

DENGUE FEVER OUTBREAK IN TWIN CITIES; A TERTIARY CARE CENTER EXPERIENCE

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ABSTRACT

Objective: To characterize the clinical presentations and laboratory markers (as disease predictors and markers) and severity of disease in patients admitted with dengue fever.

Study Design: Prospective observational study.

Place and Duration of Study: Department of Infectious Diseases, Pak Emirates Military Hospital Rawalpindi, from May to Oct 2018

Methodology: In our study, we included the patients treated for dengue fever. Data were recorded on predesigned proforma and analyzed using Microsoft excel 365 and Social Package for Statistical Sciences version 23.

Results: A total of 160 patients were included in this study, all were males. All cases were positive for Nonstructural Protein 1 Antigen. Symptoms seen in abundance were fever with rigors, chills, backache, retro-orbital pain, nausea and vomiting. Manual platelet count at admission ranged from $15-396 \times 10^3$ (mean $107.5 \pm 6.8 \times 10^3$). Platelet count on discharge ranged from $102-577 \times 10^3$ (mean $207.9 \pm 95.4 \times 10^3$). A total of 34 (21.25%) patients out of 160 confirmed and admitted dengue fever cases had Dengue Hemorrhagic Fever (Nonstructural Protein 1 Antigen positive, thrombocytopenia and leukopenia) and 2 patient went into dengue shock syndrome. The derangement in alanine aminotransferase and alkaline phosphatase levels were shown in 98 (61.2%) and 62 (31.2%) of patients. All these patients were immunoglobulin M and Nonstructural Protein 1 Antigen positive.

Conclusion: Raised serum alanine aminotransferase and alkaline phosphatase levels along with early positive Nonstructural Protein 1 Antigen is a marker of disease severity.

Keywords: Alanine aminotransferase, Alkaline phosphatase, Dengue fever, Dengue hemorrhagic fever, Liver enzymes, Nonstructural protein 1 antigen.

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INTRODUCTION

Dengue is one of the most widely transmitted vector-borne diseases in the world. It has become a global problem since World war II, effecting over 110 countries. As per estimates, 390 million dengue cases are reported every year with over 24,000 cases resulting in death.^{1,2}

Dengue virus is from the Flavivirus family and belongs to the Flavivirus genus, comprising of predominantly 4 serotypes (i.e. DENV-1, DENV-2, DENV-3 and DENV-4), with the most recent fifth serotype (DENV-5) discovered in October 2013.³ It spreads using the mosquito from the Aedes family as a vector, predominantly the *Aedes aegypti*. However, other mosquitos from the Aedes family have also been noted to act as the vectors which include *Aedes albopictus*, *Aedes polynesiensis* and *Aedes scutellaris*. *Aedes aegypti* is a

daytime feeder with peak number of mosquito bites usually seen at early mornings and dusk. It usually infects individuals below the height of 1000 meters above sea level.³

Dengue typically begins as a sudden-onset high grade bi-modal (saddle back) fever, headache that is characterized by patient's description of pain behind the eyes (retroorbital pain), myalgias, arthralgias, rash and may or may not have thrombocytopenic purpuric rash. The disease is divided into 2 phases i.e. febrile and recovery phase, with another phase 'critical phase' usually seen in children, young adults or debilitated adults. Women who develop dengue while pregnant may be at a greater risk of low birth weight baby and miscarriage.⁴

Dengue can be diagnosed on clinical findings coupled with evidence on laboratory investigations that include detection of Nonstructural Protein 1 (NS1) Antigen, IgM and IgG antibodies to the virus. The infection also causes a transient derangement in platelet number, Liver Functions Tests (LFTs); Alanine

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Aminotransferase (ALT) and Alkaline Phosphatase (ALP) and PT/PTTK.^{5,6}

In Pakistan, serological testing of Anti-Dengue viral antibodies i.e. IgM and IgG, are generally used for confirmation of diagnosis of dengue. However, more accurate tests such as Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and detection of Non-structural Protein-1 (NS-1) have emerged as more reliable methods of early diagnosis of dengue. The lack of resources and infrastructure, however, has limited the use of RT-PCR and NS-1 to only resourceful tertiary care hospitals of Pakistan.⁷

NS-1, is one of the seven non-structural proteins encoded by the single strand RNA genome of the virus. It is an important diagnostic marker for the disease since it can be detected from the first day of onset of infection, whereas, the IgM is detected usually after the 4th day of onset of disease.⁸

Infection with dengue virus can lead to Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS). An individual infected with one dengue serotype becomes immune to re-infection from the same serotype; however, a re-infection with a different serotype generates a strong immune response leading to DHF which can be life threatening.⁹

Keeping in mind the great burden of disease of dengue worldwide and in our country, we conducted a prospective study to characterize the clinical presentations and laboratory markers (as disease predictors and markers) and severity of disease in patients admitted with dengue fever.

