

CASE REPORT

Leptospira-induced acute disseminated encephalomyelitis

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Abstract

We describe a patient with acute disseminated encephalomyelitis following leptospira infection. This case highlights the importance of complete investigation for diagnosis and early treatment, leading to a better prognosis and reduction in morbidity and mortality.

Introduction

Leptospirosis-induced acute disseminated encephalomyelitis (ADEM) has rarely been reported in the literature with almost all cases originating from Asian countries. We describe a case of ADEM after leptospirosis acquired in the Netherlands.

Case report

We describe a 69-year-old male patient with a previous medical history of non-erosive gastritis, osteoporosis, depressive disorder and pneumonia requiring mechanical ventilation five months prior to presentation. This pneumonia was complicated by delirium and a cryptogenic organising pneumonitis requiring long-term, high-dose steroids. On presentation, his medication consisted of venlafaxine 75 mg, prednisone 5 mg and calcium carbonate/colecalciferol 500 mg/440 units, all once daily.

During a heat wave in the Netherlands with maximal temperatures of 37.5 °C, the patient complained of severe abdominal pain with loss of appetite and uncontrollable vomiting. After a day he visited his general practitioner who considered gastritis and started metoclopramide 10 mg three times daily, omeprazole 40 mg twice daily and ranitidine 150 mg twice daily. The prednisone was discontinued. Due to persistent complaints he was seen in the emergency department of his local hospital four days later. An ECG and laboratory tests were performed showing reassuring results and he was discharged home without a classifying diagnosis and prescribed oxycodone.

In the following three days, his symptoms worsened in combination with darkened urine, oliguria and marked confusion with erratic behaviour and fever. The patient presented again to the same hospital and laboratory testing now showed severe rhabdomyolysis with creatine kinase 148,795 U/l (0-171 U/l), urea 25 mmol/l (2.5-6.4 mmol/l), creatinine 494 µmol/l (53-119 µmol/l), aspartate aminotransferase 2912 U/l (0-35 U/l), alanine aminotransferase 564 U/l (0-45 U/l), lactate dehydrogenase 2955 U/l (0-248 U/l), and a C-reactive protein of 65 mg/l (0-10 mg/l). There was a mild leukocytosis of $14.4 \times 10^9/l$ ($4.0-10 \times 10^9/l$) and mild thrombocytosis of $579 \times 10^9/l$ ($150-400 \times 10^9/l$).

CT angiography of the abdomen showed no apparent pathology besides possible infiltrate of the right lower lobe of the lung, for which a short three-day course of cefuroxime was started.

No definite cause was found for this rhabdomyolysis and the confused state was thought to be caused by delirium. Hyperhydration with balanced solutions, frusemide and sodium bicarbonate solution was commenced. The differential diagnosis with these findings was cryptogenic organising pneumonia, hypersensitivity pneumonitis (extrinsic allergic alveolitis) due to known activity with birds, or iatrogenic pneumonitis following the use of venlafaxine, which was withdrawn.

After hyperhydration, the rhabdomyolysis and acute kidney injury improved. No renal replacement therapy was necessary. Severe confusion resulted in exhaustion making sedation and mechanical ventilation necessary. Prior to intubation, tremors and myoclonus were witnessed. Lumbar puncture was performed, showing a clear aspect with normal glucose and lactate but an increased white blood cell count ($20 \times 10^6/l$ ($3-14 \times 10^6/l$)) and a high protein (1620 mg/l (206-629 mg/l)). Blood cultures and liquor cultures remained sterile.

A gastroscopy and colonoscopy were performed but showed no abnormalities.

