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REVIEW

Dengue hemorrhagic fever and the kidney

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Abstract Dengue virus infection (DVI)/dengue hemorrhagic fever (DHF) is a common febrile illness with a variety of severities. The mortality rate is high in dengue shock syndrome (DSS), caused by circulatory failure due to plasma leakage resulting in multi-organ failure. However, acute kidney injury (AKI) is rarely reported. In areas of endemic DVI, the prevalence of AKI due to DVI has been reported to be as high as 6.0 % in children with AKI, and 0.9 % in children with DVI who were admitted to a hospital. The mechanism of AKI in DVI is not clear. It may result from (a) direct injury as in other infectious diseases, (b) an indirect mechanism such as via the immune system, since DHF is an immunological disease, or (c) hypotensive DSS, leading in turn to reduced renal blood supply and renal failure. The mortality rates of DF/DHF, DSS and DHF/DSS-related AKI are <1 %, 12-44 %, and >60 %, respectively. Kidney involvement is not actually that rare, but is under-recognized and often only reported when microscopic hematuria, proteinuria, electrolyte imbalance, or even AKI is found. The prevalence of proteinuria and hematuria has been reported as high as 70-80 % in DVI. A correct diagnosis depends on basic investigations of kidney function such as urinalysis, serum creatinine and electrolytes. Although DVI-related renal involvement is treated supportively, it is still important to make an early diagnosis to prevent AKI and its complications, and if AKI does occur, dialysis may be required. Fortunately, in patients who recover, kidney function usually completely recovers as well.

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Introduction

Dengue virus infection (DVI) originated in Southeast Asia and then over the years spread to South America and Africa, and it is now found over almost half of the world. The spread of DVI has also been increasing in recent years, as increased world travel has led to the introduction of many diseases such as DVI to places where they were formerly unknown [1–6]. A history of travel to a tropical or subtropical region is essential for obtaining a diagnosis of DVI in a patient with signs and symptom of DVI who is from a non-endemic DVI area [7, 8]. Currently DVI affects about 1 % of the world's population annually and costs billions of dollars to treat [9–12], although the number at risk ranges from 30-55 % [13].

DVI is associated with the high morbidity of an acute febrile illness. Dengue is defined as either dengue ± warning signs or severe dengue according to the 2009 classification by WHO [14] as shown in Figure 1.

Prior to 2009, DHI was classified according to the severity of plasma leakage as classical dengue fever (DF: acute febrile illness with bleeding disorder), dengue hemorrhagic fever (DHF: DF with plasma leakage), or dengue shock syndrome (DSS: DHF with shock) [14, 15]. As most references referred to in this review article use the earlier classification system, we will use it also.

DVI is a disease that primarily affects children. However, since 2000 it has become increasingly found in adults [1, 16–19]. It is generally more severe in adults than in children, and it is more severe in older children than in

