Anti-ganglioside antibodies-mediated leptospiral meningomyeloencephalopolyneuritis

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Anti-ganglioside antibodies-mediated leptospiral meningomyeloencephalopolyneuritis

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Abstract

A case of leptospirosis complicated with meningomyeloencephalopolyneuritis and nephrotic syndrome is presented. Anti-ganglioside antibodies were detected for the first time in a patient with neurological complications of leptospirosis. Possible pathogenic mechanisms and treatment options of these rare manifestations are discussed.

Introduction

Leptospirosis is an important zoonosis with worldwide distribution. The severity of Leptospira infection ranges from a subclinical illness to 2 clinically recognizable syndromes: a self-limited, systemic illness and a severe illness (Weil's disease).

The course of disease is biphasic. The first is an acute, septic phase, which lasts from 3 to 7 d. This is followed by an immune phase which lasts from 4 to 30 d. Systemic vasculitis accounts for protean clinical manifestations of the disease, while circulating antibodies are responsible for the development of aseptic meningitis, uveitis, iritis, iridocyclitis and chorioretinitis [1].

Aseptic meningitis occurs in up to 80% of patients in the second, immune phase of the disease. It usually has a benign clinical course. More severe neurological complications of leptospirosis are rare [2–4].

Renal involvement is common in leptospirosis. Interstitial nephritis and tubular necrosis are common renal lesions that may progress to acute renal failure. Haemodynamic alterations, immune response, and direct nephrotoxicity may all lead to renal damage in patients with leptospirosis. Damage to the glomerular capillary wall is usually not apparent and therefore not of clinical significance [5].

We report a case of leptospirosis complicated with severe meningomyeloencephalopolyneuritis and nephrotic syndrome treated in our intensive care unit.

Case report

A 69-y-old white male was admitted to another, county hospital in October 2005 with a 4-d history of fever, jaundice, lack of appetite and malaise. Three d after admission he was transferred to our hospital for suspected Weil's disease. He received ampicillin for 3 d at the county hospital.

The patient’s medical history revealed arterial hypertension and peptic ulcer disease. He was a heavy smoker. The patient came from a rural area where leptospirosis is endemic.

On physical examination he was afebrile and icteric. Neurological examination revealed no abnormalities. Glasgow Coma score was 15. Antibiotic treatment was continued.

Laboratory tests revealed a leukocyte count of 25.3 × 10⁹/l (lymphocytes 2.5 × 10⁹/l, neutrophils 22.3 × 10⁹/l and monocytes 0.5 × 10⁹/l), thrombo-
erythrocyte count of 60 × 10^9/l and a mild normocytic normochromic anaemia (erythrocyte count 3.78 × 10^{12}/l, haemoglobin concentration 10.5 g/dl, MCV 80 fl, MCH 27.8 pg and MCHC 34.4 g/dl). Erythrocyte sedimentation rate was 54 mm per h.

Urinalysis revealed moderate albuminuria, microhaematuria and bilirubinuria. Urine pH was 5.0 and specific gravity 1.018. Blood levels of glucose, lactate and creatinine were normal. Prothrombin and partial-thromboplastin times were normal. Other laboratory findings at admission are shown in Table I. Chest radiography and electrocardiogram showed no abnormalities.

Over the next 2 d the patient's condition deteriorated. He became febrile, lethargic and developed respiratory failure. Meningeal signs were positive. Neurological examinations revealed simultaneous and rapidly progressive flaccid quadriparesis, areflexia, intercostal and diaphragmatic palsy. Plantar responses were absent. There were no signs of ophthalmoplegia, pupillary abnormality, facial or bulbar palsy. The patient was intubated and mechanical ventilation was started.

Lumbar puncture revealed meningitis with white cells 507/mm³, 58% neutrophils and 42% monocytes. Glucose and chloride levels were normal and the total protein level was 1.615 g/l. Blood-brain barrier dysfunction with intrathecal antibody synthesis was found. Cerebrospinal fluid (CSF), urine and blood cultures were negative. Calcium, magnesium and phosphorus concentrations were normal.

Within the same period of time, the patient developed heavy proteinuria (2220 mg/24 h) with severe hypoalbuminaemia (18 g/l), peripheral oedema and bilateral pleural effusion. A diagnosis of nephrotic syndrome was established.

Brain and cervical spine MRI and CT scan were normal. Electroencephalogram showed marked diffuse slowing. Unfortunately, electrophysiological examination was not performed for technical reasons.

