

ELECTROLYTE DISTURBANCE AND KIDNEY DYSFUNCTION IN DENGUE VIRAL INFECTION

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Abstract. Dengue virus infection (DVI) is endemic in tropical countries in both children and adults. The classical presentation includes fever, hepatomegaly, thrombocytopenia-related bleeding disorders, and plasma leakage. Multi-organ involvement, including kidneys is found in complex cases. Asymptomatic electrolyte disturbances, abnormal urinalysis, and more severe manifestation such as acute kidney injury (AKI) usually indicate kidney involvement. Such manifestations are not rare in DVI, but are often not recognized and can cause the physician to misread the real situation of the patient. The prevalence of electrolyte disturbances or kidney involvement reported in studies varies widely by country and mainly depends on the severity of DVI and age of the patients. The prevalence of DVI-induced AKI ranges from 0.2%-10.0% in children and 2.2%-35.7% in adults. The prevalence among all age groups appears to be increasing in the last decade. Dengue shock syndrome (DSS) has been reported to be an independent risk factor for AKI development. The mechanism of DVI-induced AKI is complex and the details are to date undetermined. Urinalysis, serum electrolytes and creatinine measurements should be performed to document renal involvement in DVI patients for early detection and initiation of appropriate fluid therapy with close monitoring. Renal replacement therapy may be required in some cases. The presence of AKI dramatically increases the mortality rate among both childhood and adulthood DVI from 12%-44% to more than 60%.

Keywords: acute kidney injury, dengue hemorrhagic fever, dengue shock syndrome, dengue viral infection, electrolyte disturbance, kidney involvement

INTRODUCTION

Dengue viral infection (DVI) has been a serious concern in terms of being widespread and incurring large expenses for many countries, especially tropical area, for several decades. Attempts to eradicate the DVI have not been successful despite the

dramatic increase in the incidence of DVI worldwide. Additionally, the characteristics of dengue hemorrhagic fever and dengue shock syndrome (DHF/DSS) have become more complex in some cases. In DVI, the kidney is one of the major organs affected. The manifestations of kidney involvement vary from electrolyte disturbance, hematuria, proteinuria, and glomerulonephritis to severe acute kidney injury (AKI) (Futrakul *et al*, 1973; Hommel *et al*, 1999; Abboud, 2003; Mendez and Gonzalez, 2003; Nair *et al*, 2005; Vachvanichsanong *et al*, 2006;

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Lima *et al*, 2007; Khan *et al*, 2008; Kuo *et al*, 2008; Lima and Nogueira, 2008; Lee *et al*, 2009; Vasanwala *et al*, 2009; Laoprasopwattana *et al*, 2010; Lumpaopong *et al*, 2010; Basu *et al*, 2011; Bunnag and Kalyanarooj, 2011; Khalil *et al*, 2012; Mehra *et al*, 2012).

PREVALENCE

The prevalence of kidney dysfunction or electrolyte disturbance due to DVI may be under-recognized depending on the frequency of laboratory tests performed. The stage and severity of DVI are also important; if tests are performed too early, then the chance of detecting an abnormality is lower than when tests are performed at later stages. Evidences of kidney involvements in DVI may also be under-reported or ignored if the findings are mild or do not significantly affect the clinical condition or result in modification of therapy. Additionally, abnormal findings may not be a direct result of the DVI, but can result from a DVI-caused complication, such as hypotension, shock or associated septicemia.

ABNORMAL URINALYSIS

A general feature of kidney involvement is an abnormal urinalysis. To our knowledge, the first study in the literature that reported results of abnormal urinalysis in DVI was from a study of 24 DHF children in 1973 (Futrakul *et al*, 1973). Proteinuria, glycosuria, ketonuria, occult blood, microscopic hematuria and an abnormally high number of tubular cells were found in 71%, 19%, 38%, 38%, 80%, and 90% of the cases, respectively. Table 1 shows two recent studies from Thailand conducted in children with DVI, which demonstrated

abnormal findings of the urine based on urinalysis (Lumpaopong *et al*, 2010; Vachvanichsanong *et al*, 2010). The rate of hematuria was significantly different between the two studies, which may have been due to various reasons, including stage of illness and timing of urine collection, particularly relative to when fluid therapy was initiated, all of which can affect the test results.

