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CLINICAL PROFILE AND PREDICTORS OF SEVERE DENGUE DISEASE: A STUDY FROM PAKISTAN

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Abstract:

Background: *Dengue is endemic and prevalent in tropical and sub-tropical countries including Pakistan and can cause significant mortality and morbidity. There are limited studies available on factors associated with severe dengue from Pakistan, to investigate the predictors of severe dengue in patients.*

Study Design: *A cross-sectional study was conducted in Services Hospital Lahore, for the duration of one year, from March 2019 to March 2020.*

Methods: *We recruited 334 patients with dengue admitted in Services Hospital, Lahore. Based on clinical symptoms, we divided patients into severe dengue and non-severe dengue. Univariate and multivariate analysis was performed for prognostic factors of severe dengue.*

Results: *Out of 334 patients, there were 186(55.6%) males with mean age 30.3±14.3 39 years (age range: 10-73 years), severe dengue was seen in 117(35%) and non-severe dengue in 217(65%). Clinical symptoms of diabetes, low platelet count (5days after onset) elevated hematocrit, lymphadenopathy, hepatomegaly, splenomegaly, convulsions and mortality were significantly associated with severe dengue. After multivariate analysis, diabetes (OR: 2.12; 95% CI: 1.34-4.65) (5days) were independently associated with severe dengue.*

Conclusion: *Clinical features and laboratory findings are closely related to confirmed and probable dengue cases. The incidence of dengue fever was much higher during the hot and humid months between August and October.*

Keywords: *Clinical manifestation, Univariate, multivariate, elevated hematocrit, lymphadenopathy.*

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INTRODUCTION:

Dengue infection has become a common mosquito-borne viral disease, occurs in tropical and subtropical countries especially South and Southeast Asia countries, the Caribbean, Central and South America, and Africa (1). Worldwide every year, 50-200 million are affected with dengue infection, with over 20,000 dengue-related deaths and the incidence has risen 30 times during the past six decades (2). In Pakistan, dengue infection is seen all over the country including rural and urban areas (3). Dengue virus belongs to Arbovirus group, and infection is characterized by disease, headache, loss of appetite, arthralgia, rash, abdominal pain, nausea and vomiting (2). The complication of dengue disease was not treated properly, the mortality rate increased more than 20% . Recent studies have identified a subset with more complications and high mortality in severe dengue compared to non-severe dengue (4). The aim of the study was to investigate the clinical symptoms, laboratory findings and mortality in severe dengue. Very limited studies are available on this topic from Pakistan. During the first infection; residual antibodies produced cannot deactivate a 2nd infection with alternative serotype, and 2nd infection results in a serious infection and a disease under the influence of the improved antibodies. This spectacle is known as antibody-dependent healing. In one of three ways: Clinically dengue virus infection manifests itself as dengue haemorrhagic fever (DHF), classic dengue fever (DF) and dengue shock syndrome. DF is defined by musculoskeletal pain, high fever, morbilliform skin rash and retrobulbar headaches. The arrival of haemorrhagic symptoms or haemorrhagic rash characterizes dengue haemorrhagic fever (FHD) in addition to conventional DF. Dengue syndrome is categorized by altered mental status, delayed capillary filling and hypotension (5). This study was conducted to determine the incidence of dengue fever in acute febrile patients during the study period. In addition, it has been found that the features of the disease detect any differences in clinical and haematological presentation of the disease in possible cases and are proven by dengue.

METHODS:

A total of 334 patients with primary presumptive diagnosis of dengue and were admitted in the Department of Medicine at Services Hospital, Lahore. This study was conducted between March 2019 and March 2020. Severe dengue was defined by World Health Organization (WHO) criteria (3, 5). This study was approved by the Institutional Ethics Committee (IEC) and consent was obtained from all the patients. Out of the 400 patients, 66 patients were excluded (twenty-seven patients had incomplete data, and 39 patients left against medical advice (LAMA) within 3 days of admission), remaining 334 patients were included in the study. Patients underwent laboratory investigations including complete blood test, liver function tests, urine analysis (including urine albumin), abdominal ultrasound examination, serum creatinine, blood urea, serum albumin, serum glucose, cerebrospinal fluid analysis and chest x-ray reports were collected. In the present study, 120 (35.4%) had hepatic tenderness (35.9%), 14 (4.1%) with jaundice, 312(93.4%) had elevated liver enzyme, aspartate aminotransferase (AST) ranged 33- 1082 U/L and 29-1028U/L for alanine aminotransferase (ALT).

