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Haematological and Clinical Findings Especially Third Space Fluid Accumulation Observed in Major Dengue Outbreaks of Pakistan

Hira Babar, Zunairah Mughal, Sobia Ashraf, Sindhu Rehman, Arsala Rashid, Samina Qamar
Department of Pathology, King Edward Medical University, Lahore.

ABSTRACT

Introduction: Dengue fever is a mosquito-borne disease caused by the bite of female aedes mosquito. It is a flavivirus and belongs to the family of arboviruses. According to WHO estimate about 50 million people are afflicted with dengue each year. The outbreak of dengue fever has serious implications on public health and should be dealt efficiently.
Aims & Objectives: The purpose of this study was to observe the haematological parameters, frequency of third space fluid accumulation (TSFA) and its association with these parameters so that this fatal complication can be detected early to improve patient management.
Place and duration of study: It was a cross-sectional study conducted in Haematology Department KEMU, in collaboration with Dengue Unit, Mayo Hospital Lahore between December 2021 to February 2022.
Material & Methods: This was a cross-sectional study conducted at Hematology Department King Edward Medical University Lahore. The patients of dengue fever diagnosed on serology were included in our study. The complete blood counts, ALT and third space fluid accumulation on radiological examination was noted in all patients. The data was analyzed using SPSS version 20 and association among the variables was seen.
Results: Total 200 patients were included with mean age 35.03 ± 15 years and male to female ratio of 2.07:1. TSFA was seen in (60) 30% patients, and showed positive correlation with increased hematocrit, low platelet count, increased lymphocyte, and monocyte count. The results were compared with previous outbreaks in 2008 and 2012.
Conclusion: Haematological parameters are helpful in disease monitoring and predicting the development of complications especially third space fluid accumulation which has high mortality rate. Early follow-up of haematological findings with clinical correlation can help to prevent the disease complications and increase overall survival.

Keywords: Dengue, Dengue fever, TSFA, platelets, morbidity, HCT

INTRODUCTION

Dengue fever is a mosquito borne disease caused by bite female aedes mosquito. It is a flavivirus and belongs to family of arbovirus. According to WHO estimate about 50 million people are affected from dengue each year. Out of these 0.5 million are diagnosed each year resulting in 24000 deaths per annum approximately. It is mainly endemic in the regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia, and the Western Pacific regions and the Caribbean.[1]

There are four serological types of dengue virus which are DEN-1,2,3 and 4. A person can be infected 4 times with this virus and each one offers long life immunity against its own serotype. Subsequent infection presents as severe disease and carries poor prognosis.[2, 3]

This is triphasic virus beginning from stage of fever, which is high grade associated with rigors and chills, myalgias, vomiting, rash ecchymoses at pressure site and bleeding from any site of body. The biochemical and haematological parameters are important in the diagnosis of the virus. NS1 IGM by ELISA is by far the most reliable parameter. In addition, there are marked haematological manifestations such as thrombocytopenia, leukocytosis, anemia and raised hematocrit. The biochemical findings include a rise in ALT level.[4,5] Third space fluid accumulation is another important finding in the critical phase called dengue haemorrhagic fever. There is extravasation of fluid into the third space finally leading to a phase of shock manifesting as bleeding, ascitic or pleural effusion, respiratory distress and finally multi organ failure.[6]

The leading contributory factors of this virus spread are rapid urbanization of population, poor sanitation facilities leading to the availability of breeding areas to the virus, lack of vector control and climate changes since the hot humid temperature favor the growth of mosquito larva.[7] Currently in 2021 dengue fever outbreaks, a continuous rise in patients

suffering from the disease was seen. Till mid-November, 2,36,773 cases of dengue fever had been detected all over the country, with highest mortality rates in Lahore according to WHO. The outbreak of dengue fever has serious implications on public health and should be dealt proficiently.[8]

The purpose of this study was to observe the haematological parameters, frequency of third space fluid accumulation and its association with these parameters so that this fatal complication can be detected early to improve patient management. Also, we compared these findings with the previous outbreaks of the disease in Pakistan to see the evolution and virulence of the disease in the past years.

MATERIAL AND METHODS

This was a cross-sectional study carried out in Hematology Department of KEMU, in collaboration with the Dengue Unit Mayo Hospital Lahore from December 2021 to February 2022. The patients who presented in the ward after testing positive for IgM antibody by ELISA method were chosen whereas those who had fever of unknown cause, those with IgG positive at the time of presentation and those with definite focus of infection based on investigation were excluded from the study. The personal profile of the patient was noted with detailed history and physical examination. All the baseline investigations such as CBC, LFTS, RFTS and urine complete were done as per protocol. The different parameters of complete blood picture such as haematocrit, WBC count, lymphocyte count, monocyte count and platelet count were noted. Last wave of dengue also showed derangement of liver enzymes especially alkaline transferase (ALT). Its value was also noted. Next the patient's clinical condition at the time of presentation was assessed to look for third space fluid accumulation (TSFA). The extra vascular fluid accumulation results in many clinical presentations such as ascites, generalized body edema and pulmonary edema. All such clinical manifestations were recorded. The data was recorded, and results were analyzed in SPSS v20. Descriptive variables were analyzed as mean and standard deviation like age, CBCs and LFTs. Categorical variables were described in terms of percentage and frequencies. Chi-square test was applied to determine the relationship amongst the variables considering a pvalue ≤ 0.05 as significant.

