leukopenia are common in such patients. NS1 (dengue antigen) and IgM when tested were positive in 100% and 48.6% of the patients. Out of total 6.6% of the patients progressed to DHF. Diagnostic clinical features are myalgia (most common), orbital pain, anorexia in dengue fever while vomiting, diarrhea and rash were more common in DHF. In addition, 22.7% of the patients presented with bleeding manifestation, gum bleed (most common), Petechiae, epistaxis and hematuria. Only 2 patients developed acute kidney injury. Among total 10% of the patients also developed plasma leakage syndrome. Mean hospital stay was higher for patients who developed DHF.

Conclusion: Dengue fever incidence is greater in males. Thrombocytopenia and leucopenia are associated with the disease. Bleeding tendency increases with severe thrombocytopenia. Myalgia is the common symptoms and rash the least common. Vomiting, diarrhea and rash is more common in DHF patients. Peri-orbital puffiness was a relatively newer finding in patients suffering from this disease. NS1 dengue antigen and IgM dengue antibodies testing when combined has a higher diagnostic sensitivity. Hospital stay is lengthened by higher drops in platelet counts, bleeding tendency, renal failure and with the development of plasma leakage syndrome

Keywords: Dengue fever, thrombocytopenia, leukopenia, Bleeding tendency, renal failure, plasma leakage syndrome

Introduction

Acute dengue fever (ADF) is a viral infection which is prevalent globally and significantly emerging in the tropical and subtropical countries, considered endemic by the WHO.[1] Almost 390 million people suffer from dengue fever every year, a quarter of which are symptomatic.[1] DF has become a public health concern in the last five decades due to its widespread expansion amounting to 30-fold rise in incidence.[2]

In an analytic report about the incidence of ADF in various parts of the country by Khanani et al described that ADF was reported in Pakistan for the first time in children under the 16 years of age in 1985 followed by 132 cases in 1995.[3-5] The incidence of ADF has significantly increased many folds since then.

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Major outbreaks had been recorded in the years 2003, 2006, 2007, 2008, 2010 and 2011 with 397 deaths and a total number of 3500, 5400, 2700, 1800, 5000 and 20,000 confirmed cases of ADF respectively.[6-9,4] This only accounts for the documented cases which signify that Pakistan had greatly been affected by epidemics of ADF over the years. The high ratio of mortality shows that the protocol for management and training of health professional in this regard in Pakistan is not up to the mark.

The dengue virus is included in the genus flavivirus in the Flaviviridae family. The mosquito 'Aedesaegypti' is most often the vector for spread of the disease.[1]The virus has an incubation period of 3-7 days. This disease has 3 stages, 2-7 days of febrile phase, 1-3 days of critical phase and 3-5 days of recovery phase.[10] Myalgia, arthralgia, orbital pain, anorexia, nausea, vomiting, diarrhea and development of rash are the most common clinical features of the

disease[3].Mild hemorrhagic manifestations, fever, thrombocytopenia and leucopenia have been reported in the febrile phase of the illness.[3] Patients may recover without experiencing the critical phase which includes abdominal pain with a progressive increase in thrombocytopenia/ leucopenia with a rise in hematocrit, hemorrhagic manifestations, plasma leak, hypovolemic shock, acute kidney injury and death. Increased mortality rate is associated with co-morbidities like hypertension, diabetes mellitus, asthma, ischemic heart disease and some other chronic diseases.[11] WHO has categorized dengue fever into mild, moderate and severe dengue infections. Severe dengue infection has the features of hemorrhagic events called Dengue Hemorrhagic Fever (DHF) and hypovolemic shock (dengue shock syndrome).[10]

In our study we assessed the demographic analysis, clinical features and outcome, sensitivity of diagnostic tests for early diagnosis and the predictors for a longer hospital stay in patients of ADF and DHF.

