DERMATOLOGIC SPECTRUM OF PATIENTS PRESENTING WITH DENGUE INFECTION AND THEIR CO-RELATION WITH SEVERITY OF THE DISEASE

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Abstract

Objectives: To observe dermatologic spectrum of patients presenting with dengue infection and their co-relation with severity of the disease.

Material and Methods: This prospective cross-sectional study was conducted at Khyber teaching hospital Peshawar, from July 2017 to January 2018. Two hundred and twenty eight patients were enrolled in the study. Patients fulfilling the inclusion criteria were subjected to detailed history, clinical, mucocutaneous and systemic examination. Relevant investigations were done. Data was recorded in pre-designed pro forma and analyzed.

Results: Among a total of 228 patients included in the study, 123 were male and 105 were female. The mean age was 34.57 ± 14.9 years. There was significant association of mucosal manifestations with dengue fever and dengue hemorrhagic fever, while cutaneous manifestations had significant association with dengue shock syndrome with p-value of less than 0.05. Mucosal findings in dengue disease were found to be significantly associated with headache, bleeding, abdominal pain, epistaxis, deranged liver function tests, deranged renal function tests, thrombocytopenia, deranged PT, deranged APTT, high hematocrit level and unfavorable outcome, while bleeding, high hematocrit, ascites, abdominal tenderness and unfavorable outcome of the disease were found to have significant correlation with cutaneous manifestations, with p-value of less than 0.05.

Conclusion: Mucocutaneous manifestations can be used as an earlier marker to predict the development of complications, laboratory abnormalities and severe dengue disease.

Key Words: Dengue fever, dengue hemorrhagic fever, dengue shock syndrome, mucocutaneous manifestations, dermatological spectrum

Abbreviations: DF (dengue fever), DHF(dengue hemorrhagic fever), DSS(dengue shock syndrome)

INTRODUCTION

Dengue, described as "break bone fever" by Benjamin Rush, is fast emerging mosquito borne viral infection caused by dengue virus (DENV).[1] The condition is endemic in both subtropical and tropical areas.[2]Dengue patients present with wide spectrum of clinical manifestations. Patient may have silent infection with no symptoms, or may have flu-like illness, dengue fever (DF). Few patients, however, presents with severe dengue disease (SDD), including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[3]

About 2.5 billion population worldwide are at risk of developing this infection. In 100 endemic countries, approximately 50 million cases have been reported, including hospitalization of nearly half a million cases, and death of 22,000 cases.[4,5] The mortality rate of DHF/

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DSS is 1% in treated cases, which escalates to 20% in untreated cases.[4]

Dengue is febrile illness, that can affect infants, young children and adults of all ages.[6] Dengue patients present with wide spectrum of clinical manifestations. Patient may have silent infection with no symptoms, or may have flu-like illness, dengue fever (DF). However, patients may present with severe dengue disease (SDD), including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[2,3]

The symptoms of dengue fever appear in 3-14 days after the bite of infective mosquito.[6] It is an acute illness, with sudden onset of high grade fever, with headache and skin rash. This triad is called 'dengue triad'. There may be exhaustion, muscle aches and severe joints pain and swollen glands. Laboratory findings in dengue patients may show thrombocytopenia, relative leukopenia, haemoconcentration, deranged liver function tests, deranged renal function tests.[7] Disseminated intravascular coagulation may be mediated in cases in which dengue antigen-antibody complexes mediate complement activation and release of vasoactive amines.[8] However, most of the patients presenting with classical dengue fever recover completely without any complications.[9] In addition to classical dengue

fever, if there is appearance of hemorrhagic rash or hemorrhagic manifestationsin patient, then it is called dengue hemorrhagic fever.[10]Dengue shock syndrome is associated with low blood pressure, altered sensorium and delayed capillary refilling. [10] Dengue hemorrhagic fever and dengue shock fever has higher mortality rate, unless prompt and adequately treated.[6] Sequential infection increases the chance of dengue hemorrhagic fever and dengue shock syndrome.[10]

