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Risk Factors for Dengue Shock Syndrome in Children Admitted in Federal Govt. Polyclinic Hospital (FGPC) Islamabad

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[1]Conception, synthesis, planning of research and writing of manuscript
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ABSTRACT

Objective: To determine the risk factors for dengue shock syndrome in children admitted in Federal Govt. Polyclinic Hospital (FGPC) Islamabad.

Methodology: A cross sectional study, conducted at Pediatric department of FGPC hospital from August 2019 to October 2019, included 102 children of less than 12 years of age. All the children with acute febrile illness, who tested positive for NS1 antigen visiting the outpatient and emergency department, admitted in Pediatric department were considered eligible for enrollment in the study. Demographic and clinical characteristics were reported and correlated with disease prognosis and clinical outcomes.

Results: Out of 102 patients, 13 (12.7%) developed dengue shock syndrome (DSS). Patients with capillary refill time of more than 3 seconds were found to be 2.44 times more likely to develop dengue shock syndrome (OR=2.44, 95% CI 1.47 – 4.03, p<0.001). Similarly, patients with thrombocytopenia (platelet count less than 150x103 cells) and leukopenia (TLC less than 4000x103 cells) were found to be at increased risk of developing dengue shock syndrome as compared to others (OR=1.28, 95% CI 1.12 – 1.48, p=0.001 and OR=1.6, 95% CI 1.12 – 5.21, p=0.01 respectively). Out of 13(12.7%) patients with DSS 1 patient (7.7%) died but no mortality observed in DHF.

Conclusion: Increased capillary refill time, thrombocytopenia, and leukopenia were found to be significant predictors of DSS in children with dengue fever. Early identification of these risk factors can help in timely management and potentially reduce morbidity and mortality associated with DSS.

Key words: Dengue Fever (DF); Dengue Hemorrhagic fever (DHF); Dengue Shock Syndrome (DSS); Risk Factor

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Introduction

The incidence of dengue, a virus-borne illness spread by mosquitoes, has increased significantly worldwide. About half of the world's population is now at risk as the frequency of dengue has increased globally. Even though there are thought to be 100–400 million infections every year, more than 80% of them are often moderate and asymptomatic.[1]

The number of dengue fever cases has shown a significant global rise in recent years. According to the World Health Organization (WHO), reported cases increased from 505,430 in 2000 to 5.2 million in 2019. Another study estimated that approximately 3.9 billion individuals are at risk of dengue virus infection. This disease is now becoming endemic in over 100 countries across Africa, the Americas, the Eastern Mediterranean, South-East Asia, and the Western Pacific regions, as classified by WHO.

The Americas, South-East Asia and Western Pacific regions are the most seriously affected, with Asia representing around 70% of the global disease burden.[1] Dengue fever is endemic in Pakistan and according to the National Institute of Health-Islamabad, a study conducted

between 1 January to 27 September 2022, showed a cumulative total of 25 932 confirmed dengue cases and 62 deaths have been reported nationally. In the majority of reported cases, Three-fourth 74% occurred in September, accounting for 83% of the total reported cases (n=21777). Regionally, Sindh contributed 32% (n=6888), Punjab (including the Islamabad Capital Territory) accounted for 29% (n=6255), Khyber Pakhtunkhwa contributed 25% (n=5506), and Balochistan accounted for 14% (n=3128).[2]

It is mostly spread by female Aedes aegypti and Aedes albopictus mosquitoes. A member of the Flaviviridae family[3] with four distinct serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) is responsible for causing dengue. Infection with one serotype gives lifelong immunity against that serotype but subsequent infection by another serotype increases the risk of developing DSS. [4-6]

A broad spectrum of clinical characteristics is brought on by dengue. They can be classified as DF, DHF, and DSS since they can have anything from a fever to a serious sickness.[7] According to WHO, Dengue Fever (DF) is defined as an acute febrile illness associated with headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, leukopenia and positive antigen or serology for dengue. Dengue Haemorrhagic Fever (DHF) is defined as fever for 2-7 days, Haemorrhagic tendencies in the form of petechiae, bruises or mucosal bleeding, gastrointestinal tract bleeding (hematemesis, melena), bleeding from injection sites with Thrombocytopenia (equal to or less than 100000 cells per mm3) and evidence of plasma leakage because of increased vascular permeability, demonstrated by 20% increase in the hematocrit.[7] Dengue Shock Syndrome (DSS) is characterized by hypotension, altered mental status and delayed capillary filling.[8]