Patients & Methods

Study design and Patients:

This was a retrospective cross-sectional analysis in which 150 dengue patients admitted to the Northwest General Hospital (NWGH) Peshawar, Pakistan in 2017 who fulfilled the WHO criterion for dengue fever (DF) were included, which is fever and two or more of the following: myalgia, headache, orbital pain, arthralgia, leukopenia, rash and bleeding and who had a confirmed infection on laboratory test. DF patients were distinguished from DHF by the WHO criterion which is 1) fever (> than 99° F for more than 2 days, (2) Hemorrhagic manifestation, (3) Platelet Count < 100,000 platelets/ µL, (4) Plasma Leakage[3]. We did not witness any patients of dengue shock syndrome. Patients with other infections which overlap dengue symptoms were excluded from the study.

Ethical Statement

The data was obtained from the operating system after the approval of the ethical board of Northwest General Hospital Peshawar, Pakistan.

Variables and Definitions

The electronic system contains data regarding Admission/ Discharge notes, clinical features and laboratory tests is stored electronically on the Operating systems of the hospital which in specific provided information about the age, gender, ethnicity, address, travel history, signs and symptoms (Myalgia, Orbital pain, anorexia, vomiting, diarrhea, rash, petechiae, gum bleed, epistaxis and hematuria) , vitals (pulse & Blood pressure), transfusion reaction, co-morbidities, hospital stay, test results (Complete blood picture, Renal profile, NS1, dengue antibody profile and radiological test results), treatment protocol, platelet transfusions, documented complications (plasma leakage, bleeding events and organ failure) and death/ recovery data.

Severe thrombocytopenia was defined as platelet count < 20,000 platelets/ µL based on the practice in the area. Prophylactic platelet transfusion was defined as platelet transfusion in the absence of clinical bleeding and or severe thrombocytopenia. Therapeutic transfusion was defined as platelet transfusion in presence of clinical bleeding and or severe thrombocytopenia. The patients were categorized into ADF and DHF only, since we did not witness any cases of dengue shock syndrome. Clinical bleeding was defined as bleed other than petechiae, gum bleed, epistaxis and hematuria.

DHF in our study was defined according to the WHO criterion as stated above. High grader fever was defined as core temperature higher than 102 F.

Statistical Analysis

The data was analyzed through SPSS 23. Frequencies and percentages were calculated for categorical variables, whereas, mean and standard deviations were calculated for continuous variables. A p-value of 5 was considered significant. Variable with 10% missing data were not considered in the study.

Results

In 2017, 150 patients presented to our OPD who fulfilled the WHO criterion for Dengue Fever. The median age was 31, with the range of 14–70 years. Gender analysis showed 81 patients (54%) were male and 69 patients (46%) were female (Table 1).

Laboratory Testing:

All the patients were positive for NS1(100%). Dengue antibodies testing showed that seven patients (4.7%), 53 patients (35.3%), 20 patients (13.3%) patients were reactive for IgG, IgM and both respectively, while 70(46.7%) patients were found to be non-reactive.

Of the total 74.7% of the patients had thrombocytopenia at the time of presentation. The patients were divided into three categories after finding their platelet counts.

Considering patients with thrombocytopenia 24.7% of the patients had a count of 1-49×10^3 platelets/µL, 23. 3% of the patients had a count of 50-99×10^3 platelets/µL,26.7% of the patients had a count of 100-149×10^3 platelets/µL, 25.3% patients had a count of more than Or equal to 150×10^3 platelets/µL.

In addition 52.6% of the patients had a Total Leucocyte Count less than 4.0 × 10^9/L. 42.6% patients had a TLC of 4.0-11.0 × 10^9/L while 4.7% of the patients had a raised total leucocyte count.

Only 13 patients had a raised hematocrit (male 40-45% and female 36-48% was considered normal)

Table 1: Demographic Distribution of Patients

Variable	Number	Percentage
Age groups(years)		
14-28	65	43.3
29-42	42	28.0
43-56	27	18.0
57-70	16	10.7
Gender		
Male	81	54
Female	69	46
Length of hospital stay		
≤3	37	24.7
4-5days	76	50.7
6-8days	37	24.7