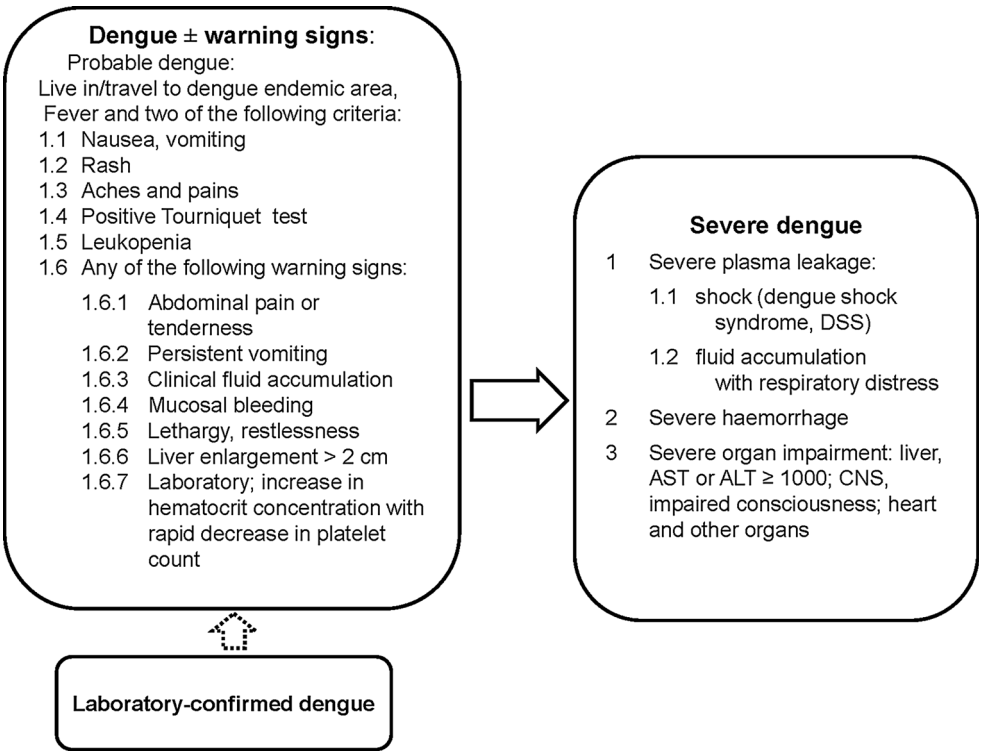

Fig. 1 Dengue case classification and severity level

younger children [9, 18, 20–22]. One reason DVI may be more severe in adults is that since DVI is well known in hyperendemic areas, parents are educated about DVI as a pediatric infection and usually take a possibly infected child to seek medical care at the first sign of disease, which leads to decreased morbidity and mortality [7, 23].

Hemorrhagic fever with renal involvement is the most common presentation of Hantaan virus infection [24–31], while dengue infection with renal injury is less commonly reported, although it has been known for many years [32]. Renal manifestations are only rarely reported with DVI and are usually associated with severe multi-organ involvement [33].

Acute kidney injury (AKI) following DVI has only rarely been studied, and in the few studies that have been done, case reports of adult instances have been more common than childhood cases [18, 34–37].

The objective of this review article is to remind physicians who regularly encounter cases of acute febrile illness to be aware of DVI, and especially to be aware of potential renal involvement in DVI, particularly AKI.

Incidence

The exact incidence of DVI is unknown, since in developing countries, large numbers of people have no access to medical treatment, and even when a medical facility is available, very often there are insufficient laboratories to confirm all cases [16, 38, 39]. If the physician is not aware of potential kidney involvement, then the appropriate investigations are unlikely to be performed (e.g., looking for microscopic hematuria, proteinuria, glomerulonephritis and/or AKI), and kidney involvement in DVI becomes under-diagnosed and under-reported [40]. In 1973, Futrakul et al. [32] performed urinalysis in 24 children with DHF, and proteinuria, glycosuria, ketonuria, occult blood, microscopic hematuria and an increased number of tubular cells were found in 71 %, 19 %, 38 %, 38 %, 80 % and 90 % of the cases, respectively.

Table 1 shows urinalysis and serum electrolyte results from two studies [41, 42]. In a study from our institute, the percentage of patients with abnormal urinalysis increased with dengue severity (p-value < 0.001): 19.4 % with dengue fever (DF), 27.0 % with dengue hemorrhagic fever (DHF), and 36.7 % with dengue shock syndrome (DSS) [42]. Higher electrolyte imbalances were also associated with dengue severity ($p < 0.001$): 25.1 % with DF, 33.5 % with DHF, and 39.8 % with DSS [42]. Interestingly, a report from another hospital in Bangkok demonstrated a higher prevalence of electrolyte imbalances in DF and DHF patients than was found our study [41].

