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Original Article

Severity of Acute Kidney Injury and its Effect on Outcome in Patients of Dengue Virus Infection

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Abstract

Background: Dengue fever is a mosquito borne viral illness that has endangered a vast population of tropical and sub-tropical areas. Dengue has multi-system involvement including liver, hematological, respiratory and central nervous systems. Spectrum of renal disorders is least studied in dengue infection and its presence in dengue may be linked to increased morbidity and mortality.
Objective: To find the frequency of acute kidney injury (AKI), its stages of severity and to compare the frequency of mortality and morbidity in various stages of AKI among dengue patients.
Study type, settings & duration: This retrospective cross sectional analysis was carried out at Nephrology Department, Multan Institute of Kidney Diseases, Multan from May to October 2019.
Methodology: Data of ninety patients was retrieved from hospital medical record system through non-probability consecutive sampling technique. Male and female patients of 15-50 years age with dengue virus infection were included in the study as per operational definition. Patients diagnosed with chronic kidney disease (CKD) and diabetes mellitus on the basis of history and medical record were excluded. Record of serum creatinine done at the time of admission, 48 hours later and seven days after hospital admission was taken. Presence and severity of AKI were classified according to acute kidney injury network (AKIN) criteria into stage-I, stage-I and stage-III AKI. Outcome was categorized as morbidity of patients having persistent renal dysfunction manifested by serum creatinine > 1 mg/dl assessed 7 days after admission and number of patients who died within 7 days of hospital admission. SPSS 16.0 version was used for statistical analysis of this data.
Results: Out of 90 patients, 19 (21.1%) developed AKI. Out of them 10 (52.6%) patients had stage I, 8 (42.1%) had stage II and 1 (5.3%) had stage III AKI. After 7 days, the mean serum creatinine of 19 patients was 1.36±0.56mg/dl. Out of 19 patients, 11 showed outcome i.e. 7 (63.6%) had morbidity (persistent AKI) while 4 (36.4%) had mortality (died). In patients with stage I AKI, 2 (100%) had morbidity. In patients with stage II AKI, 5 (62.5%) had morbidity while 3 (37.5%) had mortality. In patients with stage III AKI, 1 (100%) had mortality. SPSS 16.0 version was used for statistical analysis of this data.
Conclusion: Frequency of AKI is although low but not negligible and among these patients, complications are high. This warrants implementation of screening of renal functions in dengue fever patients in future. This practice can help us in early diagnosis of AKI and we can adopt measures to reduce morbidity and mortality associated with AKI among dengue fever patients.
Key words: Dengue fever, acute kidney injury, mortality and morbidity in dengue fever.

Introduction

Dengue fever is a mosquito borne viral illness that has endangered a vast population of tropical and sub-tropical areas. According to world mosquito program, about 40% population of the world is at risk of dengue infection. Each year, almost 50 million people are infected with dengue and an estimate indicates that 3.9 billion people in 128 countries are at risk of infection with dengue virus.[1] Dengue was documented in 1982 for the first time in Pakistan.[2] There were multiple epidemics in later years after the first episode. Dengue is now endemic all over the country.[3]

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Authors Contribution

MTA & MA conceptualized the project and did the literature search. MNA, MNH & MRA did the data collection. MRA & KB performed the statistical analysis. Drafting, revision & writing of manuscript were done by MTA, MA & MNA.

Dengue virus (DENV) is a small single-stranded RNA flavivirus comprising of four antigenically distinct serotypes (DENV-1 to 4). Dengue virus causes a wide spectrum of clinical illnesses previously classified as undifferentiated fever, dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[4] Later on, clinical experts faced difficulties in applying the criteria of DHF to clinically severe cases of dengue and this led to evolution of a new classification based on severity of illness. In accordance with WHO guidelines 2009, presence of warning signs (severe plasma leakage, severe hemorrhage and severe organ impairment) differentiates severe dengue from dengue.

