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Minireview

Acute kidney injury in dengue virus infection

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Abstract

Background. Dengue is a growing public health problem in Pakistan and acute kidney injury (AKI) is one of the least studied complications of dengue virus infection (DVI). The aim of this study was to determine the frequency, severity and predictors of AKI in patients with DVI and to study the impact of AKI on the length of hospital stay and mortality.

Methods. We retrospectively reviewed medical records of patients aged ≥14 years hospitalized with a primary diagnosis of DVI at Aga Khan University Hospital Karachi between January 2008 and December 2010. Binary logistic regression models were constructed to identify factors associated with the development of AKI and to study the impact of AKI on hospital stays of more than 3 days.

Results. Out of 532 patients, AKI was present in 13.3% (71/532). Approximately two-thirds (64.8%) of these patients had mild AKI and a third (35.2%) had moderate to severe AKI. Independent predictors for AKI were male gender [odds ratio (OD) 4.43; 95% CI 1.92–10.23], presence of dengue hemorrhagic and dengue shock syndrome (DSS, OD 2.14; 95% CI 1.06–4.32), neurological involvement (OD 12.08; 95% CI 2.82–51.77) and prolonged activated partial thromboplastin time (aPTT, OD 1.81; 95% CI 1.003–3.26). AKI was associated with a length of stay ≥3 days when compared with those who did not have AKI (OD 2.98; 95% CI 1.66–5.34). Eight patients (11.3%) with AKI died whereas there were no mortalities in patients without AKI ($P < 0.001$). Only 5 patients (7%) had persistent kidney dysfunction at discharge.

Conclusions. AKI in DVI is associated with neurological involvement, prolongation of aPTT, greater length of hospital stay and increased mortality.

Keywords: acute kidney injury; dengue; length of hospital stay; mortality; predictors for AKI

Introduction

Dengue is one of the commonest mosquito-borne infections caused by the flavi virus. Owing to rising trade activities and tourism across the world, the virus has been transported from the endemic region to various other parts of the world [1, 2]. As a result, compared with nine reporting countries in 1950, currently the geographic distribution includes >100 countries. Each year 50 million people are affected by dengue and around 2.5 billion people are at risk [3]. Dengue was first documented in 1982 in Pakistan [4]. Pakistan has had multiple epidemics ever since the first episode in 1994 [5]. The virus is now endemic in all provinces of the country [6]. Dengue can affect various organs of the body including liver, hematological system, respiratory system and brain. Acute kidney injury (AKI) is one of the least studied complications of dengue.

The majority of previous studies used variable definition of AKI in dengue virus infection (DVI), and included only patients with dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The Acute Kidney Injury Network (AKIN) definition of AKI can potentially pick up from mild to severe AKI [7] and hence is used in our study. We included all cases with primary diagnosis of DVI, irrespective of severity of the DVI using the World Health Organization (WHO) 1997 definition.

There are only a few case reports [8–15] in the literature and very few studies done on AKI in DVI [16–18]. Due to the frequent epidemics and endemic nature of infection in Pakistan, this retrospective study was planned to gather more information about AKI in dengue. We report the largest case series from South Asia (Pakistan) on AKI in DVI. Our aim was to study the frequency, severity and predictors of AKI. In addition, the impact of AKI on the length of stay and mortality was also studied.

Materials and methods

Setting and study population

This was a retrospective case series study conducted at Aga Khan University Hospital Karachi, Pakistan. Aga Khan University Hospital is a tertiary care health facility located in the largest city of Pakistan, Karachi, which has a population of around 15 million. It has 15 inpatient units with a total capacity of 563 beds. Data were collected after

receiving approval from the ethics review committee of the institution. Study subjects included inpatients admitted with a primary diagnosis of DVI. They were identified from a central computerized record for a period of 3 years from January 2008 to December 2010 with the help of the Department of Health Information Management System. Records of the cases were retrieved through codes using International Classification of Diseases 9th Revision Clinical Modification (ICD-9 CM) 061 for DVI and ICD-9 CM 065.4 for DHF and DSS. Study subjects included patients aged >14 years admitted with the primary diagnosis of DVI and confirmed dengue IgM antibodies, irrespective of severity of DVI. Patients with chronic kidney disease, those with no laboratory evidence of DVI and malaria were excluded. Patients were divided into two cohorts (those with and those without AKI) in order to determine independent predictors of AKI. Similarly, two cohorts for length of stay inside the hospital were also made in order to study impact of AKI on the length of hospital stay. Data on demographics, clinical features, laboratory data, length of stay, recovery of renal functions and mortality were noted on a pro forma. We used the AKIN definition for classification of AKI Stages [7]. Stage 1 AKI was defined as an increase in serum creatinine >26.5 μmole/L (≥0.3 mg/dL) or 1.5 to 2-fold increase from baseline. Stage 2 AKI was defined as an increase in serum creatinine of >2–3-fold from baseline. Stage 3 AKI was defined as an increase in serum creatinine of >3-fold from baseline or an absolute serum creatinine of >354 μmol/L (≥4 mg/dL). The WHO 1997 classification was used to classify DVI into dengue fever (DF), DHF and DSS [19].