Out of 334 dengue patients, 270 had gallbladder (GB) wall thickening, 210 with pleural effusion, 179 had ascites, and 22(6.5%) subjects were found with splenomegaly and hepatomegaly in 26(7.7%) patients. In our patients, there were no history of disease like Japanese encephalitis virus (JEV), St. Louis encephalitis virus (SLE), West Nile virus (WNV) leptospirosis, yellow fever, malaria and hepatitis A, B, and C. Twenty (5.9%) patients had electroencephalogram. Thirty five (10.4%) patients had brain CT scan, forty patients (11.1%) underwent 2D echogram (26 patients had normal echocardiography, 10 had 1.5) melena, skin rash, delayed in admission (>5days), and lymphadenopathy) for sever dengue. All tests were two-sided and a p-value less than 0.05 was considered statistically significant.

RESULTS:

Out of 334 patients with dengue, 213(63.7%) were men with mean age of 30.3±14.3 years and age range of 10-73 years. Most common symptoms were fever seen in 100%, followed by myalgia in 88%, chills in 74.5% nausea/ vomiting 65.5% and headache in 38% of patients. On clinical examination were severe dengue in 35%, and nonsevere dengue in 64.9%, convulsion was a rare complication seen in 4.1% of patients. Elevated hematocrit (>40%) was present in 41% and mean platelet count was 0.82±0.67.

Table 1. Comparison of basal characteristics between severe dengue and non-severe dengue

	(includes deaths) (n=117)	(n=217)		
Men	66(56.4%)	120(55.2%)	186 (55.6%)	0.8
Women	51(43.5%)	97(44.7%)	148 (44.4%)	0.8
Mean age (years)	30.4±11.8	30.3±15.4	30.3±14.3	0.9
Hypertensive	15(12.8%)	18(8.2%)	33 (9.8%)	0.4
Diabetes	45(38.4%)	37(17%)	82 (24.5%)	0.001
Delay in admission (>5days)	43(36.7%)	31(14.2%)	74 (22.1%)	0.0001
Low platelet count(<50,000 mm^3)	69(58.9%)	23(10.5%)	92 (28.7%)	0.0001
Chills	79(67.5%)	170(78.3%)	249 (74.5%)	0.1
Headache	51(43.5%)	76(35%)	127 (38%)	0.0001
Myalgia	97(82.9%)	197(90.7%)	294 (88%)	0.5
Arthralgia	49(41.8%)	63(29.8%)	112 (33.5%)	0.09
Melena	40(34.1%)	33(15.2%)	73 (21.8%)	0.0001
Rashes	53(45.2%)	50(23%)	103 (30.8%)	0.0001
Nausea and vomiting	82(70%)	137(63.1%)	219 (65.5%)	0.6
Abdominal Pain	71(60.6%)	110(50.6%)	181 (54%)	0.1
Lymphadenopathy	27(23%)	13(5.9%)	40 (11.9%)	0.0001
Fever >39^{0}C	48(41%)	92(42.3%)	140 (41.9%)	0.8
Elevated hematocrit (>40%)	76(64.9%)	61(28.1%)	137 (41%)	0.0001
Hypotension	18(15.3%)	20(9.2%)	38 (11.3%)	0.1
Bradycardia	12(10.2%)	0	12 (3.5%)	0.0001
Elevated Plasma Thromboplastin Time (>1.5)	58(49.5%)	67(30.8%)	125 (37.4%)	003
Splenomegaly	22(18.8%)	0	22 (6.5%)	0.0001
Convulsions	14(11.9%)	0	14 (4.1%)	0.02
Hepatomegaly	26(22.2%)	0	26 (7.7%)	0.0001
Deaths	5(4.2%)	0	5 (1.4%)	0.02

Among the 334 patients with dengue, IgM positivity was seen in 203 (60.7%), IgG positivity in 73(21.8%), while 8.9% had both IgM and IgG antibodies positive and 140 (41.9%) were NS1 antigen test positive patients. Delay in admission (>5 days onset) (p1.5) (p=0.003), splenomegaly (p5days and mortality (p=0.02) were significantly more prevalent in severe dengue compared to non-severe dengue. After multivariate analysis, we established that the major predictors of severe dengue were diabetes

Table: II

	Univariate		Multivariate		p value
	Odds ratio	95% CI	Odds ratio	95% CI	
Diabetes	3.04	1.81-5.08	2.12	1.34-4.65	<0.0001
Elevated hematocrit (>40%)	4.74	2.92-7.67	3.14	2.17-6.14	<0.0001
Elevated Plasma Thromboplastin Time (>1.5)	2.20	1.38-3.49	0.91	0.51-1.92	<0.03
Skin rash	2.76	1.70-4.47	1.99	1.11-3.55	<0.0001
Melena	3.26	1.72-6.18	2.59	1.40-4.93	<0.0001
Low platelet count	12.1	6.87-23.3	6.71	4.12-13.6	<0.0001
Headache	1.45	0.93-2.34	0.99	0.51-1.84	0.04
Abdominal pain	2.01	1.27-3.19	0.8	0.05-1.91	0.02
Lymphadenopathy	4.70	2.32-9.54	3.12	1.91-7.85	<0.0001
Delay in admission (>5days)	2.91	1.82-4.66	2.40	1.31-3.41	<0.0001

