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Impact of clinical and laboratory findings on prognosis in leptospirosis

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Summary

Objective: The aim of this study was to evaluate epidemiological, clinical and laboratory features, and risk factors for mortality in leptospisrosis.

Methods: Seventy-two adult leptospirosis cases were reviewed. Categorical clinical and laboratory findings of survivors and non-survivors were assessed by Chi square analysis. Non-categorical findings were assessed by the student t test. Clinical findings and laboratory data with $p < 0.05$ were assessed by stepwise logistic regression analysis for mortality.

Results: Of all patients, mean age was 47.3 ± 15.7 years, 82% were men and, 51% were farmers. Icterus occurred in 75%, and high fever was seen in 61 of the patients. The most frequently detected serotype was Leptospira icterohaemorrhagiae (30%). Overall mortality rate was 17%. In those non-survivors, altered mental status ($p = 0.002$), hepatomegaly ($p = 0.037$), haemorrhage ($p = 0.019$), ALT level ($p = 0.008$), AST level ($p = 0.02$), prolonged prothrombin time ($p = 0.02$) and increased serum potassium levels ($p = 0.004$) were seen more frequently than in survivors. Altered mental status ($p = 0.01$, OR: 8.9, CI 95%: 1.6–50.7) and serum potassium levels at hospital admission ($p = 0.01$, OR: 4.2, CI 95%: 1.4–13.1) were detected as independent risk factors for mortality.

Conclusions: Leptospirosis patients with altered mental status and hyperpotassaemia at hospital admission are at high risk for mortality and should be followed up more closely at the intensive care unit.

Key words: leptospirosis; mortality; risk factors; potassium; altered mental status

Introduction

Leptospirosis is a zoonosis which is caused by serotypes of the Leptospira interrogans group, which may run a course with multiple organ insufficiency (liver, lung and renal) at a subclinical level but can lead to death. Most symptomatic cases are admitted to hospitals. The incidence of the disease varies from sporadic cases in temperate climates [1] to endemic cases in tropical countries [2, 3], and it can even lead to epidemics [4, 5]. The agent of the disease is transmitted to humans through direct or indirect contact with the urine of infected animals. In certain regions of Turkey, leptospirosis is reported sporadically [6, 7]. Samsun is a city hosting two of Turkey's biggest rivers flanking the city and creating two vast plains where hydrated cultivation is done. The majority of the people in the region earn their living by four-season farming. The city, with a population of 2 million and a hinterland with 4 million people, receives rain all year round. The rat population is very high in agricultural area. In a previous study we were able to show that the rats in our region carry the agent of the disease abundantly in their kidneys [8]. In another study conducted in central and Eastern Anatolia, cattle and domestic fowl seem to have antibodies against *L. gryppotyphosa*, *L. serjoe* and *L. grippomoscov* [9]. However, no similar study has been conducted on rats except in our region.

Leptospirosis can vary from a mild non-specific influenza-like infection to Weil's disease, where serious complications can occur. In various publications, mortality rates are reported between 3% and 54% according to the affected organ-system [10–12]. In early phases of the disease, there are no serious criteria for the diagnosis. In this study, we aimed to evaluate the clinical and laboratory features of our patients with leptospirosis, and to identify the aspects for diagnosis, treatment and risk of mortality.

Patients and methods

Hospitalised patients with the diagnosis of leptospirosis at Ondokuz Mayıs University, Faculty of Medicine, Infectious Diseases Clinic between 1991–2002 were reviewed retrospectively. Our hospital is a referral central with 900 beds. Mostly selected patients with severe disease are admitted to our hospital. Direct admission without referral is rare. This is a retrospective study, selected patients with severe disease were admitted to the hospital and the study population includes only hospitalised patients with leptospirosis.

