Int.j.pathol.2020;18(2): 53-57

Original Article

Clinicopathological Features of Dengue Fever–a Single Center Study

Aliya Batool[1], Bushra Anwar[2], Amina Rasul[3], Sadaf Khalid[4], Naghmi Asif[5] and Hijab Shah[6].

[1]Bone marrow transplant unit/department of Pathology Islamabad Medical and Dental College, [2] Department of Pathology Fazaia Medical College, [3]Department of Physiology Watim Medical and Dental College. [4] Department of Community Medicine Islamabad Medical and Dental college. [5] Department of Pathology Department of Community Medicine Islamabad Medical and Dental college. [6] Department of Pathology Department of Community Medicine Islamabad Medical and Dental college

ABSTRACT

Background: Dengue viral infection is an important and rapidly spreading mosquito borne infection of humans worldwide.

Objective: To evaluate the clinicopathological features of patients with dengue fever.

Methodology: A descriptive cross sectional study was conducted to evaluate the clinicopathological features of patients with dengue viral infection in Pakistan Atomic Energy Commission General Hospital, Islamabad. A total of 62 patients of Dengue infection were followed and documented in this study. A detailed clinical history, physical examination, and investigations were noted using a structured Performa. Tests included complete blood count (CBC), serum Aminotransferases including Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and dengue serology.

Results: Out of 62 patients with diagnosis of Dengue viral infection through Dengue serology test, 59 cases fulfilled the WHO diagnostic criteria of probable Dengue fever and 3 cases fulfilled the diagnostic criteria of Dengue Hemorrhagic Fever (DHF), including Dengue Shock Syndrome (DSS). Male to female ratio was 5:1 and median age of the patients was 34 years (ranged from 4 to 70 years). Fever was the main symptom (100% of cases), followed by generalized body aches and pains (in 73% of cases), at the time of presentation. Mean hemoglobin level was 14 ± 1.8 gm/dl, while total leukocyte count (TLC) was <4000/µl in 84%, and platelets were <150,000/µl in 100% of the cases. Serum aminotransferases (AST, ALT) were deranged in 70% of the cases.

Conclusion: This study shows slight difference in clinicopathological features of patients with dengue infection compared to those in other parts of the world, which can help the clinicians in early detection of dengue infection and on those basis further workup and management can be planned.

Keywords: Dengue fever, Dengue hemorrhagic fever

Introduction

Dengue infection is an important and rapidly spreading mosquito borne infection of humans worldwide.[1,2] It is caused by an enveloped, positive-strand RNA virus, a member of genus Flavivirus and family Flaviviridae. There are four virus serotypes which are designated as DENV- 1, 2, 3 and 4.[3]

CORRESPONDENCE AUTHOR
Dr Aliya Batool
Consultant Hematologist/Assistant Professor,
Bone Marrow Transplant Unit,
Akbar Niazi Teaching Hospital,
Islamabad Medical & Dental College
aliyabatool@cure2children.org
Contact #: 0301/5140525

Infection with one serotype confers lifelong immunity to patient against that virus serotype but in such patients exposure to other serotypes can lead to severe form of Dengue infection.[4,5] Two species of mosquitoes; Aedes aegypti and Aedes albopictus act as a vector for transmission of virus to human beings. It is endemic in America, South East Asia, and more than hundred countries of Africa and Eastern Mediterranean.[3,4,6] Dengue spreads rapidly and may affect large number of people during an epidemic, resulting in reduced work productivity and most importantly, in loss of lives.

Dengue infection may be asymptomatic or may cause undifferentiated febrile illness (viral syndrome), dengue fever or dengue hemorrhagic fever (DHF) including dengue shock syndrome (DSS). Incubation period of dengue virus is 4 to 6 days (range 3-14 days),

and is followed by 3 phases: febrile, critical, and recovery phase. In febrile phase there is abrupt onset of fever. Fever is associated with malaise, headaches, retro-orbital pain, and myalgia. It is frequently accompanied by sore throat, nausea, vomiting, epigastric pain and diarrhea. The critical phase occurs towards the late febrile phase or around defervescence when a rapid drop in temperature may coincide with increase in capillary permeability in some patients which leads to DHF/DSS, if critical volume of plasma is lost. Otherwise critical phase lasts for 24 to 48 hours and is followed by recovery phase when plasma leakage stops and patient's general well-being improves. Some patients may have classical rash (isles of white in sea of red), minor hemorrhagic phenomena (petechia, purpura, epistaxis) or maculopapular or pruritic rash on body.[7-8]