DISCUSSION:

In our study, we established 35% of severe dengue, other studies found similar findings (6-12). Ledika et al. noted 24.6% in their studies (6), Aung et al. 27.9% (7), Mena-Lora et al. 26% (8) of patients with severe dengue. Some studies showed the lower prevalence of severe dengue at 9.0% (9). The present study revealed no significant association between age and severe dengue when dichotomized into in this cohort. Seventy three (21.9%) cases of dengue had melena and previous studies showed comparable outcome (4, 20-23). In the studies of Mohan et al. Laul et al and Mandal et al. a prevalence of 19% (20), 26% (21) and 26.8% respectively they reported (22). In the present study, we identified a significantly higher prevalence of melena among severe dengue patients (34.1%). On multivariate analysis, we found an independent association with severe dengue (odds: 2.59; 95% CI: 1.40-4.93), our findings were supported by other researchers (4). Skin rashes are frequently present in dengue disease and the present study established an independent association with severe dengue (OR: 1.99; 95% CI:1.11-3.55). Our finding was supported by Zhang et al. (odds: 2.03; 95% CI:1.26- 3.25) (4) and Khan et al. (OR;9.16; 95% CI:4.04- 20.78) (24), while few studies showed no association (23). An immunological mechanism may be the explanation for developing these rashes. Dengue virus can incite the production of cytokines with stimulation of vascular endothelial changes, infiltration of mononuclear cells and perivascular edema, consequently leading to a skin rash (25). The present study showed 23% in lymphadenopathy with severe dengue and the previous studies have noted lymphadenopathy in 5-40% of patients with severe dengue (26). In our study showed lymphadenopathy was found to be an independent predictor of severe dengue (OR: 3.12; 95% CI: 1.91-7.85). Headache and retro-orbital pain are wellestablished symptoms in dengue (26) and are present in 60- 90% of cases with dengue (22). Our study showed no significant association of headache with severe dengue. These findings were supported by other researchers (4). Central nervous system (CNS) features are rare but can occur in dengue and in our study, we found convulsion in 14 (11.9%) patients who were significantly associated with severe dengue, our findings were advocated by others (10). Seizures can be associated with encephalopathy, hemorrhages, infarction or metabolic disorders the may effect dengue encephalitis (27) or secondary to immunological mechanism (28). Elevated hematocrit suggests a vasculopathy along with leakage, secondary to increasing vascular permeability is an indirect measure of the cytokines being produced and the possibility of severe vascular endothelial dysfunction and usually predate shock. Recent studies have established hematocrit > 40% as a prognostic factor for severe dengue (28). Additionally, in our study, hematocrit (≥40%) emerged as a strong independent predictor of severe dengue (OR: 3.14; 95% CI: 2.17-6.14). Nonetheless, a recent study has not found any association between elevated hematocrit and severe dengue infection in children (29). Thrombocytopenia is one of the potential indicators of severe dengue (6). In our study, platelet count ≤50,000/ mm3 was significantly higher in patients with severe dengue (58.9%) compared to nonsevere dengue (10.5%)

The exact pathophysiology of thrombocytopenia in dengue is not yet clearly elucidated. Dengue virus may have a direct effect on the bone marrow - specially the progenitor cells causing a reduction in their capacity to replicate. An aberrant immunological response, implicated in severe dengue seems to play a significant role by dysregulation of plasma-kinin system. This leads to an increased consumption of platelets by disseminated intravascular coagulation (DIC). The damage is enhanced by increased apoptosis of platelets and generation of antiplatelet antibodies (6). Our study further emphasizes low platelet count (≤50,000/ mm3) as an independent factor for severe dengue (OR: 6.71; 95% CI: 4.12-13.6). Admission delay was one of the major risk factor for severe dengue which may have contributed to death. The present study noted delay in admission (≥5days onset) was significantly higher among the patients with severe dengue 43(36.7%) our study was advocated by others (6, 17). Ledika et al. (6) in his study noted a delay of more than 4 days of onset was significantly associated with severe dengue. In our study, we established a delay in admission as an independent predictor of severe dengue (OR: 2.40; 95% CI:1.31-3.41), these findings were supported by other researchers (6, 12). Delay in admission in severe cases may be due to the administrative issues such as lack of knowledge, misdiagnosis or lack of funds. Besides, the immunological dysfunction may manifest a couple of days after the viral infection itself, resulting in a severe disease, eventually getting medical assistance. Studies have established the mortality rate of 1-4% in severe dengue (30). The present study demonstrated a mortality rate of 2.4%. Mortality was significantly associated with severe dengue in our study and there was no mortality among non-severe dengue patients. Similar studies found a case fatality note of 1.2% in severe dengue (6, 7). Severity is defined as having more risk of mortality associated with severe bleeding, plasma leakage, shock and other organ involvement (5). In our study, we found 5 patients who died with elevated transaminase levels and delayed admission (>5 days). Three patients had

