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Clinical, Hematological and Biochemical Manifestations Among Dengue Patients of Lahore Region

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ABSTRACT

The aim of this study was to develop a criteria on the basis of impact of dengue infection on various clinical, hematological and biochemical parameters in dengue patients for the quick diagnosis and detection of dengue stage for the proper treatment of infection. This cross-sectional study was conducted at Institute of Biochemistry and Biotechnology, University of Veterinary and Animal Sciences, Lahore and Jinnah Hospital Lahore (JHL) from January to December 2013. Total 345 clinically suspected patients reporting to JHL were serologically diagnosed for dengue specific antigen and antibodies. In this study 20 patients of febrile illness other than Dengue (OFI), were selected as control. The frequency of various clinical features and alterations in hematological and biochemical parameters were assessed for both cases and controls. Total 108 (31.3%) patients were serologically confirmed for dengue infection. Seropositive 108 cases were classified as classical DF 81(75%), DHF 22(20.4%) and DSS 5 (4.6%). Mean age was 32.3±12.4 years, which comprises of male 80 (74%) and female 28 (25.9%). Common symptoms for dengue were fever and headache (100%), arthralgia (82%), myalgia (80.5%), retro-orbital pain (68.5%), bleeding tendencies (38%), rash (51%) and vomiting (48%). Thrombocytopenia (90%), leukopenia (62.5%), elevated transaminases (ALT 56.5% and AST 70.5%), hyponatremia (51.8%), hypokalemia (40.7%) and hypocalcemia (81.4%) was recorded among dengue patient. It was concluded that bleeding tendencies, retro-orbital pain, rash and vomiting were more frequent in DHF and DSS cases. Thrombocytopenia, leukopenia, deranged hematocrit, raised transaminases, urea and creatinine levels and decreased serum levels of albumin, cholesterol, sodium, potassium and calcium were commonly associated with severe form of disease.

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Dengue fever, Dengue hemorrhagic fever, Dengue shock syndrome, Clinical manifestations, Hematology

INTRODUCTION

Dengue is a global threat as it is expanding in almost 125 countries located in tropical and subtropical regions of the world where climatic condition and rapid growth of population favors their expansion (Ali *et al*., 2021; Asghar *et al*., 2021). Dengue is caused by the five circulating serotypes of dengue virus namely DENV-1, DENV-2, DENV-3, DENV-4, DENV-5 that are transmitted through the bite of female mosquitoes of genus Aedes, mainly *Aedes aegypti* and *Aedes albopictus* species (Mustafa *et al*., 2015; Ahmad *et al*., 2017; Ayyadevara, 2021) According to the severity of disease dengue infection has been classified into three groups i.e., classic dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Ayyadevara, 2021; Wang *et al*., 2022).

Pakistan has been suffering from dengue out breaks for decades and increase in dengue cases at alarming rate has been reported by Pakistani officials. Total dengue cases 48,906 with 183 deaths from January 01 to November 25, 2021 and total 47,120, cases of dengue in 2020 including 75 deaths were reported in Pakistan (Islam *et al*., 2022). According to National institute of health (NIH) Islamabad, there were 53,498 cases in 2019, more than 3200 cases in 2018, 22,938 fever cases in 2017. During year 2013 a major dengue outbreak adversely affected Khyber Pakhtunkhwa province and total 8546 dengue cases with 33 deaths were reported from Pakistan (Fatima *et al*., 2016; Shahid *et*

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al., 2017). During the period of 2010 and 2011, Pakistan faced adverse floods that had not only destroyed property and lives of the people but also increased breeding sites for dengue virus. As a result, worst outbreaks with 22,562 dengue cases and 363 deaths have been reported out of which (17493) cases with 290 deaths were reported from Lahore, Punjab alone (Rasheed *et al*., 2013). Keeping in view the severity of dengue infection in Lahore during the year 2011, and its consistent presence in other parts of the country, comprehensive study was conducted in one of the major tertiary level hospital to monitor dengue infection effects on various clinical, hematological and biochemical parameters in three different forms of dengue, including DF, DHF, and DSS. Significant alterations in hematological and biochemical parameters can be used as predictor to severity of disease and to monitor the patient condition.