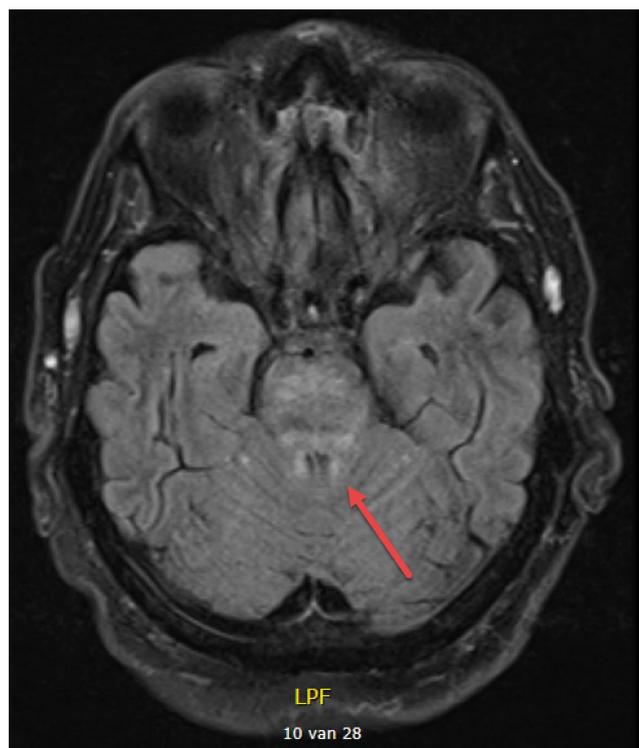
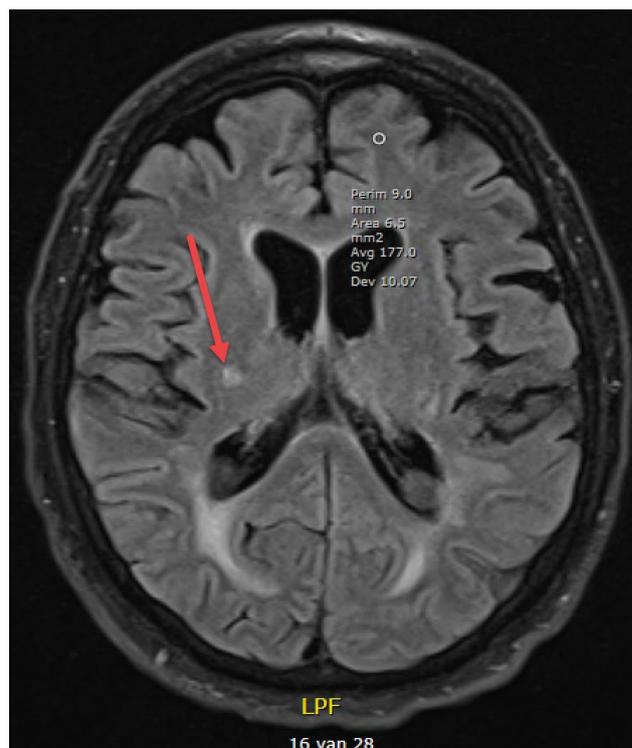


Figure 1. T2-flair, first MRI

An EEG showed diffuse delta and theta activity compatible with severe encephalopathy. He was transferred to our university hospital for expert neurology consultation and advanced imaging. An MRI was performed (*figure 1*) which showed multifocal high T2 signals from the proximal cervical myelum towards the rear of the capsula interna on both sides, also including the thalamus, periventricular white matter and the corpus callosum. Multifocal diffusion restriction was present in the corpus callosum and the ependymal borders of both ventricles and the left parafalcine cortical grey matter. We considered a differential diagnosis of heatstroke, infective encephalitis, autoimmune encephalitis or a serotonin syndrome due to interaction of venlafaxine, metoclopramide and oxycodone.

Serological testing for autoimmune antibodies (ANA, ANCA, myositis blot, anti-TPO) and paraneoplastic antibodies in serum and liquor were all negative. Testing for human herpesvirus 6, herpes simplex virus 1 and 2, varicella zoster virus, toxoplasmosis, enterovirus, mycoplasma, *Chlamydia psittaci*, HIV, lues and *Cryptococcus* was negative.

Unexpectedly, rapid testing for leptospirosis (leptocheck) was positive and hereafter we also found a positive ELISA for leptospirosis. The first microscopic agglutination test (MAT) was negative but three days later the MAT tested positive for leptospirosis (*Leptospira interrogans* serovar icterohaemorrhagiae Kantorowicz and serovar icterohaemorrhagiae Copenhageni Wijnberg with a titre of 1:40 and 1:20, respectively). PCR on blood and a urine leptospirosis



culture were negative, potentially due to the previous antibiotic administration. The patient had not travelled abroad for the past two years. Approximately two weeks before disease onset, however, he was exposed to brackish water next to a petting zoo while he was fishing with his grandson.

