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Original Article

Clinical Manifestations of Dengue in a Recent Outbreak in Muzaffarabad

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Abstract:

Objective: Assessment of clinical manifestations of dengue fever in area of Muzaffarabad during first ever outbreak of dengue fever.

Design: Prospective, cross sectional

Material & Methods: Patients who were diagnosed as suffering from dengue fever were included in the study. Clinical manifestations of all patients were recorded in study Performa designed for the study. All routine laboratory investigations including Blood complete examination including platelet counts, total leukocyte count and hematocrit, Blood Sugar, Urea, Creatinine, Serum Electrolytes, LFTS and Urine examination were performed in all patients. The diagnosis of dengue fever was confirmed with serological tests (NS1 Antigen or IgM/IgG Anti-dengue virus antibody titers).

Results: In most patients, typical diagnostic clinical findings on physical examination were high fever (1020 to 1040 F), suffused conjunctivae (45%) and facial flushing (82%) including external ears. The other prominent feature was diffuse erythematous rash (18%) over extremities and truck. The early features at presentation were facial flushing and suffused conjunctivae while rash appeared after 3-4 days of febrile illness in most patients. There was only small percentage (5%) of patients with insignificant cervical lymphadenopathy.

Conclusion: Dengue fever has become an emerging significant health problem in our country. It is imperative to have updated and sound knowledge of clinical manifestations of dengue fever, otherwise; many cases of dengue fever will be misdiagnosed due to inappropriate assessment and misinterpretation of clinical signs and symptoms.

Keywords: Dengue Fever

Introduction

Dengue feveris caused by a virus belonging to family Flaviviradae and is transmitted by *Aedes Aegypti* mosquitoes. There are four different virus serotypes DENV-1, DENV-2,DENV-3 and DENV-4. Infection with any one serotype confers lifelong immunity to that serotype. Secondary infection with any other serotypeor multiple infections with different serotypes results in severe forms of dengue fever (Dengue hemorrhagic fever or Dengue Shock Syndrome).

About 2/3rd of world population living in tropical and sub-tropical regions is at risk for this infectious disease. Dengue fever is endemic in some regions of South East Asia.

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The first reported outbreak of dengue fever in Pakistan was in Karachi in1994[1].There were few but significant outbreaks of dengue fever in other areas of Pakistan during the last 5 years. After a major outbreak of dengue fever in Lahore in 2014, patients have been reported from different areas of Sindh, Punjab and KPK provinces of Pakistan.

There were no reports of dengue cases from Northern Areas and Azad Jammu and Kashmir (AJK). The first ever outbreak of dengue fever in AJK was observed in Muzaffarabad from September to October 2016. A large majority of patients reported and admitted in Abbas institute of Medical Sciences (AIMS) Muzaffarabad, which is a tertiary care, teaching hospital in public sector. A separate dengue ward was established in this hospital due to large influx of patients suffering from dengue fever. The study was conducted in AIMS during outbreak of dengue fever.

Objectives

Assessment of clinical manifestations of dengue fever in area of Muzaffarabad during first ever outbreak of dengue fever.

Material and Methods

All patients who were diagnosed as suffering from dengue fever were included in the study. The provisional diagnosis of dengue fever was clinical which was confirmed by serological testing. A study Performa was designed and used for data collection for the purpose of the study. The following criteria for inclusion and exclusion of patients were used:

Inclusion Criteria

1. Acute febrile illness of less than 1 week duration
2. Serological evidence of dengue fever (Positive one or combination of following serological tests: NS1 Ag, IgM antibodies)

Exclusion Criteria

1. Febrile illness of more than 1 week duration
2. No serological evidence of dengue fever

After clinical evaluation following investigation were performed in all patients. Blood complete examination including platelet counts, total leukocyte count and hematocrit. Those patients presented early in the course of the disease (less than 4 days of febrile illness) NS1 Antigen for dengue virus was performed while IgM/IgG Anti-dengue virus antibody titers was performed after 4 days of illness. The other routine biochemicaltests were Blood Sugar, Urea, Creatinine, Serum Electrolytes, LFTS and Urine examination in all patients. Following operational definitions were used in the study.

Mild Hemorrhage: mild oozing from gums, epistaxis orecchymosis.

Moderate Hemorrhage: Bleeding associated with thrombocytopenia which required platelet or blood transfusion.

Severe Bleeding: Hemorrhage associated with shock, required intensive care and more than one units of blood transfusion.

