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Clinical and laboratory manifestation and outcome of icterohemorrhagic leptospirosis patients in Northern Iran

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Abstract

Background: Icterohemorrhagic form of leptospirosis has a high mortality rate. In this study, the clinical manifestations, epidemiologic and laboratory findings and outcome of Weil's disease were investigated.

Methods: A descriptive cross- sectional study was conducted on 66 consecutive patients with icterohemorrhagic leptospirosis who were admitted to Razi Hospital (The Therapeutic Center of Infectious Diseases in the North of Iran) in 2013. The inclusion criteria were as follows: All patients who had clinical and epidemiological data suggestive of leptospirosis and displayed icterohemorrhagic form at the time of admission or during hospitalization. All patients were visited on admission, one, two and six weeks later. Demographic data, clinical, laboratory features and complications were evaluated, and statistical analysis was performed using SPSS version 13.0.

Results: Among 66 patients, 89.4% (n = 59) were male, 60% (n = 40) were farmers and 9.1% (n= 6) had a history of swimming in rivers. The most common complaints were fever and jaundice, respectively. The most common clinical symptoms were fever (90.9%), myalgia (75.8%), chills (70.8%) and headache (65.1%). Hyponatremia and hypernatremia were seen in 7.6% and 72.8% of the participants, respectively. Also, hypokalemia was observed in two patients (3%). Approximately, half of the cases had leukocytosis and 90% had thrombocytopenia. Rise of AST, ALT, ALP and bilirubin were seen in 95.2%, 93.6%, 76.2% and 100% of the patients, respectively. Of the patients, 42.4% experienced complications of icterohemorrhagic leptospirosis including acute renal failure (30.3%) pneumonia (25.8%), pancreatitis (4.5%), subarachnoid hemorrhage (1.5%) and gastrointestinal bleeding (1.5%). Three cases (4.5%) died, 42 cases (63.7%) were discharged with residual effects and 52 patients (78.8%) had positive serology.

Conclusion: The most significant biochemical abnormalities were thrombocytopenia, hyperbilirubinemia, hyponatremia and hypernatremia and azotemia and the latter remained stable in 2% of the patients at least until the end of the 6-week period.

Keywords: Leptospirosis, Weil's syndrome, Icterohemorrhagic.

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Introduction

Leptospirosis is a zoonosis caused by infection that comes from pathogenic spirochetes of the genus Leptospira. Humans most often become infected after exposure to environmental sources such as animal

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urine, contaminated water or so il, or infected animal tissue. The disease often occurs to farmers, ranchers, abattoir workers, trappers, veterinarians, sewer workers, rice field workers, military personnel and laboratory workers; it is named rice-field fever and many rice field workers are hospitalized because of this disease annually in the North of Iran (1). Leptospirosis is associated with a variable clinical course. Nearly 90% of leptospira infections result in a self-limited systemic disease manifestation with signs and symptoms of unspecific anicteric myalgia febrile illness that mimics those of other diseases (2). Fatality rate in the self-limited type is less than 1%, but rises in elder patients who have comorbidity (3,4). Weil's disease, a severe, potentially fatal illness, may be accompanied by any combination of renal failure, liver failure, and pneumonitis with hemorrhagic diathesis. Acute renal failure develops into acute tubular necrosis with oliguria or anuria in two weeks. The pulmonary involvement can occur in this form and can be recognized by cough, chest pain, hemoptysis, dyspnea or even acute respiratory distress syndrome. Common hemorrhagic manifestations of Weil's syndrome are epistaxis, petechial, purpura and ecchymosis; however, gastrointestinal bleeding and subarachnoid hemorrhage are uncommon. Neurologic involvement of leptospirosis can occur too and include meningitis, encephalitis, inflammatory myelopathy and intracranial hemorrhage (5, 6). Rhabdomyolysis, hemolysis, myocarditis, necrotizing pancreatitis and multi organ failure are less common complications of this syndrome (1, 7). Mortality rate of Weil's syndrome is high (>10%) (8). The aim of this study was to examine the clinical manifestations, epidemiologic and laboratory findings, outcome and mortality risk factors of Weil's disease.

