

AN OLD ZONOSIS COMING FROM AFAR: LEPTOSPIROSIS

Ozlem Bilir*

Faculty of Medicine, Recep Tayyip Erdogan University, Rize, Karadeniz, Turkey

Article History: Received 10th May 2016; Accepted 27th June 2016; Published 30th June 2016

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 antibiotherapy (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 $\geq 1/800$ 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 \pm 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 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

Table 1: Demographic and clinical data of the patients with leptospirosis.

Characteristics	n (%)
Age	59.0 ± 10.82 (41-77 years)
Gender	
Female	8 (57.1%)
Complaints on Admission	
Weakness	6 (42.9%)
Fever	5 (35.7%)
Nausea-vomiting	4 (28.6%)
Low urine output	4 (28.6%)
Headache	3 (21.4%)
Loss of appetite	3 (21.4%)
Month in which the Disease Appeared	
July	2 (14.3%)
August	5 (35.7%)
September	3 (21.4%)
Risk Factor	
Agricultural works	12 (85.7%)
Sewage worker	1 (7.1%)
Contact with wild animals	1 (7.1%)
Concomitant Disease	
Hypertension	5 (35.7%)
Diabetes Mellitus	4 (28.6%)
Clinical Characteristics	
Anuria	1 (7.1%)
Oliguria	8 (57.1%)
Oliguria + Hyperacidemia	3 (21.4%)
Oliguria + Hepatic failure	2 (14.3%)
Treatment	
Antibiotherapy	14 (100%)
Supportive Care	14 (100%)
Hemodialysis	5 (35.7%)
Follow-up	
Internal Medicine Clinic	10 (71.4%)
Intensive Care Unit	4 (28.6%)
Outcome	
Death	0 (0%)

Table 2: Minimum, maximum and mean values of laboratory parameters on admission in the presence of active disease

Parameters	Values		
	min	mean	max
Urea (mg/dL)	66	138 ± 63.3	268
Creatinine (mg/dL)	1.68	1.88 ± 2.2	9.03
Total bilirubin (mg/dL)	0.7	2.59 ± 2.4	9.81
Direct bilirubin (mg/dL)	0.3	1.72 ± 1.9	7.59
AST (U/L)	19	61.57 ± 38.8	168
ALT (U/L)	16	42.85 ± 29.5	120
GGT (U/L)	22	133 ± 105.7	331
CPK (U/L)	27	815.85 ± 1207.3	4267
Albumin (g/dL)	2.7	3.32 ± 0.3	3.8
WBCs (count/mm ³)	2580	10001 ± 4137.0	18000
Platelets (count/mm ³)	7150	103117.85 ± 67734.43	262000
Hemoglobin (mg/dL)	8.88	12.25 ± 1.84	15.2
Hematocrit (%)	26.2	36.2 ± 4.80	43.6
CRP (mg/L)	3.26	20.2 ± 9.0	31.61

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

anicteric form, of which the incidence rate is 60 to 70%, patients present with fever and influenza-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 (Resano Igal *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 (Sitprijia *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 hypoalbuminemia 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

- Adler, B., (2015). History of leptospirosis and leptospira. *Curr Top Microbiol Immunol*, 387: 1-9.
- Cengiz, K., Sahan, C., Sünbül, M., Leblebicioğlu, H. and Cüner, E., (2002). Acute renal failure in leptospirosis in the black-sea region in Turkey. *Int Urol Nephrol*, 33: 133-136.

- Cetin, B.D., Harmankaya, O., Hasman, H., Gunduz, A. and Oktar, M., (2004). Acute renal failure: a common manifestation of leptospirosis. *Ren Fail*, 26: 655-661.
- Chandy, S., Abraham, P. and Sridharan, G., (2008). Hantaviruses: an emerging public health threat in India? A review. *J Biosci* 33: 495-504.
- Edwards, C.N., Nicholson, G.D., Hassel, T.A., Everard, C.O. and Callender, J., (1986). Thrombocytopenia in leptospirosis: the absence of evidence for disseminated intravascular coagulation. *Am J Trop Med HYG*, 35: 352-4.
- Erdinc, F.S., Koruk, S.T., Hatipoğlu, C.A., Kinikli, S. and Demiroz, A.P., (2006). Three cases of anicteric leptospirosis from Turkey: mild to sever complications. *J Infect*, 52: e45-48.
- Felzemburgh, R.D., Ribeiro, G.S., Costa, F., Reis, R.B. and Hagan, J.E., (2014). Prospective study of leptospirosis transmission in an urban slum community: role of poor environment in repeated exposures to the *Leptospira* agent. *PLoS Negl Trop Dis*, 8: e2927.
- Ghasemian, R., Shokri, M., Makhloogh, A. and Suraki-Azad, M.A., (2016). The course and outcome of renal failure due to human leptospirosis referred to a hospital in North of Iran; A follow-up study. *Caspian J Intern Med* 7: 7-12.
- Lau, C.L., Smythe, L.D., Craig, S.B. and Weinstein, P., (2010). Climate change, flooding, urbanisation and leptospirosis: fuelling the fire? *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 104: 631-638.
- Levett, P.N., (2001). Leptospirosis. *Clin. Microbiol. Rev.* 14: 296-326.
- Lim, V.K., (2011). Leptospirosis: a re-emerging infection. *Malays J Pathol*, 33: 1-5.
- Pappas, G. and Cascio, A., (2006). Optimal treatment of leptospirosis: queries and projections. *Int J Antimicrob Agents*, 28: 491-496.
- Pappas, G., Papadimitriou, P., Siozopoulou, V., Christou, L. and Akritidis, N., (2008). The globalization of leptospirosis: worldwide incidence trends. *Int J Infect Dis*, 12: 351-357.
- ResanoIgal, A.B., Camino Ortiz De Baroon, X., UrbeCastelruiz, P.K., ErroGarzaron, A. and Larruscain Garmendia, J., (1999). Leptospirosis. Review of 5 cases. *An Med Interna*, 16: 527-529.
- Sanchez, R.P., (2000). Care of a patient with leptospirosis icterohemorrhagica. *Enferm Intensiva*, 11: 17-22.
- Sitprija, V., Losuwanrak, K. and Kanjanabuch, T., (2003). Leptospirosis nephropathy. *Semin Nephrol*, 23: 42-48.
- Stull, J.W., Peregrine, A.S., Sargeant, J.M. and Weese, J.S., (2012). Household knowledge, attitudes and practices related to pet contact and associated zoonoses in Ontario, Canada. *BMC Public Health*, 12: 553.
- Turhan, V. and Hatipoğlu, M., (2012). Leptospirosis: "Newly discerning but an ancient infectious disease". *J Exp Clin Med*, 29: 163-168.
- Turhan, V., Karagöz, E., Eroğlu, M., Ülçay, A., Önem, Y., et al., (2013). Leptospirosis in a geriatric patient who frequently walks barefoot on the beach. *Turkish Journal of Geriatrics*, 16: 352-355.
- Turgut, M., Sünbül, M., bayırlı, D., Bilge, A., Leblebicioğlu, H., et al., (2002). Thrombocytopenia complicating the clinical course of leptospiral infection. *J Int Med Res*, 30: 535-540.