

# Leptospirosis in a Dutch catfish farm

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## ABSTRACT

A 51-year-old farm worker presented with jaundice and fever. There had been a rat infestation around the farm ponds and in the shed. He was admitted to our hospital with acute renal and liver failure, thrombocytopenia and rhabdomyolysis. Because of the clinical clues, leptospirosis was suspected and diagnosed in blood by polymerase chain reaction and serology. Also his son, a co-worker on the farm, showed a positive serology. Clinicians should be aware of these occupational outbreaks and should recognise the clinical picture.

## KEYWORDS

Jarisch-Herxheimer, leptospirosis, outbreak, rhabdomyolysis, Weil's disease

## INTRODUCTION

Leptospirosis has been classified as an emerging infectious disease, particularly in (sub)tropical areas.<sup>1</sup> In the Netherlands, leptospirosis historically has been associated with agricultural or recreational exposure risks.<sup>2</sup> Exposures related to travelling to endemic countries have recently emerged as an important new cause of infection.<sup>3</sup> However, occupational exposures continue to exist, which requires an on-going alertness in low endemic locations.

Fish workers are at considerable risk of leptospirosis as a result of rats attracted to the ponds and sheds where the fish food is stored. We describe a small outbreak among workers on a catfish farm and present a case of a patient with an acute life-threatening form of leptospirosis.

## CASE REPORT

A 51-year-old man who had been ill for five days with fever, sweating, headache, myalgia and limb weakness was

### What was known on this topic?

Leptospirosis is a zoonotic bacterial disease caused by pathogenic *Leptospira*, frequently carried by rodents. After infection, only a subset of patients develop the icteric form of the disease with severe late manifestations (Weil's disease). In the Netherlands, leptospirosis is most frequently associated with recreational exposure or travelling to (sub)tropical countries.

### What does this case add?

We describe a small outbreak of leptospirosis on a catfish farm and show that the severity of infection may range from subclinical to life-threatening. The icteric leptospirosis in our patient was complicated by rhabdomyolysis and a Jarisch-Herxheimer reaction, both of which are uncommon findings. Clinicians should be aware of this clinical picture. Additionally, the value of polymerase chain reaction for early diagnosis of leptospirosis was established. This case report stipulates the importance of exposure history, even in low-endemic countries such as the Netherlands.

admitted to our hospital. The patient's medical history was, besides a history of fibromyalgia, unremarkable. He worked on a family-owned catfish farm. Physical examination showed a blood pressure of 134/87 mmHg, pulse of 110 beats/min, oxygen saturation of 96% and temperature of 36.4 °C. There was an obvious jaundice and extreme tenderness of the legs. Lung and heart sounds were normal. Abdominal examination showed right upper quadrant pain without rebound tenderness or guarding. The laboratory findings were: creatine kinase

(CK) 3547 U/l (<400 U/l), serum bilirubin 219 µmol/l (total), 193 µmol/l (conjugated), aspartate aminotransferase 169 U/l (<40), alanine aminotransferase 37 U/l (<45), alkaline phosphatase (AF) 82 U/l (<150), gamma-glutamyl-transferase 71 U/l (<65), serum urea 24.7 mmol/l (2.5 to 7.5), creatinine 262 µmol/l (60 to 110), C-reactive protein 348 mg/l (<5), white cell count 16.2 x 10<sup>9</sup>/l, and platelets 30 x 10<sup>9</sup>/l. Chest radiography and abdominal ultrasound showed no abnormalities. He was admitted to the intensive care unit with acute renal and liver failure, thrombocytopenia and signs of rhabdomyolysis. Heteroanamnestic information revealed that there had been a recent rat plague on the catfish farm. The rats were eradicated by poisoning and subsequently eliminated from the shed with a high-pressure sprayer by our patient. Of the other employees on the family-owned fish farm, only the patient's son had a history of an influenza-like illness during the previous month. The patient's occupation and clinical presentation suggested the possibility of leptospirosis and intravenous cefotaxim was started. Rehydration, dialysis and platelet transfusion were necessary. One hour after the infusion of cefotaxim, he suddenly experienced rigors and a rapid decline in blood pressure which was attributed to a Jarisch-Herxheimer reaction. After ten days of treatment, the serum bilirubin, CK and platelets nearly normalised but the creatinine increased to 499 µmol/l. In total, the patient received dialysis for approximately six weeks. His urine output gradually increased and his kidney function slowly recovered.

