

Characteristics of dengue shock syndrome during 2014 dengue epidemic in Rawalpindi, Pakistan

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Objective: To study the characteristics of dengue shock syndrome (DSS) patients managed during Rawalpindi dengue epidemic 2014.

Methodology: This observational study was conducted at Dengue Ward of Holy Family Hospital, Rawalpindi, Pakistan during epidemic. Patients fulfilling Dengue Expert Advisory Group (DEAG) criteria for DSS were included. Data regarding patient characteristics, clinical features, diagnostic basis, laboratory parameters, treatment, and outcome were noted.

Result: Out of 25 patients, 52% were male. Mean patient age was 26.8 ± 11.52 years. Mean duration of pre hospitalization illness was 5.4 ± 1.5 days. Vomiting, aches, and headache were frequently noted symptoms. Mean day of illness at which DSS developed was 5.7 ± 2.04 days. 24% had additional illnesses. 56% had secondary infection.

84% were PCR positive for DEN3. At admission, mean TLC, platelets, and hematocrit were 3.68×10^3 microL, 60.5×10^3 microL and 39.61%, respectively. 96% had ultrasonographic leak. Alanine transferase was deranged in 59% and Aspartate transferase in 86.66%. Mean amount of intravenous fluids administered was 5011.33 ± 1754.24 ml. 60%, and 28% received Dextran and blood transfusion, respectively. One patient expired. Mean duration of hospital stay was 5.08 ± 1.28 days.

Conclusion: Young adults who had DEN-3 infection suffered from DSS this dengue epidemic. Primary infection was frequently noted in these patients. Mortality in these patients was 4%. (Rawal Med J 2014;41:142-147).

Key words: Dengue, dengue shock syndrome, dengue hemorrhagic fever

INTRODUCTION

Dengue fever is caused by a dengue virus which belongs to Flavivirus family. It is a mosquito borne infection transmitted by *Aedes Aegypti* and *Aedes Albopictus*.^{1,2} Worldwide, around 50 million people are infected with dengue annually.³ Four strains (DEN 1-4) of dengue virus have been described.¹⁻³ Dengue infection may remain asymptomatic, cause dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).^{3,4} DHF and DSS are severe versions of dengue infection.^{1,4} Plasma leak is hallmark of DHF, which differentiates it from DF.^{1,5} DSS is a complicated form of DHF.¹ It is diagnosed when DHF patient develops shock manifested by narrow pulse pressure, hypotension for age, and decreased urine output and DSS is associated with high mortality.⁶

Outbreaks of dengue infections occur in countries where it is endemic and Pakistan is one of them.

First outbreak of dengue fever in Pakistan was reported in 1994.^{2,3} Number of outbreaks have been reported, especially during monsoon season in Pakistan since then.⁶ Rawalpindi, is one of the biggest cities of Pakistan's Punjab province which is being hit by dengue epidemics repetitively. In the two consecutive years of 2013 and 2014, 1223 and 1571 patients of dengue infection were diagnosed at public sector hospitals of Rawalpindi, respectively.⁷ Several studies focusing various characteristics of DSS patients have been conducted internationally.^{4,8,9} At Rawalpindi, most of the dengue patients generally and DHF/DSS patients specifically are managed at Holy Family Hospital, Rawalpindi.^{1,7} We conducted this study to note patient, clinical, viral, laboratory investigation characteristics, DHF/DSS diagnostic basis, and outcome of DSS patients managed during the dengue, Rawalpindi epidemic 2014.

METHODOLOGY

This observational study was conducted at Dengue Ward of Holy Family Hospital, Rawalpindi, Pakistan from 1st September to 1st February 2015 during dengue epidemic. Institutional Research Forum & Ethical Committee approved the study and an informed consent was taken. All patients with diagnosis of DSS were included in the study. Patients with diseases associated with findings similar to plasma leak like chronic liver disease, tuberculosis, autoimmune disorders, renal failure, and cardiac failure and patients with hematological diseases and/or taking treatment for the same were excluded from the study.

