LEPTOSPIROSIS IN NORTHEASTERN THAILAND: HYPOTENSION AND COMPLICATIONS

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Abstract. During an outbreak of leptospirosis in northeastern Thailand, 148 patients with serologically diagnosed leptospirosis were seen in Loei Hospital. The clinical features were consistent with those described for the classic manifestation of the disease. However, hypotension was a common finding: noted in 94 patients (64%) upon admission or early in the course of the disease. Of these hypotensive patients, 64 (68%) had impaired renal function: 30 patients (32%) had prerenal azotemia and 34 (36%) were in renal failure. Pulmonary complications, including pulmonary edema, hemorrhage, ARDS, and interstitial pneumonitis, occurred in 22% of patients and were often associated with renal failure. A clear association existed between hypotension and renal failure and pulmonary complications. The overall mortality rate was 3.4%. The causes of death were pulmonary complications, renal failure, and sepsis. The death rate among patients with complications was 11.6%. Blood exchange, in addition to conventional treatment, was beneficial in severe leptospirosis with complications and hyperbilirubinemia.

INTRODUCTION

Leptospirosis is a common zoonotic disease in the tropics. The disease is seen sporadically among farmers, fishermen, and sewage workers. Although the clinical features of the disease may follow the classic description (Sitprija, 1996), there are often differences in the prevalence of symptoms, the severity of the disease and its complications (Zaki and Shieh, 1996; Daher *et al*, 1999; Marotto *et al*, 1999) which might reflect variations in bacterial virulence, bacterial load, and clinical management. In recent years there has been an outbreak of the disease in northeastern Thailand. We report on our clinical experience of leptospirosis in Loei Hospital, a general hospital in northeastern Thailand; we have given special attention to the hypotension that may develop early in the course of the disease and to the other severe complications of leptospirosis.

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MATERIALS AND METHODS

From January 1999 to August 31, 2000, 475 patients admitted to Loei Hospital fulfilled WHO criteria for the clinical diagnosis of leptospirosis (Faine, 1982). One hundred and forty-eight of these patients had their diagnosis of leptospirosis confirmed by positive serology (microagglutination). The common serotypes were *L. pyrogenes* and *L. sejroe*; other serotypes included *L. bratislava, L. pomona, L. copenhageni, L. javanica, L. ballico, L. bangkok, L. wollfi* and *L. akiyami*. One hundred and seven were male and 41 were female; in ages ranged from 8 to 76 years with an average of 36 years; the patients were farmers and fishermen. They were admitted to the hospital between 1 and 14 days after the onset of fever (average 4 days).

Penicillin was given intravenously (2 megaunits) every 6 hours for 7 days; ceftriaxone (2 g/day) was given if there was evidence of associated sepsis. Vital signs were recorded every 30 minutes on the first day of admission and every 4 hours thereafter. For those with hypotension (mean arterial pressure < 70 mmHg) 200 ml of normal saline were given intrave-

nously within 15 minutes; the rate was then adjusted to 300 ml/h with close observation of blood pressure, lung signs, central venous pressure, and urine output. If there was no rise in blood pressure and no increase in urine output within 2 hours, dopamine (2 μg/kg/min) was given. If the urine flow remained low despite the correction of hypotension, intravenous furosemide (40-120 mg) was given. When the urinary output had responded adequately, intravenous fluid administration was maintained to match the urine flow rate for 48 hours; in the absence of a response in the urinary output, or in the presence of pulmonary crepitations, intravenous fluid was restricted.

Early intubation and ventilatory support, using 100% oxygen and positive end-expiratory pressure (10 cm water), were instituted for patients with pulmonary complications [acute respiratory distress syndrome (ARDS), pulmonary edema or hemorrhage]. Platelet transfusions were given to those with pulmonary hemorrhage and severe thrombocytopenia (platelets < 50,000/mm^3). In ARDS and pulmonary edema, fluid intake was restricted.

Either hemodialysis or peritoneal dialysis was performed for the patients with blood urea nitrogen (BUN) over 70 mg% and hypercatabolism (BUN increment >20 mg/dl/day). In addition to dialysis, blood exchange (1.5 blood volume) was instituted for the patients with pulmonary complications or hyperbilirubinemia (total bilirubin >25 mg/dl). In early cases, when hemodialysis was not available, only blood exchange was performed.

