AN OLD ZOONOSIS COMING FROM AFAR: LEPTOSPIROSIS

Ozlem Bilir*
Faculty of Medicine, Recep Tayyip Erdogan University, Rize, Karadeniz, Turkey

INTRODUCTION

Leptospirosis is a zoonotic infection which has started to take place in emergency departments in our country during recent years due to the increasing trend toward keeping pets as well as the climatic changes becoming more and more prominent (Stull et al., 2012, Lau et al., 2010). Especially the squatter settlements, developing in urban areas, have caused it to become an important health issue by providing conditions for transmission through rats (Felzemburgh et al., 2014).

The zoonotic agent causing the disease is released from the renal tubules of mammal hosts spreading across a broad spectrum (Pappas et al., 2008). Following the incubation period, it enters into body through lacerations or abrasions, mucosa, conjunctiva, aerosol inhalation and rarely through the digestive system and disseminates through blood. Its incubation period in humans ranges from 4 days to 4 weeks. Being overlooked most of the time, this disease may manifest as anicteric leptospirosis or as the mortal clinical entity known as Weil’s disease (Adler, 2015).

It should be considered in differential diagnosis in patients with fever being admitted to emergency departments with non-specific complaints if impaired hepatic and renal functions are present. Delayed diagnosis and treatment can result in multi-organ failure leading to death. Patients are treated by hospitalization but most of them require dialysis and antibiotic therapy (Ghasemian et al., 2016). In this study we aimed to retrospectively evaluate the patients who had been admitted to the emergency department due to fever with non-specific complaints and had been diagnosed with Leptospirosis following detection of impaired renal and hepatic functions.

MATERIALS AND METHODS

Study design and patient characteristics

The records of the patients diagnosed with Leptospirosis among the patients who had been admitted to the emergency department of Recep Tayyip Erdogan University Training and Research Hospital between January 2015 and December 2015 and had been hospitalized due to renal and hepatic failure were retrospectively reviewed. The blood samples taken from the patients were analyzed by Ministry of Food, Agriculture and Livestock Veterinary Control Central Research Institute Directorate. Our country in the necessary diagnostic tests for the diagnosis of leptospirosis reference laboratory to be studied by The Food and Agriculture Ministry control. Leptospirosis was diagnosed by microscopic agglutination test (MAT) using ELISA method considering titers of ≥ 1/800 as positive.

The demographic data, complaints on admission, symptoms, chronic diseases, time of onset of the symptoms, risk factors, clinical and laboratory findings, follow-up areas and durations, use of hemodialysis and received treatments of 14 patients diagnosed with Leptospirosis among the patients who had been admitted to the emergency department with fever and renal and hepatic failure were retrospectively evaluated for the mentioned 1-year period of the study.

The data were analyzed using Statistical Packages for the Social Sciences 17 (SPSS, Chicago, IL, USA). The collected data were expressed as frequency and mean ± standard deviation.

RESULTS

Patient characteristics

The records of 561 patients who had been admitted to the emergency department with fever and renal and hepatic failure during the mentioned 1-year period of the study were retrospectively evaluated. Among this patient group, the files of the 14 patients (2.49%) who had been followed-up with the pre-diagnosis of Leptospirosis but confirmed through MAT were retrospectively evaluated.

57.1% (8/14) of the patients were female and the mean age range was 59.0 ± 10.8 (41-77 years). The most common cause of admission was weakness (42.9%, n=6). The other causes, in descending order, were fever (35.7%, n=5), nausea-vomiting (28.6%, n=4), low urine output (28.6%, n=4), headache (21.4%, n=3) and loss of appetite (21.4%, n=3). It was seen that the mean time from the onset of the event to the admission to the emergency department was 5.86 ± 2.28 days (2-10 days). The patients had been followed-up mostly with the diagnosis of Leptospirosis but confirmed through MAT were retrospectively evaluated.