Dengue fever is diagnosed my several methods. However, an accurate means that can help to predict the severity and prognosis of the disease at an early stage of disease is not available. Patients initially asymptomatic or with mild dengue fever can develop severe dengue disease later.[3] It is important to look for those signs and symptoms of the disease that can help to determine the progression of disease to severe dengue disease. This will also help to provide necessary care to patients, who are at risk of developing SDD and to reduce unnecessary hospitalization of stable cases.[3]It will also help in reducing disease burden and will play role in controlling the progression of disease to severe dengue disease.[11, 12] The dengue guidelines in 2009, regarded abdominal tenderness or pain, vomiting, lethargy, restlessness and mucosal bleeding as warning signs and symptoms of severe dengue disease. Correlation was found between the frequency of nausea, vomiting, abdominal pain, cutaneous rash, bleeding and severe dengue disease.[11,12] It was also found that certain viral factors, host immune reactions and laboratory tests can also help in predicting severe dengue disease.[13] Few studies show effect of age and sex on the clinical presentation of disease as well.[14,15,16,17]

The clinical manifestations of dengue fever can be used as an earliest marker to predict severe dengue disease. At their presentation, there is a need to identify those the patients who need critical care in ICU depending upon the presence of warning signs.[18] The reports on to predict severe dengue fever on basis of presence or absence of warning signs are inconsistent. We conducted a study to identify the cutaneous manifestations, systemic signs and symptoms, and laboratory tests that are associated with severe dengue disease. This will help to find better methods to predict the development of severe dengue disease in patients presenting with dengue fever in both outpatient and inpatient departments.

MATERIAL AND METHODS

The study was conducted in Department of Dermatology, Khyber Teaching Hospital, Peshawar from July 2017 to January 2018. Patients presenting with positive NS.1 test and diagnosed with dengue fever were enrolled in the study from outpatient and inpatient departments. All ages and both gender were included. Patients with other acute or chronic concurrent ailments besides dengue fever were excluded from the study.

An informed consent was taken. A detail history was obtained. Clinical, mucocutaneous and systemic examination was carried out. Relevant investigations such as hematocrit, platelet count, white blood cells count, coagulation profile, liver function test, renal function tests, dengue serology (IgG, IgM) and dengue NS.1 were done. The data was entered on pre-designed proforma and later analyzed.

Type of study

A Prospective cross sectional study

Statistics

Analysis of results was made using SPSS version 22. Frequencies and percentages were calculated for all the categorical variables like gender, age, skin findings, mucosal manifestations. Mean $\pm$ standard deviation was calculated for continuous variables like age, temperature, onset of fever, blood pressure, pulse etc. Post stratification Chi-square test was applied, in which p-value less than 0.05 was considered as significant. Pearson's correlation coefficient was calculated, and one sample T-test was used wherever applicable. The results were expressed as percentages and significance.

RESULTS

A total of 228 patients were included in the study. Majority of the cases, 123 (53.9%) were males and 105 (46.1%) were females. Mean age of patients in the study was 34.57+_14.94 years, with age range of 1 to 72 years. Maximum patients, 64 (28.1%) belonged to the age group of 21-30 years as shown in table 1. Number of cases reported among the under the age of 10 years were 10 (4.4%).

Total number of patients who presented with cutaneous manifestations was 108(47%), while mucosal findings were present in 59(25.9%) cases. 37(16.2%) patients had both cutaneous and mucosal manifestation. 147(64.5%) patients had classical dengue fever, 61 (26.8%) patients had dengue hemorrhagic fever and 20(8.7%) patients had dengue shock syndrome as shown in table 2.

In this study, 35 patients with dengue fever had mucosal, and 95 patients with dengue fever had cutaneous manifestations. Among the mucosal lesions, erythema was present in 14, oral thrush in 13, purpura in 4, aphthous ulcers in 2 patients. 2 patients had any other mucosal findings. Pruritis was present in 35 and maculo-papular rash was present in 29 patients. 12 patients had purpura and similar number of patients had burning sensation on skin. Only 7 patients had other skin rash as shown in table 2.

In patients with dengue hemorrhagic fever, 17 had mucosal and 48 had cutaneous manifestations. 10 patients had erythema of mucosal surfaces, 05 had

Table 1: Demographic characteristics of patients with dengue fever (n=228)

Characteristics		Number	Percentage
Age groups	Up to 10	10	4.4%
	11-20	31	13.6%
	21-30	64	28.1%
	31-40	53	23.2%
	41-50	38	16.7%
	51-60	20	8.8%
	>60	12	5.3%
Gender	Male	123	53.9%
	Female	105	46.1%

Table 2: Mucocutaneous manifestations in patients with dengue fever, dengue hemorrhagic fever and dengue shock syndrome.