Mild proteinuria is a well-known, non-specific manifestation of renal involvement in many conditions, including fever [43, 44], so when proteinuria is found, it is impossible to be certain if it is from fever or DVI. One

Table 1 Abnormal findings in urinalysis and electrolyte disturbances in dengue virus infection

	Lumpaopong et al. [41]		Vachvanichsanong et al. [42]
	DF	DHF	DF + DHF + DSS
Urine	(n = 67)	(n = 73)	(n = 1342)
Abnormal UA	-	-	28.5 %
Glycosuria	-	-	3.7 %
Hematuria	18 %	27 %	6.3 %
Proteinuria	15 %	27 %	22.1 %
Electrolytes	(n = 73)	(n = 77)	(n = 1249)
Hyponatremia	61 %	72 %	19.9 %
Hypernatremia	-	-	0.3 %
Hypokalemia	14 %	17 %	11.6 %
Hyperkalemia	-	-	5.0 %

DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; UA, urinalysis

Table 2 The prevalence of acute kidney injury induced by dengue virus infection

Author	Year of study	N	Age (years)	Country	DVI	AKI (%)
Vachvanichsanong et al. [42]	1987-2007	2,221	<15	Thailand	DF/DHF/DSS	0.2
Laoprasopwattana et al. [47]	1989-2007	2,893	<15	Thailand	DF/DHF/DSS	0.9
Mendez and Gonalez [48]	1992-2002	617	<13	Columbia	DHF	1.6
Khan et al. [37]	2004	91	6-94	Saudi Arabia	DHF	2.2
Lee et al. [22]	2002	304	> 18	Taiwan	DHF/DSS	3.3
Kuo et al. [49]	2002	273	48 ± 18	Taiwan	DF/DHF/DSS	5.5†
						27.1‡
Bunnag et al. [50]	2008-2009	50	Children	Thailand	DSS	10.0
Mehra et al. [51]	-	223	26.2 ± 18.2	India	DF/DHF	10.8
Khalil et al. [52]	2008-2010	532	15-85	Pakistan	DF/DHF/DSS	13.3
Basu et al. [53]	2007-2008	28	Adults	India	-	35.7

† GFR ↓ >50 %

‡ GFR ↓ >25 %

DVI, dengue virus infection; AKI, acute kidney injury; DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome

report from Singapore found that two adults with DHF had heavy proteinuria, with readings in the nephrotic range, but there were no clinical manifestations of nephrotic syndrome [45].

In a study from our institute, we reviewed cases of AKI in children over a 22-year period, and DHF was found in 6 % of cases (19/318) [46].

Table 2 shows the prevalences of AKI in DVI in various studies. The prevalence varied widely from 0.2 % to 35.7 % due to varying definitions of AKI, severity of DVI, age of the patients, and country of study. Another study from our institute found that 0.9 % (25/2893) of DVI children had AKI, and of those 24 of 25 had DSS [47]. A study from Taiwan regarding a DVI outbreak in 2002 found that DHF prevalence was higher in adults than in children (14.1 % vs. 3.6 %, p = 0.026). The rate of renal insufficiency and AKI in adults was 68/376 (18.1 %) and 7/606 (1.2 %), respectively, while no AKI occurred in 55 DVI children [18]. Yet another study from that outbreak found that among 304 hospitalized adults, 10 had AKI (two with DHF and eight with DSS) [22].

Pathophysiology

The pathophysiology of kidney involvement in DVI is still unclear, since it is usually not a serious manifestation, and the severe form, AKI, is not common. The mortality rate of AKI-related DVI is high, and there are few opportunities to perform any studies. There are also various confounding factors, for instance, dengue virus itself can cause direct injury to the kidney, or the injury can result from an

indirect mechanism such as another acute infectious disease, which can make the diagnosis of AKI late or unmade altogether [36].

The mechanism of kidney injury in DHF may be through hemorrhage or via the immune mechanism, as DHF is an immunological disease. Immune complexes have been found in kidney biopsy tissue [54]. Other related causes may be hemolysis or rhabdomyolysis. AKI-related DVI is usually associated with shock or hemolysis or rhabdomyolysis [40]. Rhabdomyolysis, one of the unusual manifestations in DHF, can cause multi-organ failure, including AKI [34, 55, 56]. There have been two earlier reports describing three men who developed rhabdomyolysis following DHF, although fortunately, they did not develop AKI [57, 58].