Data of patients was collected on a detailed specifically designed proforma with focus on patient characteristics, clinical features, diagnostic basis, laboratory investigation characteristics (hematological parameters, biochemical findings, ultrasonographic abnormalities, dengue serological diagnosis, PCR findings), treatment, and outcome. At admission and discharge/before expiry; total leukocyte count (TLC), platelets, and hematocrit were noted. Type of leak and its amount was also noted. Alanine transferase (ALT), aspartate transferase (AST), sodium, potassium, urea, creatinine, albumin, cholesterol, prothrombin time (PT), activated partial thromboplastin time (APTT), urinary abnormalities (hematuria, proteinuria, casts, pus cells), and abnormal ECG findings (ST-T, and rhythm abnormalities) were also recorded wherever available. Total amount of IV fluids administered during critical period with focus on Dextran and blood products was recorded. Whether patients received antibiotics and or antimalarial was also noted. Outcome was noted in terms of recovery and discharge or expiry. Duration of admission was also noted.

Dengue fever was diagnosed per Dengue Expert Advisory Group (DEAG) criteria.¹⁰ DHF diagnosis was made when a confirmed case of DF and hemorrhagic tendency had evidence of plasma leakage due to increased capillary permeability manifested by one of the following; 1) >20% rise in hematocrit for age and gender, 2) >20% drop in

hematocrit following treatment with fluids as compared to baseline, and 3) signs of plasma leakage (pleural effusion, ascites or hypoproteinemia).^{6,10} DSS patients had DHF along with one or more of the following, 1) circulatory failure manifested by rapid and weak pulse, 2) narrow pulse pressure (<20 mm Hg), 3) hypotension for age, 4) cold and clammy skin, and 5) restlessness and other neurological features like drowsiness, confusion, disorientation, convulsions and coma.⁶

Serological diagnosis of dengue fever was done employing SD Dengue Capture ELISA kit for dengue NS1 antigen, IgM antibody and IgG antibodies. Dengue fever was diagnosed in a probable case of dengue infection when NS1 and or IgM antibody were positive, negative to positive seroconversion of IgM in acute and convalescent sera samples, and negative/positive to positive/4times increase in IgG level.^{1,8,10}

Primary dengue infection was diagnosed when patients were; NS1 and or IgM positive and were IgG negative or ratio of IgM to IgG was >1.2 when they were IgG positive.^{1,11} Secondary dengue infection was diagnosed when serology was positive for IgG; 1) along with NS1 or IgM, or NS1 and IgM positivity, 2) or ratio of IgM to IgG was <1.2 when they were IgG positive.^{1,11} Polymerase chain reaction (PCR) for Dengue were sent whenever a patient was positive for Dengue NS1.

Every patient was managed according to DEAG protocol, which is locally modified version of dengue management based on international guidelines.¹⁰ All data were analyzed employing SPSS version 10. Descriptive statistics were applied.

RESULTS

Out of 25 patients, 13 (52%) were male and 12 (48%) female. Mean patient age was 26.8±11.52 years. Occupation wise 8 (32%) were student, 8 (32%) were house wives, and 2 (8%) were laborers. One (4%) patient was smoker and none had addictions. Five (20%) patients had recent contact with dengue patient and 5 (20%) had history of recent travel.

Table 1. Symptoms and at admission clinical findings.

| | | |
|-----------------------|---------------------------------|-------------|
| Vomiting | 23 (92%) | |
| Aches & pains | 22 (88%) | |
| Headache | 21 (84%) | |
| Decrease Urine output | 12 (48%) | |
| Bleeding at admission | 10 (40%) | |
| Bleeding Site | Gum bleed | 4 (16%) |
| | Hematemesis | 2 (8%) |
| | Rectal bleed | 1 (4%) |
| | Hematuria | 1 (4%) |
| | Vaginal bleed | 2 (8%) |
| Clinical features | Pulse (/minute) | 84.56±13.52 |
| | Pulse Pressure (mm Hg) | 21.4±6.21 |
| | Systolic blood pressure (mm Hg) | 97.8±13.15 |
| | Respiratory rate (/minute) | 21.2±3.1 |
| | Hepatomegaly | 5 (20%) |

Mean duration of pre hospitalization illness was 5.4 ± 1.5 days. Vomiting, aches pains, and headache were most frequently noted symptoms. 11 (44%) patients received treatments before hospitalization. Mean day of illness at which DSS developed was 5.7 ± 2.04 days (Table 1). Six (24%) patients has associated illnesses. Five patients suffered from asthma, multiple sclerosis, brain space occupying lesion, hypertension, and hypoparathyroidism. One patient suffered from multiple comorbidities; diabetes, hypertension, ischemic heart disease, and acute hepatitis A.

