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Leptospirosis; Diagnosis, Treatment and Prevention: A Review

Ozgur Aslan[1*]

[1]*Artvin Coruh University, Turkey.*

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Leptospirosis is one of the most common and zoonotic infections on earth, induced by *Leptospira* genus spirochetes. Although leptospirosis is defined as a zoonotic infection induced by *Leptospira interrogans* serotypes and characterized by jaundice, high fever and hemoglobinuria, it exhibits a complex clinical picture and difficult to diagnose only with clinical pictures. It could be confused with diseases such as meningitis, typhoid fever, brucella, tuberculosis and pneumonia. Definitive diagnosis of leptospirosis is established by the isolation of microorganism in clinical samples accompanied with clinical symptoms, determination of seroconversion or observation of a four-fold or more increase in antibody titer.

Keywords: Leptospirosis; diagnostic methods for leptospirosis; treatment and prevention.

1. INTRODUCTION

Leptospirosis is an infectious disease, induced by genus *leptospira* species and observed in all domestic animals and humans, and generally characterized by symptoms such as hemoglobinemia, icterohemoglobinemia, icterus, septicemia, anemia, abortus, agalactia and mastitis [1].

Primary modes of transmission to humans are water contaminated with the urine of infected

**Corresponding author: E-mail: Ozguraslan36@hotmail.com;*

animals and contact with disintegrated derma-mucosa. Rarely, transmission via digestive track could be observed via consumption of contaminated water or milk, vegetables grown in contaminated water or raw meat contaminated with urine. Transmission could also occur by inhalation of particles containing *leptospira*, or contact with mucous membranes. It was reported that leptospirosis is also very rarely transmitted with mouse, dog or rat bites [2].

2. DIAGNOSTIC METHODS

Leptospirosis is characteristically a two-phase disease: Septicemic phase (lasting 4 – 9 days) and immunogenic phase (lasting 4 – 30 days). During the first period (septicemic phase) leptospira could be observed in the blood and cerebrospinal fluid (CF). Leptospiremia lasts about one week. Symptoms start to disappear and the fever is reduced with the formation of IgM type antibodies. During the second, sometimes the third week a short relapse with fever is observed. Symptoms are repeated. It was accepted that this second phase is observed due to an immune mechanism induced by hypersensitivity. In this period (immune phase), nervous system such as meningeal irritation symptoms, iridocyclitis, optic neuritis or encephalomyelitis, peripheral neuropathy, and abortion in pregnant women could be observed. In the immune period, the agent is not found in blood or CF, while it could be found in the urine, kidneys and humor aqueous [3].

Definitive leptospirosis diagnosis is made in the presence of clinical symptoms by isolation of microorganism in clinical samples, determination of seroconversion or observation of a four-fold or more increase in antibody titer [4]. During the first week of the disease *leptospira* could be isolated in blood and cerebrospinal fluid. Samples planted in special media (Korthoff or Flethcher semi-solid media) are incubated at 30℃, and reproduced *leptospira* could be observed after 5 – 10 days in darkness. *Leptospira* could survive for almost 10 days ın blood containing anticoagulants. After the first week, it is possible to isolate *leptospira* in patient's urine. Serological methods are used more frequently in identification of *leptospira* antibodies since culture methods could not be applied in every laboratory and culture results take a long time to complete [5,6]. Several methods are used for serologic diagnosis. However, several studies accepted positive blood culture and Microscopic agglutination test (MAT) tests as standard leptospirosis diagnosis methods [7].

2.1 Microscopic Examination

It is possible to identify *leptospira* in blood during leptospiremia period occasionally. Also during septicemia phase, it could rarely be identified in blood, and a few days later in cerebrospinal fluid. After the the first week of the disease, it would be possible to observe *leptospira* in urine after high-speed centrifuge, since they start to be excreted in urine, albeit rare [8]. When slides prepared with plasma, urine and cerebrospinal fluid (CF) samples are examined under dark field microscope, spiral bacteria are observed as mobile white sparkles [9]. In a study conducted by Yarkın et al. [10] in Çukurova region in Turkey to identify leptospirosis prevalence and predominant *leptospira* serotypes, they have identified *leptospira* in 9 of the serum samples, in 7 of the CT samples and in 5 of the urine samples obtained from 13 patients diagnosed with leptospirosis using dark field microscope examination.