METHODOLOGY

This was a prospective observational study carried out in the department of infectious diseases, Pak Emirates Military Hospital (PEMH), Rawalpindi. A total of total of 567 suspected patients of dengue fever were evaluated in outpatient department and 160 confirmed cases of dengue fever who received inpatient care in the study period were included in this study. Universal sampling technique was used for sampling and we included 160 consecutive indoor patients in our study who fulfilled inclusion/exclusion criteria. Study was conducted from May to October 2018 and data was collected for the patients admitted with dengue fever in dengue ward over a period of 6 months during the dengue outbreak in twin cities of Rawalpindi and Islamabad. Data including age, gender, residential area, marital status, presenting

complaints with duration, physical examination findings, results of lab reports, treatment administered, and duration of hospitalization were recorded on pre-designed proforma by a single investigator. The series of investigations were carried out at the time of admission and on each day of hospital stay, which included blood complete picture with manual platelet count, liver function tests (Serum total bilirubin, ALT, ALP), renal function tests (i.e. Serum urea, creatinine, potassium and sodium levels), urine routine examination, ICT Malaria, dengue IgM & IgG serology.

Inclusion Criteria: Patients with clinical examination supporting dengue fever and positive NS1 Antigen test at the time of admission or during the hospital stay, were included in the study.

Exclusion Criteria: Patients with any other known cause of acute febrile illness, hematological disorder, and or chronic liver disease were excluded.

Strict inclusion and exclusion criteria were followed. All patients were admitted in isolated infectious diseases' ward. Those with hemodynamical instability and or any other danger signs were shifted to ward H.D.U or medical ITC for further management. Leucopenia was characterized by white cells count $<4 \times 10^9/L$ & for leukocytosis it was $>10 \times 10^9/L$. Normal reference range for ALT was up to 42 U/L and for ALP, normal reference range is 21-100 IU/L. Acute kidney injury was labelled on the basis of KDIGO guidelines.¹⁰ All the laboratory tests were performed and reported by a single expert pathologist from the same hospital's laboratory.

Written informed consent was taken from all the participants. Ethical approval was sought from the hospital ethical committee and institutional review board of PEMH Rawalpindi.

Data were analyzed using Microsoft excel 365 and Social Package for Statistical Sciences (SPSS) version 23. Descriptive analysis frequencies and percentages were calculated for all the qualitative variables. Mean and standard deviation were calculated for quantitative variables.

RESULTS

A total of 160 patients were included in this study and all were of male gender. At the time of presentation, they were residing in different areas of Rawalpindi and Islamabad city. All patients were diagnosed with dengue fever for the first time in their medical history at this presentation or hospital stay. The age

range was 11-63 years with mean age of 32.9 ± 11.5 years, shown in Table-I.

Mean duration of hospital stay was 5.5 ± 2.1 days (range 2-12 days). Presenting complaints and physical examination findings of the patients are given in Table-II, III with frequencies and percentages.

Table-I: Age distribution.

Age Group	n (%)
11-22 years	22 (13.8)
23-32 years	72 (45)
33-42 years	32 (20)
43-52 years	24 (15)
53-62 years	6 (3.8)
>62 years	4 (2.5)

Table-II: Presenting complaints.

Presenting Complaint	n (%)	
Fever	High Grade	148 (92.5)
	Low Grade	12 (7.5)
Rigors	116 (72.5)	
Chills	128 (80)	
Backache	134 (83.7)	
Generalized Body Aches	84 (52.5)	
Nausea	60 (37.5)	
Vomiting	50 (31.3)	
Retro-Orbital Pain	44 (27.5)	
Cough	14 (8.8)	
Burning Micturition	4 (2.5)	
Sore Throat	32 (20)	

Table-III: Physical examination findings.

Physical Examination	n (%)
Hepatomegaly	4 (2.5)
Splenomegaly	16 (10)
Congested throat	50 (31.3)
Rash	12 (7.5)
Dehydration	36 (22.5)
Conjunctival congestion	8 (5)
Post-auricular lymphadenopathy	6 (3.8)
Tourniquet test	42 (26.2)

Table-IV: Range of platelets on admission and discharge.

