CASE REPORT

HEAVY PROTEINURIA FOLLOWING DENGUE HEMORRHAGIC FEVER

Sakara Hutspardol, Olarn Prommalikit, Nuttaphol Upiya, Jintana Chataroopwijit, Khemika Khemakanok and Kesara Assadamongkol

Department of Pediatrics, Faculty of Medicine, Srinakharinwirot University, Nakhon Nayok, Thailand

Abstract. We report a case of nephrotic range proteinuria with 24-hour urine protein level of 335.7 mg/kg/day which developed following dengue hemorrhagic fever. Due to prolonged hypoalbuminemia from renal loss, right pleural effusion persisted and required pleuracentesis. The patient did not have classical nephrotic syndrome. The proteinuria improved without specific treatment. A renal biopsy was not performed due to self-resolution of the proteinuria and azotemia. Heavy proteinuria is not a typical characteristic of dengue virus infection, therefore the pathophysiology of this nephropathy has not been well described to date.

Keywords: nephrotic range proteinuria, acute kidney injury, dengue hemorrhagic fever

INTRODUCTION

Dengue virus infection is one of the most prevalent viral induced hemorrhagic disorders in Thailand. Various clinical manifestations have been described during the viremic stage. Bleeding diathesis and vascular leakage are major complications responsible for the majority of clinical symptoms. Renal problems have been observed, including acute renal insufficiency from dengue shock syndrome (DSS) and transient IgA nephropathy. Massive proteinuria is not a common finding in patients with dengue hemorrhagic fever (DHF), only two cases of this rare problem have been reported (Thaha *et al*, 2008; Wasanwala *et al*, 2009; Dinda *et al*, 2010). We report a case of DHF with proteinuria in the nephrotic range.

Correspondence: Dr Sakara Hutspardol, Department of Pediatrics, Faculty of Medicine, Srinakharinwirot University, 62 Moo7, Rangsit-Ongkharak Road, Ongkharak, Nakhon Nayok 26120, Thailand.
Tel: 66 (0) 3739-5085 ext 10901; Fax: 66 (0) 3739-5085 ext 10903
E-mail: sakara4695@yahoo.com

CASE REPORT

A 9-year-old boy with no significant medical history presented with a 4-day history of high grade fever, headache and watery diarrhea. He was admitted to the hospital with fever, hepatomegaly and a positive tourniquet test suggestive of dengue virus infection. Dengue IgM antibodies were found in the patient's plasma.

By Day 7 of fever, he had a 22% increase in hematocrit and a platelet count of 22,000/ l. A urine analysis was negative

Table 1
Laboratory results.

Day of illness	4	6	7	8	14	20	45	65
Hematocrit (%)	36	36	44	36	30	33	30	35
Platelets (x 10^6/l)	210	54	22	91	428	355	510	453
BUN (mg/dl)		29	36	22	20	17	11	10
Creatinine (mg/dl)		1.3	1.4	0.9	0.8	1.0	0.6	0.5
AST (U/l)		628	10,803	3,622	555	425	61	44
ALT (U/l)		210	3,611	1,694	369	236	98	59
Albumin (g/l)		23	19	17	29	28	35	44
Urine dipstick protein	Negative	3+	3+	3+	1+	1+	Negative	Negative
Urine protein (mg/dl)				1,356	49		20	33
Urine creatinine (mg/dl)				127	57		58	124
Urine protein/creatinine ratio				10.7	0.86		0.34	0.27
24-hour urine protein (mg/kg/day)				335.7	25.1			
Cholesterol (mg/dl)				83				167
Triglyceride (mg/dl)				290				199
Prothrombin time (seconds)					20.8	12.3		
INR					1.7	1.04		
Partial thromboplastin time (seconds)					50.7	29.5		

for protein, red blood cells and white blood cells on admission (Table 1). Vascular leakage progressed also on the Day 7 while a fever of 40.5ºC persisted. Postural hypotension, bilateral pleural effusions, ascites and further hemoconcentration revealed ongoing plasma leakage and intravascular volume depletion. The patient was treated with 40% dextran and fresh frozen plasma (FFP) to maintain stable vital signs and urine output.

Urinalysis showed 3+ proteinuria on dipstick (CYBOW 11 Reagent test strips for Urinalysis - Urine Qualitative Dipstick Protein; K052525, Difco) by Day 6 of fever and before shock developed. Mild azotemia with a serum creatinine of 1.3 was determined to be due to insufficient intravascular volume and managed with intravenous fluid administration. No urine sediment or casts were seen on microscopy. After the shock was treated the patient developed hepatic encephalopathy with elevated liver enzymes. The patient had depressed level of conscious and mild personality change. The maximum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were on Day 7, being 10,803 U/l and 3,611 U/l, consecutively. A serum blood urea nitrogen (BUN) of 36 mg/dl, creatinine of 1.4 mg/dl, and hypoalbuminemia of 19 g/l were seen. The urine protein/creatinine ratio was 10.7 (normal range 0.2, nephrotic range > 2.0). The 24-hour urine protein level was 335.7 mg/kg/day (nephrotic range >50 mg/kg/day).

Because heavy proteinuria is not a typical feature in DHF, other possible causes of nephrotic syndrome and glomerulonephritis had to be excluded. The antinuclear antibody (ANA), anti-cytoplasmic antibody, and anti-streptolysin O titer were all negative. But the C3 level was high at 360 mg/dl (90-180).