severe bleeding, two with convulsions, three patients had concomitant diabetes and hypertension. The present study has few limitations: we were unable to analyze seasonal variation, rural and urban area and quantitative analysis of levels of IgM and IgG antibodies against dengue or the glycemic control in diabetic patients with severe dengue. The strengths of our study was conducted at a single center and a single laboratory to confirm dengue. In addition, this study followed current WHO guidelines for severe dengue and we did multiple regression analysis for predictors of severe dengue. In the current study, we established that elevated hematocrit (>40%), low platelet count (5days) were independently associated with severe dengue disease. The was a low mortality rate (4.2%) in our cohort. Further studies to compare the strength of association of these factors can help in creating an algorithm for predicting the occurrence of severe dengue.

CONCLUSION:

Clinical features and laboratory findings are closely related to confirmed and probable dengue cases. The incidence of dengue fever was much higher during the hot and humid months between August and October.

REFERENCES:

1. Chen CM, Chan KS, Yu WL, et al. The outcomes of patients with severe dengue admitted to intensive care units. Medicine (Baltimore) 2016; 95: e4376.
2. Kaur P, Kaur G. Transfusion support in patients with dengue fever. Int J Appl Basic Med 2014; 4: S8-S12.
3. Gupta E, Ballani N. Current perspectives on the spread of dengue in India. Infect Drug Resist 2014; 7: 337-42.
4. Zhang H, Zhou YP, Peng HJ, et al. Predictive symptoms and signs of severe dengue disease for patients with dengue fever: a meta-analysis. Biomed Res Int 2014; 2014: 359308.
5. Narvaez F, Gutierrez G, Perez MA, et al. Evaluation of the traditional and revised WHO classifications of Dengue disease severity. PLoSNegl Trop Dis 2011; 5: e1397.
6. Ledika MA, Setiabudi D, Dhamayanti M. Association between clinical profiles and severe Dengue infection in children in developing country. Am J Epidemiol Infect Dis 2015; 3: 45-9.
7. Aung KLL, Thanachartwet V, Desakorn V, et al. Factors associated with severe clinical manifestation of dengue among adults in Thailand. Southeast Asian J Trop Med Public Health 2013; 44: 602-12.
8. Mena Lora AJ, Fernandez J, Morales A, et al. Disease severity and mortality caused by dengue in a Dominican pediatric population. Am J Trop Med Hyg 2014; 90: 169- 72.
9. Tamibmaniam J, Hussin N, Cheah WK, Ng KS, Muninathan P. Proposal of a clinical decision tree algorithm using factors associated with severe dengue infection. PLoS One 2016; 11: e0161696.
10. Chatterijee N, Mukhopadhyay M, Ghosh S, et al. An observational study of dengue fever in a tertiary care hospital of eastern India. J Assoc Physicians India2014; 62: 224-7.
11. Thomas L, Brouste Y, Najioullah F, et al. Predictors of severe manifestations in a cohort of adult dengue patients. J Clin Virol 2010; 48: 96-9.
12. Carrasco LR, Leo YS, Cook AR, et al. Predictive tools for severe dengue conforming to World Health Organization 2009 criteria. PLoS Negl Trop Dis 2014; 8: e2972.
13. Pang, J, Thein TL, Leo YS, Lye DC. Early clinical and laboratory risk factors of intensive care unit requirement during 2004-2008 dengue epidemics in Singapore: a matched case-control study. BMC Infecti Dis 2014; 14: 649.
14. Saqib MA, Rafique I, Bashir S, et al. A retrospective analysis of dengue fever. Case management and frequency of co-morbidities associated with death. BMC Res Notes 2014; 7: 205.
15. Htun NS, Odermatt P, Eze IC, et al. Is diabetes a risk factor for a severe clinical presentation of dengue?-- review and meta-analysis. PLoSNegl Trop Dis 2015; 9: e0003741.