MATERIALS AND METHODS

This study was conducted at Institute of Biochemistry and Biotechnology, University of Veterinary and Animal Sciences, Lahore and Jinnah Hospital Lahore. Blood samples from 345 suspected dengue patients were collected, who were reported during a period of one year from January to December 2013. Blood samples of 20 individuals with febrile illness other than dengue (OFI) were taken as control.

Inclusion criteria

According to WHO criteria suspected dengue patients with more than two days of acute febrile illness with any two or more of the symptoms including headache, retro orbital pain, myalgia, rash, bleeding manifestation, leucopenia, were included in the current study (WHO, 1997, 2012; Gregory *et al*., 2010).

Exclusion criteria

Patients with identified bacterial infection, any other specified chronic infection and only IgG positive were not included in the study.

Data collection technique

The detailed information including name, age, gender, days of fever, previous history of dengue and the location for all 345 suspected patients and 20 control samples was recorded. Consent from all the patients and control was taken to be the part of this study. Blood sample (10 mL) from each individual was taken and divided into three vacutainers for hematological, biochemical and diagnostic studies. Blood samples for diagnostic and biochemical studies were centrifuged and serums were stored at 4°C for further analysis within a week. Hematological parameters were performed on the same day.

Dengue infection identification

Patients' blood were subjected to dengue test as non-structural protein 1 (NS1) antigen and dengue specific IgG/IgM antibodies *in vitro* by standard laboratory procedure as Immunochromatographic test (ICT) using commercially available SD BIOLINE Dengue Duo rapid test dengue diagnostic kit (Standard Diagnostic Inc; Seoul, Korea) and by Enzyme linked immunosorbent assay (ELISA) using commercially available kits for NS1 antigen, IgM and IgG antibodies (Diagnostic Automation/ Cortez Diagnostics Inc, California, USA). All samples were analyzed according to manufacturer protocol.

Blood samples confirmed serologically positive by both ICT and ELISA methods were divided into three groups DF, DHF and DSS revealing severity of disease as per WHO criteria and were included for further evaluation (WHO, 1997).

Hematological parameters

Complete blood count including hemoglobin (HB), hematocrit (HCT) or packed cell volume (PCV), total leucocyte count (TLC) and platelet count (PT) in blood samples of dengue patients was performed on Hematology analyzer Sysmex KX-21 (Sysmex America Inc, Lincolnshire, Illinois, USA).

Biochemical parameters

Biochemical markers determined for liver function test (LFT) were, total protein (TP), albumin, bilirubin (Bili), alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP). Parameters included in renal function tests (RFT) were urea, creatinine (Crea) and uric acid (UA) while parameters estimated for lipid profile were cholesterol, triglyceride (TG), high density lipoprotein-cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c) and very low-density lipoprotein cholesterol (VLDL-c). For heart profile, cardiac enzymes including creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and creatine kinase-MB (CK-MB) were estimated. Serum electrolytes including calcium, phosphorus, sodium and potassium were also assessed. Serum calcium and phosphorus were estimated by using AU kits (Beckman Coulter Inc. Brea California, USA) while serum sodium and potassium electrolyte were analyzed by ion selective electrode method using the EasyLyte analyzer (Medica Corporation, Bedford, USA). Biochemical parameters were estimated on automatic chemistry analyzer Beckman Coulter AU 480 by standard AU reagent (Beckman Coulter Inc. Brea California, USA) according to the manufacturer instructions.

Statistical analysis

The SPSS software version 21 was used for statistical analysis. Continuous variables were expressed as mean ± SD and categorical variables were expressed as frequency and percentages. Association between clinical features and severity of dengue fever was analyzed by Chi-square and Fisher's Test. ANOVA was used to determine the relationship of hematological and biochemical parameters with severity of dengue fever. P-value $P<0.05$ is considered to be statistically significant.