Table 2. Complete blood count parameters.

| Parameters | Mean Values | |
|---------------------------------|--------------|---------------|
| TLC ($\times 10^3$ microL) | At admission | 3.68± 1.46 |
| | At discharge | 5.51± 2.74 |
| Platelet count (10^3 microL) | At admission | 60.50± 37.81 |
| | At discharge | 131.92± 67.38 |
| HCT** (%) | At admission | 39.61± 6.72 |
| | At discharge | 35.82± 5.61 |
| PT*** (seconds) | 16.36± 6.57 | |
| PPTK**** (seconds) | 38.40± 12.01 | |

*TLC- total leukocyte count,

**HCT- hematocrit,

***PT- prothrombin time,

****APTT- activated partial thromboplastin time

Secondary dengue infection was noted in 14 (56%) patients while the rest had primary dengue infection. In 21 (84%) patients dengue PCR was positive, and in 1 (4%) it was negative. PCR results of 3 (12%) patients were not available. DEN 3 was noted in all (100%) patients in whom PCR was positive. Leukopenia and thrombocytopenia were noted on admission (Table 2). Hypoalbuminemia was noted in 12 (66.66%) patients and ALT was deranged in 13 (59%) and AST in 13 (86.66%) patients (Table 3). ECG abnormalities were noted in 5 (41.66%) of 12 patients in which it was sought. Urine abnormalities were noted in 8 (61.53%) of 13 patients in whom the report was present.

Table 3. Biochemical parameters.

| | |
|--|---------------|
| At admission ALT (alanine transferase) | 60.7±36.81 |
| At admission AST (aspartate transferase) | 87.31± 65.5 |
| At admission Albumin (g%) | 3.0± 1.2 |
| At admission Cholesterol (mg%) | 74.2± 21.9 |
| At admission Neutrophils ($\times 10^3$ microL) | 2.03± 0.92 |
| At admission Lymphocytes ($\times 10^3$ microL) | 0.94± 0.39 |
| CPK (creatinine phospho kinase) | 461.6± 653.09 |
| LDH (lactic dehydrogenase) | 722 ±365 |
| Total Calcium (mg%) | 8.93± 1.17 |
| Na+ (meq/L) | 138.52± 3.35 |
| K+ (meq/l) | 3.92± 0.38 |
| Urea (mg%) | 26.6± 13.54 |
| Creatinine (mg%) | 0.94± 0.29 |

All patients were treated with IV fluids, mean amount of IV fluid (Normal Saline, Dextran, and Blood or products) administered during critical period was 5011.33 ± 1754.24 ml. 15(60%) patients received amount of 721.76 ± 837.27 ml dextran. Whole blood was administered to 7(28%) patients. Mean amount of blood transfused to a patient was 500 ± 433.01 ml. None of the patients received platelets. Antibiotics were administered to 16(64%) and anti-malarial to 4(16%) of patients. 24(96%) patient recovered while 1(4%) expired. Patient who expired had multiple co morbidities. Mean duration of hospital admission was 5.08 ± 1.28 days.

DISCUSSION

Dengue shock syndrome has been subject of a number of studies. DHF patients were however, mixed with DSS patients in most of these.^{6,8,9,11}

Importantly, although DSS has been more frequently noted in adult patients, number of pediatric DSS patients in various studies is generally more compared to studies focusing adult population.^{11,12} Our study stands distinct as it focuses adult DSS patients in an epidemic setting.

Statistically significant association has been noted between DHF/DSS development and age >30 years.⁸ In a Pakistani study focusing dengue epidemic in Karachi, most of the DHF/DSS patients were in the age range 20-30 years.⁶ Mean age of patients in a study focusing risk factors of Lahore dengue outbreak was 34±16.5 years.³ At our Dengue Unit, both adult and pediatric patients are managed. Mean age of our patients was 26.8±11.52 years and none was in pediatric age group.

Risk of acquiring dengue infection is considered more in males compared to females.¹³ In a Pakistani study, equal number of males and females had DHF/DSS.⁶ Male preponderance has been noted in other studies from Pakistan focusing dengue infection.² 46.29% patients were male in a study of 54 DSS patients from Sri Lanka.¹⁴ In another study 65.78% DHF/DSS patients were female.⁸ Gender distribution in our study was almost equal (1.09:1). Student and house wife were most frequently noted occupations in our study. House wives have been however, noted to have less knowledge about dengue that may increase their chance of getting dengue infection.¹⁵

Generally, duration of pre hospital admission symptoms in dengue is 4.8-5 days, although it may range from 2-12 days.^{9,11} Our results are similar. Fever, nausea/vomiting, anorexia, headache, abdominal pain/tenderness, myalgia, and rash are common clinical features in dengue infected adults and children.¹⁶ In a Pakistani study, bleeding (81%), nausea vomiting (76%), and epigastric pain (56%) were most frequently noted clinical features in DHF/DSS patients.⁶ In our patients, it was noted on day 5.7±2.04.

