



Original Contribution

HAEMORRHAGIC SYNDROME IN LEPTOSPIROSIS

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ABSTRACT

PURPOSE: This study is aimed at making analysis of haemorrhagic syndrome in leptospirosis.

METHODS: Clinical symptoms and laboratory parameters of 84 cases with leptospirosis, which have been treated in the Clinic of Infectious Diseases at University Hospital, Pleven (1982 – 2005), are studied retrospectively.

RESULTS: Haemorrhagic syndrome appears within five to nine days after clinical onset and occurs in 30,95% of cases. It is presented by petechial rash (30,95%) and bleeding from viscera (haematuria in 28,57%, melaena in 14,28%, haematemesis in 10,71%, epistaxis in 5,95%). Haemorrhages have been observed in 75% of fatal cases and are risk factors for death. Laboratory investigations demonstrate anaemia (73,81%), thrombocytopenia (42,86%), increased fibrinogen (73,81%), prolonged prothrombin time (11,90%). Treatment includes antibiotics, corticoids, vessels stabilising drugs, diuretics, substitution with thrombocyte or erythrocyte concentrate, hemodiaperfusion.

CONCLUSIONS: Hemorrhagic syndrome is with important significance for severity of leptospirosis. Vasculitis, thrombocytopenia and increased excessive nitrogen products play important role in pathogenesis of haemorrhage in this severe infectious disease.

Key words: leptospires, haemorrhage, acute renal failure, jaundice, anaemia, thrombocytopenia, fibrinogen, clotting factors.

INTRODUCTION

Leptospirosis is an acute infectious disease with worldwide distribution and is caused by leptospires of complex *Leptospira interrogans*. The pathogenesis of leptospirosis is not fully clear. The illness progresses through an acute (septicaemic) phase, which is followed by an immune phase. The clinical manifestations are in broad spectrum including fever, myalgia, headache, acute renal failure, jaundice, cardiovascular, and pulmonary disorders. Pancreatic involvement with clinical signs and/ or laboratory changes is not rare. In immune phase appear aseptic meningitis (rarely encephalitis), peripheral neuritis, cranial nerve palsies, radiculitis, and myelitis. Ocular disturbances as uveitis, iritis, iridocyclitis, and chorioretinitis have been observed. Leptospirosis is with variable severity from mild to severe forms with multi-

organ disorders. Case fatality rate is higher in elder patients and ranges from 5 to 40% (1, 2). The illness requires early diagnosis and multidisciplinary approach in the treatment. One of the major clinical syndromes with a great significance for severity and mortality in leptospirosis is haemorrhagic syndrome.

PURPOSE of this study is analysis of the haemorrhagic syndrome in leptospirosis.

MATERIALS AND METHODS

Epidemiological data, clinical signs and laboratory parameters have been studied retrospectively in 84 cases with leptospirosis, treated in the Clinic of Infectious Diseases at University Hospital, Pleven in Bulgaria (1982 to 2005).

RESULTS

The patients are aged 14 to 78 years; men in 90,48%. Sources of infection are found in 82,14%. Clinical analysis reveals acute onset with fever (100%), hepatosplenomegaly (100%), nausea and vomiting (86,90%),

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oliguria or anuria (75%), jaundice (75%), cardiovascular disorders as tachycardia (59,52%), hypotension (33,33%), myocarditis (20,24%), cardiac arrhythmia (11,90%); diarrhoea (21,43%). Haemorrhagic syndrome has been observed in 30,95% of cases. Its presence is a criterion for severe course of the illness. Haemorrhagic skin lesions have been observed in 30,95%; visceral bleeding in 28,75%, including haematuria (28,57%), melaena (14,29%), haematemesis (10,71%), epistaxis (5,95%). Haemorrhagic symptoms appear within five to nine days after clinical onset of cases. The severity of cases is as follows: mild course (serum creatinine level up to 200 $\mu\text{m/L}$; without haemorrhagic symptoms) in 52,38%, moderate (serum creatinine level from 200 to 600 $\mu\text{m/L}$; presence of haemorrhagic skin lesions without visceral bleeding) in 19,05%, and severe course (serum creatinine level above 600 $\mu\text{m/L}$; with skin haemorrhages and visceral bleeding) in 28,57%. Fatal cases are in 14,29%; in 75% of them haemorrhagic symptoms present. Risk factors for death are haemorrhage and acute renal failure. Routine laboratory investigations demonstrate leucocytosis in 73,81% (average $14,9 \cdot 10^9/\text{L}$) with left shift in 97,62%, increased erythrocytes sedimentation rate in 86,90% (av. 51 mm), anaemia in 73,81%, thrombocytopenia in 42,86% (av. $112 \cdot 10^9/\text{L}$, less than $10 \cdot 10^9/\text{L}$), increased fibrinogen in 73,81% (av. 6,4 g/L with range from 3,2 to over 10 g/L), prolonged prothrombin time in 11,90%, hypoproteinaemia and hypoalbuminaemia in 29,76%. Blood urea nitrogen levels above 8,3 mmol/L have been found in 80,95% (av. 26,1 mmol/L), serum creatinine levels above 135 $\mu\text{mol/L}$ in 72,62% (av. 303 $\mu\text{mol/L}$; range 74 to 860 $\mu\text{mol/L}$). Serum bilirubin level is elevated in 70,24% (av. 168 $\mu\text{mol/L}$; up to 1273 $\mu\text{mol/L}$) with prevalence of conjugated fraction. Alanine aminotransferase is elevated in 73,81% (av. 92 U/L; up to 382 U/L). Alkaline phosphatase is elevated in 54,76% (av. 315 U/L). Flow cytometry of lymphocytes reveals extremely decreased total T-lymphocytes (CD3+), helpers (CD4+), and suppressors (CD8+); increased natural killer cells (NK), decreased CD3+DR+. There are not found anti-thrombocyte antibodies. These investigations need further examination. The patients have been treated with penicillin (94,05%) or ceftriaxon (5,95%), followed in 11,90% of cases with cefuroxim or cefperazone.