Diagnosis of dengue fever is carried out by viral markers (NS1 antigen), Serology including IgM & IgG antibodies titer by ELISA (Enzyme Linked Immunosorbents Assay), PCR for specific genotyping for dengue to isolate the different serotypes. NS1 is detectable during the acute phase and it is not recommended after 7th days of fever. IgM antibody is detectable from 4th day of illness up to 12th weeks and IgG remains detectable for life. PCR to detect different serotypes is positive during the first week of illness only.[4]

Dengue fever is mostly a self-limiting disease but few patients can develop complications in the form of serious bleeding, multi organ failure, plasma leakage, and a higher risk of mortality if treated improperly.[8,9] Currently no curative treatment is available for Dengue fever, therefore treatment is mostly symptomatic with antipyretics, hydrating the patient and occasionally blood products transfusion. Drugs causing decreased platelets count like aspirin ibuprofen should be avoided. Close monitoring of clinical and hematological parameters is necessary to identify shock as early as possible. Only way to prevent dengue is by taking preventive measures including stoppage of transmission through mosquito killers/repellant, vaccination by Dengvaxia and early detection of clinic-pathological signs may help in decreasing morbidity and mortality from Dengue fever.[1] Previous studies has shown that timely treatment of Severe Dengue may reduce the mortality from more than 20% to less than 1%.[10]

Due to nonspecific symptoms and lack of necessary laboratory facilities, it is difficult to differentiate from dengue from other febrile illness, resulting in delay in diagnosis and management.[11] In our study, we wanted to point out significance of history, examination, laboratory findings and their correlation with the severity of the disease. Early diagnosis and treatment of Severe Dengue could lower mortality and cut down on hospital stays and expenditures, hence it is crucial to identify the risk factors for DSS.

Methodology

This study was conducted in the Department of Pediatric, Federal Govt. Polyclinic Hospital, Islamabad from August 2019 to October 2019. All the children with acute febrile illness, who tested positive for NS1 antigen visiting the outpatient and emergency department, admitted in Pediatric department were considered eligible for enrollment in the study. Despite the increasing outbreak of dengue fever with years, limited data is available regarding the prevalence of the disease among pediatric population. A total of 102 consecutive patients meeting the inclusion criteria were included in the study over a three-month period. Written informed consent was obtained from the parents, and the study was approved by the hospital's ethical committee.

Inclusion criteria for enrollment in the study were children aged >1 month and <12 years, presenting with acute febrile illness and testing positive for NS1 antigen. Exclusion criteria included children outside the specified age range, presence of hematological disorders, hemorrhagic fever other than dengue, and comorbid

diseases such as typhoid fever, pneumonia, urinary tract infection, and malaria.

We collected data according to clinical presentation including fever, duration of illness, abdominal pain, vomiting, bleeding (petechiae, spontaneous bleeding, melena, gum bleeding, hematemesis, epistaxis), rash, pleural effusion, ascites, hepatomegaly and capillary refill time. Laboratory investigations including total leucocyte count (TLC), hemoglobulin (Hb), hematocrit (HCT), platelet count and dengue NS1 antigen were reported. Treatment was started according to severity of illness. Clinical outcomes including hospital stay and discharge status were noted.

The collected data was entered and analyzed using IBM SPSS software (version 23.0). Descriptive statistics were used to express categorical variables as percentages and frequencies, while continuous variables were represented by mean and standard deviation. Statistical comparisons were performed using Chi-Square test or Fischer-exact test for categorical variables, and independent samples T-test or one-way ANOVA for comparing mean values between two groups, depending on the number of categories. Binary logistic regression was employed for univariate and multivariate analysis, with odds ratios, 95% confidence intervals, and p-values reported. Dengue shock syndrome was considered the dependent variable, and various clinical/demographic risk factors were treated as independent variables. A significance level of $p \leq 0.05$ was used to determine statistical significance in the study.

Results

A total of 102 patients were enrolled in the study, there were 63 (61.8%) males and 39 (38.2%) females with mean age of 91.55±36.7 months. Out of 102 patients admitted with dengue fever (DF) and dengue hemorrhagic fever (DHF), 13 (12.7%) developed ascites, pleural effusion and increase capillary refill time to >3 second, who were labelled as experiencing dengue shock syndrome (DSS).

There were 9 (69.2%) males and 4 (30.8%) females in dengue shock syndrome group with mean age of 96.17±35.94 months. Majority of the patients had fever, that is 98.9% (88) and 100% (13) among DF/DHF and DSS groups respectively. Overall, 28 (27.4%) patients experienced bleeding, among DF/DHF group 20 (22.5%) and among DSS group 8 (61.5%) patients had bleeding, out of which epistaxis was most common type of bleeding manifestation observed followed by petechiae, melena, hematemesis and gum bleed.