Mild Thrombocytopenia: platelet counts less than 100 x 10^3/ml

Moderate Thrombocytopenia: platelet count less than 50 x 10^3/ml

Severe Thrombocytopenia: platelet count less than 20 x 10^3/ml

Results

A total number of 376 patients were diagnosed as cases of dengue fever. The typical presentation in most patients was sudden onset of fever (100%), associated with chills and rigors without any prodromal symptoms while in the usual state of health. The mean duration of fever was 4.6 days (table-1). The majority of patients had febrile period of 4 days while minimum duration of illness was 2 days and maximum was 8 days. The fever was associated with myalgias (95%) and weakness (92%). The typical reported symptom of severe backache was absent in most of patients in the study. The other common associated symptoms (table-2) were headache (90%) and retro-orbital pain (57%). Nausea (80%) was the predominant symptom, most often appeared in the early phase of convalescence after defervescense; some patients had nausea and vomiting (57%) while most patients were symptomatic only with nausea. In 52% of patients pruritus was a distressing symptom usually after the end of the febrile illness. Other symptoms during illness were altered taste sensations (92%) sore throat (41%),and loose motions (18%).

Bleeding was infrequent and there was no hemorrhage in 69% of cases. There was mild bleeding in 26% and moderate bleeding in 5% of patients. There was no case of severe bleeding in the cohort of patients included in the study.

In most patients, typical diagnostic clinical findings on physical examination were high fever (102^0 to 104^0 F), suffused conjunctivae (45%) and facial flushing (82%) including external ears. The other prominent feature was diffuse erythematous rash (18%) over extremities and truck. The early features at presentation were facial flushing and suffused conjunctivae while rash appeared after 3-4 days of febrile illness in most patients. There was only small percentage (5%) of patients with insignificant cervical lymphadenopathy. There was no enlargement of liver or spleen and examination of respiratory and cardiovascular systems were also normal in majority of patients.

The majority of affected patients were male (Gender ratio M:F 3:1). Young adults were the most common victims, though a wide range of different ages were involved.

Another significant finding was early leukopenia. In 62% of patients leukocyte count was less than 4 x 10^3/mlon admission while platelet count was still more than 100 x 10^3/ml (table-3).40% patients were still leukopenic when they were discharged from the hospital. The platelet count was less than 150 x 10^3/ml

in 72% on admission and in 82% patient on discharge. The platelet count was less than 100 x 10^3/ml in 37% on admission and in 57% patient on discharge.
In 29 % patients NS1 antigen was positive early in the course of the disease while IgM serology was negative. IgM anti-Dengue antibody test was positive after 6 days of illness in 71 % of patients. Out of these 71% patients who presented late during the illness, in 10 % of cases IgG antibody was positive along with IgM antibody.

Table-1 Duration of Fever

DURATION OF FEBRILE ILLNESS	
Minimum	2 days
Maximum	8 days
Mean	4.6 days
Mode	4 days

Table-2 Sign and symptoms of dengue fever

SYMPTOMS OF DENGUE FEVER	
Sign and symptoms	**Frequency (percentage of patients)**
Fever	100
Chills	95
Myalgias	95
Anorexia	95
Weakness	92
Altered taste sensations	92
Headache	90
Nausea	80
Retro-orbital pain	57
Vomiting	57
Pruritus	52
Sore throat	41
Loose motions	18
SIGNS OF DENGUE FEVER	
Fever	100
Facial flushing	82
Conjunctival injection	45
Rash	18
Lymphadenopathy	5

Table-3 Cell Counts and serological markers

PLATELET COUNT		
On admission	< 100 x 10^3/ml	37%
	< 150 x 10^3/ml	72%
During illness	< 100 x 10^3/ml	66%
	< 150 x 10^3/ml	89%
At Discharge	< 100 x 10^3/ml	56%
	< 150 x 10^3/ml	84%
LEUKOCYTE COUNT		
On admission	< 4 x 10^3/ml	62%
During Illness	< 4 x 10^3/ml	63%
At discharge	< 4 x 10^3/ml	40%
SEROLOGICAL MARKERS		
NS1 Antigen	29%	
IgM Antibody	71%	
IgM Antibody +IgG Antibody	10%	

Discussion

The incidence of Dengue fever has been increasing globally during the last three decades and it has now become a major health problem in most developing countries. There were large out breaks of dengue fever in central and northern areas of Punjab and some area of KPK in Pakistan. The State of Azad Jammu and Kashmir was free of dengue fever as no case was ever reported till August 2016.
The firstever outbreak of dengue fever in this community was recorded from August to October 2016. A large number of patients were reported with high grade fever and 376 patients were admitted in Abbas Institute of Medical Sciences Muzaffarabad with diagnosis of Dengue fever.
There are wide variations in clinical presentation of Dengue virus infection[2,3]. It may be asymptomatic or may cause undifferentiated febrile illness (viralsyndrome), dengue fever (DF), or dengue hemorrhagic fever (DHF) including dengue shock syndrome (DSS).
The most typical finding was the onset of high grade feverwith chills and rigors in previously healthy individuals. The duration of fever was 4-7(mean 4.6) days in 72% of patients. This finding was similar to findingsin other studies[4,5]. The other common associated symptoms were myalgias, weakness and altered taste sensations. “Bone Pains” which lead to the acronym “bone breaking fever” was only reported by few patients. The most ignored symptom which has gained little attention in literature appeared to be altered taste sensations. A large majority of patients (92%) reported this symptom. Nausea was another