	Dengue fever	Dengue hemorrhagic fever	Dengue shock syndrome
Total patients	147(64.5%)	61(26.8%)	20(8.7%)
Mucosal manifestations			
Erythema	14	10	5
Thrush	13	0	0
Purpura	4	0	1
Aphthous ulcers	2	5	1
Anyother	2	2	0
Total	35 (23.8%)	17 (27.8%)	7 (35%)
p-value	0.022(0.744)	0.018(0.790)	0.065(0.332)
Cutaneous manifestations			
Pruritis	35	31	9
Maculopapular rash	29	15	3
Purpura	12	4	1
Burning	12	5	3
Other skin rash	7	6	1
Total	95 (64.6%)	48 (78.6%)	17 (85%)
p-value	0.163(0.014)	0.158(0.017)	0.027(0.683)

aphthus ulcers and 02 had other mucosal findings. 31 patients had pruritis, 15 had maculo-papular rash, 05 had burning and 04 had purpura on the skin. Only 6 patients had other cutaneous manifestations shown in table 2.

Among patients with dengue shock syndrome, mucosal erythema was present in 05 patients, while aphthous ulcers and purpura were noted in a single patient each. On the other hand, 09 patients had pruritis, 03 patients had maculo-papular rash, 03 had burning sensation, with one patient having cutaneous purpura. Only one patient in dengue shock syndrome presented in erythroderma as shown in table 2.

The association of mucosal manifestations with dengue fever was statistically significant, with p-value of less than 0.05. Dengue hemorrhagic fever also had significant association with mucosal findings as well. The association of cutaneous manifestations was, however, not significant with dengue fever and dengue hemorrhagic fever. In dengue shock syndrome, association with cutaneous manifestations was found significant as shown in table 2. Gender was found to have significant association with severity of dengue disease, while age was found to have association with mucosal and cutaneous manifestations of dengue disease as shown in table 3.

In this study, Fever was present in 82 (35.96%) pa-

Table 3: Frequency of clinical features, complications and laboratory abnormalities in patients with dengue viral illness and their association with mucocutaneous manifestations of dengue disease

Clinical signs and symptoms	Present		P-value	
	Number (n=228)	Frequency	Mucosal manifestations	Cutaneous manifestations
Fever	82	35.96%	0.064	0.102
Anorexia	157	68.9%	0.051	0.097
Headache	155	68%	0.002	0.059
Bleeding	41	18%	0.042	0.026
Malaise	141	61.8%	0.155	0.113
Vomiting	133	58.5%	0.073	0.059
Abdominal pain	95	41.7%	0.049	0.095
Epistaxis	27	11.8%	0.031	0.116
Laboratory investigations				
Deranged liver function tests	84	36.8%	0.026	0.059
Deranged renal function tests	6	2.6%	0.028	0.058
Thrombocytopenia	119	83.8%	0.018	0.077
Leukopenia	94	41.3%	0.072	0.092
Deranged PT	11	4.8%	0.040	0.106
Deranged APTT	6	2.6%	0.028	0.058
High hematocrit(>52%)	87	38.15%	0.042	0.002
Complications				
Ascites	21	9.2%	0.054	0.040
Pleural effusion	33	14.4%	0.070	0.055
Abdominal tenderness	39	17.1%	0.051	0.043
Pericarditis	0	0	0	0
Unfavorable outcome (admitted)	67	29.38%	0.009	0.011

tients at the time of examination, anorexia in 157(68.9%), headache in 155 (68%), malaise in 141(61.8%), Vomiting in 133(58.5%), Abdominal pain in 95(41.7%), Bleeding in 41(18%) and Epistaxis was present in 27(11.8%). There was significant association between presence of mucosal manifestations and abdominal pain, epistaxis, headache and bleeding as shown in table 3. Cutaneous manifestations of dengue viral illness was found to have correlation with bleeding only, with p-value of <0.05, as shown in table 3.

Hematocrit was found to be greater than 52% in 87 (38.15%) patients, and was found to have significant correlation with both mucosal and cutaneous manifestations as shown in table 3. 119 (83.8%) patients had

thrombocytopenia, with 116 (50.9%) patients having platelets of less than 50,000/mm3. Leukopenia was found in 94(41.3%) patients, among which 2(0.8%) patients had total leukocyte count of less than 1000/mm3. PT was found deranged in 11 (4.8%) patients while APTT was deranged in 6(2.6%) patients. PT, APTT and platelets count had significant correlation with mucosal manifestations of the disease only as shown in table 3. Liver function tests were above the normal range in 84 (36.8%) cases and renal function tests were abnormal in 6(2.6%) cases, with both of these biochemical abnormalities of the disease showing positive association with mucosal findings of dengue viral illness as shown in table 3.

