The Journal of International Medical Research
2002; 30: 535 – 540

Thrombocytopenia Complicating the Clinical Course of Leptospiral Infection

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Leptospirosis can present with a wide clinical spectrum, and haematological manifestations are often apparent. We retrospectively analysed platelet counts in 49 patients with leptospirosis. Forty-three patients (87.8%) had thrombocytopenia. Mean baseline platelet counts rose from 69 × 10^9/l to 151 × 10^9/l following treatment. Haemorrhagic episodes were observed in 11 patients. Platelet nadir was 29 × 10^9/l in the group experiencing bleeding and 64 × 10^9/l in the remainder. Six patients died due to bleeding and one due to sepsis. Thirty-six patients (73.5%) had acute renal failure; their mean platelet count was 46 × 10^9/l. Liver enzyme levels were elevated in all patients. Thrombocyte count, liver enzyme levels and bilirubin levels were significantly correlated. Forty-three (87.8%) patients showed signs of sepsis; mean thrombocyte count was 46 × 10^9/l in these patients, and 133 × 10^9/l in those without sepsis. Multiple organ involvement and fulminant disease is usually associated with renal failure and/or thrombocytopenia in leptospirosis.

KEY WORDS: Leptospirosis; haemorrhage; thrombocytopenia; mortality

Introduction

Leptospirosis is a spirochetal zoonosis that can cause clinical illness in animals and humans. The disease predominantly affects farmers, trappers, veterinarians, rice-field workers and military personnel who have contact with infected animals or their urine. Leptospirosis has a wide clinical spectrum ranging from mild febrile illness to severe, sometimes fatal, icteric disease with renal failure (Weil's disease).[1 – 3] Haematological manifestations are relatively common in leptospirosis, the most common being thrombocytopenia.[4 – 10] The aim of this study was to analyse platelet counts during the course of leptospiral infection, and to explore the relationship between thrombocytopenia and mortality in Turkish adult patients with *Leptospira icterohaemorrhagiae* and other *Leptospirae* species.

Patients and methods

Forty-nine patients (40 men and nine women, aged 48 ± 15 years) with leptospirosis, admitted to our hospital between January 1991 and October 2001, were included in this retrospective study. Leptospirosis was considered in patients with fever, jaundice, myalgia and renal failure. Infection was confirmed by the presence of *Leptospirae* in circulating blood using dark-field microscopy

or by determining agglutinating antibodies with a microscopic agglutination test and/or enzyme-linked immunosorbent assay.

Complete blood counts and biochemical analyses were carried out on hospital admission and throughout the course of the illness. Platelet counts below 150×10^9/l were considered to be indicative of thrombocytopenia. When clinically indicated, bone-marrow examinations were performed in these patients to exclude other causes of thrombocytopenia. The examinations were undertaken if there was any cause to doubt the diagnosis, and not if the clinical and laboratory findings (e.g. fever, jaundice, myalgia, renal failure) were strongly suggestive of leptospirosis at initial presentation.

Therapy was initiated when the diagnosis had been confirmed. Platelet transfusions were performed when platelet counts fell below 20×10^9/l. Sepsis was determined by clinical evidence of infection, plus a systemic inflammatory response to the infection, which included two or more of the following conditions:

(i) Temperature > 38 °C or < 36 °C;
(ii) Heart rate > 90 beats/min;
(iii) White blood cell count > 12 000 cells/mm^3, < 4000 cells/mm^3 or > 10% immature forms.

Mann–Whitney *U*-test and regression analyses were used to evaluate the data. $P < 0.05$ was considered statistically significant.