prominent symptom (80% of patients) which was not associated with vomiting and appeared after the febrile illness in majority of cases. In more than half of the patients (52%) pruritus was a distressing symptom. This symptom has also been mentioned infrequently in the literature. The treatment with sedative anti histamines was satisfactory in majority of cases. Headache and retro-orbital pain (which was aggravated by movements of the eyeballs in some patients)were also significant symptoms.

The differential diagnosis of dengue fever includes a wide range of acute febrile illnesses according to the presentation of dengue fever (asymptotic, undifferentiated fever or dengue hemorrhagic fever). The undifferentiated dengue fever with non-specific mild symptoms mimics any other acute febrile condition. The typical dengue fever presents with severe headache, retro-orbital eye pain, myalgias, arthralgias, a diffuse erythematous maculo-papular rash, and mild hemorrhagic manifestation[6, 7].

The sudden onset of high grade fever and myalgias, redness of pinna and conjunctival injection observed during the study wereearly differential diagnostic clinical features from other common acute febrile illnesses.

There is wide spectrum of hemorrhagic manifestations in Dengue fever which may include epistaxis, bruises, hematuria, gingival bleeding, hemoptysis, hematemesis, vaginal bleed, hematochezia and sub-conjuctival hemorrhages[8, 9, 10].

In this cohort of patients there was no bleeding in majority(69%) of patients admitted for treatment during the study. There was infrequent, minor and insignificant bleeding in 26% patients. The bleeding was usually mucosal in the form of oozing from the gums or epistaxis. It was intermittent, self-limiting and settled in 1-2 days in all patients without any specific supportive therapy. Only 5% patients had thrombocytopenia and required platelet transfusions. Majority of these patients were given four to six units of platelet transfusions and there was quick recovery and improvement in platelet counts. There was no incident of severe bleeding, shock or need of intensive care treatment.

In a retrospective Cross-Sectional Study conducted by Erum Khan and colleagues in Agha Khan University hospital Karachi "Demographic and Clinical Features of Dengue Fever in Pakistan from 2003–2007" following clinical features were common: nausea (59.3%), rash (36.4%), myalgia (25.8%), hemorrhage (18.2%), diarrhea (16.3%), cough (11.0%) and headache (11.0%)[11].

In other study by Asif Humayun and colleagues "Multiple dengue serotypes and high frequency of dengue hemorrhagic fever at two tertiary care hospitals in Lahore during the 2008 dengue virus outbreak in Punjab, Pakistan" following frequency of common clinical features was found in majority of patients: Fever (100 %), rash (51 %), epistaxis (15 %), bruise (10 %), hematuria (9 %), gingival bleeding (8 %)[12].

These clinical finding were also observed in our study while there were also other significant findings like retro-orbital pain, facial flushing, weakness, altered taste sensations and pruritus.

Another finding in the study was leukopenia, which has received less attention in the literature. In significant majority of patients (62%) initial blood examination showed leukocyte count of less than 4 x 10^3/ml when platelet counts were still more than 100 x 10^3/ml. The initial drop of leukocyte count was followed by drop in platelets. There was steady improvement in leukocyte count during the course of illness in most patients. However, the leukocyte count was less than 4 x 10^3/ml in 40% of patients while they were discharged from the hospital.

In 37% of patients platelet count was less than 100 x 10^3/ml on admission. The platelet counts dropped below this level in 66 % of patients during hospital stay while 56% patients had platelet counts less than 100 x 10^3/ml on discharge.

The clinical suspicion of dengue fever needs confirmation by serologic evidence for dengue virus infection[13]. The serological diagnosis was confirmed with NS1 Antigen, IgM and IgG anti-dengue virus antibodies. NS1 antigen was positive in 29 % of patients who presented early in the course of disease while IgM was negative. About 2/3rd of patients (71%) were diagnosed by IgM antibody tests. Among these (71%), 10 % cases who presented late during the course of illness, IgG anti-dengue antibody was also positive in the serum.