2.2 Microscopic Agglutination Test (MAT)

MAT, where alive *leptospira* are used as antigens, is a reference method for leptospirosis diagnosis. Despite speed, sensitivity and high specificity advantages of MAT, it has also numerous disadvantages such as its subjective assessment, observation of poor agglutination when the incubation period of the infection is longer, and its use only in reference laboratories because of its utilization as the test antigen for alive *leptospira* and laboratory infections it causes [2].

Factors such as the stage of the disease, living in an epidemic region and the properties of agglutination identified serotype are significant in interpretation of the results of microscopic agglutination test. While titers such as 1/40 could be significant for a clinician in leptospirosis in a non-epidemic region, in regions with high prevalence, titers such as <1/200 could not be related to acute leptospirosis [2,11]. Generally, in acute infection, for results with <1/400 titers, a 4 times titer increase should be identified in the samples two weeks later. Titers higher than 1/400–1/800, are mostly considered as leptospirosis [2,11]. Positivity in 1/100 titer is significant in demonstrating contact in epidemiological studies [8]. MAT antigen panel is determined based on the epidemiological properties of the country or the region. Generally, each serum sample is studies with an antigen panel containing 15 – 23 serotypes. Serogroups

could include antigen pools or the most frequent 2 – 3 serotypes, which facilitate epidemiological studies [2].

2.3 Enzyme Linked Immunosorbent Assay (ELISA)

ELISA test is utilized as type-specific screening test in humans. ELISA method, where dead antigens are used, is commonly utilized due to its rapid and facile application, objective assessments and availability of specific IgM and IgG identification. It is more sensitive than MAT test for IgM identification during the first week of the disease. ELISA method identifies IgM and IgG type antibodies that correspond to the disease agent. A positive IgM demonstrates acute infection [2,3,9].

In a study by Sargın et al. titled "Weil Disease with acute cholecystitis without stone and severe thrombocytopenia: A case study," ELISA test was conducted to identify *leptospira* antibodies before the treatment of the patient and determined ELISA IgM Positive. At the end of the therapy, ELISA test conducted again on patient blood sample exhibited ELISA IgM negative and ELISA IgG positive [12].

Deodhar and Jojn, conducted Dri Dot and ELISA tests on 647 patients, who applied to a tertiary care hospital in India for seven days within a year with inflammatory diseases. They have reported 244 positive patients out of 647 (37.7%) with Dri Dot test and 200 positive patients out of these 244 patients (82%) with ELISA test [13].

2.4 Polymerase Chain Reaction (PCR)

PCR methods were developed to identify *leptospira* in tissue, serum and urine. This method is more precise compared to culture and direct identification methods. Furthermore, the method identifies all alive and dead bacteria [9]. PCR-based methods are widely used for pathogenic determination of *leptospira* strain, due to their high precision and early diagnosis abilities. Since PCR is prepared using Tagman technology, it provides more rapid results when compared to conventional PCR and has the advantage of showing less tendency to contamination. Conventional and real time PCR are developed for all target leptospirosis localization, are limited to pathogenic types with or without gene sequences, and exemplified with SecY and lipL.32, respectively. A positive PCR generally demonstrates a pathogenic member. However, it is not used to predict the leptospira serotype in the sample [14]. Kucerova et al. investigated 216 leptospirosis suspect patient during 2010 – 2011 using real time PCT to determine the gene coding *leptospira* surface lipoprotein LipP32 to confirm acute form of leptospirosis and achieved positive results in total 14 biological material (9 urine, 4 blood, 1 bronchoalveolar) obtained from 8 (3.70%) patients [15].