RESULTS

Dengue cases were not reported through the months of January to June. Dengue frequency was seen on increase through the months of July to September and then declined through months of October to December. Most of the cases 74 (68.5%) were reported from the month of July to September. Figure 1 shows the number of dengue cases from June to December 2013.

Blood samples of 345 suspected dengue patients and 20 as control were subjected to serological testing. 114 (33%) samples were confirmed positive by ICT method while 110 (31.8%) were found to be positive by ELISA. Total 108 (31.3%) samples confirmed positive by both the ICT and ELISA techniques were utilized for further studies.

The mean age of the patients in this study was 32 years with a range of 11-70 years. The maximum number of patients 55 (50.9%) belonged to age 11-30 years. Most dengue patients were 44(40.7%) belongs to age 31-50 years while least patients were 9(8.3%), with age 51-70 years. Out of 108 serologically positive patient 28 (25.9%) were females and 80 (74%) were male. Among the positive cases 81 (75%) patients were classified as DF, 22 (20.4%) patients as DHF and 5 (4.6%) as DSS.

Clinical parameters

Patients were presented with different clinical features such as fever, headache, chills, arthralgia, myalgia, vomiting, diarrhea, and maculopapular rash. Analysis of symptoms demonstrated that all patients presented with fever and headache during their first hospital visit. Myalgia, arthralgia, retro-orbital pain, chills, abdominal pain, rash, vomiting and bleeding manifestation were found to be significantly more frequent in patients of DHF and DSS (Table I).

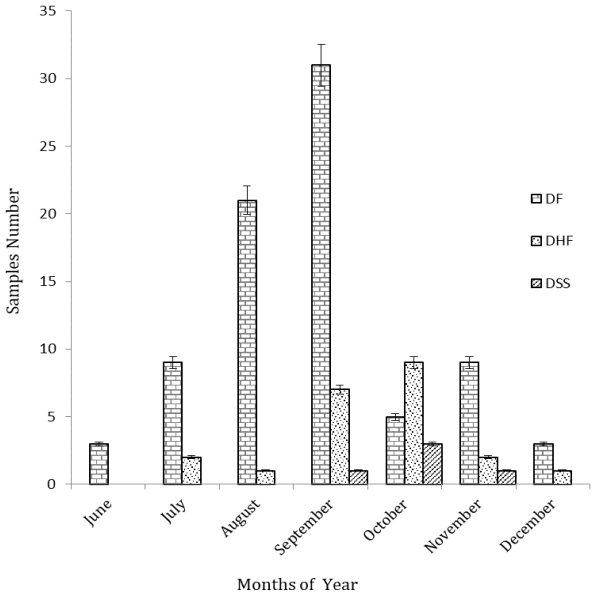

Fig. 1. Number of dengue cases during the months of June, to December, 2013.

Table I. Comparison of clinical parameters in patients with dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Symptoms	Total dengue positive patients number (%)	DF number (%)	DHF number (%)	DSS number (%)	Control number (%)	P value
Fever	108 (100)	81 (100)	22 (100)	5 (100)	20 (100)	-
Myalgia	87 (80.5)	64(79.0)	19 (86.4)	4 (80)	9 (45)	.008
Headache	108 (100)	81 (100)	22 (100)	5 (100)	20(100)	-
Chills	84 (77.7)	63 (77.7)	16 (72.7)	5 (100)	11 (55)	.104
Retro orbital pain	74 (68.5)	51 (63)	18 (81.8)	5 (100)	4 (21.1)	.000
Abdominal pain	44(40.7)	21 (25.9)	19 (86.3)	4 (80)	4 (20)	.000
Arthralgia	89 (82)	65 (80.2)	20 (90.9)	4 (80)	6 (30)	.000
Hemorrhagic manifestations	42 (38)	16 (19.8)	21 (95.5)	5(100)	0 (0)	.000
Rash	56 (51)	35 (43.2)	17 (77.3)	5 (100)	0 (0)	.000
Vomiting	52 (48)	31 (38.3)	17 (77.3)	4 (80)	6 (30)	.000