Methods

A retrospective cross-sectional study was conducted on 66 consecutive patients with confirmed diagnosis of icterohemorrhagic leptospirosis who were admitted to Razi Hospital (The Therapeutic Center of Infectious Diseases in the North of Iran) in 2013. This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences (Code No: 89116, Date: January 05, 2011). The inclusion criteria were as follows: Those patients who had clinical and epidemiological data suggestive of leptospirosis, and displayed icterohemorrhagic form at the time of their admission or during hospitalization. These symptoms include jaundice, oliguria, skin rash, shock, altered sensorium, skin or conjunctiva diathesis and pulmonary hemorrhage.

Exclusion criteria were as follows:

1. Those patients who had no icterohemorrhagic form in spite of having clinical characteristics suggesting leptospirosis.
2. Patients who had no serologic findings of leptospirosis.
3. Patients who did not return for the follow up.
4. Patients who referred to the hospital after 10 days of initiation of the disease.

Serum samples for IFA (immunofluorescence assay) were sent to Pasture Institute of Amol; if the IFA was negative, a second serum sample was obtained and sent for MAT (microscopic agglutination test) to Razi laboratory of Hesarak, a referral research laboratory located in Iran. The MAT results were interpreted as "definitely positive" with a single titer $\geq$ 1/800.

Clinical investigation included a record of all signs and symptoms presented by each patient, as well as arterial systolic and diastolic blood pressure at hospital's admission.

A standard questionnaire was used to obtain demographic information, exposure history to animals and various sources of ground water, and clinical data and risk factors of the patients. Then all patients were visited at the first, second and sixth weeks after admission.

Laboratory data included blood urea, creatinine, potassium, bilirubin, transaminases, Creatino- Kinase, lactate dehydrogenase, total blood count and prothrombin time was performed. Statistical analysis was per-

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formed using the software SPSS 13.0 (SPSS Inc. Chicago, IL, USA). The p value < 0.05 was considered statistically significant.

Results

Sixty six patients were selected for this study; of whom, 59 were male (89.4%) and 7 were female (10.6%).The difference was statistically significant (p= 0.02). Age range of the cases was from 22 to 79 years; the average age was 53.6 years. The highest prevalence of icterohemorrhagic leptospirosis was in the age group of 50-60 years with 25 cases (37.9%) and the least frequent was in the age group of 70-80 years with two cases (3%). Approximately, 60% of the patients were farmers and six (9.1%) had a history of swimming in rivers. Thirty five patients (53%) were admitted in in June, 15 (22.7%) in July, 9 (13.6%) in August, 4 (6.2%) in September and 3 (4.5%) in May. The most common complaints of the patients were fever (45.2%) and jaundice (39.8%), respectively. The frequency of clinical signs and symptoms is demonstrated in Table 1. Jaundice was observed in 100% of the patients at the time of admission, and its percentage at the first, second and 1.5 months post admission was

Table 1. Frequency Distribution of Signs and Symptoms of Patients with Icterohemorrhagic form of Leptospirosis Hospitalized in Razi Hospital

Finding	n	%	Finding	n	%
Icter	66	100	Cough	13	19.7
Fever	60	90.9	Arthralgia	12	18.2
Myalgia	50	75.8	Conjunctivitis	12	18.2
Headache	43	65.1	Itching	9	13.6
Abdominal pain	42	63.6	Backache	9	13.6
Nausea	40	60.6	Extremity edema	8	12.1
Vomiting	38	56.1	Sore throat	7	10.6
Weakness	37	56	hemoptysis	6	9.1
Anorexia	30	45.5	Diarrhea	3	4.5
Dizziness	21	31.8	Splenomegaly	3	4.5
Sweating	16	24.2	Lymphadenopathy	2	3
Constipation	13	19.7	Periorbital edema	1	1.5

Table 2. The Rate of Laboratory Abnormalities of Patients with Icterohemorrhagic Form of Leptospirosis Hospitalized in Razi Hospital