RESULTS

Our study included total 200 patients confirmed by dengue specific IgM, out of which out of which 135 (67.5%) males and 65 (32.5%) were females with a male to female ratio of 2.07:1. The mean age of all the patients was 35.03 ±SD 15 years. The patients presented to us with fever (97%), anorexia (72%), rash (38%), myalgias (68.5%) and pruritis (28.8%). The haematological parameters obtained from all the patients are described in Table-1.

Sr. #	Test	Min.	Max.	Mean	Standard Deviation
01	Age (years)	10.0	82.00	35.1	15.01
02	Platelet ($x10^3uL$)	4.00	545.0	81.67	95.24
03	TLC ($x10^3uL$)	1.30	40.00	6.53	4.21
04	Lympho's Count ($x10^3uL$)	3.00	67.00	37.65	15.35
05	Mono's Count ($x10^3uL$)	1.00	34.00	11.01	6.30
06	ALT (U/L)	5.00	1277.0	170.2	244.50
07	Hematocrit (%)	11.0	63.00	42.80	7.40

Table-1: The haematological parameters of patients presented with dengue.

The patients were followed for the development of third space fluid accumulation by radiological assessment. The main findings included were ascites, gall bladder edema, pleural and peritoneal effusions. Out of 200 patients, 60 (30%) patients showed the presence of TSFA. The haematological parameters were compared between patients with and without TSFA and correlation was established.

As shown in Table-2, TSFA presented positive association with low platelet count, increased lymphocyte and monocyte count and raised hematocrit.

The results of our study were compared with the previous studies conducted in Pakistan in the Dengue outbreaks in 2008 and 2012 and the results are shown in Table-3.

TSFA		AGE	PLTS *	TLC *	LYM *	MON *	HEM-CR*	ALT *
No	* Mean	35.4	105.6	6.90	36.09	10.4	41.6	152.4
	*±SD	15.5	99.8	3.71	15.9	6.12	7.24	235.7
YES	Mean	34.3	25.8	5.66	41.3	12.5	45.6	211.7
	±SD	13.8	51.0	5.1	13.4	6.5	7.02	261.2
	P-Value	0.64	<0.001	0.05	0.03	0.028	<0.001	0.12

Table-2: Correlation of TSFA with haematological parameters

* Mean±S.D

*Lym's &*Mono's =Lymphocyte &Monocyte Count

*PLTS & Hemcr =Platelets& Hematocrit

*ALT = Alanine Amino Transferase

*TSFA = Third Space Fluid Accumulation

Sr. #	Test	Mean ± S.D	STUDY 2012 [11]	STUDY 2008 [21]
01	AGE (YEARS)	35.1 ± 15.01	45.5 ± 12	39.68 ± 11.2
02	PLATELETS (10^3µL)	81.67 ± 95.24	55 ±15	74.44 ± 41.90
03	TLC (10^3/µL)	6.53 ± 4.21	1.2 ± 1.8	4.60 ± 2.29
04	LYMPHOCYTE COUNT (10^3µL)	37.65 ± 15.35	53.6 ± 5.2	45.64 ± 8.97
05	MONOCYTE COUNT (10^3µL)	11.01 ± 6.30	3 ± 0.7	4.5 ± 3.89
06	HCT (%)	42.80 ± 7.34	38.46 ± 6.78	39.76 ± 6.22

Table-3: Differences among 2021, 2008 and 2012 Dengue outbreak.

DISCUSSION

Dengue fever epidemic can evolve with fatal complications all around the world. The diagnosis of the disease is mainly based on clinical features, laboratory investigations and epidemiological data. The laboratory tests include complete blood count, coagulation profile, liver function tests and specific viral tests.[9] The incidence of dengue fever has been increased drastically in the past few years. In endemic areas, the dengue fever epidemic is associated with high morbidity which in turn is a burden on the health care system.[10]

In our study we aimed to focus on the haematological presentation of the patients presenting with dengue fever in Mayo Hospital Lahore. There were 200 patients enrolled in our study with male to female ratio of 2.07:1. The mean age of patients presenting to us was 35.03 ±SD 15 years. It was seen that younger and middle age groups were more affected in this dengue fever outbreak as shown in our study. Earlier studies in different setups in Pakistan showed mean ages of 45 and 39 years in 2012 and 2008 respectively.[11, 12] The patients presented with a variety of clinical features, most commonly including fever, headache, rash, vomiting and dengue hemorrhagic shock as well. Fever was seen in nearly all the patients followed by myalgias. Similar presentation of patients was seen in other studies.