Table II. Variation in hematological parameters in patients with dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Parameters	DF (n=81)	DHF (n-22)	DSS (=5)	Control (n-20)	p- value
Hemoglobin (g/dL)	12.7± 1.9	13.03± 2.1	14.3±0.54	13.4± 1.55	0.119
Hematocrit (%)	42.2±5.77	43.9±6.53	46.4±5.62	35.29±5.88	0.000
Total leucocyte (cells/µL)	3248±762	3097±895	2660±594	7024±1409	0.000
Platelet count (cells/µL)	73741±19203	33227±11803	19560±3642	327544±67556	0.000

Table III. Variation in biochemical parameters in patients with dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Biomarkers	Reference range	DF (n=81)	DHF (n=22)	DSS (n=5)	Control (n=20)	P
Liver profile						
AST(U/L)	11-50	94.3±95.0	145±128	301±109	31.7±10.2	0.00
ALT(U/L)	11-50	73.6 ±78.8	104 ±78.3	155.4±94.8	26.5±11.6	0.00
ALP(U/L)	Up-to 300	141±65.8	181.4±75.3	192.2±61.8	159.6±70.2	0.72
Bilirubin(mg/dL)	0.4-1.2	0.96±0.82	1.37±.83	1.80±0.1.3	0.64±0.20	0.00
Albumin (g/dL)	4.5-5.2	3.6±0.59	3.1±0.49	2.6±0.5	4.4±0.79	0.00
Protein (g/dL)	6.6-8.5	6.8±0.96	6.1±0.74	5.7±0.63	7.7±0.64	0.00
Renal profile						
Urea (mg/dL)	11-43	24.4±6.4	47±41.7	71.0±45	23.2±5.9	0.00
Creatinine (mg/dL)	0.7-1.1	0.64±0.22	1.03±1.18	1.9±1.21	0.68±0.15	0.00
Uric Acid (mg/dL)	3.5 -7.2	4.5±0.92	4.1±1.4	4.0±0.66	4.1±0.99	2.08
Lipid profile						
Cholesterol (mg/dL)	180-200	140±34.7	121.9± 28	112± 5.7	199 ±31.5	0.00
Triglycerides (mg/dL)	< 150	213±54.8	235±75.2	259± 59.3	193 ±60.5	0.03
HDL-c (mg/dL)	40-60	25±6.5	23.9±4.1	19.8± 0.83	36 ±6.4	0.00
LDL-c (mg/dL)	100-129	92.8±27	84.3± 22.6	80.6± 2.87	12 9±28.6	0.00
VLDL-c (mg/dL)	<35	41.6±12.2	46.6±15.1	51.6±11.8	38.6±12.0	0.25
Cardiac profile						
CPK IU/L	24-171	225±199	274±89.5	378.6±200	137±38.4	.148
CK-MB IU/L	Up-to 25	36±4.7	46±26.8	78±45.1	14±5.5	.029
LDH IU/L	208-378	341±134	467±149	504±83.1	265±106.7	.007
Electrolyte						
Sodium (mmol/L)	135-147	132±6.0	128.1±3.8	124.8±4.0	135.1±6.1	.00
Potassium (mmol/L)	3.5-5.2	4.6±1.28	3.0±0.35	2.66±0.26	4.66±0.79	.00
Calcium (mg/dL)	8.8-10.5	8.5±0.74	7.38±.70	6.8±0.39	9.0±0.92	.00
Phosphorus (mg/dL)	2.4 4.5	3.81±2.3	3.34±1.2	2.8±0.60	3.84±0.53	0.57

AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; HDL-c, high density lipoprotein-cholesterol; LDL-c, low density lipoprotein-cholesterol; VLDL-c, very low-density lipoprotein cholesterol; CK, creatine phosphokinase; CK-MB, creatine kinase-MB; LDH, lactate dehydrogenase.