First outbreak of Dengue Fever was noticed in Pakistan during 1994.[9] A second outbreak occurred in Punjab during 2003, while sporadic cases also occurred in Rawalpindi-Islamabad, Peshawar, Jhelum, Abbottabad, Mangla and Haripur.[10,11] In 2011 another outbreak occurred in Rawalpindi-Islamabad.[12] Since 2011 there has been a rise with an unprecedented intensity and magnitude of Dengue related infections in Pakistan.[13] Therefore, we undertook this prospective study to describe the clinicopathological manifestations of Dengue infection in this region of country.

Methods

This study was conducted at Pakistan Atomic Energy Commission General Hospital, Islamabad. 230 patients, who presented with acute febrile illness during the months of October and November 2013, were evaluated for Dengue fever. Out of these patients, 62 were found to be positive for IgM antibody for Dengue virus by immunochromatograhic (ICT) Dengue IgG/IgM method for the rapid qualitative and differential detection of IgG and IgM antibodies in human serum or plasma. These 62 patients were followed and documented in this study. A detailed clinical history, physical examination, and investigations were noted using a structured performa. Tests included complete blood count (CBC), serum alanine aminotransferases (ALT), aspartate aminotransferase (AST), and Dengue IgM/IgG ICT test. For this purpose, 3 ml of blood in EDTA anticoagulant, 2.8 ml blood in citrate anticoagulant, and 3 ml blood in gel tubes, was collected. Data were recorded and analyzed using statistical software (Specimen is passed entirely in version 11.0). Descriptive statistics were used to describe the symptoms and signs of dengue infection and laboratory investigations. Dengue fever and dengue hemorrhagic fever were diagnosed as per WHO criteria.[14]

Results

During study period 230 patients presented in medical outpatient department with acute febrile illness. Out of these, 62 patients were positive for IgM antibody for dengue virus by solid phase ICT dengue IgG/IgM method. 59 out of these 62 patients fulfilled the WHO criteria of probable diagnosis of dengue fever and 3 cases fulfilled the criteria of dengue hemorrhagic fever including dengue shock syndrome. Male to female ratio was 5:1. The mean age at the time of presentation was 34years (ranged from 4 to 70 years). Fever was the main feature at the time of presentation (100% of cases) which was high grade 101 ± 1°F, associated with chills and rigors. Average duration of fever was 6 ± 4 days. Percentage of occurrence of other significant clinical features is shown in Table 1.

TABLE.1: Frequency of Clinical Features of Patients with Dengue Fever

Sr.#	Clinical Features	No.(%AGE)
1.	Generalized body aches & pain	45 (73)
2.	Vomiting	37 (60)
3.	Rash	25 (40)
4.	Epistaxis	25 (40)
5.	Sore throat	22 (36)
6.	Nausea	20 (31)
7.	Hepatosplenomegaly	15 (24)
8.	Cough	12 (20)
9.	Toxic look	12 (20)
10.	Gum bleed	11 (18)

3/62 patients fell in the category of dengue hemorrhagic fever/dengue shock syndrome; they were shifted to intensive care unit and had 100% mortality. The salient features of these patients are given in Table 2.

TABLE 2: Salient Features of Patients with diagnosis of DHF/DSS

Clinical features	Patient –1	Patient –2	Patient-3
Sex	Male	Male	Female
Age (years)	70	59	60
Fever duration (day/s)	7	1	10
Associated features	Body aches, vomiting, hematemesis , malena, toxic look	Shortness of breath, orthopnea, toxic look	Shortness of breath, toxic look
Premorbid condition	Hypertensiv e, Diabetic	Hypertensi ve, Diabetic	Nil
Cause Of death	Respiratory Failure	Respiratory Failure	Disseminated intravascular coagulation(DIC)
Minimum Platelet Count/µL	14,000	12,000	16,000

Laboratory Findings:

Blood complete picture showed average Hemoglobin of 14gm/dl ± 1.8 SD, with minimal value of 10.2 gm/dl to maximum value of 19 gm/dl. TLC was <4000/µl in 84% of cases with mean value of 1550/µl ± 0.712. Differential Leukocyte showed absolute neutropenia in 52% of cases. Platelet count of <150, 000/µl was seen in 100% of the cases with minimum value of platelets being 5,000/µl and mean value of 62,370/ µl ± 36939, as shown in Figure 1. On peripheral smear examination >40% of patients showed activated/plasmacytoid lymphocytes with features of activation like, abundant basophilic cytoplasm and eccentric nucleus, as shown in one of our patients in Figure 2. Serum aminotransferases were deranged in 70% of the patients with AST having mean value of 155 U/L ± 45 and ALT having mean value of 70U/L ± 55.71.