Leptospirosis was diagnosed by clinical and laboratory findings and positivity of IgM specific ELISA (VIRION ALISA; Institut, Virion GmbH, Würzburg, Germany) and/or microscopic agglutination test (MAT), which were applied to suspected patients. The diagnosis of leptospirosis was confirmed in all cases by MAT. Where the result of MAT was negative or <1/200, the diagnosis was confirmed by ELISA IgM positivity. Demographic data (age, sex, profession), epidemiological data (type of contact, duration between onset of symptoms and admission to hospital, place of residence) and possible symptoms and findings related to the disease (fever, nausea, vomiting, diarrhoea, headache, abdominal pain, muscle pain, icterus, oliguria, hypotension, tachypnoea, cough, disturbance of consciousness, neck stiffness) were recorded. In the laboratory investigation, complete blood count, coagulation parameters and serum biochemical measurements were assessed including the leukocyte and platelet counts, serum potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, blood urea nitrogen (BUN), creatinine phosphokinase (CPK), bilirubin and alkaline phosphatase levels. Assessment of chest radiography was made for the presence and the type of infiltration.

Statistics

Categorical clinical and laboratory findings of survivors and non-survivors were assessed by Chi square analysis. Non-categorical findings were assessed by the student t test, p values <0.05 were defined as meaningful. Those with a statistically meaningful p-value (potassium levels, altered mental status, ALT, AST, prolonged PT time, haemorrhage, hepatomegaly) and the risk factors which were already described in the literature (age over 37 years, renal insufficiency, and respiratory insufficiency, dyspnoea, white blood cell count) were taken to logistic regression analysis due to the possibility of risk factor for mortality.

SPSS for Windows 10.0 software was used for these analyses.

Results

Demographic features

The study population consisted of 72 patients; 59 men (81.9%) and 13 women (18.1%) with mean age 47.3 ± 15.7 years (min: 17, max: 75). The majority were farmers (51.4%). The other most frequent professions were the pensioners (9.7%), housewives (8.3%) and fishermen (4.2%).

65.4% of the patients were from the Samsun city centre and 50 kilometres surrounding. Of the patients 77.8% were referred by other hospitals.

Considering the seasonal distribution of cases, 66.6% of cases had occurred in summer and autumn. Distribution of cases according to months is given in figure 1.

Clinical findings

The most common symptoms were respiratory symptoms (72.1%), muscle pain (65.7%) and nausea-vomiting (65.3%). The most common clinical findings in patients were icterus (75.0%), fever (61.1%), tachycardia (52.9%) and conjunctival suffusion (31.9%) (table 1).

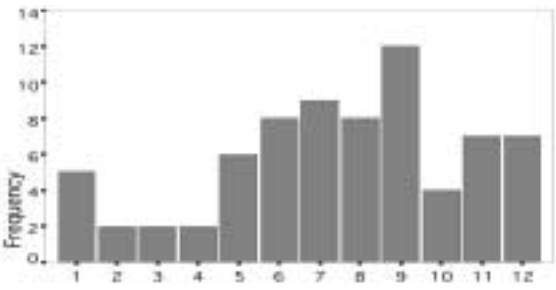

Figure 1
Distribution of leptospirosis cases according to months.

Laboratory findings

In the non-survivors, the mean ALT and AST levels were higher than in the survivors. ALT levels were within normal limits in 16 (22.2%) patients, between the upper limit of normal and 200 IU in 44 (61.1%) patients, 200–500 IU in 6 (8.3%) patients, 500–1000 IU in 5 patients (6.9%) and over 1000 IU in 1 patient (1.4%). AST levels were within normal limits in 10 patients (13.9%), between the upper limit of normal and 200 IU in 47 patients (65.3%), 200–500 IU in 9 patients (12.5%), 500–1000 IU in 3 patients (4.2%) and over 1000 IU in 3 patients (4.2%). 19 patients (26.4%) had severe thrombocytopenia requiring transfusion (lower than 20 000 mm^3), 8.3% had leukopenia (<4000/mm^3) and 38.9% had leukocytosis (>12 000/mm^3) (table 2). Of all the patients 58.3% had elevated creatinine kinase levels (>195 IU). 31.9% of the cases had infiltration on chest x-ray (diffuse or localised alveolar infiltrates, an interstitial pattern, multiple nodular densities or lobar pneumonia). The most frequent types were diffuse or localised alveolar infiltrates (73.9%).