Results

Laboratory findings for the 49 patients with leptospirosis are shown in Table 1. Thrombocytopenia was detected in 43 (87.8%) patients. Mean platelet count at presentation was 69×10^9/l (range, $4 - 300 \times 10^9$/l), mean platelet nadir was 56×10^9/l (range, $4 - 235 \times 10^9$/l) and mean post-treatment platelet count was 151×10^9/l (range, $31 - 587 \times 10^9$/l). A thrombocyte count below the level of 100×10^9/l was observed in 41 patients. Bone-marrow aspirations revealed hypercellularity with increased megakaryocytes in the thrombocytopenic patients who had undergone bone-marrow examinations, indicating that leptospirosis thrombocytopenia is due mainly to peripheral platelet destruction. Haemorrhagic episodes were observed in 11 patients: five patients suffered from gastrointestinal system (GIS) bleeding, two experienced genitourinary system (GUS) haemorrhage, two experienced respiratory tract bleeding, one suffered from both GIS and GUS haemorrhage, and one experienced nasal bleeding. Platelet nadir was 29×10^9/l (range, $9 - 60 \times 10^9$/l) in the group experiencing bleeding and 64×10^9/l (range, $7 - 92 \times 10^9$/l) in the non-bleeding group ($P > 0.05$). Seven patients died, six due to bleeding and one due to sepsis. Mean thrombocyte counts of the lost and recovered patients were 22×10^9/l (range, $9 - 40 \times 10^9$/l) and 62×10^9/l (range, $4 - 235 \times 10^9$/l), respectively. Mean white blood cell count was 11×10^9/l (range, $1.4 - 32.0 \times 10^9$/l) with neutrophil predominance. Mean haemoglobin was 11.8 g/dl (range, 6 – 16 g/dl). There was no correlation between white blood cell counts, haemoglobin levels and mortality.

Fever was observed in 31 patients. The mean thrombocyte count in patients with fever was 54×10^9/l (range, $4 - 235 \times 10^9$/l) and 61×10^9/l (range, $9 - 218 \times 10^9$/l) in those without fever. Hepatosplenomegaly was observed in 19 patients. Mean thrombocyte count was 40×10^9/l (range, $5 - 135 \times 10^9$/l) and 61×10^9/l (range, $4 - 235 \times 10^9$/l) in patients with and without hepatosplenomegaly, respectively. Mean duration of complaints (fever, jaundice, olyguria, myalgia) was 8.5 days (range, 2 – 30 days). There was no correlation between the

TABLE 1:
Clinical characteristics and laboratory findings of 49 patients with leptospirosis with or without thrombocytopenia

Characteristic	Mean values	
	Thrombocytopenic patients (n = 43)	Non-thrombocytopenic patients (n = 6)
Age (years)	48.3	31.2
Female/male (n)	8/35	1/5
Haemoglobin (g/dl)	11.8	13.0
White blood cells ($\times 10^3$ mm^3)	11.1	10.1
Thrombocytes ($\times 10^9$/l)	56.0	201.0
Blood urea nitrogen (mg/dl)	84.0	39.3
Creatinine (mg/dl)	4.2	1.3
Alanine aminotransferase (IU/l)	140.3	401.3
Alanine aspartate (IU/l)	143.7	194.7
Alkaline phosphatase (IU/l)	379.4	387.7
Creatine phosphokinase (IU/l)	853.0	170.7
Bleeding (n)	11	0
Hepatosplenomegaly (n)	18	0
Total/direct bilirubin (mg/dl)	17.0/15.0	27.1/18.3
Renal failure (n)	35	1
Microscopic agglutination test	5 *Leptospira grippotyphosa* 8 *Leptospira icterohaemorrhagiae* 11 *Leptospira patoc*	1 *Leptospira icterohaemorrhagiae* 2 *Leptospira patoc*
Mortality (n)	7	0
Duration of jaundice (day)	4.1	–
Sepsis (n)	42	1

duration of complaints and the severity of thrombocytopenia. Conjunctival bleeding was observed in 22 patients and mean platelet count in this group was 39×10^9/l (range, 5 – 96 $\times 10^9$/l). Mean platelet count in patients without conjunctival bleeding was 71 $\times 10^9$/l (range, 4 – 235 $\times 10^9$/l). Clouding of consciousness was observed in 11 patients and mean platelet count in these patients was 39×10^9/l (range, 9 – 109 $\times 10^9$/l). Mean platelet count in patients without impaired consciousness was 62×10^9/l (range, 4 – 235 $\times 10^9$/l). Acute renal failure was observed in 36 patients (73.5%) and mean platelet count in this group was 46 $\times 10^9$/l (range, 5 – 170 $\times 10^9$/l). Mean platelet count in patients with normal renal function was 86 $\times 10^9$/l (range, 4 – 235 $\times 10^9$/l). Mean

