Neuroleptospirosis: Aseptic Meningoencephalitis or Invasion into the Central Nervous System?

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Abstract

Leptospirosis is a zoonotic disease of global importance with a mortality of up to 50% among patients requiring intensive care medicine. Meningitis or meningoencephalitis due to leptospires are considered to be an immunologically mediated disease and to occur mainly during the second phase of disease. Herein, we report a patient with severe meningo-encephalitis due to leptospirosis with evidence of direct bacterial invasion into the central nervous system (CNS). A 36-year-old otherwise healthy male farmer, without recent travel history, presented with recurrent fever, peaking >39°C, cough and conjunctivitis 10 days after high-pressure cleaning of a piggery without eye protection. Diagnostic work-up revealed meningitis due to Leptospira species (spp.). Serology (microscopic agglutination test) yielded elevated antibody titers (1:400) for Leptospira interrogans. Polymerase chain reaction (PCR) and electron micrograph of cerebrospinal fluid (CSF) demonstrated direct invasion of Leptospira into the CSF. Magnetic resonance imaging (MRI) of the brain and spine did not reveal any pathologic findings; electroencephalography (EEG) indicated right-hemispheric slowing. Due to severe abdominal pain, gastroscopy was performed. Histology showed signs of vasculitis. Conventional abdominal angiography demonstrated vasculitis resembling panarteritis nodosa. Combined antibiotic and steroid therapy lead to clinical improvement.

Neuroleptospirosis is an important differential diagnosis of occupational meningoencephalitis in Central Europe. This case supports the hypothesis of direct invasion of leptospires into the CNS.

Introduction

Leptospirosis is a zoonotic disease of global importance with a mortality of up to 50% among patients requiring intensive care medicine [1]. In developing countries, urban leptospirosis is mainly caused by hygienic problems. In high-income countries, farmers still represent a major risk group [2]. Typical domestic or feral mammalian hosts include rats, dogs, cats or pigs which serve as reservoirs for spirochaetes of the type Leptospira [1]. Leptospirosis has a typical biphasic course of disease: The first, initial septicemic phase and the second, mostly immunologic mediated phase of disease [1]. Meningitis and meningoencephalitis due to leptospires are considered to be an immunologically mediated disease and to occur mainly during the second phase of disease [1]. It is very uncommon that leptospirosis presents as a primary neurologic disease [3]. Herein, we report a patient with severe meningo-encephalitis due to leptospirosis with evidence of direct bacterial invasion into the central nervous system (CNS).