43 of 67 patients (64.2%) analysed by MAT were positive. Only three patients had a titre of 1/50 MAT positivity and all of them had simultaneous IgM positivity with ELISA. 36% of ELISA positive cases were MAT negative. No relationship between serogroup and mortality was found. Serogroup distribution according to MAT results is given in table 3.

Table 1

Clinical findings of patients.

	Non-survivors %	Survivors %	Total %	p-value
Clinical findings				
Icterus	83.3	73.3	75.0	0.28
Respiratory system symptoms	80.0	70.7	72.1	1.0
Muscle pain	63.6	66.1	65.7	1.0
Nausea/vomiting	75.0	63.3	65.3	0.74
Fever (>38 °C)	66.7	60.0	61.1	0.75
Tachycardia	80.0	48.3	52.9	0.08
Headache	45.5	38.3	39.4	0.74
Oliguria	54.5	35.0	38.0	0.31
Bleeding	66.7	26.7	33.3	0.019
Conjunctival suffusion	28.3	50.0	31.9	0.16
Abdominal pain	33.3	28.3	29.2	0.74
Diarrhoea	36.4	20.0	22.5	0.25
Cough	18.2	21.7	21.1	1.0
Hepato-splenomegaly	66.7	30.0	36.1	0.037
Altered mental status	58.3	13.3	20.8	0.002
Neck stiffness	–	3.3	2.8	1.0
Onset of symptoms-period until hospital admission	7.7 ± 4.8 days	8.3 ± 5.8 days	8.2 days	1.0
Pathological auscultation on chest examination	15.5	18.2	15.7	0.17
Renal insufficiency requiring haemodialysis	33.3	16.7	19.4	0.11

Table 2

Laboratory test results.

	Non-survivors	Survivors	p-value
Potassium mEq/L	4.57 ± 0.70	3.84 ± 0.84	0.004
Leukocyte (/mm^3)	15681 ± 12788	12648 ± 7363	0.59
Thrombocyte (/mm^3)	56220 ± 56649	91573 ± 89220	0.09
Total bilirubin mg/dl	17.98 ± 18.08	18.17 ± 19.31	0.97
Direct bilirubin mg/dl	12.59 ± 11.80	12.26 ± 13.36	0.80
Alkaline phosphatase IU (95–280)	556 ± 497	287 ± 171	0.12
Blood urea nitrogen mg/dl (5–24)	85.42 ± 49.56	82.17 ± 60.90	0.86
Creatinin mg/dl (0.4–1.4)	4.3 ± 3.1	4.0 ± 3.0	0.75
Creatin phosphokinase (CK) IU (35–195)	940 ± 878	890 ± 1277	0.63
Aspartate aminotransferase (AST) IU (8–46)	297 ± 326	166 ± 236	0.03
Alanine aminotransferase (ALT) IU (7–46)	354 ± 467	127 ± 135	0.008
Erythrocyte sedimentation rate (mm/hour)	49.8 ± 47	66.0 ± 31	0.23
Haemoglobin g/dl	10.08 ± 2.98	11.24 ± 2.59	0.18
Leukopenia (<4000/mm^3)	16.7%	6.7%	0.26
Leukocytosis (>12000/mm^3)	41.7%	38.3%	1.0
Protrombine time (PT) prolongation	66.7%	22.2%	0.02
Pathology in PA radiographs	50.0%	28.3%	0.18
Thrombocytopenia (<100000/mm^3)	83.3%	75.0%	0.72

Table 3

43 MAT test results

Serotypes	n	%
Patoc (diagnosed by biflexa group)	16	37.2
L. icterohaemorrhagiae	13	30.2
L. grippotyphosa	5	11.6
L. bratislava	5	11.6
L. hardjo	2	4.7
L. canicola	1	2.3
L. copenhageni	1	2.3
Total	43	100