3. TREATMENT

Leptospirosis treatment includes antibiotic treatment to eliminate the cause of the disease, severity and duration of symptoms, and to reduce the morbidity, in addition to supportive treatment for hypoxemia, hypotension, hemorrhage and kidney failure. It was established that *leptospira* are sensitive for a wide spectrum of antibiotics and do not develop resistance. Antibiotic treatment in leptospirosis shortens the duration and reduces the severity of the disease.

Duration of the disease is reduced as the antibiotic treatment is started as soon as possible. It was reported that duration of illness is significantly reduced when the treatment is started during the initial two days, there was a significant difference between the illness durations of cases, which were started on antibiotics during the initial seven days and after the initial seven days, and the treatment that was started after seven days was not effective on the duration of the disease [16].

Primary choice is penicillin group in leptospirosis treatment. In cases that are not responsive to penicillin, doxycycline is a good alternative. Certain studies reported that penicillin treatment in late stage leptospirosis affects prognosis negatively. There are studies, which reported that penicillin treatment after the fourth day of leptospirosis has no benefits [17]. Treatment is successful if it is started during the two days after the onset of symptoms and before the development of vasculitis. In addition to penicillin, antibiotics such as doxycycline, ampicillin, and amoxicillin could be used in the treatment. Several examples could be given for these antibiotics that were used in leptospirosis case studies. In leptospirosis case with hearing loss prognosis reported by Özgüneş et al. [18], ampicillin-sulbactam was used and the patient completely recovered on the tenth day of treatment, however a sudden hearing loss

developed. Çelikbaş et al. [17] obtained successful results with sulbactam-ampicillin and ceftriaxone treatment in two leptospirosis cases they reported. Furuncuoğlu et al. [5] applied initially ceftriaxone and clarithromycin treatment to the patient and could not receive a response to treatment in leptospira induced myocarditis cases. They altered the treatment on the third day and crystallized penicillin was started and the patient completely recovered on the tenth day and discharged. Ünsal et al. [19] started ceftriaxone treatment in an icteric leptospirosis case that developed in a garbage collector and discharged the patient on the tenth day following antibiotic therapy. Gürcüoğlu et al. [20], in three cases they reported in South Marmara region, applied doxycycline treatment and received a rapid response. Narita et al. [21] applied ampicillin treatment in 14 cases they reported in Japan, and achieved recovery in all cases without long-term complications. Hakyemez et al. [4] applied meropenem in a sepsis syndrome case and the patient completely recovered on the third week of treatment.

4. PREVENTION

Adaptation of general rules of hygiene and rodent control have high significance. “Panama Channel Experience” among soldiers under leptospirosis risk demonstrated that once a week 200 mg doxycycline was effective. This scheme is 95% effective; attack rate was 4.2% in placebo group, while it was 0.2% in treatment group. Certain current reports claimed that doxycycline chemoprophylaxis was not effective.

Leptospirosis vaccine is commonly used in veterinary medicine and stock farming and vaccination is recommended. It was demonstrated that cattle vaccination prevented infection and as a result fetal waste. However, carriers could not be prevented and periodic vaccination is required [3].

Vaccination for prophylaxis in humans is only reported in countries such as Russia, China and Vietnam and the action of the vaccine is not completely known. Furthermore, the existence of several serotypes renders general prevention via immunization almost impossible. However, the most significant studies on leptospirosis are focused on developing a vaccine that could successfully be used in human medicine [6]. Despite studies conducted, there is yet a reliable and successful vaccine that could be utilized in humans to be found for leptospirosis [22].

5. CONCLUSION

As a result, leptospirosis is an easily overlooked disease transmitted with water. Leptospirosis is a significant infectious disease today as the global climate change becomes increasingly evident It should be considered in inflammatory diseases with multi-organ involvement, primarily hepato-nephritis encountered especially after natural disasters. Severe leptospirosis is a public health issue that could be life threatening in several countries. Leptospirosis should be considered in differential diagnosis, since the fatality of the disease is high in patients among individuals with risk factors with fever, jaundice, muscle pain, conjunctival rash, non-hemorrhagic hyperemia and headache complaints accompanied by azotemia and high transaminase with thrombocytopenia and/or high CPK [3]. An active vaccine and increased sensibility among physicians are required.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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