Haematological findings can be used as diagnostic and prognostic tools in dengue fever. These findings can predict the severity of the disease and monitor the disease progression. In our study it was seen that mean platelet count of the patients was 81.67 ±SD95.2 which was below the average range of platelets. The pathophysiology of thrombocytopenia includes different processes including bone marrow suppression in acute phase and direct invasion of megakaryocytes by virus thus causing their destruction. Also, the presence of antiplatelet antibody has been described leading to sequestration of platelets.[13] The low platelet count at presentation in patients with dengue fever was associated with rash, bleeding manifestations and third space fluid accumulation.[14] earlier studies have also shown that thrombocytopenia to be an important haematological abnormality seen in dengue fever.[15]

Hemo-concentration is another important haematological finding seen in patients with dengue fever. It is considered as an early diagnostic marker of the disease and is related to disease progression. [6] in our study the mean hematocrit of patients was 42.80 ±7.40. Also, it was observed that the patients with raised hematocrit presented signs and symptoms of dengue hemorrhagic fever. An Indian study showed patients with raised hematocrit at presentation to be likely to have a prolonged hospital stay.[16] Another study conducted in Pakistan also demonstrated positive association of raised hematocrit, low platelet count and raised amino transferase with the poor outcome of dengue fever.[12]

Leucopenia with relative lymphocytosis is another important finding in dengue fever. Various studies have shown that early detection of leucopenia helps to predict the clinical severity of the disease.[9] Especially the presence of atypical lymphocytes is correlated with the development of severe disease

and complications. The mean TLC in our patients was 6.53 ± 4.2x10^3 It was observed that patients presenting to us had wide and variable range with minimum TLC of 1.60 µl and maximum TLC of 40x10^3 µl respectively. Relative lymphocytosis was also one of the main findings in our patients. Another important finding in our patients was increased monocyte count. The mean value of monocyte count was 11.01±6.30 was higher than shown in previous studies. A study conducted in Nawaloka Hospital Sirilanka described that the patients with higher percentage of lymphocytes and monocytes had strong association with the development of hypotension, bleeding, and respiratory compromise.[17]

Radiological examination can be regarded as a diagnostic and prognostic investigation for dengue fever. The most common radiological findings include gall bladder wall edema, ascites, pleural and peritoneal effusion and hepatosplenomegaly. In our study, 60 patients had third space fluid accumulation and presented with combination of these findings. Total 68% patients had gall bladder wall thickening, 59% patients had ascites, and 37% patients has pleural effusion. Hepatosplenomegaly was seen in 14% patients. We divided our patients in two groups depending upon the development of TSFA to study its correlation with haematological parameters. It was seen that the group of patients with third space fluid accumulation had a mean platelet count 25.8 ±51.015 and the patients' group without TSFA had mean platelet count 105.61 ± 99.80. There was a positive correlation between development of TSFA and low platelet count in our study (p-value <0.001). Similarly, it was seen that the patients who developed TSFA had low TLC (p-value 0.05), relative lymphocytosis (p-value <0.029), raised monocyte count (p-value <0.028), increased mean hematocrit (p-value <0.001) and raised ALT values as compared to the other group without TSFA. Other studies were conducted before to highlight the importance of radiological findings in dengue fever. Also, it was seen that patients with low platelet count have positive correlation with third space fluid accumulation and can be helpful in predicting the severity of the disease.[18, 19] In another study it was seen that a rapid reduction in platelets, progressive reduction in white blood cells, percentage rises in Haemoglobin (Hb), and PCV, and rises in aspartate aminotransferase and alanine aminotransferase were observed in patients with TSFA and therefore with the development of severe illness.[20]

Various studies have been conducted in Pakistan to describe the haematological features of Dengue fever that might help n diagnosis and follow up of the disease. Dengue fever is an emerging infectious disease in Pakistan that has increased multifold in the past few years. It is however a preventable disease and can be managed effectively by early diagnosis. Haematological parameters are helpful in disease monitoring and predicting the development of complications especially third space fluid accumulation which has high mortality rate. Early follow-up of haematological findings with clinical correlation can help to prevent the disease complications and increase overall survival.

CONCLUSION

Haematological parameters are really helpful in disease monitoring and predicting the development of complications especially third space fluid accumulation which has a high mortality rate. Early follow-up of haematological findings with clinical correlation can help to prevent the disease complications and increase overall survival.

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The Authors:

Dr. Hira Babar
Post Graduate Resident,
Department of Pathology,
King Edward Medical University, Lahore.

Dr. Zunairah Mughal
Post Graduate Resident,
Department of Pathology,
King Edward Medical University, Lahore.

Dr. Sobia Ashraf
Associate Professor,
Department of Pathology,
King Edward Medical University, Lahore.

Dr. Sindhu Rehman
Demonstrator,
Department of Pathology,
King Edward Medical University, Lahore.

Dr. Arsala Rashid
Demonstrator,
Department of Pathology,
King Edward Medical University, Lahore.

Dr. Samina Qamar
Associate Professor,
Department of Pathology,
King Edward Medical University, Lahore.

Corresponding Author:

Dr. Zunairah Mughal
Post Graduate Resident,
Department of Pathology,
King Edward Medical University, Lahore.
Email: zunairahkemu@gmail.com