The length of stay was divided into ≤3 days and >3 days. Mild hepatitis was defined as alanine aminotransferase (ALT) 0.75–5.01 μkat/L (45–300 IU/L) and severe hepatitis was defined as ALT > 5.01 μkat/L (>300 IU/L).

Data analysis

Descriptive statistics were used to summarize baseline values and demographic data. Quantitative and qualitative data were expressed as mean, median, interquartile range and standard deviation (SD) and number of observations with percentage (%), respectively. To evaluate the association between outcomes (AKI and without AKI group, length of hospital stay) and each of the factors, χ^2-test or Fisher's exact tests of independence were used to compare proportions where appropriate, and the Student's t-test was used to analyze continuous data. Odds ratios (OR) and their 95% confidence intervals (CI) were estimated using binary logistic regression, with AKI and length of hospital stay (≤3 versus >3 days) as outcomes. Multivariable models were constructed, including variables that showed an effect in the prediction of AKI and length of hospital stay >3 days in the univariate analysis. All P-values were based on two-sided tests and significance was set at a P-value <0.05. The analyses were performed using SPSS version 19.

Results

General characteristics of the study population

Out of 532 patients, two-thirds (70.9%) were male. The mean age was 35.2 ± 14.7 years (range 15–85 years). DF was found in the majority of patients (84.4%). DHF was present only in 76 (14.3%) patients, followed by DSS in only 7 (1.3%) patients. Seventy-one (13.3%) patients developed AKI. Approximately two-thirds (64.8%) of the subjects had AKIN Stage 1 AKI. AKIN Stage 2 AKI was present in 13 (18.3%) patients and Stage 3 AKI was present in 12 (16.9%) patients. Among other manifestations, 329 (61.8%) had mild hepatitis with ALT 0.75–5.01 μkat/L (45–300 IU/L) and 47 patients (8.8%) had severe hepatitis with ALT > 5.01 μkat/L (>300 IU/L). Prolongation of prothrombin time was found in 64 (12%), while 225 (42.3%) patients had prolonged aPTT. Fourteen

Table 1. General characteristics of the study population ($n = 532$)

Variables	Mean ± SD	Median/range/ percentages
Age (years)	35.29 ± 14.70	32 (15–85)
Gender		
Male	377	70.9%
Female	155	29.1%
Length of hospital stay	3.46 ± 3.45	3 (1–33 days)
Peak creatinine (μmol/L)	98.124 ± 83.98	79.56 (17.68–875.16)
Peak creatinine in AKI (μmol/L)	229.84 ± 174.15	149.6 (114.92–875.16)
Admission creatinine (μmol/L)	90.16 ± 61.88	79.56 (17.68–857.48)
Admission hematocrit (Proportion of 1.0)	0.4102 ± 0.063	0.415 (0.199–0.58)
Peak hematocrit (Proportion of 1.0)	0.422 ± 0.0563	0.424 (0.264–0.58)
Platelets	38.65 ± 42.14	23 (2–427)
Alanine aminotransferase (μkat/L)	2.73 ± 5.86	1.27 (0.050–60.55)
Prothrombin time (s)	12.82 ± 8.70	11.10 (3–120)
aPTT (s)	36.02 ± 15.12	33.35 (11.2–120)
Central nervous system involvement	11	2.1%
Vasopressin	5	0.9%
Respiratory failure	14	2.6%
WHO classification		
DF	449	84.4%
DHF	76	14.3%
DSS	7	1.3%
Length of stay in hospital (days)		
≤3	386	72.6%
>3	146	27.4%
Alanine aminotransferase		
Normal	156	29.3%
Mild hepatitis 0.75–5.01 μkat/L	329	61.8%
Severe hepatitis >5.01 μkat/L	47	8.8%
Prothrombin time (s)		
≤15	468	88%
>15	64	12%
aPTT (s)		
≤35	307	57.7%
>35	225	42.3%
Platelets (per μL)		
<50 000	406	76.3%
50 000–100 000	93	17.5%
100 000–150 000	23	4.3%
>150 000	10	1.9%