Tumor necrosis factor alpha (TNFα) in the serum was determined on the second or third day of admission by enzyme-linked immunosorbent assay (Cytoscreen; Biosource International, Camarillo, CA) in 28 patients.

RESULTS

General clinical findings

The common symptoms, seen in more than 60% of the patients, included fever, headache, myalgia, conjunctival suffusion, and hypotension (mean arterial pressure < 70 mmHg). Impaired renal function (serum creatinine > 1.5 mg/dl) was found in 58% of patients; jaundice was found in 41%; pulmonary complications in 22%; nausea and vomiting in 20%; abdominal pain in 12%; and diarrhea in 5%. Interestingly, hyperbilirubinemia (total serum bilirubin > 25 mg/dl) was present in 21 patients (14%); thrombocytopenia (platelet count >100,000/mm^3) in 61 (41%); hyponatremia (Na <125 mmol/l) in 13 (9%); hyperkalemia (K>5 mmol/l) in 9 (6%); and hypokalemia (K<3.5 mmol/l) in 38 (26%). Mild proteinuria (trace to 1+) with red blood cells and white blood cells was observed in 61% of the patients. Thirty-four patients (24%) had G6PD deficiency.

Hypotension

Hypotension upon admission or early in the course of disease (within 24 hours of admission) was present in 94 patients (64%), and was not specific for any serotype of leptospires. Interestingly, most patients were alert despite hypotension; hypotension was a feature of 61% of patients with anicteric leptospirosis and of 67% of patients with icteric leptospirosis. Ninety-four hypotensive patients responsed to intravenous fluid, with or without dopamine: their blood pressure was restored; good urine flow and improved renal function was noted in 60 patients, whose illness ran a short clinical course. The restoration of blood pressure with the persistent impairment of renal function was seen in 34 patients: these patients were in acute renal feature admission. Twenty-nine patients had pulmonary complications. Forty-nine of 54 patients who were not hypotensive had an illness of mild clinical course. Only 5 patients developed acute renal failure after admission (Table 1). The patients with hypotension had much higher serum TNFα levels than the normotensive patients.

Impaired renal function

Impaired renal function, with serum creatinine above 1.5 mg/dl, was noted in 85 patients (57%).

Prerenal azotemia: Forty-six patients had prerenal azotemia. The mean serum creatinine

was 3.0±0.9 mg/dl and the mean BUN was 60.4±11.2 mg/dl. Twenty-eight patients were icteric while 18 patients were anicteric. The urine specific gravity averaged 1.019. These patients were admitted to hospital on the third day (average) after the onset of fever; 30 patients were hypotensive on admission (Table 1). Response to intravenous fluid therapy was good and urine output increased. The serum creatinine fell to less than 1.3 mg/dl within 48 hours. Interstitial pneumonitis, one type of pulmonary complications diagnosed by chest X-ray was found in 2 patients; another patient had pulmonary hemorrhage (Table 2). The mean clinical course was 5 days.

Acute renal failure: Acute renal failure was present in 39 patients: these patients entered the hospital 2-7 days (average 4 days) after the onset of fever. Thirty-four patients had hypotension during admission. The mean serum creatinine was 6.5±2.1 mg/dl; the mean BUN was 88.6±12.4 mg/dl. The urine specific gravity averaged 1.012. Renal failure was catabolic; 50% of patients were oliguric. Thirteen patients were anicteric; 26 were icteric. Twenty patients were hyperbilirubinemic (total serum bilirubin >25 mg/dl). The serum creatinine and BUN levels were higher in patients with icteric leptospirosis than in anicteric patients. Pulmonary complications were common in the patients with renal failure: 29 patients had pulmonary complications (Table 2), 26 patients had thrombocytopenia. The duration of renal failure varied from 4 to 40 days (average 12 days).

There was a clear association between hypotension and impaired renal function (Table 1). Of the 94 patients with hypotension, 64 (68%) had impaired renal function. Thirty patients (32%) had prerenal azotenia and 34 (36%) had acute renal failure (Table 1). Only 21 normotensive patients (39%) had impaired renal function, with renal failure in 5 (9%). The patients with acute renal failure had significantly higher levels of serum TNFα than prerenal azotemic patients (Table 2).