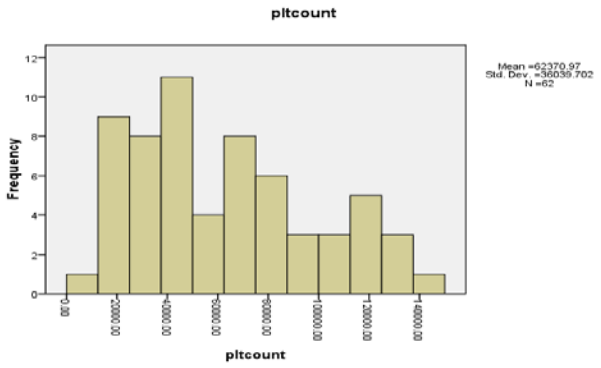

Figure 1: Histogram showing Platelet count of Patients

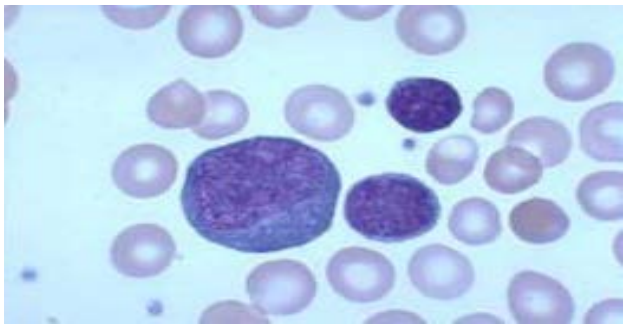

Figure 2: Peripheral Film showing activated Lymphocyte

Discussion

Dengue infection has evolved as a major health problem with variable presentation depending upon the age, immune status and viral strain.[15-17] worldwide dengue infection has been recognized as the disease of children but in this region it is more observed in adult males. In our study male to female ratio was 5:1 which may be due to the fact that males are more exposed to the vector or because they have to report to their medical facility to get medical leave. Typically, this disease presents with sudden onset of fever which is high grade, between 390C to 400C (102.2 to 1040F), however we noticed that although patients presented with sudden onset of fever but it was not that high grade at the time of presentation. It was most likely because of use of the antipyretics or maybe due to less severity of disease. In our study 26.95%of all the cases of acute febrile illness presenting in medical outpatient department were due to Dengue infection. In a study conducted by Karoli R, it is reported that 39% of all cases of acute febrile illness were due to Dengue infection.[18] Another study revealed 97% of patients with febrile illness had dengue infection, however this depends upon the severity of infection in region.[19] WHO has described this as short febrile illness of 2-7 days.[7] In our study the main duration of illness was 6 ± 4 days, but a study in neighboring country showed mean duration of 15 days. The clinical features of dengue fever shown in our study are more or less similar to those shown in a study conducted at Jamshoro tertiary care hospital, Sindh, except that we noticed generalized rash in 40% of our cases as compared to 25% of cases from Jamshoro, while other studies revealed 69.7%, 40% and 56.9%.[18,19,20,21] This difference may be due to the fact that short-lived rash without itching, may go un-noticed in dark skinned Pakistani population, or maybe with passage of time dengue infection has evolved with more serious presentations. We did not perform the Tourniquet test

on our patients which is now recommended by WHO and recent studies have included this test in screening test for dengue.[22] Among atypical presentation of dengue fever we noticed hepatosplenomegaly in 24% of our patients. Although hepatomegaly is among the clinical criteria of Dengue fever, splenomegaly is not generally a feature of it. A recent study from India has reported 50% of cases with hepatomegaly or hepatosplenomegaly in patients with Dengue infection, so it should be kept in mind when evaluating patients suspected of having dengue.[23]

