Leptospirosis: an underrecognized and underdiagnosed disease

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In this issue of the Netherlands Journal of Critical Care, van Leeuwaarde et al. [1] describe the course and histopathological post mortem examination of a patient with severe myocarditis as complication of leptospirosis. This case report nicely illustrates the clinical and laboratory diagnosis and the potential devastating effects of the host immune response in this emerging infectious disease.

Pathogenic leptospires of the genus Leptospira colonize the proximal renal tubules of carrier animals like rodents. Consequently, coming into contact with urine containing leptospires, either directly or through contamination of soil or water, may lead to leptospirosis. Many species are recognized and they are classified into a number of species based on their degree of genetic relationship. Leptospirosis occurs worldwide with the highest incidence in the humid tropics. The exact number of infections is unknown since the disease is often overlooked and underreported, but it is estimated that more than 500,000 cases occur each year worldwide [2, 3]. In the Netherlands, around 30 cases are reported annually, the icterohaemorrhagiae serogroup being responsible for the majority of cases [4]. Three decades ago the incidence of leptospirosis was higher, mainly due to occupational disease among cattle farmers caused by L. interrogans serovar Hardjo (‘dairy farm fever’) [5]. A successful eradication programme nearly eliminated the carriage in cattle and nowadays outdoor recreational activities, particularly in Southern America and South East Asia are important contributors to infection. Increased and adventurous travelling to endemic regions render many people susceptible to possible contamination and is a potential for increased incidence of this disease [3].

The clinical manifestations range from subclinical infection to a severe illness known as Weil’s disease characterized by jaundice, renal failure and haemorrhage with a case fatality rate of up to 15% [6]. Although leptospirosis may mimic many other diseases, muscle pain, typically in the calves and lumbar region, and conjunctival suffusion (redness without exudate) should raise the suspicion of leptospirosis. Although the diagnosis was made at autopsy in the case described by van Leeuwaarde et al., in retrospect, the myalgia, the conjunctival suffusion and the history of sewer maintenance work were clues that could have led to an earlier diagnosis.

Some patients have biphasic pattern: initially a sepsis phase with normalization of the temperature at the end followed by an immune phase with severe symptoms like aseptic meningitis. Cardiac involvement is a known complication of leptospirosis, but probably goes unnoticed in many cases. Autopsy studies reveal myocarditis in over 90% of patients, most of whom died of pulmonary haemorrhages [7, 8]. As in the case presented by van Leeuwaarde et al., interstitial myocarditis and intimitis of coronary artery vessels are prominent features in post mortem analysis suggesting an important immunological role in the pathogenesis of this manifestation. An exaggerated immune response of the host, besides vasculitis mediated by toxins, has been postulated as a principal mechanism of leptospiric pneumonitis and forms the rationale for a randomized double-blind clinical trial to evaluate the use of pulse treatment with methylprednisolone in patients with lung involvement in leptospirosis [9].

Recognition of a disease is the basis of diagnosis. Unfortunately, many cases of leptospirosis will go unnoticed due to non-specific signs and symptoms. Thrombocytopenia, mildly elevated creatine kinase, raised creatinine and hyperbilirubinaemia may point towards leptospirosis, but confirmation requires microbiological testing. Culture of Leptospira requires specialized media and growth takes weeks. Therefore, serology is the cornerstone of microbiological diagnosis. Microscopic agglutination test (MAT) is the reference test for serology testing, however, only reference centres offer this assay because highly experienced laboratory personnel are required for performing this test. Furthermore, false negative results due to delayed seroconversion are common. In contrast, PCR seems suited for early recognition of the disease. In 2009 a real-time PCR (RT-PCR) for the detection of pathogenic Leptospira was developed and validated [10]. RT-PCR on blood has excellent test characteristics: a sensitivity of 100% and a specificity of 93% (based on culture as golden standard). Sensitivity is highest in the first four days and for early diagnosis RT-PCR on blood can be of great diagnostic value. Urine contains significant inhibitory activity and is not yet suited for amplification of leptospiral DNA. In the Netherlands, the Tropical.
Institute of Biomedical Research in Amsterdam can perform the MAT and the PRT-PCR tests.

In conclusion, leptospirosis is an important and potentially lethal zoonosis. Insufficient sewage disposal systems in enlarging cities and flooding may lead to epidemics in developing countries. In the Netherlands, few cases are reported annually, but increased outdoor recreational activities abroad place more people at risk of exposure to the pathogen. Increased awareness and the introduction of RT-PCR on blood upon presentation are essential for early diagnosis. The immune system plays an important role in morbidity observed in this disease. It is hoped that future studies will show us how to best intervene in the immune phase in order to reduce mortality.

References