Platelets on Admission	
Range ($\times 10^3$)	n (%)
0-50	24 (15)
51-100	60 (37.5)
101-150	52 (32.5)
151-200	14 (8.8)
>200	10 (6.3)
Platelets at Discharge	
Range ($\times 10^3$)	n (%)
101-150	46 (28.7)
151-200	50 (31.3)
201-250	22 (13.8)
251-400	34 (21.3)
>400	8 (5)

Manual platelet count at admission ranged from $15-396 \times 10^3$ while mean was $107.5 \pm 6.8 \times 10^3$. Platelet

count on discharge ranged from $102-577 \times 10^3$ (mean $207.9 \pm 95.4 \times 10^3$). Range of platelets in groups shown in Table-IV.

Mean hematocrit at admission was $42 \pm 3.8\%$ while $41 \pm 4.3\%$ at discharge. Thirty four patients had leucopenia while only 4 had leukocytosis. Acute liver injury was reported as per the operational definition in 28 patients (17.5%). The ALT levels were deranged in 98 (61.2%) patients. In 48 patients ALT was >2 times, >3 times upper reference limit in 18 patients, >4 times in 4, >5 times in 2 and >6 times of upper reference limit in 4 patients. All these cases were positive for IgM serology ALP was deranged in 62 (31%) of the patients.

All patients were NS1 antigen positive while dengue serology has varying results i.e. IgM was positive in 68 (42.5%), IgG positive in 4 (2.5%), Both IgM & IgG positive in 2 (1.3%) and in 86 (53.3%) patients both IgM and IgG were negative. There was no clinical difference in severity of the patients with positive IgG. Four (2.5%) patients had co-infection of malaria in which ICT malaria was positive.

A total of 34 patients out of 160 confirmed DF cases had DHF (NS1 antigen positive, thrombocytopenia and leukopenia) and only two patient went into DSS. No patient in our study population was expired and all were discharged home after indoor management at the hospital.

Table-V: Mean laboratory parameters.

Laboratory Test	Mean Value \pm SD	Range
Hemoglobin g/dl	14.2 ± 1 g/dl	12-16
TLC $10^9/L$	4.9 ± 1.5 $10^9/L$	2-11
ALT U/L	76 ± 8.1 U/L	4-599
ALP IU/L	94 ± 4.3 IU/L	29-229
Total Bilirubin $\mu\text{mol/L}$	10.9 ± 5.1 $\mu\text{mol/L}$	7-41
Serum Urea mmol/L	4.3 ± 1.2 mmol/L	2-7.7
Serum Creatinine $\mu\text{mol/L}$	97 ± 2.1 $\mu\text{mol/L}$	50-148

DISCUSSION

The first documented dengue infections in Pakistan date back to the years 1994-95.¹¹ There have been 10 major dengue outbreaks ever since. In 2011, there were 50,000 reported cases in Lahore alone. It was followed by another major outbreak in KPK two years later in 2013 when 8546 cases were reported. In 2013 district Swat alone had 6000 cases reported out of which 69% were seen to be males.^{12,13} As one of the most common vectorborne diseases of Pakistan, dengue presents as a challenge to our health care setup owing to the lack of diagnostic facilities and due to the varying clinical presentation of disease. Thus, due to

lack of surveillance and paucity of diagnostic facilities many cases of dengue go unreported every year. As per an epidemiological study conducted in the 1960's and 1980's, significant numbers of normal healthy population were found to be positive for dengue specific antibodies.¹⁴

Hepatic involvement in the course of dengue infection is seen in the form of elevated levels of aminotransferases. With more acute and abrupt rise seen in children, immunocompromised and in secondary dengue infections leading to DHF and DSS.^{15,16} Hence, an elevated level of aminotransferases can serve as an indicator of hepatic dysfunction which can be due to hepatotoxic drugs administered during the hospital stay and because of the virus itself.

In the current study, clinical features, diagnostic and laboratory tests of all patients who were admitted in Dengue Ward of PEMH in 2018, were studied. All patients admitted presented with fever as a predominant feature. Other symptoms seen in abundance were rigors, chills, backache, retro-orbital pain, nausea and vomiting. A study conducted in Peshawar (Pakistan) showed almost similar findings of fever, generalized weakness and vomiting being present in 100%, 73% and 43% percent of cases respectively. However, one stark difference was noted as the study showed 70% of cases having hepatomegaly in contrast to our study where only 2.5% of cases had hepatomegaly and 10% had splenomegaly upon presentation to the clinic.¹² The prevalence of disease (38%) predominantly in the age groups between 21-40 years was in correspondence to our study where 45% of patients admitted in dengue ward were in between the ages of 23-32 years.