Complications, like ascites were present in 21 (9.2%) patients, pleural effusion was present in 33 (14.4%) patients, and 39 (17.1%) patients had abdominal tenderness. Pericarditis was not documented in any patient. Presence of ascites and abdominal tenderness had significant association with presence of cutaneous manifestations of dengue disease as shown in table 3.

Among 228 enrolled patients, 151(66.2%) patients were stable at the time of examination and were treated as an outpatient. 67(29.38%) patients were admitted in the hospital, while 10(4.3%) patients presented to dermatology department at the time of discharge. Disease unfavorable outcome like admission for the presence of complications was found to have significant association with cutaneous and mucosal manifestations of dengue disease with p-value of less than 0.05, as shown in table 3.

DISCUSSION

Dengue fever incidence is increasing worldwide and is becoming one of the most challenging problem for public health sectors in tropical and subtropical countries.[19] Dengue has wide range of clinical presentations. It can present as dengue fever (DF), with mild flu-like symptoms, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), however, the published studies about the signs and symptoms and their association with dengue hemorrhagic fever and dengue shock syndrome are inconclusive. [20]

A total of 228 patients were enrolled in the study. Majority of the patients were male, with male to female ratio of 1.17:1. This finding was consistent with Giraldo et al in which male to female ratio of patients with fever was 1.04:1.[12] Mean age of patients was 34.57±14.9 years with maximum patients belonging to the age group between 21-30 years which was consistent with Afzal et al.[21]

Total number of patients with mucosal manifestations was 25.9%. Chadwich et al showed that the mucosal involvement was found in 14% cases. In another study it was estimated to be 15- 30%, in which more mucosal involvement was seen in patients with dengue hemorrhagic fever. In this study, the percentage of patients with dengue hemorrhagic fever, the mucosal involvement was more as compared to dengue fever, which was again consistent with Thomas et al.[22] Total number of patients who presented with cutaneous manifestations was 108(47%), which was consistent again with Thomas et al where cutaneous manifestations was present in 46% cases.[23]

This study showed that the frequency of patients developing mucocuatenous manifestations was increasing with increase in severity of dengue viral illness, being highest for patients with dengue shock syndrome. Zhang et al concluded that there is 14 fold increase in the chance of developing severe dengue disease if patient develop hemorrhagic manifestations like purpura. Zhang et al also proved that cutaneous manifestations can be helpful to predict the progression of dengue viral illness to severe dengue disease. [20] Similarly, in the study, there was significant correlation between cutaneous manifestations and dengue shock syndrome with p-value of <0.05.

The study showed significant correlation of mucosal manifestations with dengue fever and dengue hemorrhagic fever, which was similar to findings in the study where mucocutaneous signs were used as warning signs to help identify patients at risk of shock in dengue viral illness.[24]

In the study, maximum patients had anorexia (68.9%), followed by headache (68%), malaise(61.8), vomiting (58.5%), abdominal pain 41.7%, bleeding (18%) and Epistaxis (11.8%). In Kumar et al, maximum number of patients had malaise (64.6%) followed by headache (47.6%), vomiting (47.6%) and abdominal pain (37.5%) in the same order which was surprisingly consistent with the study. [25]

In this study, 83.8% patients had thrombocytopenia and 41.3% had leukopenia, which was contrary to Saleem et al, in which all the patients with dengue fever presented with thrombocytopenia and leukopenia.[23] Liver function tests were found to be deranged in 5.8% patients among Thai patients in Wichkam et al, while in this study, liver function tests were found deranged in 36.8%.[26] In another study, 28% patients had deranged liver function tests. Hematocrit was abnormal in 38.15% which was consistent with Ali et al in which deranged hematocrit level was a common finding.[27] Only 1.5% patients had renal failure in Kumar et al, which was found in 2.6% in this study.[25]

Among the complications, pleural effusion was present in 30.3% cases in the study while in this study the frequency of pleural effusion in patients with dengue disease was 14.4%.[25]

CONCLUSION

This study highlights that mucosal and cutaneous manifestations has association with the severity of dengue disease, and can be used as one of the warning sign to predict the prognosis of the illness at the time of presentation. The mucocutanous manifestations are also found to be significantly associated with laboratory abnormalities and organ involvement in dengue disease, and so can help to prevent the development of complications by managing these cases vigilantly.

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