The DNA of pathogenic leptospires was detected by polymerase chain reaction (PCR) in the blood (i.e. five days after the onset of illness). At that time, serological tests on the same blood sample were negative. A second serum sample was tested on hospital day 9, which showed a positive ELISA IgM with a titre of 1:1280. The microscopic agglutination test (MAT) was moderately positive, demonstrating weak reactions with eight of the ten leptospiral serogroup antigens but gave the strongest reaction with serotype *icterohaemorrhagiae* of the *Icterohaemorrhagiae* serogroup. Two months after

the onset of illness, the MAT showed reactions with the serotype *icterohaemorrhagiae* of the *Icterohaemorrhagiae* serogroup and the serotype *poi* of the serogroup *Javanica* (table 1). Additionally, sera from the other family members were tested. The MAT of the son who had experienced an influenza-like illness showed an antibody titre of 1:2560 against serotype *icterohaemorrhagiae* of the *Icterohaemorrhagiae* serogroup. The IgM was positive as well, indicating a very recent infection. The sera of the remaining family members were negative (table 1).

## DISCUSSION

The diagnosis of an uncommon disease usually depends on recognising an unusual combination of clinical findings. In the present case, jaundice, isolated hyperbilirubinaemia, high creatine kinase levels and renal failure following a febrile illness could be recognised as a pattern characteristic of leptospirosis. Crucial to these clinical findings is to realise the importance of the patient's exposure history. Detailed information regarding the rat plague on the catfish farm was a major clue to the correct diagnosis.

Leptospirosis is a bacterial infectious disease caused by pathogenic leptospires of the genus *Leptospira*.<sup>4</sup> The disease is maintained in nature by chronic renal infection of carrier animals, such as rodents, which transmit them through urine and consequently contaminate lakes or standing water. The portal of entry is generally through cuts in the skin or via conjunctiva, but inhalation of aerosols also may result in infection.<sup>1</sup>

After a seven to ten day incubation period, leptospirosis starts with a bacteraemic phase marked by non-specific influenza-like illness of approximately one week followed by a second phase with production of antibodies, disappearance of leptospires from the blood and the appearance of spirochetes in urine (figure 1). In humans, the majority of infections caused by leptospires are subclinical. However, a subset (5 to 15%) of patients develop the icteric form of the disease with severe late