Fever is the most common clinical presentation in dengue infection accompanied by vomiting, headache, body aches, abdominal discomfort and generalized rash all over the body.[5] Plasma leakage, due to an increase in capillary permeability, is a cardinal feature of dengue hemorrhagic fever. Dengue has multi-system clinical involvement including liver, hematological system, respiratory system and central nervous system. The presence of nonstructural protein 1 (NS1) antigen has highest diagnostic yield of dengue infection in early stages.[6] Improved appetite, bradycardia, rash, fatigue and mood changes are usually observed during recovery period.[7]

Acute kidney injury (AKI) is a decline in kidney function during 48 hours as demonstrated by an increase in serum creatinine of more than 0.3 mg/dl, an increase in serum creatinine of more than 50%, or the development of oliguria.[8] Spectrum of renal disorders is least studied in dengue infection that varies from mild glomerulonephritis to AKI. There is paucity of published data about incidence of renal involvement in dengue patients.[9] Acute kidney injury is rare but a well-known complication of dengue infection. Its prevalence among dengue patients has been found to be 0.3 to 3.3% worldwide.[9]

Dengue infection has been a growing health problem in Pakistan and AKI is a least studied complication.[10] Its presence in dengue may be linked to increased morbidity and mortality. Due to frequent dengue epidemics in Pakistan, this study was conducted to find the frequency of stages of AKI on the basis of its severity and to compare the frequency of mortality and morbidity in various stages of AKI among dengue patients.

Methodology

This retrospective cross sectional analysis was carried out at Nephrology Department, Multan Institute of Kidney Diseases, Multan. After approval from hospital ethical review committee, data of ninety (90) male and female dengue patients between 15-50 years age was retrieved from hospital medical record system from May to October 2019. These patients were categorized into severe dengue (with warning signs) and dengue (with no warnings signs). The presence of warning signs was established by the evidence of nasal or gum bleeding, abdominal pain or persistent vomiting. On the basis of history and medical record available in hospital medical record system, patients with chronic kidney disease (glomerular filtration rate < 30 ml/min/1.73m2) and those with diabetes mellitus were excluded from the study. Diagnostic criteria of dengue fever was according to WHO definition i.e. febrile illness with or without warning signs (severe plasma leakage, severe hemorrhage, and severe organ impairment). IgM antibodies detected by enzyme linked immunosorbent assay (ELISA) were used as a serological test for dengue infection. Presence of AKI and its severity were classified according to AKIN criteria into stage-1 (serum creatinine of 1.5-1.9 times from the baseline at 48 hours from admission), stage-2 (serum creatinine of 2.0- 2.9 times from baseline at 48 hours from admission) and stage-3 (serum creatinine of more than 3.0 times from the baseline at 48 hours from admission or requiring dialysis) AKI.

Outcome of patients was categorized into morbidity (persistent renal dysfunction expressed by serum creatinine >1mg/dl seven days after admission) and mortality (death of dengue patients due to AKI within seven days of their admission).

Data of 90 male and female cases from 15 to 50 years of age, with confirmed dengue IgM antibodies by ELISA were taken from the hospital medical record system using universal sampling technique (all who fit the selection criteria were taken as sample size i.e 90 patients record, further sampling was done according to specific objective of the study i.e. 19 patients record). The history and examination findings were reviewed from the medical record for evidence of mucosal bleeding, abdominal pain and persistent vomiting. On the basis of presence or absence of these warning signs, patients were categorized into dengue and severe dengue. The record of serum creatinine, done at the time of admission, 48 hours later and then 7 days after hospital admission was taken. The follow up record of patients, discharged within 7 days after admission was taken from medical record of consultant clinic. Presence of AKI and its severity were classified according to AKIN criteria into stage-1, stage-2 and stage-3 AKI. Outcome was categorized as morbidity of patients having persistent renal dysfunction

manifested by serum creatinine >1 mg/dl assessed 7 days after admission and mortality of patients who died within 7 days of hospital admission. All information was recorded by researcher himself using a structured performa.