Laboratory findings revealed that mean hemoglobin and hematocrit values were comparable among two groups (p=1.021, p=0.583 respectively), the mean total leukocyte count (TLC) was also same among two groups (p=0.491), but when TLC was subdivided into categories then it was revealed that more patients from DSS group had TLC of less than 4000 as compared to DF/DHF group (76.9% vs 41.6%, p=0.039), similarly mean platelet count was significantly lower among DSS group as compared to DF/DHF (69.33±53.17 vs 177.77±190.34, p=0.045) and more patients from DSS group had platelet count of less than $50x10^3$ as compared to DF/DHF group i.e. 8 (61.5%) vs 2 (2.2%) p<0.001. Distribution of demographics, clinical signs/symptoms and laboratory findings among two groups is summarized in table I.

Table I: Distribution of demographics, clinical signs/symptoms and laboratory findings among two groups.

Characteristics	Study Groups		p
	DF/DHF (n=89)	DSS (n=13)	
Demographics			
Age in months (Mean±SD)	91.06±37.18	96.17±35.94	0.655
Gender n (%)			
Male	54 (60.7%)	9 (69.2%)	0.553
Female	35 (39.3%)	4 (30.8%)	
Clinical Signs & Symptoms			
Fever	88 (98.9%)	13 (100%)	0.701
Days of fever (Mean±SD)	3.66±2.16	5.15±3.13	0.031
Days of fever n(%)			
<7	81 (91.0%)	9 (69.2%)	0.023
>7	8 (9.0%)	4 (30.8%)	
Bleeding n(%)	20 (22.5%	8 (61.5%)	0.003
Bleeding type n(%)			
Epistaxis	17 (19.1%)	5 (38.5%)	0.147
Petechie	-	3 (23.1%)	0.002
Malena	1 (1.1%)	2 (15.4%)	0.042
Hematemesis	1 (1.1%)	2 (15.4%)	0.042
Gum bleed	1 (1.1%)	3 (23.1%)	0.006
Vomiting n(%)	38 (42.7%)	5 (38.5%)	1.000
Abdominal pain n(%)	14 (15.7%)	2 (15.4%)	0.147
Rash n(%)	2 (1.1%)	1 (7.7%)	0.240
Hepatomegaly n(%)	3 (3.4%)	2 (15.4%)	1.000
Ascitis n(%)	8 (9.0%)	13 (100%)	<0.001
Pleural effusion n(%)	5 (5.6%)	13 (100.0%)	<0.001
Effusion type n (%)			
Unilateral	5 (5.6%)	2 (15.4%)	0.193
Bilateral	-	11 (84.6%)	<0.001
Capillary refill time n(%)			
Less than 2 seconds	80 (89.9%)	-	<0.001
More than 2 seconds	9 (10.1%)	13 (100.0%)	

Laboratory Findings			
Hemoglobin (Mean±SD)	11.76±1.38	11.70±2.51	1.021
Hematocrit (Mean±SD)	35.24±3.75	34.58±5.55	0.582
Hematocrit n (%)			
<40	82 (92.1%)	11 (84.6%)	0.372
>40	7 (7.9%)	2 (15.4%)	
Total Leukocyte Count ($x10^3$) (Mean±SD)	5.01±2.43	4.54±1.45	0.491
Total Leukocyte Count ($x10^3$) n (%)			
<4	37 (41.6%)	10 (76.9%)	0.039
4 – 7	33 (37.1%)	3 (23.1%)	
>7	19 (21.3%)	-	
Leukopenia n(%)	38 (42.7%)	6 (46.2%)	0.814
Platelet Count (Mean±SD)	177.77±190.34	69.33±53.17	0.045
Platelet Count ($x10^3$) n(%)			
<50	2 (2.2%)	8 (61.5%)	<0.001
51 – 150	43 (48.3%)	5 (38.5%)	
>151	44 (49.4%)	-	
Thrombocytopenia n(%)	46 (52.3%)	12 (92.3%)	
Outcome			
Hospital stay (days) Mean±SD	3.87±1.97	5.15±1.21	0.025
Status n (%)			
Discharged Alive	89 (100%)	12 (92.3%)	0.127
Death	-	1 (7.7%)	

The univariate analysis revealed capillary refill time, thrombocytopenia and leukopenia to be significant predictors of dengue shock syndrome (DSS). Patients with capillary refill time of more than 3 seconds were found to be 2.44 times more likely to develop dengue shock syndrome (OR=2.44, 95% CI 1.47 – 4.03, p<0.001). Similarly, patients with thrombocytopenia (platelet count less than $150x10^3$ cells) and leukocytopenia (TLC less than $4000x10^3$ cells) were found to be at increased risk of developing dengue shock syndrome as compared to others (OR=1.28, 95% CI 1.12 – 1.48, p=0.001 and OR=1.6, 95% CI 1.12 – 5.21, p=0.01 respectively). (Table II)

Table II: Univariate analysis of potential predictors for dengue shock syndrome.