**Table 1.** Diagnostic tests on the family members of the catfish farm

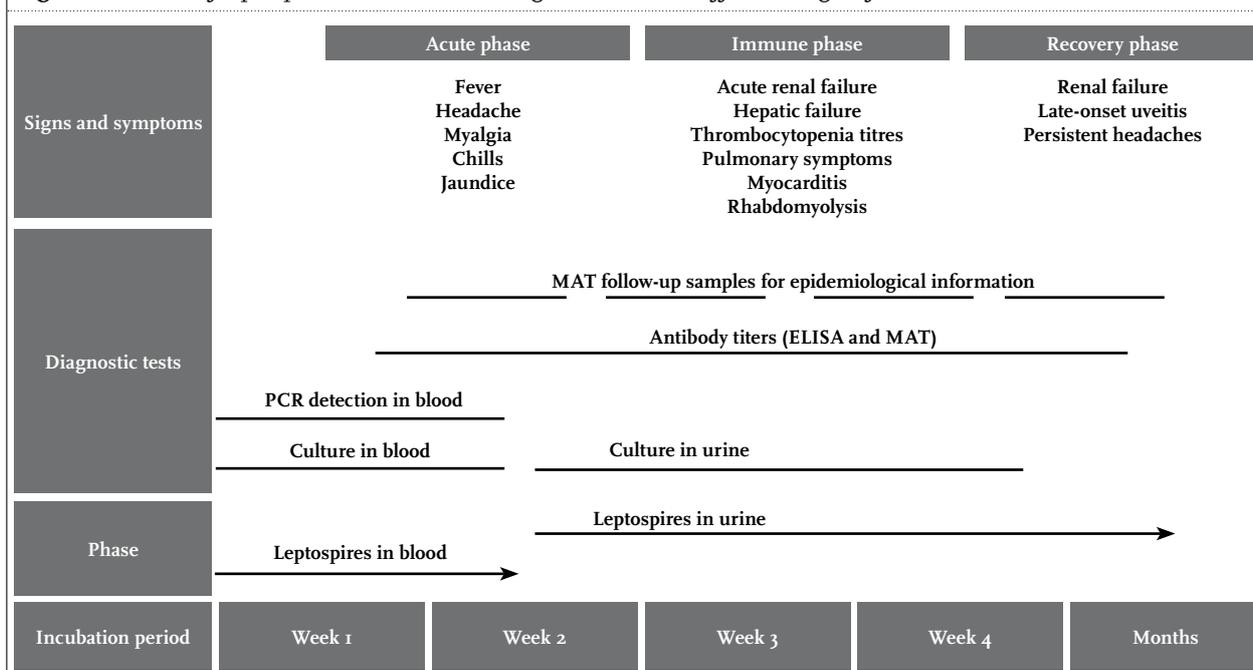
Farm workers	Age (years)	Symptoms	IgM ELISA (titre)	MAT (titre)	Serogroup (serotype)	PCR (blood)	Culture (blood)
Father (patient)	51	Jaundice, renal failure	640-1280	160-320	<i>Icterohaemorrhagiae</i> ( <i>icterohaemorrhagiae</i> ) <i>Javanica</i> ( <i>poi</i> )	Positive	Negative
Mother	49	Healthy	Negative	Negative	-	n.p.	n.p.
Child 1	21	Healthy	Negative	Negative	-	n.p.	n.p.
Child 2	19	Flu-like illness	320	2560	<i>Icterohaemorrhagiae</i> ( <i>icterohaemorrhagiae</i> )	n.p.	n.p.
Child 3	16	Healthy	Negative	Negative	-	n.p.	n.p.

n.p. = not performed, MAT = microscopic agglutination test.

manifestations four to six days after the onset of illness. The complications of icteric leptospirosis (Weil's disease) emphasise the multisystemic nature of the disease, which is characterised by reversible generalised vasculitis and endothelial damage. The liver, kidneys and lungs are most frequently involved. In our patient, serum bilirubin levels were markedly elevated compared with the moderate rises in transaminase levels and AF, which is typical for leptospirosis.<sup>5</sup> Acute renal failure is a result of interstitial nephritis caused by the invasion of leptospires in the interstitial tissue and tubules. In our patient, the renal failure was probably also the result of rhabdomyolysis. Rhabdomyolysis is characterised by extremely high serum levels of muscle components, due to focal muscle necrosis, which might precipitate in the glomerular filtrate, resulting in renal tubular obstruction and direct nephrotoxicity.<sup>6</sup> Because *Leptospira* take weeks to grow on specialised media, the diagnosis of leptospirosis is usually made by serological testing (figure 1). The current reference method is the microscopic agglutination test (MAT), in which patient sera are incubated with live antigen suspensions of multiple leptospiral serovars. Interpretation of the MAT is complicated by the high degree of cross-reaction that occurs between different serovars, especially in the acute phase samples.<sup>7</sup> Two months after the onset of illness, the MAT of our patient's serum showed reactions with two different serotypes. This might be explained by either cross-reaction or exposure to more than one serotype. ELISA has repeatedly been shown to be more sensitive