Table 2. Frequency, severity and outcome of AKI at discharge

Total number of patients	532
AKI	71 (13.3%)
AKIN-1 AKI	46 (64.8%)
AKIN-2 AKI	13 (18.3%)
AKIN-3 AKI	12 (16.9%)
Outcome at discharge	Fully recovered = 58 (81.7%) Persistence kidney dysfunction = 5 (7%) Mortality = 8 (11.3%)

Table 3. Predictors of AKI in individuals aged ≥14 years hospitalized for DVI ($n = 532$)

Variables	Univariate analysis			Multivariate analysis	
	AKI	No AKI	P-value	OD [95% CI]	P-value
Age (years)	43 ± 18.39	34.12 ± 13.70	<0.001	1.02 (1.007–1.04)	0.006
Gender					
Male	62 (87.3)	315 (68.3)	0.001	4.43 (1.92–10.23)	<0.001
Female	9 (12.7)	146 (31.7)			
CNS	7 (9.9)	4 (0.9)	<0.001	12.08 (2.82–51.77)	0.001
Respiratory failure	9 (12.7)	5 (1.1)	<0.001		
DF	52 (73.2)	397 (86.1)	<0.001		
DHF	12 (16.9)	64 (13.9)		2.14 (1.06–4.32)	0.03
DSS	7 (9.9)	0			
Normal	20 (28.2)	136 (29.5)	0.01		
Mild hepatitis 0.75–5.01 μkat/L	38 (53.5)	291 (63.1)			
Severe hepatitis >5.01 μkat/L	13 (18.3)	34 (7.4)			
Length of hospital stay (days)					
≤3	29 (40.8)	357 (77.4)	<0.001		
>3	42 (59.2)	104 (22.6)		3.07 (1.68–5.62)	<0.001
Prothrombin time (s)					
≤15	54 (76.1)	414 (89.8)	0.001		
>15	17 (23.9)	47 (10.2)			
aPTT				1.81 (1.003–3.26)	0.04
<35	26 (36.6)	281 (61)	<0.001		
>35	45 (63.4)	180 (39)			
Platelets (per μL)					
<50 000	61 (85.9)	345 (74.8)	0.12		
50000–100 000	7 (9.9)	86 (18.7)			
100000–150 000	1 (1.4)	22 (4.8)			
>150000	2 (2.8)	8 (1.7)			

(2.6%) patients had respiratory failure and 11 (2.1%) patients had neurological involvement. Among those with AKI, eight patients (11.3%) died, whereas there was no mortality in patients who did not have AKI. Among survivors at the time of discharge from hospital, 58 patients (81.7%) had complete recovery of the kidney function and only 5 (7%) continued to have some degree of renal dysfunction (Table 1).

Independent predictor for AKI

On binary logistic regression male gender (OD 4.43; 95% CI 1.92–10.23), presence of DHF and DSS (OD 2.14; 95% CI 1.06–4.32), neurological involvement (OD 12.08; 95% CI 2.82–51.77) and prolongation of aPTT (OD 1.81; 95% CI 1.003–3.26) were found to be independent predictors for the development of AKI (Tables 2 and 3).

Independent predictor for the length of hospital stay

Three hundred and eighty-six patients (72.6%) had length of hospital stay <3 days, while the rest (27.4%) had length of stay >3 days. We found that AKI was an independent predictor for increased length of hospital stay (OD 2.98; 95% CI 1.66–5.34) (Table 4).

Table 4. Impact of AKI on the length of hospital stay and mortality

Length of stay in hospital			
AKI ≤ 3 days	AKI > 3 days	Univariate analysis	Multivariate analysis
29 (7.5%)	42 (28.8%)	P < 0.001	OD [95%CI 2.98 (1.66–5.34)] P ≤ 0.001
Mortality			
AKI	No AKI	Univariate analysis	Multivariate analysis
8 (11.3%)	0 (0%)	P < 0.001	

Discussion

Tropical acute febrile illnesses are common causes of AKI in developing countries. DF along with other tropical infections like malaria, scrub typhus, enteric fever, leptospirosis and hantavirus have been reported to cause AKI [20]. AKI is a complication of DVI which has not been studied much. There are multiple proposed mechanisms for etiopathogenesis of renal impairment in DVI. Dengue causes capillary leakage and loss of fluid from the intravascular compartment leading to shock [9, 10] which may lead to decreased kidney perfusion and acute tubular necrosis. Possible etiological factors for AKI in DF include hypotension with either hemolysis or rhabdomyolysis and shock as reported in various case reports [8, 11–14]. On the other hand, unexplained AKI has also been reported in the literature [15]. Interestingly, dengue may cause glomerular injury in addition to the above-mentioned mechanisms as reported in one study [21]. The presence of viral antigen in tubular epithelial cells has been demonstrated [22]. Two experimental studies also provide evidence supporting possible glomerular injury in DVI [23, 24].