Co morbidities like diabetes, hypertension and ischemic heart disease have been noted in DHF patients. Variable relationship between dengue severity and co morbidities has however, been noted in studies.^{3,17} Secondary dengue infections are

commonly noted in patients with severe dengue.^{1,3,4} Up to 1% of primary and 9% of secondary dengue infection patients develop DSS.¹⁴ Fatalities in primary dengue infection have also been noted.¹⁵ Secondary to primary dengue infection status in our patients was 56%:44%. DEN 2 and 3 are most important causes of dengue related morbidity in our geographical area.¹⁸ Den 3 serotype was isolated in our patients.

Leukopenia is important characteristic of dengue infection.⁶ We noted the same. Interestingly platelet count <40000×10⁶/L has been considered predictor of DSS.⁴ HCT in DSS patients on day of defervescence can rise >45%.⁴ Serial USG is important for early diagnosis of leak in dengue.⁵ In 96% of our patients diagnosis of leak was based on USG evidence. Hypoalbuminemia has been noted in DSS, it however doesn't has prognostic association.⁹ It was commonly noted in our patients and so was hypocholesterolemia.⁹ Liver enzymes are deranged in DSS.⁶ As AST has sources other than liver it may be more deranged.^{6,9}

Renal abnormalities are frequently noted in dengue infection and include proteinuria (74%), hematuria (12,5%), and acute renal failure (2-5%) etc.¹⁹ Our results are similar in this regard. ECG abnormalities like bradycardia, ST-T wave abnormalities and heart blocks are common in dengue infected patients.²⁰ These may be sole indicator of cardiac involvement or progress to functional cardiac abnormalities.²⁰ We noted abnormalities in 41.66% patients whose ECG was performed.

We managed patients according to guidelines provided by DEAG,¹⁰ which recommends 4600 ml as total fluid intake during the critical period of adult DHF/DSS patients. Mean amount of IV fluids administered in our patients was more than that. Dextran is administered in dengue when fluid resuscitation with crystalloids fail.²¹ Dextran was administered to 60% of our patients. Blood transfusion is indicated in DSS patients with falling HCT.²¹ 28% of our patients were transfused blood.

In dengue platelet transfusions are advocated in high risk patients with platelet count <20000×10⁶/L and bleeding risk.²² Platelets transfusion have however, not found to reduced duration or risk of bleeding in

dengue.²² None of our patients was transfused platelets. Antibiotics and antimalarial were frequently used in our patients. This is indicative of treating physicians concern of coinfections or complicating infections in settings of DSS.

Mortality in dengue infected patients is 1-2%.²³ In DSS patients, much higher mortality has however been noted.¹⁶ 41.6% DSS patients expired in a Pakistani study.³ We noted 4% mortality. Mean duration of hospitalization in dengue patients varies from 3.4-6.2 days.³⁰ Duration of hospitalization in DSS can be variable. In a Pakistani study, duration of hospitalization of 85.7% DSS patients was 7-33 days, respectively.²⁴ Increasing age, renal damage, and coagulation profile abnormalities correlated with increased duration of hospital stay in the same study. In a study from Singapore that focused adult fatal DHF cases duration of hospitalization varied from 2-33 days.⁹ Multiple co morbidities lead to increase chances of mortality in dengue, our findings are similar.

This study has certain limitations, which should be kept in mind before generalizing its findings. It focused a dengue epidemic, DEN-3 infection was noted in all patients and it is representative of a drainage area of a single hospital. Variations from findings are definitely possible in endemic settings, and infection with other dengue serotypes.

CONCLUSION

Dengue shock syndrome due to DEN-3 infection was noted in young adults without predominant gender predilection during the 2014 Rawalpindi Dengue epidemic. Primary dengue infection was frequently noted. No patient had rash. Leukopenia, thrombocytopenia, hypocholesterolemia, hypoalbuminemia, deranged LFTs, urine and ECG abnormalities were common findings. Crystalloid, dextran and blood transfusion remained mainstay of treatment. No patient was transfused platelets. Antibiotics and anti-malarial were frequently used. 4% mortality was noted.

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