In DSS, the mechanism of kidney injury may be as above or via hypotensive mechanisms resulting from prolonged shock [59]. One study using multivariate analysis indicated that DSS was an independent risk factor for AKI (OR, 220.0; 95 % CI, 19.8-2443.9) [22]. Nair et al. [60] reported DF in a boy who developed AKI, although there was no bleeding, fluid leakage or shock, and another report noted a similar phenomenon in two adults [61]. Wiersinga et al. [62] reported DVI-induced hemolytic uremic syndrome in a 48-year-old man.

Clinical manifestations

There is a wide variety of clinical manifestations of DVI, ranging from subclinical to systemic and up to death. The principal symptoms are fever, bleeding due to thrombocytopenia, and hypotension due to vascular permeability impairment, which causes serum leakage, resulting in intravascular volume depletion, pleural effusion, ascites and hypotension. If the leakage is not replaced, severe hypotension and hypovolemic shock can result.

Multiple organ involvement is occasionally reported in severe cases, including CNS, renal, hepatic and/or respiratory involvement [3, 61, 63]. Multi-organ involvement is usually found in the presence of hypotension and severe bleeding; however, it can occur in the absence of hypotension or severe bleeding as well. Laoprasopwattana et al. [47] found that in 25 AKI-related DHF/DSS cases in children, respiratory failure, hepatic failure and severe bleeding disorder were associated with 80.0 %, 96.0 % and 84.0 % of the cases, respectively. A report from Taiwan of 10 DHF/DSS adults with AKI found 80 % with gastrointestinal bleeding [22].

There has been a report of adults with chronic kidney disease (CKD) also having DHF/DSS, but the diagnoses were difficult and delayed due to the mimicked symptoms in CKD and DHF/DSS. The treatment of these cases was also a dilemma, since fluid and electrolyte manipulation is difficult in CKD, and all the patients died [64]. This study is a good reminder, however, for physicians to seek for associated diseases in CKD patients.

Rare manifestations of DVI include liver damage, neuropathy and cardiomyopathy, and electrolyte imbalance has also been occasionally reported [61, 65, 66]. AKI has been reported in the absence of hypotension, hemolysis, rhabdomyolysis, or nephrotoxic drug use [67].

Interestingly, dual infections in DHF/DSS are occasionally reported and may be a cause of AKI, particularly septicemia [34]. For example, in a report from Taiwan of 127 DHF/DSS patients, seven (5.5 %) had concurrent bacteremia. The patients who had bacteremia had a higher median age and more prolonged fever than the patients who did not have bacteremia (70.0 vs 52.0 years and 8.0 vs 4.0 days, respectively). A similar study found that DSS and unusual manifestations were more common in patients who had bacteremia than in those who did not (3/7 [42.8 %] vs. 3/93 [3.2 %] and 3/7 [42.8 %] vs. 5/93 [5.3 %], respectively) [34]. It is important to remember that in dual infections, such as are reported in these studies, synergistic effects may induce AKI. The multivariate analysis from the Taiwan study showed that AKI and fever >5 days were independent risk factors for the development of bacteremia in DHF/DSS patients (OR, 51.5; 95 % CI, 4.4-607.6 vs. 26.1 (95 % CI, 1.8-381.5, respectively). In another report, also from Taiwan, of 10 DHF/DSS cases with AKI, three also had bacteremia [22].

Another report found disseminated candidiasis as a co-infection with DVI, leading to AKI [68], and in yet another, Thaha et al. [69] reported AKI in patients who had severe malaria and DSS. Both diseases can cause AKI, but to determine the specific disease that causes the AKI is not possible, and it is unnecessary in terms of therapy.