Pie-Chart: Clinical signs and symptoms

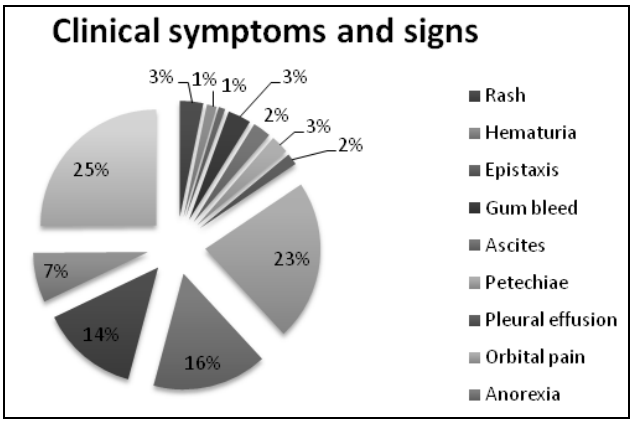

Table-2: Serological and hematological characteristics

Variable	Frequency	%age
NS1 antigen		
positive	150	100
Negative	0	0
Antibodies		
IgG	7	4.7%
IgM	53	35.3%
Both	20	13.3%
Non-reactive	70	46.7%
Total leukocyte count		
<4	64	42.6%
4-11	69	46%
>11	7	7.3%
Hematocrit value		
Normal	137	91.3%
High	13	8.6%
Transfusion history		
Yes	3	2%
No	147	98%
Platelets counts		
1-49	37	24.6%
50-99	35	23.3%
100-149	40	26.7%
≥150	38	25.3%

Clinical signs and symptoms

Regarding symptoms 90.7% of the patients had myalgia, orbital pain in 64.7%, anorexia in 46%, vomiting in 39.3%, diarrhea in 20% and 9.3% of the patients developed rash.

Among total, 33 patients (22%) presented with bleeding at the time of admission. Out of the 150 patients, Petechiae were present in 7.3% of the patients, gum bleeding in 9.3% of the patients, epistaxis in 2.7%, and hematuria in 4% of the patients. 28% of the patients presented with a high grade fever (>102 F).

7.3% of the patients developed ascites and 4.7% of the patients developed pleural effusion.
However, the values are not applied as a whole, since some of the patients developed both, hence a total of 15 patients (10%) developed plasma leak.

Clinical Outcome

Of the total 15 patients (10%) developed DHF. 2 DHF patients developed Acute kidney injury who were admitted in the ICU and had a significantly longer hospital stay. Only 3 patients out of DHF was given therapeutic platelet transfusion upon the clinician's discretion, they had platelets counts of 8, 12 and 18 ($\times 10^3$ platelets/μL) respectively with significant clinical bleeding. The overall mortality rate was zero.
Out of all 24.7% of the patients stayed in the hospital up to 3 days and 50.7% of the patients stayed in the hospital for 4-5 days. Only 24.7% of the patients stayed in the hospital for 6-8 days(Table 1).