The incidence of AKI found in our study is higher than reported in other studies. Laoprasopwattana *et al.* have reported an incidence of 0.9% [16] in Thai children. Whereas Lee *et al.* described an incidence of 3.3% [17]. This difference could be because of different selection criteria used for defining AKI. However, it is interesting to note that both of the above-mentioned studies defined AKI as a rapid elevation of serum creatinine >2 mg/dL. They might have under-recognized AKIN Stage 1 AKI, which accounted for 64.8% of the patients in our study. A more recent study by Mehra *et al.* reported an incidence of 10.8% using the AKIN definition and their findings are comparable with ours [25] (Table 5).

Table 5. Summary of case series on AKI in DVI

Author	Year	Country	Study design/size	Main theme	Outcome
Laoprasopwattana *et al*. [16]	2010	Thailand	Case series/2893 cases	Outcome of DHF-caused AKI in Thai Children	Twenty-five patients (0.9%) developed AKI. Patients with DHF induced AKI were matched with those without AKI. AKI with DHF has a mortality of 64% and was associated with DHF-Grade IV (odds ratio 16.9; 95% CI) and obesity (odds ratio 6.3; 95% CI). Respiratory and liver failure along with major bleeding was found in those with AKI
Lee *et al*. [17]	2009	Taiwan	Case series/304 cases	Clinical characteristics, risk factors and outcomes in adults experiencing DHF complicated with acute renal failure.	10 out of 304 patients with DSS had AKI. The rest were taken as control. DSS was independently associated with AKI and mortality was high in those with AKI.
Wiwanitkit *et al*. [18]	2005	Thailand	Case series	Acute renal failure in the fatal cases ofDHF, a summary in Thai death cases	AKI was found in 33.3% of cases of fatal DHF in contrast to 0.3% of all cases of DHF
Mehra *et al*. [25]	2012	India	Case series/233 cases	AKI in DF using AKIN criteria: incidence and risk factors	Twenty-four patients (10.8%). developed AKI and all-cause mortality was 9%

We found coagulopathy and derangement of both intrinsic and extrinsic pathways in our case series. However, AKI was significantly associated with prolongation of aPTT. Thus, hypotension in combination with coagulation derangement might be the possible etiology for the development of AKI. Male gender was over represented in our case series and had a higher risk of developing AKI. Increased mobility of male population in our society might be putting them at higher risk of mosquito bite or it might be just because they have better access to health care in our part of the world.

Dengue is associated with significant morbidity and mortality as well as an enormous economic burden [26, 27]. The mean length of hospital stay in patients with dengue has been reported to be 3–4 days in various studies. Khan *et al*. [28] from Saudi Arabia reported length of stay of 4 days. Similarly, a study from Singapore reported the mean stay as 3 days [29]. Parkash *et al*. [30] reported a mean hospital stay of 4 days in patients with associated hepatitis. The mean length of stay in our study was 3.46 days, which is comparable with internationally reported data. Moreover, we found that AKI was associated with a longer hospital stay and hence is an independent predictor for length of hospitalization. We did not come across any published literature looking at the impact of AKI on hospital stay in patients with DVI.

Various studies from Pakistan have reported mortality of 2.6–2.7% in the general population infected with DVI [30, 31]. International data report a variable mortality ranging from 0 to 3.7% [32–35]. However, impact of AKI on mortality in dengue is less well studied. We found a significantly increased rate of mortality (11.3%) in patients with AKI, and interestingly no mortality in patients without AKI. Therefore, the presence of AKI in DVI predicts increased morbidity and mortality.

This study has several limitations. The study is retrospective in nature and is of limited clinical use as the study focused on inpatients, therefore excluding patients who visited outpatient clinics and other hospitals. Also, the study was limited to a single center. Moreover, histopathology reports in clinically indicated cases were not available to elucidate etiopathogenesis of AKI. Patients were only followed up until discharge and there was a lack of long-term follow-up. Prospective studies are needed with renal biopsy in clinically indicated cases along with a long-term follow-up to know more about the etiopathogenesis and outcome of AKI in DVI.

Conclusions

AKI in DVI causes significant morbidity and mortality. The presence of AKI in patients with DVI should be vigilantly monitored preferably in a special care unit. The presence of AKI should alert clinicians for admission and early initiation of supportive treatment under close monitoring in order to avoid morbidity and mortality associated with this complication.

Authors' contributions

M.A.K. planned and wrote the final manuscript. S.S., M.A.C., B.M. and Z.K. carried out data collection and entry into SPSS. J.T. and S.Y. reviewed the first draft of the manuscript. S.A.H. supervised and reviewed the study protocol and gave important suggestions throughout the study and in writing the manuscript.

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Conflict of interest statement. None declared.

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