Laboratory findings

DVI is confirmed by either a serological study of dengue virus antibodies or by dengue virus isolation from blood. The principal means of checking for renal involvement is urinalysis and biochemical studies [59]. Abnormal electrolyte conditions such as hyponatremia can be due to DVI itself causing plasma leakage or to hypotonic therapy or renal salt loss. Urine sodium or fractional excretion of sodium (FENa)(FENa = UNa/SNa X SCr/UCr X 100 %) tests can determine the definite cause of hyponatremia. Hyperkalemia can also be due to DHF-induced hemolysis or rhabdomyolysis, or to AKI. Metabolic acidosis can also be due to shock from DHF or AKI.

An increase in blood urea nitrogen (BUN) and serum creatinine in DVI indicate AKI. A report from Taiwan of

10 DHF/DSS adults with AKI found a maximum creatinine level of 2.1-11.5 mg/dl, while three of eight patients who had BUN/creatinine ratios available had ratios >20, indicating renal hypoperfusion [22]. A report from our institute of DHF/DSS with AKI in 25 children found maximum serum creatinine levels up to 4.9 ± 2.9 mg/dl [47].

Abnormal renal histopathology is rarely reported, since a renal biopsy is rarely performed in dengue patients due to the risk of bleeding. However, in one study, patients who were well enough to have a renal histopathological examination were found to have red blood cells in their tubular lumens, interstitial nephritis, and immune complex glomerulonephritis, including acute tubular necrosis [59].

Renal involvement in dengue hemorrhagic fever was first demonstrated by renal biopsy more than 30 years ago in a study in which 10 out of 20 renal biopsies showed an immune complex of IgG, IgM and C_3 deposited in the glomeruli, also with focal thickening of the glomerular basement membrane and mesangial hypertrophy [54]. Dengue virus or RNA has also been found in the kidneys in fatal DHF [68, 70, 71]. Viral replication in the kidneys is unknown. However, only one study has investigated this phenomenon, with a result that viral RNA was not detected in tubular cells in the kidneys [71].

Other tests, such as a liver function test or coagulogram, should be performed to search for other organ involvement, since the association between multiorgan failure and DHF/DSS with AKI is high.

Diagnosis

The standard diagnosis of DVI follows the World Health Organization clinical and laboratory criteria, which are acute onset of high fever, hemorrhagic disorders (e.g., petechiae, purpura, a positive tourniquet test, epistaxis, bleeding of gums or gastrointestinal bleeding), hepatomegaly, evidence of plasma leakage, (e.g., ascites, pleural effusion, rapid pulse, narrow pulse pressure, or hypotension, including signs of hypovolemic shock) and oliguria [14].

Laboratory criteria include hemoconcentration (a hematocrit increase of >20 % from baseline) and thrombocytopenia (platelet count less than 100,000 cells/mm^3), possibly, but not necessarily, with leucopenia, leukocytosis and/or atypical lymphocytes.

DVI is confirmed by a serology test or blood isolation for dengue virus. Although there are four dengue serotypes, no study has yet been done to determine which serotype(s) can cause kidney injury or which serotype(s) can lead to more-serious forms of DHF/DSS. The causes of severe rather than mild DHF/DSS can be quite complex, as the severity depends not only on virus serology but also on patient susceptibility (host immunity, age, genetics) and environmental factors [16, 72, 73]. The incidence has been reported to be higher in males [1, 22].

It should be emphasized that AKI is diagnosed when the serum creatinine level increases above normal values for age and sex [74]. Additionally, abnormal electrolytes can be related to renal involvement in DVI or AKI, such as hyponatremia, hyperkalemia and metabolic acidosis, and therefore, serum electrolytes should be checked in DVI patients.

Treatment

The main strategies for dealing with DHF/DSS, are first, early detection to reduce dangerous complications, and then, once detected, careful monitoring for hypovolemia and appropriate fluid therapy (fluid and electrolyte solutions, plasma and plasma-expanders) [75]. (Although what constitutes appropriate fluid therapy is still somewhat controversial, as there is still some disagreement over which fluid or fluids are best, and the appropriate volume, rate of infusion and timing [5].) An optimal specific therapy for DVI-related kidney injury has not yet been established, but complications or unusual manifestations should be carefully watched for and dealt with immediately when they appear.