In laboratory features of patients with probable diagnosis of dengue fever the average hemoglobin was 14mg/dl. This is because most of our patients were adult males who have average of hemoglobin levels between 15 to 20 gm/dl. Hemoconcentration (hematocrit >55% from baseline) was not seen in our patients presenting with probable diagnosis of Dengue fever, but a rise in hematocrit was noticed in >20% of patients. Three patients presenting with DHF showed a fall in hematocrit during hospital stay, maybe because of intravenous infusions. Since we observed only three patients presenting with DHF, so further observation is required in this respect. Leucopenia (WBC <4000/µl) was noticed in 84% of patients with probable diagnosis of dengue fever. Differential leukocyte count showed absolute neutropenia in 52% of cases. The leukocyte count drops due to bone marrow suppression in dengue infection. In a study conducted in Jamshoro, 80% of patients had leucopenia, another study reported 78.8%.[20,24] Activated plasmacytoid lymphocytes were also seen in >40% of our patients. These lymphocytes had abundant, deeply basophilic cytoplasm, with condensed chromatin pattern. Thrombocytopenia was the striking feature among our patients with 100% of them having platelet count of less than 150, 000/µl.[3] Our findings are consistent with many studies.[20,24] It can be concluded that thrombocytopenia is a persistent finding in dengue fever and can also be regarded as a strong indicator of dengue fever. Thrombocytopenia is best used as a marker of severe disease particularly when it is < 100,000/µl, or, when there is a rapid drop in platelet count. Its usefulness is as an indicator of prognosis during the disease course, rather than a parameter for therapeutic interventions.[25] Our study shows raised serum aminotransferases in 70% of cases which is consistent with studies showing disproportionate rise in AST (about 2 to 3 times higher) as compared to ALT.21 In our study, 5% of patients which is almost like 2% of patients from a study in Hyderabad, were diagnosed with DHF/DSS with 100% mortality.[20] The poor outcome was due to the fact that they were elderly patients with comorbid conditions, like hypertension and diabetes, in 2 out of 3 cases. More comprehensive study is required for evaluating the risk factors and poor prognostic markers of patients presenting with DHF/DSS.

Conclusion

This study shows slight difference in clinicopathological features of patients with dengue infection compared to those in other parts of the world, which can help the clinicians in early detection of dengue infection and on those basis further workup and management can be planned.

References

1. Acharya KP, Chaulagain B, Acharya N, Shrestha K, Subramanya SH. Establishment and recent surge in spatio-temporal spread of dengue in Nepal. Emerging Microbes & Infections. 2020;9(1):676-679.
2. Kusnoputranto H, Sintorini MM, Utomo SW, Aliyyah N, Sinaga ERK, Pratiwi OA. Dynamic transmission of dengue hemorraghic fever and climate variability patterns in Jakarta. Indian J Public Heal Res Dev. 2019; 10(1):628-632.
3. Rodenhuis-Zybert IA, Wilschut J, Smit JM. Dengue virus life cycle: viral and host factors modulating infectivity. Cell Mol Life Sci. 2010;67(16):2773-2786.
4. Recker M, Blyuss KB, Simmons CP, et al. Immunological serotype interactions and their effect on the epidemiological pattern of dengue. Proc Biol Sci. 2009;276(1667):2541-2548.
5. Katzelnick LC, Fonville JM, Gromowski GD, et al. Dengue viruses cluster antigenically but not as discrete serotypes. Science. 2015;349(6254):1338-1343. 6.
6. Wilson ME, Chen LH. Dengue: update on epidemiology. Curr Infect Dis Rep. 2015;17(1):457.
7. Kuo HJ, Lee IK, Liu JW. Analyses of clinical and laboratory characteristics of dengue adults at their hospital presentations based on the World Health Organization clinical-phase framework: Emphasizing risk of severe dengue in the elderly. J Microbiol Immunol Infect. 2018;51(6):740-748.
8. Hasan S, Jamdar SF, Alalowi M, Al Ageel Al Beaiji SM. Dengue virus: A global human threat: Review of literature. J Int Soc Prev Community Dent. 2016;6(1):1-6. doi:10.4103/2231-0762.175416
9. Ali A, Ahmad H, Idrees M, Zahir F, Ali I. Circulating serotypes of dengue virus and their incursion into non-endemic areas of Pakistan; a serious threat. Virol J. 2016;13(1):144.
10. Ali N, Nadeem A, Anwar M, Tariq WU, Chotani RA. Dengue fever in malaria endemic areas. J Coll Physicians Surg Pak. 2006;16(5):340-342.