Hematological parameters

Hematocrit was raised in dengue patients as compared to controls. Highest mean HCT level was reported in DSS patients. In this study raised HCT level (>45%) was observed in 34 (42.5%) male and (>40%) was seen in 9 (32.I%) female. Low levels of HCT (<40%) was observed in 24 males and (<35%) was seen in 15 (53.5%) female. Leukopenia (leucocyte count< 4000 cells/µL) and thrombocytopenia (Platelet count<100000 cells/µL) were the most commonly observed hematological feature in dengue patients. Severe thrombocytopenia (Platelet count <25000 cells/µL) was reported in 4(18.1%) patients of DHF and 4(80 %) DSS group, while mild thrombocytopenia (platelet count >50000 cells/µL) was present in 70(86.4%) of the DF patients. Table II clearly demonstrates the variation in hematological parameters in

DF, DHF and DSS patients.

Biochemical parameters

The levels of transaminases (AST and ALT) were significantly high, while serum levels of TP and albumin were significantly low among dengue groups. The increased AST/ALT ratio in these studies differentiated dengue infection from other acute hepatitis caused by hepatitis A, B and C viruses. Urea and creatinine levels were increased with the increase in severity of the disease (Table III). Cholesterol, HDL-c and LDL-c levels were significantly low as compared to control. These levels were gradually decreased with the severity of the disease. Contradictory to this, elevated levels of triglycerides were recorded, which were increased with the severity of the disease. Cardiac enzymes (CK, CK-MB and LDH) levels were raised in dengue groups as compared to control due to myocardial cell injury caused by dengue infection. The estimated levels of Na^{+}, K^{+}, and Ca^{++} were significantly decreased in DHF and DSS patients as compared to control patients (Table III).

DISCUSSION

The study was planned to assess the clinical manifestations and changes in hematological and biochemical parameters in connection to severity of dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) among dengue patients of Lahore region. Number of dengue cases was higher in teenagers and young people (11-50 years) age as compared to elderly people (50-70 years) age. High frequency of disease in young group was due to large population size in this age category and more exposure to mosquitoes due their outdoor activities. Other studies on dengue patients also supported that the intensity of dengue was high in young age group as compared to the old age group (Fatima *et al*., 2016; Khan *et al*., 2018). Higher number of patients was observed in July to October months of year. Occurrence of dengue was associated to the monsoon and post moon soon season due to increase in breeding sites of mosquitoes and this finding was in accordance to other studies (Fatima *et al*., 2016; Ahmad *et al*., 2017).

This study explored the higher level dengue infection in male population as compared to female population. The male population in Pakistan typically spends more time outdoors for employment and therefore more exposed to mosquitoes than female. Moreover, females in Pakistan cover themselves with clothes more completely as compared to North America and Vietnam. Findings of this study was supported by (Gandhi and Shetty, 2013; Asghar *et al*., 2021). However, in studies from North America and Vietnam equal populations of male and female or more female than male was reported to be affected by dengue infection (Gunther *et al*., 2009). In this study 75 % cases were presented as DF, while incidences of classic DF 70% were found in other studies (Karoli *et al*., 2012; Ayyadevara and Nikhat, 2020).

The most common clinical features observed in this study were fever, headache, myalgia, and arthralgia and these findings were in consistence with other studies (Yadav, 2018; Asghar *et al*., 2021; Wang *et al*., 2022). Clinical feature such as persistent vomiting, bleeding, severe abdominal pain and petechiae were associated with severe form of dengue as DHF and DSS. The above findings are being supported by previous work (Jain *et al*., 2013).