Pulmonary complications

Pulmonary complications, in the form of interstitial pneumonitis, pulmonary edema, ARDS, and pulmonary hemorrhage, occurred in 32 patients (22%). Pulmonary complications were seen 1 day to 7 days (average 4 days) after the onset of fever. ARDS was observed in 14 patients; pulmonary hemorrhage in 9;

Table 1
Relationship between hypotension and renal function.

	Normotension (n=54)	Hypotension (n=94)	p
Serum creatinine ≤1.3 mg/dl	33 (61%)	30 (32%)	<0.05
Serum creatinine >1.3 mg/dl	21 (39%)	64 (68%)	<0.05
Prerenal azotemia	16 (30%)	30 (32%)	NS
Renal failure	5 (9%)	34 (36%)	<0.05
TNFα (pg/ml)	83.6±99 (n=10)	389.7±330.6 (n=18)	<0.05

Table 2
Relationship between renal function and pulmonary complications.

	Prerenal azotemia (n=46)	Renal failure (n=39)	p
Pulmonary complications	3 (6.5%)	29 (74.4%)	<0.05
ARDS	0	14 (35.9%)	<0.05
Pulmonary hemorrhage	1 (2.2%)	8 (20.5%)	<0.05
Interstitial pneumonitis	2 (4.3%)	4 (10.3%)	<0.05
Pulmonary edema	0	3 (7.7%)	<0.05
TNFα (pg/ml)	126.9±74.6 (n=8)	561.9±274.5 (n=12)	<0.05

interstitial pneumonitis in 6; and pulmonary edema in 3. Of the patients with pulmonary complications, 29 had renal failure while 3 patients had prerenal azotemia (Table 2). Hyperbilirubinemia was present in 5 patients; thrombocytopenia affected 25 patients. In 5 patients with pulmonary hemorrhage, the platelet count was less than 50,000/mm^3. The patients with normal renal function had no pulmonary complications.

Hyperbilirubinemia

Twenty-one patients had a serum bilirubin of greater than 25 mg/dl; 20 (95%) of these patients had renal failure; 10 (45%) had thrombocytopenia; and 5 (24%) had pulmonary complications. These patients entered the hospital 2-14 days (average 6 days) after the onset of illness. In 9 patients with hyperbilirubinemic renal failure, 5 of whom also had ARDS, blood exchange produced a good clinical outcome. Serum TNFα was decreased from 412 ± 102 pg/ml to 92 ± 24 pg/ml. One patient died from associated pneumonia and gram-negative septicemia.

Outcome

One hundred and forty-three patients completely recovered; 5 patients died (a mortality rate of 3.4%). The patients who died were between 42 and 70-years-old (average 55 years). Three had pulmonary hemorrhage and severe thrombocytopenia (two of these three also had renal failure); one patient had ARDS; one patient had pneumonia and septicemia; both of these last two patients had renal failure and hyperbilirubinemia. Among the 43 patients with complications (11 patients with acute renal failure only; 4 with pulmonary complications only; 28 with both renal failure and pulmonary involvement) the mortality was 11.6%.

DISCUSSION

The clinical manifestations and laboratory findings of leptospirosis in this report reflect those of the classic form of the disease (Sitprija, 1996). Hypotension was seen in 64% of the patients; 58% of patients impaired renal function. Hypokalemia, not uncommon in leptospinosis (Abdulkader *et al*, 1996), was noted in 26% of the cases; hyperkalemia was rare, despite the cases of renal failure. Serum TNFα levels were high in a number of patients, suggesting servere disease (Estavojer *et al*, 1996; Friedland and Warrell, 1996; Tajike and Salomar, 1996). In agreement with previous reports (Daher *et al*, 1999; Marotto *et al*, 1999), pulmonary complications, especially pulmonary hemorrhage and ARDS associated with renal failure, or bacterial sepsis were associated with a poor prognosis.