57.1% (8/14) of the patients were female and the mean age range was 59.0 ± 10.8 (41-77 years). The most common cause of admission was weakness (42.9%, n=6). The other causes, in descending order, were fever (35.7%, n=5), nausea-vomiting (28.6%, n=4), low urine output (28.6%, n=4), headache (21.4%, n=3) and loss of appetite (21.4%, n=3). It was seen that the mean time from the onset of the event to the admission to the emergency department was 5.86 ± 2.28 days (2-10 days). The patients had been followed-up mostly with the diagnosis of influenza due to their non-specific complaints in other centers. The month on which the disease had most...
commonly been seen was August (35.7%, n=5) followed by September (21.4%, n=3) and July (14.3%, n=2). With respect to chronic diseases, the most commonly seen ones are hypertension (35.7%, n=5) and diabetes mellitus (28.6%, n=4) (Table 1).

**Risk Factors**

The risk factors of the patients were active agricultural work in rural areas for 12 patients (85.7%), being a sewage worker for 1 patient (7.1%) and contacting with wild animals in the mountains (7.1%) (Table 1).

**Laboratory and clinical features**

With respect to the laboratory analyses on admission, increased levels of urea, creatinine and C-reactive protein (CRP) were observed in all patients while leukocytosis, leukopenia and thrombocytopenia were detected in 50% (n=7), 14.3% (n=2) and 78.6% (n=11) of the patients respectively (Table 2). One of the patients was anuric and 13 (92.8%) were oliguric. Co-existence of oliguria and acidosis was observed in 21.4% (n=3) and oliguria and hepatic failure in 14.3% (n=2) (Table 1).

**Follow-up and treatment**

The patients had been hospitalized, and 28.6% of them (n=4) had been hospitalized in the intensive care unit (ICU) then followed-up in the clinical setting. Ceftriaxone 2 g/day had been preferred as the antibiotherapy, 28.6% had required dialysis and all of them had been discharged after a mean of 9 ± 4.94 days (3-19 days) without any cases of death (Table 1).

**DISCUSSION**

Due to disasters and extreme weather events resulting from climatic changes and globalization, leptospirosis has started to take place in emergency departments in Turkey with the etiology of fever of unknown origin (Lau et al., 2010, Turhan et al., 2012). Zoonotic infection spreads to humans through carrier animals or through direct contact with water, soil and vegetables (Sanchez, 2010). In our country, sporadic cases frequently encountered in agricultural areas have been reported (Erdinc et al., 2006, Cetin et al., 2004). Agriculture is the most common risk factor also in the present study while, unlike the literature, 57.1% of the patients were female and the mean age range was 59.0 ± 10.8. We think that this is caused by the fact that the study population live in the East Black Sea Region and that mostly middle-aged women are engaged in agriculture in this region. The infection occurs frequently in August and July and show parallelism with the other studies in this respect (Cetin et al., 2004).

Leptospirosis infections may manifest as the self-limiting anicteric form or as the mortal form, known as Weil’s disease, which is accompanied by jaundice, proteinuria and hemorrhage (Adler, 2015). In the

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dL)</td>
<td>66</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.68</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.7</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>0.3</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>19</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>16</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>22</td>
</tr>
<tr>
<td>CPK (U/L)</td>
<td>27</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.7</td>
</tr>
<tr>
<td>WBCs (count/mm³)</td>
<td>2580</td>
</tr>
<tr>
<td>Platelets (count/mm³)</td>
<td>7150</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
<td>8.88</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>26.2</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>3.26</td>
</tr>
</tbody>
</table>

Table 2: Minimum, maximum and mean values of laboratory parameters on admission in the presence of active disease.
anicteric form, of which the incidence rate is 60 to 70%, patients present with fever and influence-like non-specific symptoms to emergency departments. Also in the present study, the patients had admitted to the emergency department with the non-specific complaints of weakness, fever, loss of appetite, body pain, and had previously been followed-up with the diagnosis of influenza.

The normal structure of the skeletal muscle is disturbed, and focal necrosis and necrobiosis are typical features. Due to this, patients present to emergency departments with myalgia described as widespread body pain (Turhan et al., 2013). In a study conducted by Resano et al., the most common symptoms of leptospirosis infections were reported as fever, myalgia and jaundice (Resanoglu et al., 1999). 21.4% of our patients had presented with widespread body pain and increased levels of Creatine Phosphokinase (CPK), which is the laboratory finding of necrosis, were observed in 50%.

