Anti-ganglioside antibodies-mediated leptospiral meningomyeloencephalopolyneuritis

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ANTI-GANGLIOSIDE ANTIBODIES - MEDIATED LEPTOSPIRAL MENINGOMYELOENCEPHALOPOLYNEURITIS

Running title: Post-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.

BACKGROUND

Leptospirosis is an important zoonosis with worldwide distribution. The severity of *Leptospira* infection ranges from a subclinical illness to two 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 3 to 7 days. This is followed by an immune phase which lasts from 4 to 30 days. 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 which may progress to acute renal failure. Hemodynamic alterations, immune response, and direct nephrotoxicity may all lead to renal damage in the 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-year-old white man was admitted to another, county hospital in October 2005 with a four-day history of fever, jaundice, lack of appetite and malaise. Three days after admission he was transferred to our hospital for suspected Weil's disease. He received ampicillin for three days 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 x 10^9/L (lymphocytes 2,5 x 10^9/L , neutrophils 22,3 x 10^9/L and monocytes 0,5 x 10^9/L), thrombocyte count of 60 x 10^9/L and a mild normocytic normochromic anemia (erythrocyte count was 3,78 x 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 hour. Urinalysis revealed moderate albuminuria, microhematuria and bilirubinuria. Urine pH was 5.0 and specific gravity was 1.018. Blood levels of glucose, lactate dehydrogenase (LDH), amylase, creatine kinase (CK), gamma-glutamyl transferase (γGT), calcium, magnesium, phosphorus and alkaline phosphatase were all normal. Prothrombin and partial-thromboplastin times were normal. Other laboratory findings at admission are shown in Table 1. Chest radiography and electrocardiogram showed no abnormalities.

Over the next two days 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 quadriplegia, 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 507 white cells per cubic millimeter with 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 edema 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 done 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 day of disease. MAT titers 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 afebrile, alert and with preserved sensorium. Motor neurological deficit with areflexia, though, remained unchanged. High-dose corticosteroid treatment (dexamethasone 4x12 mg IV) 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 days.

CSF examination during the third week of disease revealed cytoalbuminological dissociation (total protein level 1,207 g/L and leukocyte count was 3 cells per cubic millimeter). Glucose and chloride levels were normal.

Anti-ganglioside antibodies were assessed by the semiquantitative GanglioCombi ELISA test (Buhlmann Laboratories AG, Basel, Switzerland) on the 21st day 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 two weeks. The nephrotic syndrome resolved spontaneously one month after disease onset.

During the fourth week of the disease, a very slow neurological recovery began. The patient was transferred to a rehabilitation center two months after disease onset. Rehabilitation was successful and the patient was able to walk without assistance three 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 angiitis, mononeuritis multiplex, polyneuropathy, cranial nerve palsies, and movement disorders (2, 4, 6, 7, 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 clinical 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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TABLE 1 Laboratory findings at admission

	value	normal range	units
Serum			
C-reactive protein	89	<5	mg/L
fibrinogen	5,92	1,8-3,5	g/L
glucose	5,5	4,2-6,4	mmol/L
sodium	127	137-146	mmol/L
potassium	3,3	3,9-5,1	mmol/L
chloride	94	97-108	mmol/L
urea nitrogen	14,9	2,8-8,3	mmol/L
creatinin	140	79-125	μmol/L
bilirubin - total	228,4	3-20	μmol/L
direct	129,3	<5	
indirect	99,1		
aspartate aminotransferases	51	11-38	U/L
alanine aminotransferases	52	12-48	U/L
total protein	59	66-81	g/L
albumin	24	38-52	
globulin	35	24-34	
Cerebrospinal fluid			
cells/mm^3	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