Discussion

In 2017, 150 patients of dengue fever were assessed for their clinical features and outcome. Many studies have been conducted locally and internationally which have described several social factors which affects the gender wise incidence and has reported a greater incidence of dengue in male patients, which was 54% in our study. A study conducted in six Asian countries also concluded that incidence of dengue fever is higher in male patients.[12] On the other hand, a study conducted in North America concluded that the incidence of the disease is almost equal with respect to male and female population1.[13]
The commonest symptom upon presentation was myalgia (90.7%), the other common symptoms were orbital pain, anorexia, vomiting, diarrhea and rash. Rash being the least common symptom (9.3%)These symptoms have been found to be common in such patients in many other studies for both in patients of DF and DHF.[14] On the contrary a study by Premaratna et al had shown a greater incidence of rash (95%) in such patients.[15]
Though we had only smaller number of DHF patients, vomiting, diarrhea and rash were more common in patients of DHF than DF.[3] However, 7 patients among 10 patients of DHF had peri-orbital puffiness due to fluid accumulation/ plasma leak which is a feature of DHF. This finding has been reported in other studies as well.[16] The WHO criterion has been helpful in diagnosing cases of DHF as shown by Srikiatkhacorn et al who conducted a prospective analysis of dengue patients in Thailand and reported 99% specificity of the WHO criteria, but there were 72 patients in our study who had a platelet count of < 100,000 platelets/ μL, out of which only 10(13.8%) patients developed DHF.[17] Therefore the criterion cannot be taken diagnostic of DHF and clinicians should be mindful of this fact while dealing with patients of severe dengue fever.
42 patients out of 108 patients presented with high grade fever when analyzed between day 2-7 at the hospital while the mean (SD) for duration of fever prior to reporting at the hospital was 3.5 days, while the rest of patients presented with low- grade fever. 30% DHF patients presented with high grade fever. Fever has been found to be one of the earliest symptom of dengue patients. There was no significant differences in terms of duration and intensity of fever with respect to age/ gender.[18]
Bleeding is the most dreaded complication of DF which has been confirmed by many studies.[3] 34 patients (22.7%) initially presented with hemorrhagic manifestations. Gum bleeding was the most common which was 9.3% and epistaxis (2.7%) was the least common. Out of these 34 patients who developed manifestations, 10 patients (29.4%) developed DHF while the rest did not develop severe disease. 52.9% patients who had a platelet count of 1-49$\times 10^3$ platelets/μL developed bleeding manifestations while the trend of bleeding decreased with an increase in the platelet count, only 6 patients out of the 34 patients with platelet count more than100$\times 10^3$ platelets/μL developed bleeding manifestations, which could be explained by the increased capillary fragility in such patients.[22]
Our study revealed that patients displayed thrombocytopenia and leucopenia present in both patients of DF and DHF with lowest counts at 4.1 days after developing fever which is in support of other studies. The platelet counts were comparatively much lower in patients of DHF. Interestingly, 4.7% of the patients also developed leukocytosis.[19]
Out of the 150 dengue patients who presented to our hospital were all positive for NS1 (dengue antigen), while 48.6% patients were positive for IgM, out of which 56.16% were male and 43.8% were female. NS1 and dengue antibody testing (IgM & IgG) was performed on 3-5 day after the onset of fever. This shows that IgM antibodies are positive in almost half of the patients which is supported by other studies[20].
Out of the IgM positive patients there is a slightly higher number of male patients (31 patients). This also concludes that IgG antibodies are less sensitive

(20.3%) in 3-5 day after onset of fever compared to IgM. Other studies also show that NS1 and IgM when tested for in combination increase the overall dengue diagnostic sensitivity.[21]

15 patients (10%) developed plasma leakage manifested in the form of pleural effusion and ascites or both diagnosed with the help of chest X-ray and ultrasonography. Out of these 15 patients, 10 patients progressed into DHF. Many other studies advocate high value of capillary fragility measurement in DHF which leads to plasma leak.[22] High HCT in our study was a strong predictor of plasma leakage syndrome, 13 out of 15 patients with high HCT developed the features of plasma leakage. Plasma leak is a feature of DHF as described by the WHO criterion for DHF. This also shows that patients who fail this criterion still have the risk of developing complications of severe dengue fever. It is not preferable to make a valid claim with a small sample but is worth mentioning here.

As advocated by studies with large samples that prophylactic platelet transfusion has low efficacy in treating patients of DF and DHF[22], our study analyzed that none of our patients were given prophylactic platelet transfusion, only 3 out of 08 patients in our study with a platelet count lower than 20×10^3platelets/μL with significant bleeding were given platelet transfusion. The hospital stay for these patients could not be generalized due to a smaller number but is worth mentioning that it did not significantly hasten the recovery or shorten the hospital stay of the patients given platelet transfusion, though it reduced the bleeding tendency. With zero mortality this can be interpreted that prophylactic platelet transfusion has no role in decreasing mortality in patients of DF/ DHF.

DHF patients are also at the risk of developing renal failure, 2 DHF patients in our study developed AKI who were shifted to ICU and later fully recovered and were discharged from the hospital.[23]

We have analyzed platelets counts, bleeding tendency and plasma leakage are predictors of the hospitals stay and time consumed in recovery. Hospital stay is longer and recovery is delayed in patients who have higher drops in platelet counts, increased bleeding tendency and presence of features of plasma leakage syndrome.

Conflict of Interest

No conflict of interest has been found while conducting this study.

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D. Manuscript Writing
E. Critical Review
F. Facilitated for Reagents/Material/Analysis