Renal failure, characterized by changes in urinary sedimentation and interstitial involvement as the main lesion is commonly seen in such patients. Tubular necrosis and interstitial nephritis rather than glomerular lesions are the notable manifestations (Cetin et al., 2004). It may progress from dilation of the tubules to severe degeneration and necrosis. Interstitial edema and cellular infiltration are observed (Sitprija et al., 2003). Renal failure develops shortly after the onset of the disease and death mostly results from this condition (Levett, 2001). Changes in urinary sediment and increased levels of blood urea and creatinine were seen on admission in all of our patients. Additionally, while 28.6% of them had suffered from low urine output, oliguria was seen in 92.9% and anuria was seen in one patient. 35.7% of the patients, who had not responded to hydration and diuretic therapy, had required hemodialysis. However, these patients who had required hemodialysis also had had diseases that may have caused renal damage such as hypertension and diabetes. These results show parallelism with another study conducted in the Black Sea Region (Cengiz et al., 2002).

Thrombocytopenia is commonly seen in leptospirosis infection. It occurs transiently and independently from disseminated intravascular coagulation. During the infection, increased plasma levels of 11-DH-TXB2 cause induction of the activation-aggregation of the thrombocytes and the phagocytosis by Kupffer cells thereby leading to thrombocytopenia (Edwards et al., 1986). 78.6% of our patients had been thrombocytopenic; however, no cases of death had been seen although the presence of thrombocytopenia is considered as a risk factor with respect to mortality (Turgut et al., 2002). Anemia was observed in 42.9% of our patients although it has been reported in the literature that anemia may be observed due to blood loss, microangiopathies and hemorrhages caused by the effects of Leptospiral Hemolysins in 30% of patients. While it has been reported that WBC count may be normal and leucopenia or leukocytosis may rarely be seen, leukocytosis was observed in 50% of our patients.

The incidence rate of Weil’s disease is 10-15% with a mortality rate of 5-40% (Lim, 2011). It can involve the kidneys as well as causing conditions relating to liver, heart, lungs, skin, eyes and nervous system (Levett, 2001). Jaundice results from vascular damage occurring in the hepatic capillaries (Cetin et al., 2004). In 64.3% of our patients, increased bilirubin levels as well as hypalbuminemia and increased levels of hepatic enzymes had been observed. Additionally, two patients had had hemorrhagia requiring transfusion accompanied by proteinuria and hepatic failure. Although being hospitalized in the ICU, these patients survived.

Leptospirosis may be confused with Hantavirus infections which cause hemorrhagic fever with renal syndrome. Leukocytosis and thrombocytopenia in the hemogram as well as proteinuria, hematuria, pyuria and increased levels of hepatic enzymes and CPK are seen also in such patients (Chandy et al., 2008). Besides Hantavirus, Rickettsia and Crimean-Congo Hemorrhagic Fever, which are seen with fever and renal failure, should also be considered in the differential diagnosis.

Antibiotherapy is recommended for the treatment to shorten the duration of the disease and to prevent urinary involvement. Oral doxycycline, azithromycin, penicillin and amoxicillin are preferred as antibiotics in patients with mild disease who are planned to be followed-up as outpatients. On the other hand, parenteral penicillin, cefotaxime, doxycycline ceftriaxone are recommended for patients with severe clinical presentation. All of our patients had received intravenous ceftriaxone. However, no consensus could be reached in the studies relating to use of antibiotics with respect to mortality and improvement in the disease manifestation (Pappas et al., 2006). Supportive care is important in such patients, and hemodialysis may be required if renal failure occurs in those who do not respond to intravenous fluids and diuretic therapy. 35.7% of the patients had required dialysis in addition to the supportive care.

In conclusion, Leptospirosis infection should certainly be kept in mind in patients presenting to emergency departments with non-specific complaints. Although sporadic cases have been seen in Turkey, the disease has started to take place with the etiology of fever of unknown origin. Consideration of this disease will allow preventing its high level of mortality.

REFERENCES