Lab Data	Admission (%)	1 Week Later (%)	2 Weeks Later (%)	1.5 Months Later (%)
Leukocytosis	47.6	38.4	3.1	-
Thrombocytopenia	88.8	56.4	14.2	-
Anemia Hb <12 g/dL for female Hb <14 g/dL for male	96.8	75.0	14.2	-
Increased AST	95.2	62.5	19.7	10.6
Increased ALT	93.6	60.3	22.7	12.1
Increased ALP	76.2	54.3	10.6	7.6
Hyperbilirubinemia	100	68.7	21.2	7.6
Azotemia	31.7	28.2	3.2	2
Hyponatremia	7.6	2.1	-	-
Hypernatremia	72.7	7.9	4.5	1.5
Hypokalemia	3	-	-	-
Hyperkalemia	7.6	-	-	-
Hyperglycemia	14.3	7.9	-	-
Pyuria	49.2	28.2	-	-
Hematuria	49.20	31.7	-	-
Rise of amylase	54.5	7.6	-	-
Rise of LDH	65.1	7.6	-	-
Rise of CPK	36.4	-	-	-
Rise of PT	48.4	-	-	-
Rise of PTT	46.9	-	-	-

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; CPK: Creatine Phosphokinase; PT: Prothrombin Time
PTT: Partial Thromboplastin Time

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60.6%, 7.9% and 3.2%, respectively. Also, weakness and lethargy were seen in 14.3%, headache in 7.9%, myalgia in 7.9% and arthralgia in 1.6% of the patients six weeks after they were discharged from the hospital.

Table 2 demonstrates the laboratory characteristics of the patients at admission, and at the first, second, and six weeks post admission. At the end of the treatment, three of the patients (4.5%) were still suffering from hypernatremia and in a test that took place 1.5 months after the discharge, one of them (1.5%) still had hypernatremia (Table 2). When the patients were discharged, elevated AST, ALT, ALP and total bilirubin were seen in 13, 15, 7, and 14 patients, respectively. In the following 1.5 months, high AST and ALT were observed in 7 and 8 patients, respectively, and elevated total bilirubin was found in 5 patients. Fifty two patients (78.8%) had positive serology. A significant association (p= 0.041) was found between the incidence of icterohemorrhagic leptospirosis form and seropositive patients. Out of the 66 patients examined in this study, 28 patients (42.4%) experienced complications of icterohemorrhagic leptospirosis; of them, 20 patients (30.3%) developed acute renal failure, 17 (25.8%) developed pneumonia, 3 (4.5%) developed pancreatitis, 1 suffered from subarachnoid hemorrhage (1.5%), and 1 patient suffered from gastrointestinal bleeding. Also, there were two cases of loss of consciousness. Finally, 21 patients (31.8%) achieved complete remission at discharge, 3 (4.5%) died and 42 (63.7%) were discharged with residual effects. The average length of hospitalization was7 ±1.3 days; the minimum stay was 3 days and the maximum stay was 25 days. The CXR abnormalities were observed in 17 patients (25.8%) from which10 cases (58.8%) had lobar infiltration, 4 (23.5%) had reticular lesions and lesions were hemorrhagic in 3 patients (17.7%). LDH was increased in all the three patients who died, and all of them had leukocytosis; also, the highest amount at the time of admission was 18,600; and all the three patients had a high BUN (maximum 292). Levels of total bilirubin in the patients who died increased substantially. Dialysis was performed for two of the three patients who died. Although the creatinine level was high in all the three cases (up to 7.2), performing dialysis was impossible in one case because of hemodynamic instability. Among the studied patients, 34 (51.5%) required platelet transfusion; the highest rate of platelet transfusion requirement was 30 units, and the minimal was 2. Electrolyte abnormalities were observed in all those three patients who died. Corticosteroids were prescribed for two (66/6%) of the patients who died. Also, all three had thrombocytopenia, and the lowest was 24,000. Serology was positive in two patients, and negative in one. In addition, pancreatitis in two cases and gastrointestinal bleeding in another case were reported. Also, ascites, acute renal failure, diabetes, pancreatitis, metabolic acidosis and heart failure were present in one of these patients who died. Diffuse infiltration was reported in CXR of two patients. Also, hemorrhagic lesion was observed in one of them. Serum amylase levels were also high in these patients in a way that one of them reached the level of 1330.The maximum AST level in these patients was 238 and the maximum ALT level was 137.