Hypotension early in the course of disease, although a common finding, has not been emphasized in the literature (Sitprija, 1996). We found that it was not serotype specific and could have been due to the high bacterial load. The pathophysiology of the disease may explain this: there is systemic vasodilation initially, with normal or raised cardiac output and renal vasoconstriction secondary to cytokines and vasoactive mediators (Cinco *et al*, 1996; Sitprija, 1999; Petros *et al*, 2000), making hypotension common in the early phase of the disease. As the disease progresses, and becomes severe, systemic vascular resistance is increased, renal vascular resistance is further increased, and cardiac output is reduced (Sitprija, 1999); this is the case in other infectious diseases, such as malaria (Malloy *et al*, 1967). Renal failure then develops; 68% of our hypotensive patients had impaired renal function, with 32% prerenal azotemia and 36% renal failure, while 39% of normotensive patients had impaired renal function, with 30% prerenal failure and 9% renal failure (Table 1). Hypotension and hemodynamic changes play an important role in the pathogenesis of renal failure, in addition to that of direct cellular injury by leptospires (Vinh *et al*, 1986; Yousneslbrahim *et al*, 1995; Yang *et al*, 2000). Treatment should aim at early fluid administration in response to increased vascular capacity in order to downregulate the vasoactive mediators that cause renal vasoconstriction. Since this may require an enormous amount of fluid, which can be harmful, the use of low-dose dopamine to decrease the size of the vascular

bed and increase the renal blood flow is logical; overhydration must be avoided; the central venous pressure and lung signs must be closely monitored. Of 94 hypotensive patients, 60 responded well to intravenous fluid administration alone or with dopamine. Intravenous fluid administration was important in the prevention of renal failure. It is indeed remarkable that, in some instances, the serum creatinine declined rapidly from 6 mg/dl to 1 mg/dl within 24 hours.

The patients who did not respond to intravenous fluid administration had already developed renal failure. Most of these patients were referred from district hospitals, and were admitted later than those with normal renal function and prevenal azotemia. While the patients without renal failure had very few complications, those with severe renal failure were often affected by pulmonary complications and hyperbilirubinemia. There was a clear association between hypotension and renal failure and pulmonary involvement; it is likely that this association reflected severe infection. However, since the patients with prerenal azotemia had fewer pulmonary complications and the patients with normal renal function had no complications, it is possible that the severity of the disease reflected the delay in treatment at the prerenal stage. It is therefore sensible to normalize hemodynamics during the prerenal stage, forestalling a progression to renal failure with severe complications. In a study of 43 hypotensive patients admitted to a district hospital, normalizing hemodynamics by intravenous fluid administration either with or without dopamine, shortened the hospital stay and prevented the development of renal failure and pulmonary complications (Kitti Losuwanrak, personal communication).

The mechanism by which hemodynamic changes cause renal failure and pulmonary complications is not well understood. The relationship between hemodynamics, mediators, cytokines, and adhesion molecules in the inflammatory process has not been investigated. Shear stress is known to modulate adhesion molecule expression (Ando *et al*, 1995; Dore *et al*, 1995). Further study in this area is warranted.

As with severe sepsis, the correct management of severe leptospirosis with pulmonary involvement hinges upon hemodynamic and ventilatory support. Sophisticated techniques, such as continuous venovenous hemofiltration (CVVH) and continuous anteriovenous hemofiltration (CAVH), which decrease circulating cytokines and mediators, have been used (Gomez *et al*, 1990). These techniques are, however, costly and not available in rural areas. Nitric oxide and CVVH have been reported to be useful in the treatment of pulmonary hemorrhage in leptospirosis (Borer *et al*, 1999). Blood exchange was found to be fruitful in the management of hyperbilirubinemic renal failure in leptospirosis (Sitprija and Chusilp, 1973; Pochanugool and Sitprija, 1978) Among our patients, blood exchange was performed, at lower cost, for those with leptospirosis with renal failure and pulmonary complications, in addition to conventional treatment. The rationale was to remove bacterial products, cytokines, chemokines, mediators, bilirubin, and bile acids, which can cause cellular injury. In the two studies cited above, blood exchange was shown to improve systemic and renal hemodynamics. In severe leptospirosis, plasmapheresis increased the cardiac output and improved the renal blood flow and the glomerular filtration rate (Sitprija, 2000). Clinical results are encouraging. The overall mortality was 3.4%; the mortality among severe and complicated cases was 11.6%, which compairs favorably with the rates given in other reports (overall mortality 5% to 19%; mortality in complicated cases 17% to 36%) (Sehgal *et al*, 1995; Trevejo *et al*, 1995; Perrocheau and Perolat, 1997; Daher *et al*, 1999; Marotto *et al*, 1999). Blood exchange or plasmapheresis should therefore be considered as an adjunctive treatment for severe leptospirosis, especially in the patient with pulmonary complications or hyperbilirubinemia.

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