

Acute kidney injury in severe dengue

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ABSTRACT

Background: Several forms of renal involvement have been identified in patients with dengue, including proteinuria, glomerulonephritis, and IgA nephropathy to acute kidney injury (AKI). **Objective:** The objective of the study was to know the type of AKI and the outcome of patients with AKI. **Materials and Methods:** All serologically proven dengue patients admitted in our wards/pediatric intensive care unit (PICU) were included in the study. A detailed history was done and a thorough clinical examination was performed on all the included patients. They were monitored for pulse pressure, urine output, hemoglobin, packed cell volume, and platelet counts regularly. On admission, renal function tests were done and assessed for pre-renal or renal AKI. Patients were managed as per the WHO protocol for dengue. **Results:** Based on the pediatric risk, injury, failure, loss, and end-stage renal disease criteria, we encountered an incidence of 61.3% of AKI, of which 45% were at risk of developing AKI and 15.9% had developed kidney injury. All the patients had pre-renal type of AKI. There were no deaths seen, but the length of stay was prolonged in patients with AKI. **Conclusion:** It is possible to detect renal involvement at an early phase, and by strict monitoring of fluid status, timely management can reduce the morbidity and mortality.

Key words: *Acute kidney injury, Pediatric risk; injury; failure; loss; end-stage renal disease, Severe dengue, Pediatric intensive care unit*

Dengue infection is a mosquito-borne systemic acute febrile illness caused by arbovirus, commonly transmitted by *Aedes aegypti*, and to a lesser extent by *Aedes albopictus* and *Aedes polynesiensis* mosquito [1]. According to antigenic characteristics, there are four serotypes of dengue virus: DEN-1, DEN-2, DEN-3, and DEN-4 [2]. A new serotype, DEN-5, was identified in serum samples collected during an epidemic of dengue in Malaysia in 2007 [3]. It is widely spreaded in tropical and subtropical countries. The reported incidence is 390 million dengue infections per year, of which 96 million present at any level of severity, that is, clinical or subclinical [4]. In 2009, the WHO revised the classification of dengue infection, and dengue was divided into probable dengue, dengue fever (DF) without warning signs, DF with warning signs, and severe dengue [5]. Recently, the WHO 2011 regional revised guidelines classified dengue into DF, dengue hemorrhagic fever (DHF) without shock or with shock hemorrhage (DSS), and expanded dengue syndrome [1].

Severe dengue is a potentially deadly complication due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. The next 24–48 h of the critical stage can be lethal; proper medical care is needed to avoid complications and risk of death. Acute kidney injury (AKI) is a potential complication of severe dengue infection and is typically associated with hypotension, rhabdomyolysis, or hemolysis [6]. Several forms of renal involvement have been identified in

patients with dengue, including proteinuria, glomerulonephritis, and IgA nephropathy to AKI [7]. Association of AKI in severe dengue diagnosed by pediatric risk, injury, failure, loss, and end-stage renal disease (pRIFLE) criteria is associated with higher mortality [8–10]. Dengue-induced AKI is a less appreciated intricacy that can occur more profoundly in DHF and DSS but less commonly in DF, and hence, this study was taken to study the occurrence of AKI in severe dengue infection with emphasis on the type of AKI so that early detection of renal involvement and immediate intervention can reduce morbidity and mortality.

METHODOLOGY

This was a cross-sectional study conducted from July 2017 to October 2017 in the Department of Pediatrics of a Tertiary Care Institute of Central India. The ethical clearance was obtained from the ethical review board of the institution. The case file information was de-identified during data collection and was coded. All the serologically proven dengue-positive patients admitted to pediatric intensive care unit (PICU) were included in the study. Their detailed history and examination were done. On admission, kidney function test was done and assessed for pre-renal or renal AKI as per pRIFLE criteria. They were regularly monitored for pulse pressure, urine output, hemoglobin, packed cell volume, and platelet counts. Patients were managed as per the WHO protocol for dengue.

Criteria for severe dengue include any sign of severe plasma leakage, leading to shock or fluid accumulation with respiratory distress, severe bleeding, and severe organ impairment. AKI was identified and staged as per pRIFLE criteria (Table 1). Reference values for serum creatinine (CR) (by Jaffe's method) were taken as follows: Infants - 0.2–0.4 mg/dl, child - 0.3–0.7 mg/dl, and adolescent - 0.5–1.0 mg/dl.

In our study, the ratio of blood urea nitrogen to serum creatinine has been taken to diagnose pre-renal (ratio >20) or renal (ratio <20) type of AKI. Glomerular filtration rate (GFR) was calculated as per Schwartz formula [11]: $GFR (ml/min/1.73 \text{ sq.m}) = k \times \text{height (cm)} / \text{plasma creatinine (mg/dl)}$, where k is proportionality constant and the value is taken as 0.34 in preterm infants, 0.45 in term infants, 0.55 in children and adolescent girls, and 0.7 in adolescent males. The obtained data were statistically analyzed by applying descriptive mean, standard deviation, t-value, and mean difference in terms of various variables. We have entered all data, and statistical analysis was done with the help of IBM SPSS-25 software.