HEMATURIA

DVI generally causes bleeding disorders due to thrombocytopenia, and it is not surprising to find microscopic hematuria in DVI patients. However, the incidence of microscopic hematuria is often not reported. Macroscopic hematuria may be found in patients who have urinary catheterization.

In a cohort study of 154 adults and 147 children with DVI, the prevalence of a positive urine blood test was similar between the children and adults (55% vs 58%), although some symptoms were different (Hanafusa *et al*, 2008). A positive urine blood test can mean hemoglobinuria or myoglobinuria as well as hematuria.

PROTEINURIA

Proteinuria is one of the most common abnormalities found by urinalysis in DVI children (Vachvanichsanong *et al*, 2010). However, proteinuria is a non-specific finding that can result from many different conditions, including even mild conditions, such as fever (Loghman-Adham, 1998; Hogg *et al*, 2000). The significance of proteinuria usually depends on the severity and condition of the patient; it can be a warning sign of renal damage and further

Table 1
Prevalence of abnormal findings in urinalysis in dengue viral infection in two studies from Thailand.

| | Lumpaopong <i>et al</i> , 2010 | | Vachvanichsanong <i>et al</i> , 2010 |
|-------------|--------------------------------|---------------|--------------------------------------|
| | DF (n=67) | DHF (n=73) | DF + DHF + DSS (n=1,342) |
| Abnormal UA | - | - | 28.50% |
| Glycosurea | - | - | 3.70% |
| Hematuria | 18% | 27% | 6.30% |
| Proteinuria | 15% | 27% | 22.10% |

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

damage can occur if it persists. Vasanwala *et al* (2009) reported on two cases of adult DHF who had heavy proteinuria in the high nephrotic range, but neither had any other characteristics of nephrotic syndrome. Hutspardol *et al* (2011) reported the case of a child with nephrotic range proteinuria who also had hypoalbuminemia, right pleural effusion and azotemia. However, both studies showed that the proteinuria was eventually self-limiting.

GLOMERULONEPHRITIS

The classical glomerulonephritis characteristics of hematuria, edema, and hypertension are unlikely to be documentable in patients with DVI. Hematuria is often seen in DVI patients; therefore, physicians may not even consider glomerulonephritis as the possible cause. Glomerulonephritis in DVI patients can only be confirmed by histopathology. In one study of 20 patients with DHF, immune complex was found in half (Boonpucknavig *et al*, 1976). Interestingly, Rajadhyaksha and Mehra (2012) reported a case of a 22-year-old woman who developed systemic lupus erythema-

tosus and lupus nephritis four weeks after diagnosis of DVI.

Other unusual findings have been reported, such as DF-induced hemolytic uremic syndrome in a 48-year-old patient (Wiersinga *et al*, 2006) and IgA nephropathy in a 15-year-old DF patient (Upadhaya *et al*, 2010).

ELECTROLYTE AND ACID-BASE DISTURBANCES

Table 2 shows electrolyte disturbance results from three studies in DVI children. Hyponatremia was found to be the most common electrolyte disturbance in these patients. In one study, hyponatremia was reported as high as 66% in 150 children with DF and DHF (Lumpaopong *et al*, 2010). However, half of these cases (50%) had mild hyponatremia (serum sodium 130-134 mEq/l), while 14.7% had serum sodium levels between 125-129 mEq/l, and only 1.3% had concentrations <125 mEq/l. In another study of 45 children with DSS, 46.7% had hyponatremia (Bunnag and Kalayanarooj, 2011), while from another study conducted in our institute, only 19.9%

Table 2
Electrolyte disturbances in dengue viral infection from three studies.

| | Lumpaopong <i>et al</i> , 2010 | | Vachvanichsanong <i>et al</i> , 2010 | Bunnag and Kalayanarooj, 2011 |
|---------------|-----------------------------------|---------------|---|----------------------------------|
| | DF (n=73) | DHF (n=77) | DF + DHF + DSS (n=1,249) | DSS (n=50) |
| Hyponatremia | 61% | 72% | 19.90% | 46.7% (n=45) |
| Hypernatremia | - | - | 0.30% | - |
| Hypokalemia | 14% | 17% | 11.60% | - |
| Hyperkalemia | - | - | 5.00% | - |
| Hypocalcemia | - | - | - | 68.3% (n=41) |

DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome.

of 1,249 DVI children had hyponatremia (Vachvanichsanong *et al*, 2010). Additionally, another study found that hyponatremia was 9.7 times more prevalent in 49 DVI children compared to 44 children with other acute febrile illnesses (Mekmullica *et al*, 2005). In an earlier study from our institution, abnormalities in urine and electrolytes significantly increased with increasing DVI severity (Vachvanichsanong *et al*, 2010).