Data was entered and analyzed using SPSS 16.0 version. Frequency and percentages were calculated for the qualitative variables i.e. gender, AKI, stages of AKI, morbidity and mortality. Quantitative variables of the study like age, BMI, were expressed as Mean±SD. Morbidity and mortality were compared in various stages of AKI by using chi-square test keeping *p*-value ≤0.05 as significant. Data was stratified for age, gender and BMI to address effect modifiers. Post-stratification, chi-square test was applied taking *p*-value ≤0.05 as significant.

The ethical approval was obtained from the Interactive research and development, Institutional review board (IRD-IRB), Multan Institute of Kidney Diseases, Multan.

Results

The median age of patients was 28.5 years. There were 51 (56.7%) males and 39 (43.3%) females. At baseline, the mean serum creatinine was 0.84±0.23mg/dl which was increased to 1.30±0.52 after 48 hours. . Overall prevalence of AKI in dengue patients was 21.1% (19 patients). Out of 19 AKI patients, 10 (52.6%) had stage I, 8 (42.1%) had stage II and 1 (5.3%) had stage III AKI (Figure).

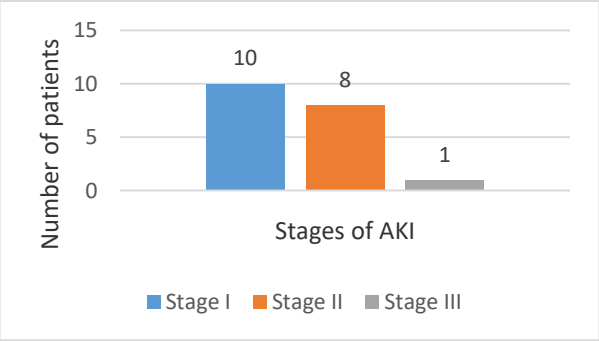

Figure: Distribution of stages of AKI: (stage I AKI 52.6%, stage II 42.1%, stage III 5.2%).

In patients aged 15-30 years, 6 (16.2%) had AKI, in patients aged 31-45years, 9 (22.5%) had AKI and in patients aged >45years, 4 (30.8%) had AKI. The difference was insignificant (*p* >0.05). In males, 14 (27.5%) had AKI and in females, 5 (12.8%) had AKI. The difference was insignificant (*p* >0.05).

After 7 days, the mean serum creatinine of 19 AKI patients was 1.36±0.56mg/dl. Out of 19 patients, 11 showed outcome i.e. 7 (63.6%) had morbidity (persistent AKI) while 4 (36.4%) had mortality.

In patients with stage I AKI, 2 (10.5%) had morbidity. In patients with stage II AKI, 5 (26.3%) had morbidity while 3 (15.7%) had mortality. In patients with stage III AKI, 1 (5.2%) had mortality. The difference was insignificant (*p* >0.05) (Table).

Table: Outcome and stages of AKI in patients.

Outcome	*Stages of AKI*			*p-value*
	Stage I n (%)	*Stage II n (%)*	*Stage III n (%)*	
Morbidity	2 (10.5)	5 (26.3)	0 (0.0)	0.235
Mortality	0 (0.0)	3 (15.7)	1 (5.2)	

Note: Percentage of morbidity and mortality was calculated out of total AKI patients. Chi-square test was applied to calculate *p*-value which was found insignificant (<0.05).

In 15-30 years of age, 1 patient with stage I AKI had morbidity while no morbidity or mortality observed in any other stage. In 31-45 years age group, 1 patient with stage I AKI had morbidity. In stage II, 3 (50%) had morbidity and 2 (40.0%) had mortality while in stage III no patient had any complications. In patients aged >45years, no morbidity or mortality observed in stage I AKI, 2 (66.7%) had morbidity and 1 (33.3%) had mortality in stage II while in stage III, 1 (100%) had mortality.