Supportive measures include adequate urine output fluids (100%), corticoids (48,81%), vessels stabilising drugs (43,81%), diuretics (75%), transfusions of plasma and thrombocyte concentrate (19,05%), and erythrocyte concentrate (14,29%); in 4,76% of cases (with extremal bleeding) substitution with whole blood. Hemodiaperfusion in anuria has been used in 19,05% of cases.

DISCUSSION

The haemostasis is a complex defence for prevention of life-threatening bleeding. It is a multifactorial process, in which participate vessels, platelets and clotting factors. The regulation of haemostatic mechanisms depends on the state and interactions of these three components. Disorders in number and functions of platelets, quantitative and quality changes in coagulating factors and pathological damage of the vessels lead to haemorrhagic manifestations (3, 4, 5). The vessels are covered with endothelial cells, integrated in membrane, which selectively prevents a passive penetration of blood cells and plasma through vessels walls into the interstitium (4). It has been known that the basic pathomorphological substrate in leptospirosis is endothelial damage, which leads to generalised vasculitis (1, 6, 7, 8, 9). Experimental studies suggest that capillary leakage and haemorrhage result from the disruption of endothelial cell membranes of small vessels via the intercalation of glycoprotein toxin, which displaces host long-chain fatty acids required to maintain vascular cell walls integrity. Because of this uncontrolled mechanism, petechial lesions reflect a systemic vasculitis allowing the migration and proliferation of leptospire into nearly all organs and tissues and accounting for a broad spectrum of clinical illness. Severe vascular injury can ensue, causing, for example, pulmonary haemorrhage, ischaemia of the renal cortex, leading to tubular epithelial cell necrosis, and destruction of the hepatic architecture resulting in jaundice and liver cells injury with or without necrosis (1). Certain pathophysiological changes that occur in infection also contribute to causing organ dysfunction. These changes include hypovolaemia, blood hyperviscosity, and intravascular coagulation. Cytokines (especially tumour necrosis factor), complement activation, and free radicals are also involved in tissue injury. Hypovolaemia in leptospirosis is attributed to decreased fluid

intake, increased fluid loss, and increased vascular permeability caused by chemical mediators released during inflammation. A low-grade intravascular coagulation is also observed, shown by the presence of fibrin degradation products in the serum. These factors can compromise the microcirculation, leading to capillary stasis and tissue anoxia. Capillary permeability is therefore further increased, resulting in fluid leakage, haemoconcentration and a further rise in blood viscosity (6). Platelets are other component in haemostasis. Thrombocytopenia may be consumptive or immune, depending on causative factors (5). In the present study we have found anti-thrombocyte antibodies. Perhaps endothelial damage causes decreasing of prostacycline synthesis, leading to increased thrombocytes adhesion and aggregation, resulting in secondary decrease of circulating platelets number (3, 4, 10). The role of coagulating factors for haemostasis in leptospirosis is not with important significance. Increased blood nitrogen products are with significance for eventual changes in blood concentrations of clotting factors (2, 3, 4, 5, 7). In the liver, there is focal centrilobular necrosis with a proliferation of Kupffer cells being responsible for jaundice. With progression to severe disease caused by more extensive ischaemia, conjugated serum bilirubin levels may rise, accompanied by modest elevations in alkaline phosphatase levels (1). The levels of serum transaminases, alanine aminotransferase and aspartate aminotransferase, rarely exceed 200 U/L (1), which fact correlates with the present study. In conclusion, the haemorrhagic syndrome is with important significance for severity of leptospirosis. Vasculitis, thrombocytopenia and increased excessive nitrogen products play important role in pathogenesis of haemorrhage in this severe infectious disease.

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