Bunnag and Kalayanarooj (2011) reported a very high rate of hypocalcemia (68.3%) among 41 DSS children.

Metabolic acidosis is usually found in shock or AKI conditions. Bunnag and Kalayanarooj (2011) reported metabolic acidosis in 14% of 50 DSS children while Lumpaopong *et al* (2010) found metabolic acidosis in only 8.6% of 150 DF/DHF children.

In another study from the northeast of Thailand, in patients aged less than 18 years who died from DVI, electrolyte and acid-base disturbances were found in 7/8 (87.5%) and 51/91 (56.0%), DF and DHF patients, respectively (Lumbiganon *et al*, 2012).

ACUTE KIDNEY INJURY

Acute kidney injury (AKI), is the current medical term for what was formerly known as acute renal failure (ARF), and it describes a sudden onset of renal dysfunction, which primarily means a decrease in the glomerular filtration rate (GFR). This in turn, results in retention of waste products, leading to metabolic acidosis, hyperkalemia, hypocalcemia, hyponatremia or hypernatremia and water retention.

There was no consensus on the precise biochemical definition of ARF. Generally it was defined as a rise in serum creatinine greater than two times the baseline value or the upper limit of normal values for age and gender in children, and a serum creatinine greater than 2 mg/dl in adults (Chan *et al*, 2002; Kellum *et al*, 2002). Although serum creatinine levels can have a wide range, its effect on mortality is abrupt rather than gradual, and once a 'tipping point' is crossed, a small change in serum creatinine can have a high impact on a patient's mortality.

The Acute Dialysis Quality Initiative (ADQI) group introduced the RIFLE (Risk

Table 3
RIFLE criteria for acute kidney injury classification (Bellomo *et al*, 2004).

| RIFLE stage | Creatinine/GFR criteria | Urine output criteria |
|--------------------------|--|--|
| Risk | Increased SCr \times 1.5 or decreased GFR > 25% | < 0.5 ml/kg/h for 6 hr |
| Injury | Increased SCr \times 2 or decreased GFR > 50% | < 0.5 ml/kg/h for 12 hr |
| Failure | Increased SCr \times 3 or decreased GFR > 75% or SCr > 4 mg/dl | < 0.3 ml/kg/h for 24 hr or anuria for 12 hr |
| Loss | Persistent renal failure > 4 weeks | |
| End-stage kidney disease | End-stage kidney disease (> 3 months) | |

GFR, glomerular filtration rate; SCr, serum creatinine.

Table 4
Modified RIFLE criteria for pediatric patients (pRIFLE) (Akcan-Arikan *et al*, 2007).

| RIFLE stage | eCCr criteria | Urine output criteria |
|--------------------------|---|--|
| Risk | Decreased by 25% | < 0.5 ml/kg/h for 8 hr |
| Injury | Decreased by 50% | < 0.5 ml/kg/h for 16 hr |
| Failure | Decreased by 75% or eCCr < 35 ml/min/1.73 m ² | < 0.5 ml/kg/h for 24 hr or anuria for 12 hr |
| Loss | Persistent renal failure > 4 weeks | |
| End-stage kidney disease | Persistent renal failure > 4 months | |

eCCr, Estimated creatinine clearance.

of renal dysfunction; Injury to the kidney; Failure of kidney function; Loss of kidney function; End-stage kidney disease) criteria to classify the stage and severity of renal dysfunction for early detection, treatment and prevention of further kidney damage (Bellomo *et al*, 2004). The criteria are listed in Table 3, with a modification of the RIFLE classification system for pediatric patients shown in Table 4 (Akcan-Arikan *et al*, 2007). The Risk, Injury and Failure stages refer to AKI, and increasing RIFLE stage indicates increasing risk of death.