Predictor Variables	OR	95% Confidence Interval	p-value
Capillary refill time	2.44	1.47 – 4.03	<0.001
Thrombocytopenia	1.28	1.12 – 1.48	0.001
Leukopenia	1.6	1.12 – 5.21	0.01

Discussion

In our study we tried to look for high risk patients with Dengue Haemorrhagic Fever (DHF) likely to develop Dengue Shock Syndrome (DSS) on clinical presentation and its correlation with complete blood counts and radiological evidence of plasma leakage. In our study all of the patients presented with fever. Vomiting, abdominal pain, rash, bleeding and hepatomegaly were noted in majority of the patients. Similarly observed in two meta-analysis[10,12] and with Md. Abdullah et al[13], Saiful Islam et al[14] & Afroze S et al.[15] In addition to above findings Amjad Mehmood et al [16] observed retrobulbar pain with headache. The most important parameter in predicting dengue shock syndrome was poor capillary refill time, pleural effusion, ascites and thrombocytopenia similarly observed by Phakhounthong et al.[11] Srikiatkhachorn et al[17] demonstrated thrombocytopenia with plasma leakage were associated with dengue severity whereas hypotension was documented with SD (Severe Dengue) by Saiful Islam et al.[14] The most common bleeding manifestations in DSS were epistaxis, petechiae, gum bleed followed by gastrointestinal bleed in the form of melena and hematemesis, similarly seen with Kang Zhuang Yuan et al.[10] Petechiae was noted by Verma P et al[18], on the other hand melena was observed with Potts JA et al.[19,20] In addition to above clinical signs, gall bladder thickness was observed with Tauqeer HM.[21] Neurological complications like fits, altered sensorium and irritability was observed incidentally by the study conducted in India. [18]

The classical hematological findings reported in dengue infection are thrombocytopenia, leucocytopenia, and hemoconcentration found in[13,14] and Jayadas TTP et al.[22] On the contrary we found no significant increase in hemoconcentration apart from leucopenia and thrombocytopenia, similarly seen with Phakhounthong et al.[11] Some studies showed Leukocytosis with increase hemoconcentration and thrombocytopenia Nandwani S etal.[23] In our study thrombocytopenia was most common finding in those with severe dengue, likewise with Tanner L et al.[24] Thrombocytopenia and sudden fall in total leukocytes counts in early phase of illness was the predictor of severe dengue reported from a study conducted in Sri Lanka, Kularatirum et al.[25] Deranged liver functions LFTs in the form of raised AST (aspartate aminotransferase) and ALT (alanine transferase) and low albumin was observed by Sri Lankan study[22], though hepatomegaly was noted but LFTs were not included in our study. Boys are more affected then girls in our study [13,14,22] while in contrast Girls were more affected in the study by Nandwani S etal.[23]

Duration of hospital stay in case of dengue shock syndrome (DSS) was more as compared to DF, similarly observed by Nandwani S etal.[23] We have observed that delay in reporting to health facility and delay in hospitalization was also led to illness severity in our study like Tauqeer HM.[21] In our study, all cases with dengue haemorrhagic fever were recovered. Among the patients with dengue shock syndrome, 12 cases have recovered and 1 child expired due to intractable shock. It was also noted that mortality in DHF/ DSS has been reduced as compare to studies done in the past. This could be due to delay in early recognition of clinical and laboratory parameters or delay in seeking medical attention in previous years.

In this study, we examine a hypothesis and identify certain clinical and laboratory indicators that can be used to predict the outcomes of patients hospitalized with dengue fever. The findings of our research offer valuable insights that can aid pediatricians, particularly in resource-limited settings, in making informed decisions.

This study was done at a single center over a brief period of time and no comparative analysis was done with adult population to see if there was a difference in clinical presentation. Other factors like association of serotype and presence of IgM and IgG antibodies indicating a primary or secondary infection respectively with the severity of dengue fever were not addressed in our study.

Conclusion

Our study highlights increased capillary refill time, thrombocytopenia, and leukopenia as crucial clinic-pathological risk factors for predicting the severity of dengue fever in children. Early identification of these risk factors through clinical and laboratory profiles can significantly reduce morbidity and mortality rates, ultimately improving patient outcomes. However, it's important to note that our study has limitations, such as the absence of PCR testing for dengue and the isolation of different dengue genotypes. Further research conducted at various institutions is necessary to determine the true burden of the disease.

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