Therapy

56 patients (77.8%) were treated with antibiotics of the penicillin group (crystallised penicillin, ampicillin, piperacillin, ampicillin-sulbactam), 7 (9.7%) with doxycycline, 4 (5.6%) with cephalosporins (ceftriaxone, cefepime), 4 (5.6%) with carbapenems, 1 (1.4%) with a combination of penicillin and doxycycline. The patient-days were observed as follows: 532 patient days in the penicillin treated group (mean 9 days), 85 patient days

in the doxycycline treated group (mean 9 days), 35 patient days in the cephalosporin treated group (mean 9 days) and 37 patient days in the carbapenem treated group (mean 9 days).

Mortality

12 patients (16.7%) died. The frequency of clinical findings in survivors and non-survivors is given in Table 1, their laboratory values in Table 2.

In the logistic regression analysis, altered mental status (p = 0.01, OR: 8.9, CI 95%: 1.6–50.7) and potassium levels at the time of hospital admission (p = 0.01, OR: 4.2, CI 95%: 1.4–13.1) were seen to be independent risk factors for mortality.

Discussion

Leptospira isolation is essential for a definitive diagnosis. However it takes 4 weeks or more for culture results to be known. Serological tests, especially MAT, have been preferred for diagnosis of leptospirosis. MAT cannot, however, measure specific IgM and IgG. The ELISA have proved to be more specific and sensitive than MAT [5, 7]. The risk factor for mortality in leptospirosis varies in reported case series [12–14]. Altered mental status, potassium levels, age over 37 years, renal insufficiency, and respiratory insufficiency, dyspnoea, white blood cell count (>12,900/mm^3), repolarisation abnormalities in electrocardiograms, and alveolar infiltrates on chest radiographs were reported as significant predictors of death [12, 15, 16]. However, these results were not the same in all case series.

Leptospirosis is mostly seen in adult men [5, 12, 17–19], with certain professions carrying additional risk for having the infection [20, 21]. Most of our patients were farmers or people who dealt with soil.

During the acute phase of the disease ELISA is more sensitive than MAT, and IgM positivity can be detected earlier with ELISA [22, 23]. Accordingly, 36% of IgM positive cases in this study were MAT negative. On the other hand, IgM by ELISA were positive in three cases having MAT titre of 1/50.

Although a relationship between the severity of the disease and the serogroup could not be established in many previous case series, Katz *et al.* [24] reported that serogroup icterohaemorrhagiae causes a disease picture with much more frequent icterus and renal insufficiency than in other serogroups. This relationship was shown neither in other case series nor in our study.

The reported mortality rate in leptospirosis is 5 to 16.6% [12, 19, 25, 26]. Our mortality rate was within these limits. In another Turkish study from another region of Turkey, Saltoglu *et al.* [6] also reported 16.6% mortality. This high variability in mortality rate may be due to the absence of standardisation of diagnostic criteria and the differing severity of clinical pictures. Another factor which can influence the severity of the disease might be the delay prior to hospital admission after the onset of the symptoms, but our data showed no difference between the onset of symptoms-hospital admission periods of survivors and non-survivors. Furthermore, patients with mild clinical symptoms are treated at private or public hospitals. Serious cases are referred to our hospital. This was reflected by a large proportion of our patients being referred after hospitalisation at other hospitals.

In our study, mental change occurred more frequently in non-survivors and this was an independent risk factor for mortality. Altered mental status has previously been reported as a powerful independent risk factor for mortality [12]. In the same study, age over 37, renal insufficiency and respiratory insufficiency were also shown to be independent risk factors [12]. We did not find any significant relationship for those parameters.

It is known that transaminase levels rarely exceed 200 IU in leptospirosis [27], though this occurred in 16.6% of our patients. Mean transaminase levels were higher in non-survivors. Thus it should be considered that transaminase levels might sometimes be higher than expected in leptospirosis cases.