Case Report

A 36-year-old otherwise healthy male farmer, without recent travel history, presented with recurrent fever, peaking >39°C, cough and conjunctivitis 10 days after high-pressure cleaning of a piggery without eye protection. Diagnostic work-up showed thrombocytopenia and hepatosplenomegaly without other clinical or laboratory abnomalities. Antibiotic treatment with clarithromycin (1000 mg per day) for 10 days was started in an outpatient clinic. After two uneventful weeks without fever, the patient developed signs and symptoms of acute meningoencephalitis. Cerebrospinal fluid (CSF) examination revealed 490 cells/µL with predominance of granulocytes, normal glucose and protein levels. Antibiotic treatment with ceftriaxon (2 g per day) and ampicillin (6 g per day) was started. Microbiological workup of the CSF included electron microscopy, which showed spiral-shaped spirochaetes with “hooked” endings, typical of Leptospira species (spp.) (Figure 1A and 1B). Serology (microscopic agglutination test) yielded elevated antibody titers (1:400) for Leptospira interogans (serotypes icterohaemorrhagiae, bratislava, copenhageni and hardjo). Polymerase chain reaction (PCR) of CSF and bronchoalveolar lavage also detected Leptospira spp. In vitro susceptibility testing of the clinical isolate revealed susceptibility against penicillin G, doxycycline, chloramphenicol, erythromycin, cefotaxim and ciprofloxacin. Magnetic resonance imaging (MRI) of the brain and spine did not reveal any pathologic lesions, electroencephalography (EEG) indicated right-hemispheric slowing. Antibiotic therapy was changed to piperacillin/tazobactam (12 g/1.5 g per day) and doxycycline (400 mg per day) for 7 days. Severe pneumonia necessitated non-invasive ventilation and chest computed tomography (CT) scan showed hemorrhagic lesions (Figure 1C). Microbiologic work-up revealed Candida krusei, Because of Mecitillicin-resistant Staphylococcus aureus...
and Leptospira species in bronchialalveolar lavage, antimicrobial treatment with meropenem (6 g per day), rifampicin (1200 mg per day) and linezolid (1200 mg per day) over two weeks was initiated. Follow-up chest CT-scan revealed pleural effusions and infiltrates resembling cryptogenic organizing pneumonia, therefore methylprednisolone (100 mg per day) was added. Renal and hepatic functions remained normal, leptospiro antibody titers (1:50) and CSF white blood count (150/µl) declined within 44 days after admission. Neurologic and pulmonary functions improved and the patient could be discharged from the neurologic intensive care unit 54 days after initial diagnosis of neuroleptospirosis. Methylprednisolon was tapered over the next four weeks. Four months later, the patient developed fever, headache, muscle and joint pain. CSF and microbiologic work-up was unremarkable. Leptospira antibody titers were normal. However, the patient complained severe abdominal pain. Gastroscopy was performed, histology showed signs of vasculitis. Abdominal CT-scan showed splenic infarctions, conventional abdominal angiography demonstrated vasculitis resembling panarteritis nodosa of the superior mesenteric artery. Treatment with methylprednisolone (60 mg per day) and acetylsalicylate (100 mg per day) was initiated. The patient clinically improved and could be discharged home.

**Discussion**

This is a very rare case of an occupational infection with Leptospira spp. in Central Europe with first in vivo evidence for direct invasion of Leptospira into the CNS.

Through periodically contractions of the axial filament and therefore rotation of the spiral shaped bacteria, leptospires are highly motile. The rotational movement of leptospires enables penetration through mucous membranes. Therefore, inhalation or direct contact with the eyes may cause invasion of leptospires through physiologic barriers into the blood stream [4].

It is hypothesized that neuroleptospirosis is rather caused by immunologic reactions to the spirochaetes than by direct invasion of the bacteria into the CNS [1]. Direct invasion of leptospires into the CNS is very rare and has been reported only in two post-mortem cases [5].

The ability of leptospires to penetrate tissues is influenced by 12 methyl-accepting chemotaxis proteins and the spiral movements [6]. The outer membrane of leptospires is rich of lipopolysaccharides and attached with proteins for evading the hosts immune system and for penetrating tissue [6]. Electron microscopy and PCR findings in this patient's CSF proofed direct bacterial invasion of leptospires into the central nervous system. Electron microscopy findings typically show a helically wound spiral shaped bacterium (0.01–0.02 µm in diameter) with characteristic hooked ends [1]. A TaqMan-based multi-gene targeted real-time PCR has a specificity of up to 100% and can detect a variety of pathogenic and non-pathogenic Leptospira strains [7]. Neurologic manifestations of leptospirosis include aseptic meningitis, polyneuritis, meningoencephalitis, subarachnoid or intracerebral hemorrhage [1,8,9]. The patient had clinical and electroencephalographic evidence of meningoencephalitis, although MRI scan did not reveal any pathologic findings. It is known from previous studies that MRI abnormalities are very rare in encephalitis caused by leptospires, but may include reversible corpus callosum T2 and FLAIR hyperintense lesions [10].

The course of disease during was prolonged in this patient. The initially combined therapy with bacteriostatic and bactericide antibiotics (doxycycline and piperacillin/tazobactam) could have caused an interaction between the bacterioci effects of penicillin and the bacteriostatic properties of tetracyclin. As observed in this patient, the association between leptospirosis and vasculitis has been reported in several cases [11-15] indicating a strong autoimmunologic response triggered by leptospires.

**Conclusion**

Neuroleptospirosis is an important differential diagnosis of occupational meningoencephalitis in Central Europe. This case supports the hypothesis of direct invasion of leptospires into the CNS.

**References**

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