The prevalence of DVI-related AKI seems to be low, because the number of

reported cases in the literature is small (George *et al*, 1988; Gunasekera *et al*, 2000; Davis and Bourke, 2004; Lim and Goh, 2005; Vachvanichsanong *et al*, 2006; Wiersinga *et al*, 2006; Karakus *et al*, 2007; Lima *et al*, 2007; Laoprasopwattana *et al*, 2010; Wijesinghe *et al*, 2013). However, in recent decades the prevalence of DVI-related AKI has significantly increased (Table 5) from 0.9% to 35.7%, with the high variation attributable to the definition of AKI used, severity of DVI, age of the study patients, and capabilities of the hospital. AKI has a high impact on hospital stay, morbidity, and mortality in DVI patients

(Laoprasopwattana *et al*, 2010; Khalil *et al*, 2012).

In our institute during an 18-year period, 25 of 2,393 (0.9%) children admitted with DVI developed AKI. The mortality rate of those who developed AKI was high at 64%. The independent risk factors of AKI were DHF grade IV (odds ratio, OR: 16.9; 95% confidence interval, CI: 4.2-68.5) and obesity (OR: 6.3; 95% CI: 1.4-28.8). The indicators of mortality were dengue grade IV, oliguria AKI, respiratory failure and prolonged prothrombin or activated partial thromboplastin greater than twice the normal values. The serum creatinine of all patients who survived returned to normal within 1-48 days (Laoprasopwattana *et al*, 2010). In a similar study in Taiwanese adults hospitalized with DHF, 10 out of 304 (3.3%) developed AKI, with a mortality rate of 60%. DSS was the only independent risk factor for development of AKI (Lee *et al*, 2009).

In a study from Taiwan of 519 adults with DVI, the estimated glomerular filtration rates (eGFR) decreased by >25%, >50%, and >75% in 21.6%, 2.9%, and 2.6%, respectively, of the 273 cases that had at least two separate measurements for serum creatinine (Kuo *et al*, 2008). Compared to DF patients, patients with DHF/DSS were five times more likely to have a >50% decrease in their eGFR (15% vs 2.9%, $p = 0.001$). Additionally, 21 patients with chronic kidney disease (CKD), defined as eGFR <60 ml/min/1.73 m², were significantly more likely to have a >50% decrease in their eGFR (36.8% vs 3.1%, $p < 0.001$) and had a significantly higher mortality rate (28.6% vs 1.2%, $p < 0.001$). One study of 99 fatal DVI cases in 2010 found that AKI and acid-base disturbances were two of the

most common complications (Lumbiganon *et al*, 2012).

MECHANISMS OF AKI IN DVI

The principle mechanism of AKI can be simply explained as hypoperfusion and hypoxia from shock (Laoprasopwattana *et al*, 2010). Moreover, DVI-induced AKI may result from various factors, such as the use of non-steroidal anti-inflammatory drugs for antipyrexia, acute tubular necrosis, immune complex mediated acute glomerulonephritis, or sepsis, any of which may require multiple drug therapy, particularly in patients with severe disease, thus making the patient more susceptible to nephrotoxicity as well (Laoprasopwattana *et al*, 2010). Lima *et al* (2007) reported a 48-year-old female with DHF-induced AKI in the absence of hypotension, rhabdomyolysis, hemolysis, or nephrotoxic drug usage, and postulated that the mechanism of AKI may be due to a direct kidney injury caused by the dengue virus.

The actual mechanism of DVI-induced AKI is still undetermined. Some reports have indicated that the mechanism may involve rhabdomyolysis-induced acute tubular necrosis (Gunasekera *et al*, 2000; Davis and Bourke, 2004; Lim and Goh, 2005; Karakus *et al*, 2007; Wijesinghe *et al*, 2013; Repizo *et al*, 2014). DVI has also been connected with muscle injury, and although, as mentioned, the mechanism has not yet been determined, creatine phosphokinase should be monitored for muscle injury, especially in DVI patients.