The acute febrile illnesses Malaria, Enteric fever, Upper respiratory tract infections, Gastroenteritis and acute viral hepatitis were important considerations in differential diagnosis in south East Asia and tropical countries[14, 15].The main clinical features predicting the diagnosis of dengue fever during this study were skin rash, facial flushing, conjunctival injection, leukopenia and thrombocytopenia. The clinical manifestations of Chikungunya fever and Zika virus infections overlap with dengue fever[16]. There are no reports of confirmed cases if Zika virus infections from Pakistan but there are recent reports of Chikungunya fever in Karachi

and it will remain an important differential diagnosis of dengue fever.

Dengue fever has been perceived as serious infection in the community and was associated with anxiety and stress. However,there was no mortality and dengue fever remained self-limiting infection during this outbreak

Conclusion

Dengue fever has become an emerging significant health problem in our country. It is imperative to have updated and sound knowledge of clinical manifestations of dengue fever, otherwise; many cases of dengue fever will be misdiagnosed due to inappropriate assessment and misinterpretation of clinical signs and symptoms. The knowledge of clinical manifestations of dengue fever and its differential diagnosis will help in accurate evaluation of patients, will prevent unnecessary hospitalization and also avoid morbidity and mortality associated with wrong treatment.

Recommendations

Large, preferably multicenter trials are recommended for future research with follow up to evaluate long term sequelae of dengue fever.

Conflict of interests: Nil

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References

1. Chan YC, Salahuddin NI, Khan J, Tan HC, Seah CL, Li J, Chow VT. Dengue haemorrhagic fever outbreak in Karachi, Pakistan, 1994. Trans R Soc Trop Med Hyg. 1995;89:619-20
2. Balmaseda, A, Standish, K, Mercado, JC et al. Trends in patterns of dengue transmission over 4 years in a pediatric cohort study in Nicaragua. J Infect Dis. 2010; 201: 5–14
3. Alves, MJ, Fernandes, PL, Amaro, F et al. Clinical presentation and laboratory findings for the first autochthonous cases of dengue fever in Madeira island, Portugal, October 2012. Euro Surveill. 2013;18: 6
4. Mehmood K, Jameel T, Huma F, Tahir M. Incidence Of Dengue Haemorrhagic Fever In Local Population Of Lahore, Pakistan. Biomedica. 2009; (25): 93 – 96
5. Faridi MMA, Aggarwal A, Kumar M, et al. Clinicaland biochemical profile of dengue haemorrhagicfever in children in Delhi. Trop Doct. 2008; 38 (1): 28-30.
6. Centers for Disease Control and Prevention. Clinical guidance: dengue virus. June 2014. http://www.cdc.gov/ (last accessed 16 June 2016).
7. Simmons CP, Farrar JJ, Nguyen VV, et al. Dengue. NEJM.2012;366:1423-1432.
8. World Health Organization, Regional Office for South-East Asia. Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever - revised and expanded edition. 2011. http://www.searo.who.int/ (last accessed 17 June 2016).
9. Halstead SB. Dengue.Lancet. 2007; (370):1644-1652.
10. Gulati S, Maheshwari A. Atypical manifestations of dengue.Trop Med Int Health. 2007; (12):1087-1095.
11. Khan E, Kisat M, Khan N, Nasir A, Ayub S, et alDemographic and Clinical Features of Dengue Fever in Pakistan from 2003–2007: A Retrospective Cross-Sectional Study. PLoS ONE.2010; 5(9): e12505. doi:10.1371/journal.
12. Humayoun M A, Wassem T, Jawa AA, Hashmi M S, AkramT.Multiple dengue serotypes and high frequency of dengue hemorrhagic fever at two tertiary care hospitals in Lahore during the 2008 dengue virusoutbreak in Punjab, Pakistan.International Journal of Infectious Diseases.2010; (14)S: 54–59
13. Lima, MR, Nogueira, RM, Schatzmayr, HG, de Filippis, AM, Limonta, D, and dos Santos, FB. A new approach to dengue fatal cases diagnosis: NS1 antigen capture in tissues. PLoSNegl Trop Dis. 2011;5: e1147
14. Lin CC, Huang YH, Shu PY, et al. Characteristic of dengue disease in Taiwan: 2002-2007. Am J Trop Med Hyg. 2010; 82(4):731-9.
15. Min-Sheng Lee, Kao-Pin Hwang, Tun-Chieh Chen, Po-Lian Lu, Tyen Chen. Clinical characteristics of dengue and dengue hemorrhagic fever in a medicalcenter of southern Taiwan during the 2002 epidemic. J Microbial Immunol Infect 2006; (39): 121-129.
16. Beltrán-Silva SL, et al. Clinical and differential diagnosis: Dengue, chikungunya and Zika. Rev Med Hosp Gen Méx. 2016. http://dx.doi.org/10.1016/j.hgmx.2016.09.011

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