The rise in hematocrit level in dengue patients was associated to plasma leakage due to increase in vascular permeability. A 20% rise in hematocrit concentration was documented previously as cut off for diagnosis of DHF (Srikiatkhachorn, 2009), but in this study, elevation in hematocrit levels was less than the expected rise. Similar findings have been reported previously with lesser rise in hematocrit level (Karoli *et al*., 2012; Jain *et al*., 2013). There is need to develop new recommendation for hematocrit rise and its use in dengue diagnosis. Most frequently observed leukopenia and thrombocytopenia in dengue patients was due to bone marrow suppression and binding of dengue antigens to platelets (Jakribettu *et al*., 2015). There was significant variation in total leucocyte count and Platelet count regarding severity of dengue infection.

Hematological abnormalities in the form of thrombocytopenia, was found in 90% of the patients. These findings are in agreement with 80 and 92% as reported previously (Yadav, 2018; Asghar *et al*., 2021). Another group of scientists from India associated the thrombocytopenia, leucopenia and hemoconcentration with dengue infection (Nandwani *et al*., 2021).

This study demonstrated the elevated transaminases in 94% of the dengue patients. These results are in agreement with the previous reports from Singapore, Vietnam and India which showed 86, 97 and 97.5% dengue patients with elevated transaminases levels (Chhina *et al*., 2008; Trung *et al*., 2010; Lee *et al*., 2012). A study from Brazil had reported elevated transaminases level in 64% that is relatively low (Souza *et al*., 2004). The serum AST/ ALT levels in dengue infection tend to be higher and this differ from the pattern in viral hepatitis. Hyperbilirubinemia was found to be quite common in DSS patients and these results were consistent with the reports from India (Chhina *et al*., 2008; Ayyadevara and Nikhat, 2020). Serum albumin levels were low in dengue patients and decrease

in albumin level was consistent with increase in severity of disease and least level was recorded in DSS. This decrease in albumin level can be correlated with the increased plasma leakage and increased vascular permeability in DSS. Decreased serum albumin level was consistent with other studies from India (Ayyadevara and Nikhat, 2020).

Renal impairment was associated to severity of disease as raised urea and creatinine levels were recorded in 18% DHF and 60% DSS. These results are in agreement with previous reports (Lee *et al*., 2006; Vachvanichsanong and McNeil, 2015; Ayyadevara and Nikhat, 2020).

Lipid profile analysis demonstrated decrease in total cholesterol, HDL-c and LDL-c and elevated triglyceride and VLDL-c level in DF, DHF and DSS. The decrease in cholesterol, HDL-c and LDL-c might be correlated to the cytokines production and its interlinkage with lipid metabolism. Dengue induced cytokines (TNF-α, IL-1) decrease cholesterol and HDL production by affecting the enzymes involved in their production. Increased levels of triglycerides are the result of increased lipolysis and de novo fatty acid synthesis in liver due to enhanced activity of specific enzyme. Finding of this study were in line with the result of previous studies (Gorp *et al*., 2002; Ayyadevara and Nikhat, 2020).

Low levels of sodium, potassium and calcium were recorded in DHF and DSS as compared to DF and control. This situation might be due to plasma leakage in severe dengue condition. These results are being supported by previous reports (Mekmullica *et al*., 2005; Lumpaopong *et al*., 2010).

CONCLUSION

On the basis of above findings, it can be concluded that the hematological parameters, thrombocytopenia, leukopenia and raised hemoconcentration were relevant to severity of the disease. Clinical recovery monitoring is dependent on hematological parameters. The hematological profile can be used as screening tool to assess early therapeutic response. This study suggested that some biochemical alterations as raised transaminases, urea, creatinine and triglyceride levels and decreased serum levels of albumin, sodium, potassium, calcium, cholesterol, HDL and LDL can be used as predictor of dengue complication. Patients with compromised parameters should be treated with extra care to avoid complication.

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IRB approval

This study was approved by the Advanced Studies Research Board of University of Veterinary and Animal Sciences, Lahore, Punjab, Pakistan.

Ethical statement

The research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements.

Statement of conflict of interest

The authors have declared no conflict of interest.

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