Dialysis can offer some improvement in some cases. An earlier study from our institute involved 25 DHF/DSS-with-AKI children, of whom 11/25 (44.0 %) had dialysis performed; although half of the patients ultimately died despite the dialysis (3/9 survivors and 8/16 deceased had dialysis), this should not be seen as an indicator that dialysis is of little or no use, as these were very severe cases whose prognosis was very poor anyway, and although kidney function can be replaced by dialysis, when other organs concurrently fail, a high death rate is to be expected [47]. In another study involving dialysis in DHF/DSS adults with AKI from Taiwan, hemodialysis was performed in three of six patients who died, but of the four who survived, the number of patients who had dialysis was not reported [20]. Dialysis is definitely beneficial in helping patients with AKI to maintain renal function when the kidneys fail or are temporarily unable to function due to disease [26].

Prognosis

If diagnosis and treatment are appropriate, the fatality rate of DVI should be less than 1 % [5, 39, 76]. When high morbidity or mortality occurs in DHF/DSS patients, it is primarily due to plasma leakage, which causes severely

inadequate intravascular volume or severe bleeding from coagulopathy associated with major organ involvement. If shock ensues, mortality dramatically increases, with reported rates as high as 12-44 % [9, 55, 77].

Even without a specific treatment, however, the outcome of mild kidney involvement in DHF is still favorable, as with kidney involvement in other acute febrile illnesses, and we can think of it as "acute reversible glomerulonephritis" [59]. However, the much more severe AKI-related DHF/DSS is much more likely to result in a poor outcome, since this is usually associated with other major organ failure or prolonged shock, uncontrolled coagulopathy and/or respiratory failure. Fatalities in DHF/DSS associated with multiorgan involvement cannot be avoided, even if optimal treatment is available and provided. The mortality rate of AKI-related DHF/DSS has been reported to be as high as 60 % (6/10) [22] and 64 % (16/25) [47]. One study comparing mortality rates found that of 519 DVI patients, of whom 12 died, the patients with AKI had a mortality rate significantly higher than those who did not (28.6 % vs 1.2 %, $p < 0.001$) [49].

AKI rates have also been found to be higher in DHF/DSS patients with bacteremia than in those without bacteremia (5/7 [71.4 %] vs 4/81 [4.9 %]); mortality rates were also found to be higher (2/7 [28.5 %] vs 1/93 [1.1 %]) [34].

The kidney is one of the vital organs, and kidney survival is normally quite directly related to patient survival. Early detection of AKI-related DHF/DSS is essential, and when found, the patient should immediately be referred to an institute where appropriate treatment, including renal replacement therapy (RRT), is available.

AKI is by itself not an indicator of a grave prognosis, since RRT as the treatment of choice gives a high survival rate. However, in situations where there is a bleeding problem, RRT is usually only reluctantly performed. In patients who do survive, kidney function usually returns to normal. In a study from our institute, the serum creatinine of nine out of 25 children who survived an episode of AKI-related DHF/DSS returned to normal on average within 32 days (range, 1-48 days) [47].

Conclusion

The variety of types of kidney involvement in hemorrhagic fever is wide, from subclinical with only nonspecific laboratory results such as microscopic hematuria or proteinuria to the most severe form of kidney injury, AKI. Treatment is based on the standard treatment for hemorrhagic fever, with more-intensive fluid and electrolyte therapy, and correction of the associated bleeding disorder. Nephrotoxic drugs must be avoided, and dialysis is essential in AKI. The prognosis then depends on whether other major organs are involved. Kidney function usually returns to normal in surviving patients.

We hope this brief discussion will alert physicians who have not previously encountered AKI in dengue to be sure to watch for it in the future.

Compliance with ethical standards

Ethical approval This study was exempt from Ethics Committe because it is a review article.

Conflict of interest None.

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