Patients testing positive for NS1, along with signs and symptoms corresponding with the disease was a part of admission criteria to our dengue ward in PEMH. Dengue serology i.e. IgM and IgG, was also tested in patients presenting to our setup. All patients admitted in our dengue ward were seen to be NS1 positive at time of presentation or during stay. A similar finding was seen in a study undertaken in Malaysia, thus, highlighting the importance of NS1 as a marker of dengue in early phases of disease.¹ A study conducted in Australia on travelers returning from dengue endemic areas showed similar diagnostic results with 33% (42% in our setup) being tested positive for IgM and NS1 both upon presentation. Two percent were seen to be positive for IgG and NS1 (2.5% in our study) whereas, 4% were positive for IgG, IgM and NS1 (1.3% in our study).¹⁷

Other laboratory tests conducted during patient stay in dengue ward showed findings like other studies conducted before. A study in Malaysia shows 80% of patients presenting with a low platelet count, mean WBC count as $3.73 \times 10^3/\mu\text{l}$, mean Hb of 10.8g/dl and mean hematocrit at 38.9%.¹ In our study, however, hematocrit was tested at time of presentation and at time of discharge showing a mean of $42 \pm 3.2\%$ and $41 \pm 4.3\%$ respectively. We also observed a mean TLC count of $4.9 \pm 1.5 \times 10^9/\text{L}$ in our study with a total of 28 (17%) patients showing leucopenia whereas, only a mere 2% showed reactive thrombocytosis. Lei *et al*, also shows majority of Dengue patients having leucopenia at time of presentation or during their stay at the hospital, with a reduction seen in absolute number of monocytes and neutrophils.¹⁸

Dengue patients were also seen to have derangement in renal function tests with the study quoted above showing a derangement in 23% of cases with a mean serum urea levels of 40.2 mg/dl and serum creatinine levels of 1.5 md/dl.¹ In our study, serum urea levels were seen to be fluctuating between 36-139 mg/dl and serum creatinine levels between 50-148 $\mu\text{mol}/\text{L}$, with a mean of $4.3 \pm 1.2 \text{ mmol}/\text{L}$ and $97 \pm 2.1 \mu\text{mol}/\text{L}$ respectively.

A stark difference is again shown in our study when trend in derangement of liver enzymes was studied. The derangement in ALT and ALP levels were shown in 61.2% and 31.2% of patients. All these patients were IgM and NS1 antigen positive. This is contrary to the results shown by Prakash *et al*, where ALT was deranged in 86% and ALP was deranged in 95% patients.¹⁹ Kuo *et al*, reported 90% of ALP derangement in dengue patients.²⁰ We assumed that low threshold for admission of the dengue fever patients for inpatient care is the cause for lesser severity of the disease and minimum possible incidence of complications including acute liver injury. Moreover, NS1 Antigen is a marker which rises early in the disease so it's quite a possibility that these liver enzymes don't usually get deranged in early phase of dengue fever.¹

Strength of this study is that it has given the trends of severity and biochemical markers of the recent dengue outbreak in Rawalpindi and Islamabad.

CONCLUSION

Raised serum ALT and ALP along with early positive NS1 antigen is a marker of disease severity. Low threshold for admissions and inpatient care in a close monitoring environment of such patients can lead to successful outcomes and minimum complications. Careful clinical examination

along with daily laboratory investigations including liver function tests and dengue NS1 antigen is invaluable in diagnosis and appropriate management of this disease.

LIMITATION OF STUDY

It was single center study with small sample size and included the patients taking inpatient care only. The study population in our study was entitled to the treatment and were only residing in one of these cities at the time of presentation and were not necessarily the permanent residents of these cities. Thus, they didn't represent the true population of the twin cities.

Conflict of Interest: None.

Authors' Contribution

TAK: Conception of design, data collection & analysis, writing and editing of manuscript, SN: Conception of design, data collection & analysis, writing and editing of manuscript, MMQ: Data collection & analysis, writing and editing of manuscript, MI: Conception of design, data collection & analysis, writing and editing of manuscript, MS: Data collection & analysis, writing and editing of manuscript.

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