On Day 14 of illness, the fever and right pleural effusion persisted. The hypoalbuminemia was treated with a 20% albumin infusion and intravenous furosemide daily. Vitamin K and FFP were given to treat a coagulopathy. Pleuracentesis was performed for pleural fluid analysis and microbiology culture. His pleural fluid revealed a transudative effusion. After the pleural effusion disappeared, fever subsided and the patient was discharged home one week later. His serum albumin level then increased to 29 g/l without further albumin infusion. The repeat urine test before hospital discharge demonstrated persistent proteinuria with a urine protein creatinine ratio of 0.86 and a 24-hour urine protein of 25.1 mg/kg/day.

At one and two months follow-up, the proteinuria had resolved and the urine protein creatinine ratios were 0.34 and 0.27, respectively. At the most recent visit, the patient was well without complications.

DISCUSSION

Renal complications in dengue virus infection are mainly associated with severity of disease. Acute renal failure and hemolytic uremic syndrome have been reported in cases of DSS (Lee *et al*, 2009). Apart from acute kidney injury as a result of shock and renal hypoperfusion, different manifestations of dengue-virus-induced nephropathy have been reported including microscopic hematuria and albuminuria (Futrakul *et al*, 1973; Horvath *et al*, 1999). However, heavy proteinuria in the nephrotic range is not common in dengue virus infection. In Southeast Asia, two patients from Singapore were reported as having self-limited heavy proteinuria secondary to DHF (Vasanwala *et al*, 2009). Renal biopsies were not performed in the aforementioned patients or in our patient due to spontaneous resolution of proteinuria. The red blood cells and proteinuria in those patients with DHF are similar to patients with acute glomerulonephritis. To clarify the main pathophysiology of kidney involvement in DHF, Boonpucknavig *et al* (1976) performed a kidney biopsy in 20 patients with DHF and renal impairment using fluorescent antibody technique to localize IgG, IgM, and C3 in glomeruli. Electron microscopy revealed focal thickening of the glomerular basement membrane and mesangial cell hypertrophy at immune complex lodging sites (Boonpucknavig *et al*, 1976). *In vivo* studies using preformed soluble dengue antigen-antibody complexes injection directed to glomerulonephritis and proteinuria with deposition of immune complexes in the glomeruli of mice (Boonpucknavig *et al*, 1980).

A correlation between dengue virus infection and nephrotic syndrome has not been well established due to insufficient numbers of patients diagnosed with these two co-morbidities. Pre-existing nephrotic syndrome or glomerulonephritis need to be excluded when systemic autoimmune disease or persistent proteinuria are seen. In our patient with self-limited nephrotic-range proteinuria and transient hypoalbuminemia, hypercholesterolemia was not seen.

Pleural effusions and ascites occur in DHF as a result of increased vascular permeability. With excessive intravenous fluid infusion and plasma leakage, large pleural effusions may form causing respiratory distress. However, thoracocentesis is rarely indicated due to spontaneous resolution of pleural fluid by reabsoption during the convalescent stage. In DHF, pleuracentesis should only be considered in patients with severe respiratory compromise due to the increased risk of bleeding. For nephrotic syndrome, pleural effusions are managed

with albumin replacement. With pleuracentesis, there is a risk of introducing infection.

Due to the low serum albumin caused by massive proteinuria and hemodilution in our patient, a right pleural effusion had not resolved one week after the patient had recovered from DHF. Pleuracentesis was performed to relieve the effusion and albumin infusion was administered to treat hypoalbuminemia. Judicious fluid therapy and nutritional support are helpful in patients with multiple organ involvement.

Awareness of the possibility of proteinuria with DHF is needed for the optimal care for patients with DHF. Albumin replacement may be started early to minimize the sequelae of dengue-virus-associated nephropathy and hasten effusion fluid resorption. Although the massive proteinuria post-DHF in our case and the two patients from Singapore was self-limited, further studies of proteinuria in DHF patients are needed to improve the understanding of the pathophysiology of proteinuria, nephrotic syndrome, and glomerulonephritis in DHF.

ACKNOWLEDGEMENTS

The authors gratefully thank Dr Johnny M Chinnapha for his assistance with the English editing.

REFERENCES

Boonpucknavig S, Siripont J. *In vitro* studies of the normal human B lymphocyte receptors for preformed soluble dengue antigen-antibody complexes. *Clin Exp Immunol* 1980; 39: 676-82.

Boonpucknavig V, Bhamarapravati N, Boonpucknavig S, *et al*. Glomerular changes in dengue hemorrhagic fever. *Arch Pathol Lab Med* 1976; 100: 206-12.

Dinda AK, Agarwal SK, Tiwari SC, *et al*. Transient IgA nephropathy with acute kidney injury in a patient with dengue fever. *Saudi J Kidney Dis Transpl* 2010; 21: 521-5.

Futrakul P, Poshyachinda V, Mitrakul C, *et al*. Renal involvement and reticulo-endothelial-system clearance in dengue hemorrhagic fever. *J Med Assoc Thai* 1973; 56: 33-9.

Horvath R, McBride WJH, Hanna J. Clinical features of hospitalized patients during Dengue-3 epidemic in far north Queensland 1997-1999. *Dengue Bull* 1999; 23: 24-9.

Lee IK, Liu JW, Yang KD. Clinical characteristics, risk factors, and outcomes in adults experiencing dengue hemorrhagic fever complicated with acute renal failure. *Am J Trop Med Hyg* 2009; 80: 651-5.

Thaha M, Pranawa, Yogiantoro M, *et al*. Acute renal failure in a patient with severe malaria and dengue shock syndrome. *Clin Nephrol* 2008; 70: 427-30.

Vasanwala FF, Puvanendran R, Ng JM, *et al*. Two cases of self-limiting nephropathies secondary to dengue haemorrhagic fever. *Singapore Med J* 2009; 50: 253-5.