than MAT in the acute phase of the disease. However, ELISA only detects antibodies reacting with a broadly reactive genus-specific antigen and thus gives no indication of the causative serovar or serogroup.<sup>7</sup> In the Netherlands PCR has not been used routinely but a recent study showed that RT-PCR on blood samples was highly sensitive during the first four days of illness.<sup>8</sup> This was confirmed in our study as leptospirosis was diagnosed by PCR on the fifth day of illness, whereas serology still remained negative at that time. PCR thus facilitates early diagnosis and enables starting treatment at the most effective time point, which is essential for optimal antibiotic therapy.<sup>9</sup> The management of severe leptospirosis requires antibiotic treatment and supportive care. Antibiotic therapy may consist of third-generation cephalosporines, doxycycline or penicillin G, which have all been shown to be equally effective.<sup>10,11</sup> A rare complication of antimicrobial treatment in leptospirosis, as is the case with other diseases caused by spirochetes such as secondary syphilis or relapsing fever, may be a Jarisch-Herxheimer reaction. This is a systemic reaction resembling a severe inflammatory response that usually begins one to two hours after initial treatment with effective antibiotics, especially penicillins. It consists of the abrupt onset of fever, rigors, tachycardia and hypotension, as was found in our patient.<sup>12</sup> This report demonstrates that leptospirosis may range from a subclinical to a life-threatening infection. The two cases of leptospirosis on a family-owned fish farm emphasise the danger associated with rat infestation and elimination, even in low-endemic countries. Although

**Figure 1.** Course of leptospirosis and relevant diagnostic tests at different stages of disease



rodent control has reduced the incidence of leptospirosis in the Netherlands,<sup>3</sup> there still is a significant risk associated with occupation and recreational exposures occurring in water sports. Therefore, a patient's exposure history and recognition of the clinical picture is of major importance for the diagnosis of leptospirosis.

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## REFERENCES

1. Levett PN. Leptospirosis. *Clin Microbiol Rev.* 2001;14:296-326.
2. Olszyna DP, Jaspars R, Speelman P, et al. Leptospirose in Nederland 1991-1995. *Ned Tijdschr Geneesk.* 1998;142:1270-3.
3. Hartskeerl R, Goris M. Leptospirose in Nederland in 2008 en 2009. *Infectieziekten Bulletin.* 2010;6:185-7.
4. Morey RE, Galloway RL, Bragg SL, et al. Species-specific identification of Leptospiraceae by 16S rRNA gene sequencing. *J Clin Microbiol.* 2006;44:3510-6.
5. Heath CW, Alexander AD, Galton MM. Leptospirosis in the United States: analysis of 483 cases in man, 1949-1961. *N Engl J Med.* 1965;273:857-64, 915-22.
6. Kahn FY. Rhabdomyolysis: a review of the literature. *Neth J Med.* 2009;67:272-82.
7. World Health Organisation, International Leptospirosis Society. Human leptospirosis: guidance for diagnosis, surveillance and control. Geneva; 2003: pp 1-109.
8. Ahmed A, Engelberts MF, Boer KR, et al. Development and validation of a real-time PCR for detection of pathogenic *Leptospira* species in clinical materials. *PLoS ONE.* 2009;4:e7093.
9. Katz AR, Ansdell VE, Effler OV, et al. Assessment of the clinical presentations and treatment of 353 cases of laboratory-confirmed leptospirosis in Hawaii, 1974-1988. *Clin Infect Dis.* 2001;33:1834-41.
10. Panaphut T, Domrongkitchaiporn S, Vibhagool A, et al. Ceftriaxone compared with sodium penicillin G for treatment of severe leptospirosis. *Clin Infect Dis.* 2003;36:1507-13.
11. Suputtamongkol Y, Niwattayakul K, Suttinont C, et al. An open, randomized, controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis. *Clin Infect Dis.* 2004;39:1417-24.
12. Pound MW, May DB. Proposed mechanisms and preventative options of Jarisch-Herxheimer reactions. *J Clin Pharm Therap.* 2005;30:291-5.