Although leptospirosis was suspected, because of the patient's unusual complications extensive microbiological diagnostic tests were carried out to exclude infections from other pathogens. Stool samples for isolation of polio I, II and III viruses, echoviruses, and coxsackieviruses were negative. Tests for antibodies (blood and CSF samples) against herpes simplex virus 1 and 2, varicella zoster virus, human herpes virus type 6, Epstein-Barr virus, cytomegalovirus, tick-borne encephalitis virus, Mycoplasma pneumoniae, Chlamydia pneumoniae, Borrelia burgdorferi, and Brucella were negative. Serology against hepatitis A, B and C was also negative.

Current leptospiral infection was serologically confirmed by microscopic agglutination test (MAT) on the tenth d of disease. MAT titres of 1:4000 to L. australis, 1:2000 to L. pomona and 1:2000 to L. hardjo serovars were found.

During the following week, the patient's condition improved. He became afibrile, alert and with preserved sensorium. However, motor neurological deficit with areflexia remained unchanged. High-dose corticosteroid treatment (dexamethasone 4 × 12 mg i.v.) was started but without any effect on neurological symptoms or nephrotic syndrome. Because of diaphragmatic palsy, prolonged mechanical ventilation was continued for up to 21 d.

CSF examination during the third week of disease revealed cytological dissociation (total protein level 1.207 g/l; leukocyte count 3 cells mm³). Glucose and chloride levels were normal.

Anti-ganglioside antibodies were assessed by the semi-quantitative GanglioCombi ELISA test (Buhlmann Laboratories AG, Basel, Switzerland) on the 21st d of disease. The serum GM1 and asialo-GM1 antibodies were weak positive, whereas GD1a antibodies were positive. Anti-GM2, anti-GD1b and anti-GQ1b were negative.

The mild renal non-oliguric failure and the liver lesion recovered completely within 2 weeks. The nephrotic syndrome resolved spontaneously 1 month after disease onset.

Table I. Laboratory findings at admission.

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein</td>
<td>89</td>
<td>&lt;5</td>
<td>mg/l</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>5.92</td>
<td>1.8–3.5</td>
<td>g/l</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.5</td>
<td>4.2–6.4</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Sodium</td>
<td>127</td>
<td>137–146</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.3</td>
<td>3.9–5.1</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Chloride</td>
<td>94</td>
<td>97–108</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>14.9</td>
<td>2.8–8.3</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Creatinin</td>
<td>140</td>
<td>79–125</td>
<td>μmol/l</td>
</tr>
<tr>
<td>Bilirubin-total</td>
<td>228.4</td>
<td>3–20</td>
<td>μmol/l</td>
</tr>
<tr>
<td>direct</td>
<td>129.3</td>
<td>&lt;5</td>
<td>μmol/l</td>
</tr>
<tr>
<td>indirect</td>
<td>99.1</td>
<td></td>
<td>μmol/l</td>
</tr>
<tr>
<td>Aspartate</td>
<td>51</td>
<td>11–38</td>
<td>U/l</td>
</tr>
<tr>
<td>Alanine aminotransferases</td>
<td>52</td>
<td>12–48</td>
<td>U/l</td>
</tr>
<tr>
<td>Total protein</td>
<td>59</td>
<td>66–81</td>
<td>g/l</td>
</tr>
<tr>
<td>albumin</td>
<td>24</td>
<td>38–52</td>
<td>g/l</td>
</tr>
<tr>
<td>globulin</td>
<td>35</td>
<td>24–34</td>
<td>g/l</td>
</tr>
</tbody>
</table>

Cerebrospinal fluid
cells/mm³ | 507 | 3–5
neutrophils | 294 |
monocytes | 213 |
protein | 1.615 | 0.15–0.45 | g/l
glucose | 3.0 | 2.25–4.0 | mmol/l
chloride | 120 | 118–132 | mmol/l
During the fourth week of the disease, a very slow neurological recovery began. The patient was transferred to a rehabilitation centre 2 months after disease onset. Rehabilitation was successful and the patient was able to walk without assistance 3 months after discharge from the hospital.

**Discussion**

We report a rare case of leptospirosis complicated with severe neurological complications and nephrotic syndrome. We, for the first time, report an association of anti-ganglioside antibodies with severe neurological complications of leptospirosis.

Neurological complications of leptospirosis affecting the central and peripheral nervous systems have been previously described. The most commonly reported syndromes include encephalitis, myelitis, cerebrovascular accidents, cerebral angitis, mononeuritis multiplex, polyneuropathy, cranial nerve palsies, and movement disorders [2,4,6–8]. The majority of these complications occur in the later course of the disease, during the immune phase. However, neurological symptoms and signs can even precede the clinically apparent leptospirosis. This fact is of outstanding clinical importance [3].