We concluded that the patient was suffering from leptospirosis with abdominal complaints and rhabdomyolysis, complicated by aseptic meningitis or possibly acute disseminated encephalomyelitis (ADEM). Treatment was started with ceftriaxone 2 g twice daily for seven days. We also treated the presumed ADEM after 8 days of intubation with a course of methylprednisolone 1 g once daily for five days followed by 1 mg/kg prednisone per day as maintenance therapy and intravenous immunoglobulin 0.4 g/kg for five days. The patient remained comatose with a Glasgow Coma Score of 3 and absent corneal, swallow and cough reflexes. Ventilator triggering was present but insufficient to maintain normocapnia. A second MRI (*figure 2*) 11 days after the first MRI and after completion of the course of intravenous immunoglobulin showed progression of the aforementioned abnormalities, with severe diffusion restriction of the periventricular white matter, brainstem and high cervical myelum. One week later, his neurological status was unchanged, with a third MRI (*figure 3*) showing the same abnormalities with a mildly reduced diffusion restriction and oedema. A second five-day course of 0.4 g/kg intravenous immunoglobulin was initiated. Five days after completing this course, there were no changes in his clinical condition and supportive treatment was withdrawn. Post-mortem examination was not performed.

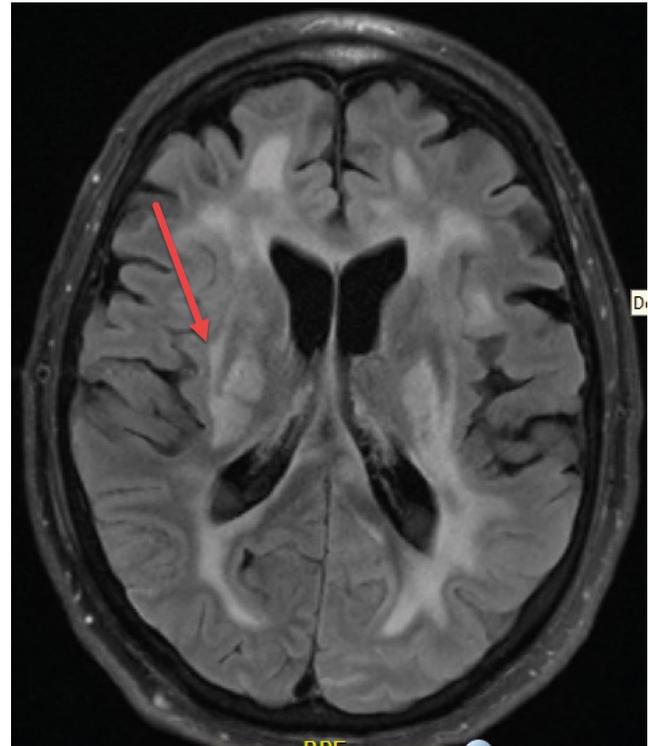


Figure 2. T2-flair, second MRI

Discussion

Leptospira spp. can cause the potentially severe zoonosis leptospirosis. Leptospirosis has a worldwide distribution with high prevalence in developing countries due to poor sanitary conditions and is underreported. Globally 1500-2000 cases are being reported every year. In the Netherlands the incidence of *Leptospira* spp. is around 0.5 per 100,000 population.^[1] The primary reservoir of *Leptospira* spp. is rodents, but it can also be transmitted via other mammals including cattle, pigs and dogs. Infection mainly occurs after human contact with urine-contaminated water through mucous membranes or breaks in the skin. The average incubation time is about 10 days with presentation of the symptoms between 2 and 30 days. The clinical spectrum of leptospirosis varies from mild and self-limiting to severe forms, such as Weil's syndrome (renal dysfunction, bleeding diathesis, icterus, liver failure, and rhabdomyolysis) and severe pulmonary haemorrhage syndrome. In about 10-15% of cases neurological symptoms are seen. With severe presentation of the disease, mortality can be as high as 10%.^[2] The diagnosis can be confirmed by several techniques including PCR, serological tests and isolation of *Leptospira* spp. in blood, urine and liquor.

Given the exposure to possible contaminated water at the petting zoo (no source confirmation was attempted) and the positive leptocheck in our case (compared with MAT: sensitivity 87.4%, specificity 73.3%), ELISA (compared with MAT: sensitivity 86%, specificity 84.5%), and MAT (sensitivity 55.3%, specificity 95.7%), the diagnosis is highly likely.^[3-5]



Leptospira are subdivided into 20 species containing over 728 different serovars. The *interrogans* species (containing the icterohaemorrhagiae serogroup) accounts for over 20% of these serovars. The species defines for a small part the gravity of the disease and the clinical symptoms; the serovars do not play a role in the clinical picture.