RESULTS

A total of 154 serologically proven dengue children were admitted in our PICU from July 2017 to October 2017. According to the WHO guidelines, 44 (28.5%) of 154 children had severe dengue. Based on the pRIFLE criteria, 27 (61.3%) patients had AKI; of which, 20 (45%) patients were at risk of developing AKI, whereas 7 (15.9%) had developed kidney injury which was statistically significant ($p < 0.05$). All the patients, 27 (100%), had pre-renal type of AKI, and the average GFR in patients who were at risk of developing AKI was 84.77 ± 48.82 and in those with injury was 20.87 ± 93.18 ($p < 0.05$). There were no deaths reported, but patients with AKI had comparatively longer duration of hospital stay (6–10 days) as compared to patients with non-AKI (5 days) (Table 2).

DISCUSSION

There are many faces of renal involvement with dengue infection; even AKI may result from various mechanisms, that is, by intense systemic inflammation, hemodynamic instability, hemolysis, rhabdomyolysis, and acute glomerulonephritis. Retrospective studies of the case series of dengue have shown that the development of AKI is associated with a longer hospital stay and higher mortality [12–14]. Careful assessment of the warning signs of severe dengue and the patient's blood volume is crucial for the prevention of AKI. The amount of infused fluid should be the minimum needed to maintain the hemodynamic conditions until there is a reversal of the increased vascular permeability. Prior knowledge of expected clinical profile and predictors of AKI development would provide information to identify patients at high risk.

In our study, 44 (28.5%) patients of a total of 154 patients had severe dengue, based on the WHO dengue guidelines. Of 44 cases of severe dengue, 27 (61.36%) patients suffered

Table 1: pRIFLE criteria to stage AKI

Stage	(CR) or GFR criteria	UO criteria
Risk	Increased CR $\times 1.5$ OR GFR decreases $>25\%$	UO $<0.5 \text{ ml/kg/h}^*$ 6 h
Injury	Increased CR $\times 2$ OR GFR decreased $>50\%$	UO $<0.5 \text{ ml/kg/h}^*$ 12 h
Failure	Increased CR $\times 3$ OR GFR decreased $>75\%$ OR CR $\geq 4 \text{ mg/dl}$ (with acute rise of $\geq 0.5 \text{ mg/dl}$)	UO $<0.3 \text{ ml/kg/h}^*$ 24 h OR Anuria $\times 12 \text{ h}$
Loss	Persistent ARF=complete loss of renal function for >4 weeks	
ESRD	End stage renal disease	

GFR: Glomerular filtration rate, ARF: Acute renal failure, pRIFLE: Pediatric risk, injury, failure, loss, end stage renal disease, UO: Urine output, AKI: Acute kidney injury

Table 2: Length of stay in AKI vs. non AKI patients

Days	AKI		Non-AKI
	Risk	Injury	
≤ 4	3	0	6
5–6	14	0	9
7–8	2	4	2
>9	1	3	0

AKI: Acute kidney injury

from AKI as per the pRIFLE criteria. We encountered 61.36% incidence of AKI which is very high as compared to a study by Laoprasopwattana *et al.*, who found a lower incidence ranging from 0.9% to 5% [6]. The incidence of AKI in dengue infection diagnosed by AKIN criteria (14.2%) and RIFLE criteria (12.6%) is superior to diagnose by conventional definition (4.2%) [15]. Mallhi *et al.* found AKI in 14.2% of severe dengue children as per AKI criteria [16]. In a study done among adults by Lee *et al.* in Taiwan, they reported an incidence of 3.3% [17–18]. Previous studies investigated for AKI among patients with DHF showed an incidence of 3.9% [13], 9.3% [12], and 12% [19].

In another study, the RIFLE classification was used to investigate the occurrence of AKI in patients with the tropical acute febrile disease. The results showed that the incidence of AKI among patients with dengue on admission to the hospital was 35.7% [20]. The nature of AKI, in our study, was pre-renal; thereby, appropriate fluid resuscitation of hypovolemia secondary to third space loss and proper maintenance of electrolyte imbalance with monitoring of pulse pressure and urine output are crucial measures to prevent AKI in all dengue patients to have a good prognosis. The limitations of this study were that we had a limited sample size along with that this research was an area-based research.

CONCLUSION

In this prospective study, we conclude that it is possible to detect renal involvement at an early phase and by strict monitoring of

fluid status and timely steps toward the management can reduce morbidity and mortality.

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