Discussion

The incidence of leptospirosis has increased in the north of Iran during the recent decade. In this study, a series of patients with icterohemorrhagic form of leptospirosis called Weil's syndrome were studied. Of the patients, 88.9% were male and 11.1% were female. Significant differences were found between icterohemorrhagic form of leptospirosis infections in different genders (p= 0.002). This ratio has been observed in most studies performed in different areas (9-11). In a study in 2008 conducted by Chawla et al. on patients with severe form of leptospirosis in India, 80% of the patients were male (10). As leptospirosis is often an occupational disease, it is

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reasonable that its incidence in men be more common than in women. In our study, the most common symptoms were fever (90.9%), jaundice (87.9%) and myalgia (75.8%), respectively. The most common symptoms in cases studied by Chawla et al. were fever (96.6%) followed by jaundice (63.3%) and conjunctival suffusion (40%). Therefore, paying enough attention to such warning signs as icter can result in a faster diagnosis and consequently in a faster treatment. In our study, decrease of platelet count was seen in more than 88% of the cases. This finding has been reported in most studies of severe leptospirosis (11-14). In a study performed by Lina et al. in the Philippines, on 15 out of 59 patients with leptospirosis the incidence of thrombocytopenia was 61%, although it existed in most of the patients suffering from severe leptospirosis (15). This difference is acceptable because all our patients were considered having severed leptospirosis. Also, an increase in the mortality rate among patients who developed thrombocytopenia and bleeding (especially pulmonary hemorrhage) was found in the mentioned study. Among patients who died during our study, all three had thrombocytopenia; and one person died due to pulmonary hemorrhage. Nearly one third of our patients had azotemia at the time of admission and it continued to remain in 2% of them, indicating that renal failure can last for a long time in patients with leptospirosis. The mortality rate in our study was 6.1%. In a study by Clerke et al. in 2000, conducted on patients with leptospirosis in India, the most commonly involved organs were liver, kidneys and lungs (13); and this finding was similar to that of our study in which more than 90% of the patients had liver disorders, 20% had kidney disorders and 32% had pulmonary dysfunction. In another study on Weil syndrome, it was demonstrated that liver and kidneys were the main organs involved, and two patients died due to a severe form of leptospirosis infection (16). In this study, 100% of the deceased had impaired liver and kidneys as well as electrolyte imbalance. In a study performed by Lecour and et al. in Brazil, it was demonstrated that 22% of the patients with leptospirosis needed dialysis. Although in our study only four out of 63 patients (34/6%) needed dialysis, the percentage was higher (17). In another study by Helmerhorst HJ conducted in Amsterdam, it was found that factors that affected the prognosis of patients included renal failure, pulmonary involvement and electrolyte abnormalities (18). The influence of these factors on prognosis was demonstrated in the present study, indicating that these disorders existed in all the patients who died. In a study of Marchiori in Cameroon, in CXR of patients with icterohemorrhagic leptospirosis alveolar infiltration, bronchopneumonia, pulmonary hemorrhage and respiratory distress syndrome were the common findings, and these abnormalities in CXR were most common and in our study (19,20).

Weaknesses of this Study

As this study was retrospective, we did not have important demographic data such as the mean time of exposure until beginning of the symptoms and exact location of exposure. Also, some laboratory data such as the serum amylase in many patients were not registered in patients' records.

Conclusion

The mortality rate of our patients with icterohemorrhagic form of leptospirosis was approximately 6%. This could be partly due to the endemic nature of the disease. The most significant biochemical abnormalities of our patients were thrombocytopenia, hyperbilirubinemia, hypo and hypernatremia and azotemia; and the latter remained stable in 2% of the patients at least until the end of the 6-week follow-up period.

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