Although initially all the symptoms seemed to resolve with supportive care, a progressive neurological syndrome developed, eventually leading to deep coma. MRI findings showed progressive encephalitis fitting ADEM. Extensive analysis including infectious, autoimmune and paraneoplastic tests demonstrated no other potential diagnosis. As leptospirosis is a known aetiological trigger for ADEM, we concluded that our patient had leptospirosis-induced ADEM.

ADEM is an inflammatory demyelinating disorder of the central nervous system. In most cases ADEM is likely to be of autoimmune aetiology after a viral infection or vaccination^[6-11] but many other cases are described without any association to an antecedent factor. It is thought that ADEM is caused by a form of molecular mimicry of the infective agent and myelin antigens, causing sensitisation of lymphocytes directed against the brain. The prevalence in developing countries is unknown, but it is thought to be more frequent than reported.^[12] The neurology is multifocal and polysymptomatic, usually with an sub acute onset. Symptoms include headache, fever, behavioural disorders, ataxia, chorea, athetosis, decreased consciousness and coma. In acute phases the mortality varies from 10 to 20%.^[13,14]



Figure 3. T2-flair, third MRI

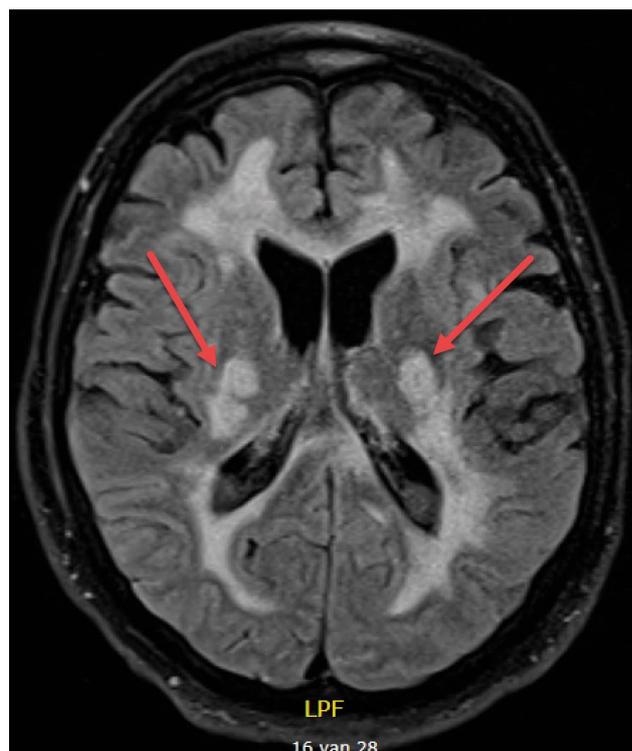
ADEM is mainly a clinical diagnosis which needs to be confirmed by MRI with T2-weighted and fluid attenuated inversion recovery approaches. These settings usually show diffuse asymmetrical multifocal lesions, with an increased T2 signal and decreased T1 signal, in the myelum and/or intracerebral parts of the brain. Changes usually occur asymmetrically in the white matter, basal ganglia, thalamus, midbrain, spinal cord and cortical grey matter. Also other pathology needs to be excluded.^[13,15-19]

Spinal fluid may show nonspecific alteration of protein levels and an increase in the cell count.^[20,21] There is no specific laboratory test for ADEM.

Leptospirosis-induced ADEM is rare, with only a few cases reported; usually the outcome is good and a complete recovery is described in most cases.^[19,22-24]

According to the literature, the therapy for leptospirosis-induced ADEM includes intravenous immunoglobulin, high-dose intravenous steroids and possibly plasma exchanges.^[25-27] In our case we initiated the therapy with a course of high-dose methylprednisolone followed by maintenance therapy of 1 mg/kg prednisone a day and intravenous immunoglobulins for five days. Follow-up with two MRIs and successive neurological examinations after a second round of five days of Intravenous immunoglobulins did not show any improvement in our patient, after which we considered a meaningful recovery unlikely.

Although challenging with intubated patients on sedation, the importance of this case lies in the need for rapid diagnosis of ADEM with central nervous system involvement after



leptospirosis, as early treatment is associated with a better prognosis, reducing morbidity and mortality.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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