Myalgia and increased creatine kinase are important indicators in differentiating leptospirosis from other icteric diseases. 65.7% of cases were complaining from muscle pain when they came to hospital. In other large series, myalgia rates were reported between 20–100% [12, 21, 28, 29].

Renal insufficiency was reported in most leptospirosis patients [30, 31]. However in many studies the diagnosis of renal insufficiency is based upon laboratory results only. Renal sufficiency requiring haemodialysis was seen in 1/5 of our cases. The rate for oliguria was 38.0%. Dupont [15] and Daher [16] showed that oliguria was an independent risk factor for mortality and Seguro [32] showed that mortality is higher in oliguric patients. Although renal insufficiency rates were higher in non-survivors in our study, the difference did not reach statistical significance. With larger case numbers, renal insufficiency could become statistically significant with regard to mortality.

Although the mean potassium levels in non-survivors were normal, we showed that hyperkalaemia was an independent risk factor for mortality (p = 0.01). The higher serum potassium levels observed in non-survivors may have been provoked by more severe renal dysfunction, metabolic derangement, or rhabdomyolysis. Nevertheless, the relationship between mortality and potassium

levels over 4 mmol/L has been described by Marotto [14]. As with our results, Lopes *et al.* [13] demonstrated that hyperkalaemia at the time of hospital admission is an independent risk factor for mortality in leptospirosis patients.

Thrombocytopenia is a frequently seen complication in leptospirosis cases [33] and might cause bleeding, leading to death. Bleeding, as a serious complication, was more frequently seen in non-survivors ($p < 0.05$), but it was not an independent risk factor for mortality.

In leptospirosis, pulmonary involvement due to capillary damage varies between 20–70% and is a complication associated with mortality [34, 35]. In reported case series, pulmonary involvement varies between 2–78% [17, 21, 29, 36]. The involvement is mostly interstitial. Meaningful pathological changes in chest x-rays were found in 31.9% of followed-up cases, whereas 15.7% had pathological findings on pulmonary examination. No statistically meaningful difference was seen in survivors and non-survivors in pulmonary involvement rates. Dupont [15] reports the pathological finding rate in chest x-rays as 49%, additionally showing that alveolar infiltrates constitute an independent risk factor for mortality. In our study, there was no relationship between the type of infiltration and mortality.

This study is the largest leptospirosis series in Turkey and provides epidemiological, clinical and laboratory data describing the extent of the problem of leptospirosis, which can be used in future cases. In conclusion, leptospirosis is a disease with high mortality. This study showed that the transaminase levels might sometimes be higher than expected in leptospirosis cases. Patients with altered mental status and hyperkalaemia at hospital admission carry a high risk for mortality and should be closely followed up on the intensive care unit.

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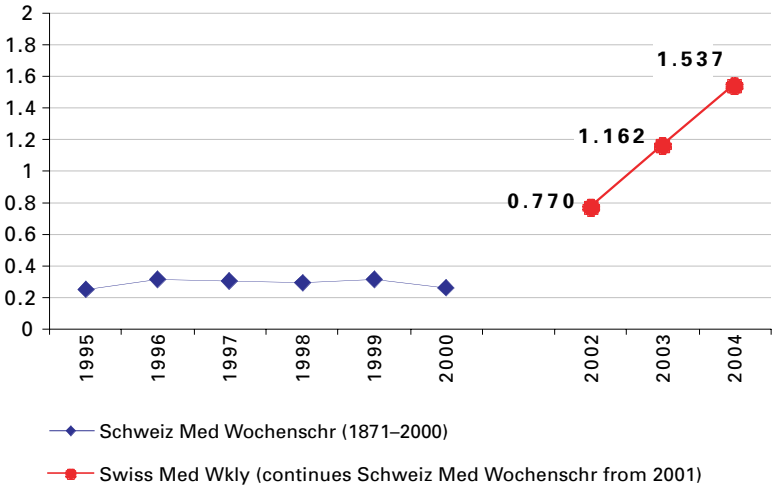

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