11. Zubair M, Ashraf M, Ahsan A, Nazir NU, Hanif H, Khan HA. Dengue viral infections in Pakistan and other Asian countries: a comprehensive review. J Pak Med Assoc. 2016;66(7):884-888.
12. Ali F, Bhatti AB, Satti SA, Binyamin M. Epidemic of Dengue and Dengue Hemorrhagic Fever in Pakistan. Int Jour of Biomed Res [Internet]. 2014Mar.28 [cited 2020Jul.26];5(3):158-60.
13. Haider Z, Ahmad FZ, Mahmood A, et al. Dengue fever in Pakistan: a paradigm shift; changing epidemiology and clinical patterns. Perspect Public Health. 2015;135(6):294-298.
14. Hadinegoro SR. The revised WHO dengue case classification: does the system need to be modified?. Paediatr Int Child Health. 2012;32:33-38.
15. Shah I, Deshpande GC, Tardeja PN. Outbreak of dengue in Mumbai and predictive markers for dengue shock syndrome. J Trop Pediatr. 2004;50(5):301-305.
16. Chadwick D, Arch B, Wilder-Smith A, Paton N. Distinguishing dengue fever from other infections on the basis of simple clinical and laboratory features: application of logistic regression analysis. J Clin Virol. 2006;35(2):147-153.
17. Mustafa MS, Rasotgi V, Jain S, Gupta V. Discovery of fifth serotype of dengue virus (DENV-5): A new public health dilemma indengue control. Med J Armed Forces India. 2015;71(1):67-70.
18. Karoli R, Fatima J, Siddiqi Z, Kazmi KI, Sultania AR. Clinical profile of dengue infection at a teaching hospital in North India. J Infect Dev Ctries. 2012;6(7):551-554.
19. Huy, B. V., Hoa, L., Thuy, D. T., Van Kinh, N., Ngan, T., Duyet, L. V., Hung, N. T., Minh, N., Truong, N. T., & Chau, N. (2019). Epidemiological and Clinical Features of Dengue Infection in Adults in the 2017 Outbreak in Vietnam. BioMed research international, 2019, 3085827. https://doi.org/10.1155/2019/3085827
20. Khan AH, Hayat AS, Masood N, Solangi NM, Shaikh TZ. Frequency and Clinical Presentation of Dengue Fever at Tertiary Care Hospital of Hyderabad/Jamshoro. JLUMHS 2010; 09 :88-94.
21. Mallhi TH, Khan AH, Adnan AS, Sarriff A, Khan YH, Jummaat F. Clinico-laboratory spectrum of dengue viral infection and risk factors associated with dengue hemorrhagic fever: a retrospective study. BMC Infect Dis. 2015;15:399.
22. Mayxay M, Phetsouvanh R, Moore CE, et al. Predictive diagnostic value of the tourniquet test for the diagnosis of dengue infection in adults. Trop Med Int Health. 2011;16(1):127-133.
23. Shukla V, Chandr A. A study of hepatic dysfunction in dengue. J Assoc Physicians India. 2013;61(7):460-461.
24. Chaloemwong J, Tantiworawit A, Rattanathammethee T, et al. Useful clinical features and hematological parameters for the diagnosis of dengue infection in patients with acute febrile illness: a retrospective study. BMC Hematol. 2018;18:20.
25. Chen CY, Lee MY, Lin KD, et al. Diabetes mellitus increases severity of thrombocytopenia in dengue-infected patients. Int J Mol Sci. 2015;16(2):3820-3830

HISTORY	
Date received:	16-06-2020
Date sent for review:	14-10-2020
Date received reviewers comments:	23-10-2020
Date received revised manuscript:	12-11-2020
Date accepted:	26-11-2020

CONTRIBUTION OF AUTHORS	
Author	**Contribution**
Dr. Aliya Batool	A,B,C
Dr. Bushra Anwar	B,C
Dr. Amina Rasul	B,C
Dr. Sadaf Khalid	C
Dr. Naghmi Asif	C
Dr. Hijab Shah	C