In male patients with stage I AKI, 1 (100%) had morbidity while no mortality. In stage II, 3 (60.0%) had morbidity while 2 (40.0%) had mortality, while in stage III, 1 (100%) had mortality. In female patients with stage I AKI, 1 (100%) had morbidity while no mortality. In stage II, 2 (66.7%) had morbidity and 1 (33.3%) had mortality while in stage III, no patient had any complications.

Discussion

The overall fequency of AKI in dengue patients in our study was 21.1%. According to a local study by Khalil et al, the prevalence of AKI among dengue patients was 13.3% [10]. He found that 64.8% patients were of AKI stage I, 18.3% stage II and 16.9% were diagnosed with stage III AKI. In another local study, morbidity associated with dengue was 62.5% and mortality was 37.5%.[11]

Although the hospital based prevalence of AKI and its morbidity and mortality are comparatively low in our study but it is important to mention that almost all of these studies were conducted during the times when dengue was endemic in our region. There has been a marked improvement in diagnostic

techniques and management of dengue fever and its complications with the passage of time. This is one of the reasons that the incidence of dengue and the resulting complications have declined over time. The development of immunity against dengue in affected patients may be another explanation to this decline.

Acute kidney injury is a significant, albeit poorly studied, complication of dengue. The data available is heterogeneous and mostly originate from retrospective case series and case reports. The reported frequency of this association exhibits wide variation in accordance to the particular population being assessed, severity of dengue, criteria used for the diagnosis of AKI and time of evaluation.[12]

Mortality is reported in 11.3% of dengue patients who developed AKI whereas 7% of the patients developed morbidity in terms of persistent renal dysfunction.[11] In another study, the frequency of AKI was 3.9% in patients of dengue virus infection.[13]

Previously, dengue was thought to affect adult population only. Later on, Laoprasop wattanaet al., reported an incidence of 0.9% among children in Thailand, and Lee et al., reported an incidence of 3.3% among adults in Taiwan.[14,15] In a Brazilian intensive care unit for infectious diseases, dengue was the cause in 4% of the cases of AKI.[16]

In a more recent study that employed the AKIN criteria for diagnosis, the incidence of AKI was 10.8%.[17] Using the AKIN criteria in a retrospective analysis, Khalil et al. identified AKI in 13.3% of a series of patients with dengue confirmed by the presence of IgM antibodies, independent of the severity of disease; 64.8% of the patients were in stage I, 18.3% stage II and 16.9% stage III of the disease.[10]

In one recent investigation, AKI was observed in 14.2% of patients with dengue fever and was accompanied by high morbidity and mortality.[18] In another study, there were 95 patients (14.2%) who had AKI, with AKIN-I, AKIN-II and AKIN-III in 76.8%, 16.8% and 6.4% patients, respectively.[19]

In another study, the RIFLE (risk, injury, failure, loss, ESRD) classification was used to investigate the occurrence of AKI in patients with tropical acute febrile disease. The results showed that the incidence of AKI among patients with dengue upon admission to the hospital was 35.7%.[20] Retrospective studies of case series of dengue have shown that the development of AKI was associated with a longer hospital stay and higher mortality.[10,21,22]

Despite an improvement in the diagnosis and management of dengue fever, the data on multi-system involvement is still insufficient. Multidisciplinary approach is required to conduct large scale researches to yield better understanding of this highly communicable infection. Studies conducted at individual centers have shown different outcomes and it is recommended to have a collaborative approach between different healthcare setups involving sharing of data and experience regarding management of dengue and its complications.

Although frequency of AKI is low but not negligible and among these patients, complications are high. This warrants implementation of screening of renal functions in dengue fever patients in future. This practice can help us in early diagnosis of AKI and we can adopt measures to reduce morbidity and mortality associated with AKI among dengue fever patients.

Conflict of interest: None declared.

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