Presumed pathogenic mechanisms include both direct effect of leptospires and immune-mediated injuries of the central nervous system. These proposed pathogenic mechanisms have not been completely elucidated [4]. Diffuse vasculitis occurring during and after the initial phase seems to be responsible for most of the neurological syndromes, while circulating immune complexes could be associated with the other syndromes observed in the second (immune) phase of the disease.

The association of some anti-ganglioside antibodies with inflammatory polyradiculoneuropathies and related diseases (e.g. Bickerstaff encephalitis) has already been established [9,10]. Furthermore, some antibodies show a particular relationship with some syndromes and triggering infectious agents (e.g. anti-GM1 with Campylobacter jejuni and acute motor axonal neuropathy (AMAN)) [9–11].

The molecular mimicry between infectious agents and gangliosides may function in the production of anti-ganglioside antibodies. Antibodies can bind to nodes of Ranvier and fix complement which results in conduction block. Anti-GD1a ganglioside antibodies are almost exclusively associated with acute motor axonal form of the post-infectious polyneuropathies [12]. Hence, such pathogenic mechanisms could explain some of the neurological syndromes seen in leptospirosis. The presence of anti-ganglioside antibodies has not been previously reported in patients with neurological complications of leptospirosis, even in those with polyradiculoneuropathy. Positive anti-ganglioside antibodies and a compatible clinical picture in our patient strongly suggest that neurological impairment was due to a diffuse, immune-mediated process. Another immunologically mediated complication, which occurred in our patient, was nephrotic syndrome.

Our findings confirm that leptospires can induce the production of anti-GD1a and anti-GM1 antibodies and cause post-infectious polyneuropathy. However, this fact does not explain diffuse affection of the nervous system. Leptospires seem to be capable of inducing a diverse spectrum of pathogenic mechanisms at the same time. That is probably the reason for steroid treatment failure previously observed in neuroleptospirosis.

Therefore, steroid use in patients suffering from severe forms of disease is controversial. Total plasma exchange (TPE) or intravenous immunoglobulins (IVIG) could be beneficial in these patients but, to date, few data support these treatment choices. In mild cases no treatment is necessary.

We conclude that our patient suffered from leptospiral immune-mediated meningomyeloencephalitis with overlapping acute motor axonal neuropathy and nephrotic syndrome. This is the first report of simultaneous diffuse nervous system dysfunction associated with the presence of anti-ganglioside antibodies and nephrotic syndrome during the course of leptospirosis.

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**References**


Pneumocystis carinii pneumonia in a rheumatoid arthritis patient treated with adalimumab

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Abstract
Patients with rheumatoid arthritis (RA) have an increased risk of infection as a result of alterations in immune regulation, debility, and comorbid illnesses. TNF-α is of central importance in the pathophysiological responses to infection and inflammation, and plays a crucial role in host defence. Pneumocystis carinii is an opportunistic pathogen that commonly affects individuals with inadequate T-cell mediated immune response. Patients with acquired immune deficiency, as well as those receiving immunosuppressive drugs for various conditions have an increased risk of P. carinii pneumonia (PCP). We report the development of PCP in a woman with RA shortly after the initiation of anti-TNF-α treatment with adalimumab.

Introduction
TNF-α is of central importance in the pathophysiological responses to infection and inflammation, and plays a crucial role in host defence. It stimulates the production of other pro-inflammatory cytokines and promotes the maturation of inflammatory cells. The importance of TNF-α in the pathogenesis of rheumatoid arthritis (RA) is now well known and treatment with TNF antagonists is highly effective. However, the safety profile of this new class of agents is not yet fully established [1].

Pneumocystis carinii is an opportunistic pathogen that commonly affects individuals with inadequate T-cell mediated immune response. Patients with acquired immune deficiency, as well as those receiving immunosuppressive drugs for various conditions have an increased risk of P. carinii pneumonia (PCP) [2].

We report the development of PCP in a woman with RA shortly after the initiation of anti-TNF-α treatment with adalimumab.

Case report
A 59-γ-old female with the diagnosis of RA fulfilling the ACR criteria was followed up from May 1998. Until March 2004, her treatment consisted of methotrexate 7.5–15 mg per week, sulfasalazine 1.5–3.0 g/d, and deflazacort 3–6 mg/d. She could not tolerate leflunomide, and although hydroxychloroquine 100 mg was also given, it had to be discontinued due to ocular toxicity. Between March 2004 and October 2005, the treatment regimen was...