Severe DHF/DSS patients usually develop multi-organ failure including hepatic failure, carditis, encephalopathy, respiratory failure, and bleeding disorders. However,

Table 5
Prevalence of dengue viral infection-induced acute kidney injury in various studies.

| Author(s) | Country | Study year(s) | DVI | N | Age (yrs) | AKI (%) |
|---------------------------------------|--------------|---------------|------------|-------|-------------|-------------------|
| Laoprasopwattana <i>et al.</i> , 2010 | Thailand | 1989 - 2007 | DF/DHF/DSS | 2,893 | < 15 | 0.9 |
| Mendez and Gonzalez, 2003 | Columbia | 1992 - 2002 | DHF | 617 | < 13 | 1.6 |
| Khan <i>et al.</i> , 2008 | Saudi Arabia | 2004 | DHF | 91 | 6-94 | 2.2 |
| Lee <i>et al.</i> , 2009 | Taiwan | 2002 | DHF/DSS | 304 | > 18 | 3.3 |
| Abboud, 2003 | - | - | - | - | - | 5.0 |
| Kuo <i>et al.</i> , 2008 | Taiwan | 2002 | DF/DHF/DSS | 273 | 48 ± 18 | 5.5 ^a |
| Bunnag and Kalayanaroj, 2011 | Thailand | 2008 - 2009 | DSS | 50 | Children | 27.1 ^b |
| Mehra <i>et al.</i> , 2012 | India | - | DF/DHF | 223 | 26.2 ± 18.2 | 10.0 |
| Khalil <i>et al.</i> , 2012 | Pakistan | 2008 - 2010 | DF/DHF/DSS | 532 | 15 - 85 | 10.8 |
| Lumbiganon <i>et al.</i> , 2012 | Thailand | 2010 | Fatal DF | 8 | < 18 | 13.3 |
| Basu <i>et al.</i> , 2011 | India | 2007 - 2008 | Fatal DHF | 91 | Adults | 25.0 |
| | | | - | 28 | | 14.3 |
| | | | | | | 35.7 |

DVI, dengue virus infection; AKI, acute kidney injury; DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome.
^aGFR decreased > 50%; ^bGFR decreased > 25%.

for patients without multi-organ failure, AKI is an unusual complication; when it does occur, it is usually associated with hypotension, rhabdomyolysis, or hemolysis (Lima and Nogueira, 2008).

Renal histopathology in DVI cases has rarely been reported in the literature due to the contraindication of performing a renal biopsy in patients with a hemorrhagic disease such as DVI. Nevertheless, some renal histopathological studies have been performed after the recovery phase or during post-mortem examinations. In one such study, the dengue virus was detected in the kidney in one third of renal necropsies performed on DHF/DSS patients, but not as high as found in the liver (5/10) (Guzman *et al*, 1999). The most important finding was generalized vascular injury.

TREATMENT

Optimizing fluid administration is the major treatment in DVI patients. Type of fluid prescribed (crystalloid or colloid), tonicity and rate of infusion are critical. Inappropriate fluid replacement can worsen the condition. A high prevalence of hyponatremia emphasizes that fluid therapy in DVI patients should be prescribed with high tonicity. Therapy is more complicated for patients who have abnormal electrolytes or impaired renal function.

Blood component transfusion may also be indicated. Renal replacement therapy (RRT) may be required in some patients who have severe metabolic acidosis, hyperkalemia, oliguric renal failure, or pulmonary edema. In two studies, 11/25 (44%) of childhood DHF/DSS cases with AKI and 3/10 (30%) adults had RRT (Lee *et al*, 2009; Laoprasopwattana *et al*, 2010).

PROGNOSIS

The mortality rate in DVI increases with severity of disease and presence of any complication. The mortality rate of DHF is less than 1%, while for DSS it is about 50 times higher (Anders *et al*, 2011). The mortality rate among DHF/DSS patients increases to more than 60% if AKI is also present (Lee *et al*, 2009; Laoprasopwattana *et al*, 2010).

SUMMARY

Asymptomatic electrolyte disturbance and deterioration of kidney function in DVI are highly prevalent in both children and adults. Transient abnormal urinalyses including heavy proteinuria are demonstrated. The number of DVI-induced AKI cases has been increasing. Kidney function impairment is one of the major potential fatal conditions, and when it occurs, accurate fluid therapy is mandatory with delicate adjustments and close monitoring required. Renal replacement therapy may be required in severe cases.

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