platelet level according to the strain of *Leptospirae* was 53×10^9/l (range, $9 - 170 \times 10^9$/l) for *Icterohaemorrhagiae*, 66×10^9/l (range, $16 - 135 \times 10^9$/l) for *Grippotyphosa* and 33×10^9/l (range, $5 - 93 \times 10^9$/l) for *Patoc* strains. The correlations between thrombocyte counts, liver enzymes and bilirubin levels were investigated. There was an inverse correlation between alanine aminotransferase/aspartate aminotransferase and thrombocyte count ($r = -0.360$; $P = 0.016$). Mean total bilirubin level was 17 mg/dl and mean direct bilirubin level was 15 mg/dl. There was no statistically significant correlation between bilirubin levels and thrombocyte count. Sepsis findings were observed in 43 patients (87.8%). Mean thrombocyte count was 46×10^9/l in patients with sepsis and 133×10^9/l in patients without sepsis ($P = 0.011$). Liver enzymes were elevated in all patients.

Discussion

Leptospirosis in humans occurs throughout the world as an acute infection. The severity of the disease ranges from an asymptomatic subclinical course to a fatal outcome.[11] The disease is apparent worldwide, but is more common in areas with wet climates.[1 – 3] Certain occupational groups are at particularly high risk, and include slaughterhouse employees, workers in the fishing industry, miners, farmers, sewer workers and veterinarians. People who swim in stagnant ponds and canals are also at risk. In some countries, recreational exposure and contact with infected domestic animals are also frequently associated with leptospirosis.[1,2,4,12,13]

Thrombocytopenia and thrombocytosis can occur during leptospiral infection, particularly when sepsis is present. Thrombocytopenia is a common finding in leptospirosis, occurring in 40.0 – 86.6% of infections. In some studies, mortality has been correlated with thrombocyte count.[4,6 – 11] Few studies, however, have focused on thrombocytopenia and its relationship to other clinical and laboratory findings. The exact pathogenesis of thrombocytopenia in leptospirosis is unknown. Vasculitis, decreased thrombocyte production, and increased peripheral destruction and consumption of thrombocytes have been considered as potential causes of thrombocytopenia.[4,6 – 11,13,14] In our study, thrombocytopenia was commonly seen in patients with leptospirosis. Statistically significant correlations were found between mortality and thrombocyte count, with haemorrhage mainly due to bleeding from mucosal surfaces.

In our study, thrombocytopenia was not due to the disseminated intravascular coagulation (DIC), as in previous reports.[4,6 – 8] We have recently reported sepsis findings in patients with leptospirosis according to the criteria described above;[15] 43 of 49 patients met these criteria. We suggest that thrombocytopenia in leptospirosis may be due to sepsis as a result of various factors. The mechanism of thrombocytopenia in sepsis in the absence of DIC is uncertain, but could include chemokinin-induced macrophage ingestion of thrombocytes, direct activation of thrombocytes by endogenous mediators of inflammation and certain microbial products. Many authors have suggested that a toxin elaborated by *Leptospirae* may mediate some of the pathophysiological effects of this zoonosis.[13,14] While classic endotoxins have not been convincingly demonstrated in these organisms, fatally infected animals exhibit many changes suggestive of endotoxaemia. The *Leptospirae* lipopolysaccharide antigens, which cause immunoglobulin M and G antibodies, may be responsible for these pathophysiological alterations, suggesting that sepsis may be a

critical prognostic factor. However, previous reports have not shown a relationship between sepsis and thrombocytopenia in patients with leptospirosis.

The association of thrombocytopenia and renal failure in leptospirosis has been suggested in a retrospective study.[10] In this particular investigation, renal failure occurred in 72.2% of thrombocytopenic patients and in 21.4% of patients with normal thrombocyte counts ($P < 0.02$).[10] In our study, we also observed renal failure, particularly among thrombocytopenic patients with leptospirosis. Leptospiral infection may induce tubulo-interstitial nephritis through a toxic component in the outer membrane, followed by expression of inflammatory genes.[16] The association with thrombotic thrombocytopenic purpura and leptospirosis has also been suggested.[17] Multiple-organ involvement and a fulminant course is usually associated with renal failure and/or thrombocytopenia in leptospirosis.[11,16,18,19] These observations should be supported by experimental studies to elucidate the complicated issues in the pathobiological basis and clinical course of leptospiral infections. Haematological manifestations, in particular thrombocytopenia in patients with fever, jaundice, myalgia and renal failure, should alert physicians to the differential diagnosis of leptospiral infection, and prompt the institution of appropriate therapy.

• Received for publication 6 May 2002 • Accepted 13 May 2002

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