Primary neuroleptospirosis complicating cerebral venous sinus thrombosis: a case report

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Abstract
Leptospirosis, caused by pathogenic spirochetes of the genus Leptospira, presents as a biphasic illness consisting of an initial leptospiremic phase followed by an immune phase. Nevertheless, leptospirosis remains undiagnosed on numerous occasions, particularly when it presents with neurological complications, due to its infrequent and atypical nature. Primary neuroleptospirosis complicated by cerebral venous sinus thrombosis emerges as an infrequent, and life-threatening complication, associated with a high mortality risk.

We report a 55-year-old man presented with fever and headache of two days duration, which progressed into clouding of consciousness on the third day. Clinical examination revealed conjunctival suffusion, Glasgow coma scale (GCS) of 11/15, disorientation, and meningism. The diagnosis was confirmed by detecting Leptospira DNA in cerebrospinal fluid through real-time PCR, and a subsequent magnetic resonance venogram revealed sigmoid and transverse sinuses thrombosis, which was performed due to the patient's persistent occipital headache.

This case report underscores the significance of recognizing rare manifestations of common tropical diseases in endemic areas and the importance of thorough patient history in diagnosis, as in this patient where leptospirosis was suspected due to recent risk exposure.

Key words: primary neuroleptospirosis, cerebral venous sinus thrombosis, cerebral vasculitis

Introduction
Leptospirosis is the most widespread zoonotic infection worldwide, caused by pathogenic Leptospira. Mammals act as a primary reservoir for Leptospira, and multiple risk behaviors make the host vulnerable to infection.

Leptospirosis can manifest in a spectrum of severity, marked by two distinct phases: the bacteremic and the immune phase. Neurological complications are common in the immune phase, with aseptic meningitis being the most common manifestation characterized by CSF lymphocytic pleocytosis, mildly elevated proteins, and negative CSF Leptospira PCR. It is rare for leptospirosis to present as a primary neurological disease and its complication with cerebral venous thrombosis is even more infrequent.

We report a case of a 55-year-old man with molecularly confirmed primary central nervous system leptospirosis infection, which was complicated by sigmoid and transverse venous sinus thrombosis.

Case presentation
A 55-year-old man presented with progressive loss of consciousness for a day preceded by low-grade-intermittent fever, vomiting, headache, and loose stools for 2 days. He had an insidious onset stabbing headache in the vertex and occipital regions, accompanied by photophobia and phonophobia, followed by three episodes of watery projectile vomiting. The headache was not relieved with simple analgesics and was exacerbated by coughing and straining. Two hours later, he developed drowsiness and a progressive reduction
of consciousness without any other neurological deficits. The rest of the systemic inquiry was unremarkable.

He was exposed to muddy water in a rodent-prevalent area ten days ago and had no recent exposure to fever or diarrheal illness. His medical and travel history is unremarkable and partakes in social drinking but abstains from smoking.

On examination, his temperature was 38.5°C, and conjunctival suffusion was noted. His sclera was muddy in colour and there was no jaundice or lymphadenopathy. GCS was 11/15 (E-4/4, V-2/5, M-5/6) and he was disoriented in time and place. There was marked neck stiffness, positive Kernig’s sign, pupils that were equal and reactive to light, and the optic fundi were normal. The cranial nerves, cerebellar, and limb examinations did not reveal any abnormality.

He was hemodynamically stable, and the rest of the respiratory and abdominal examinations were normal.

His full blood count revealed the following values: white blood cells 14.03×10⁹/L, neutrophils 87.9%, hemoglobin 15.2 g/dL, and platelets 98×10⁹/L. Blood picture suggested features of a bacterial infection with no evidence of microangiopathic hemolytic anemia. His renal profile showed serum creatinine at 0.83mg/dL (0.7-1.1), serum sodium at 137 (135-145) mmol/L, creatine phosphokinase at 129 U/L (55-170), and persistent hypokalemia in the range of 2.5 to 2.9 mmol/L. Liver profile was normal with aspartate aminotransferase (AST) at 36 U/L, alanine aminotransferase (ALT) at 17 U/L, and a total bilirubin level of 0.3 mg/dL. Inflammatory markers were elevated with C-reactive protein at 80 mg/L and an erythrocyte sedimentation rate of 64 mm in the first hour. The international normalized ratio (INR) was 1.1.

After an urgent non-contrast computed tomography (NCCT) of the brain, a lumbar puncture was performed. CSF analysis revealed protein 55mg/dl (15-45) and mixed polymorphonuclear-lymphocytic pattern (polymorphs 105/mm³, lymphocytes 175/mm³) with normal CSF sugar level (67 mg/dl). His random blood sugar was 104 mg/dl. All cultures including blood, urine, and CSF was negative. Leptospirosis was strongly suspected due to a history of muddy water exposure in an endemic area and clinical clues such as conjunctival suffusion, neutrophil leukocytosis, moderate thrombocytopenia, and persistent hypokalemia. Alongside the strong suspicion, both CSF and serum samples were sent for real-time PCR for Leptospira DNA, and they became positive. Other closely related differential diagnoses of infectious etiologies, such as dengue, malaria, scrub typhus, and hantavirus, were excluded with negative serological tests. Thrombotic thrombocytopenic purpura was
considered a non-infectious etiology with evidence of fever, altered level of consciousness, and thrombocytopenia, but the rest of the diagnostic tests were negative including the absence of microangiopathic blood picture, anemia, indirect hyperbilirubinemia, and normal lactate dehydrogenase level of 200 U/L (125-220).

Despite the resolution of meningism and altered sensorium within 12 hours following the initiation of antibiotics, he continued to experience a persistent occipital headache. An urgent repeat NCCT of the brain was carried out and revealed a hyperdense empty delta sign, indicating dural venous sinus thrombosis of the superior sagittal sinus. Subsequently, magnetic resonance imaging (MRI), angiography (MRA), and venography (MRV) of the brain were carried out showing superior sagittal, transverse, and sigmoid sinus thrombosis without signs of raised intracranial pressure.

Thrombophilia screening, which included tests for anti-nuclear antibody (ANA) and antiphospholipid antibodies, was performed and produced negative results.

His management included intravenous ceftriaxone 2g administered every 12 hours for 14 days and intravenous dexamethasone 8mg administered every 8 hours for 3 days. He regained full consciousness and sensorium within 12 hours of starting antibiotics. Ceftriaxone was continued for 14 days, resulting in significant improvement in meningism, altered sensorium, and inflammatory markers.

Anticoagulation therapy with subcutaneous low-molecular-weight-heparin (LMWH) 60mg BD and warfarin 5mg daily was initiated after brain imaging, with a target INR range of 2-3. Persistent hypokalemia was managed with initial intravenous potassium chloride (KCL) and then with a maintenance dose of oral KCL.

No renal, hepatic, or pulmonary complications were observed during the hospital stay. Six months of warfarin therapy and a repeat cerebral venogram for the resolution of thrombosis are planned.

**Discussion**

Leptospirosis, a zoonotic disease caused by pathogenic spirochetes of the genus *Leptospira*, is endemic in Sri Lanka and is considered an important notifiable disease.3 *L.interrogans* is a spiral-shaped, highly motile aerobic spirochete, which has approximately 300 serovars arranged in 64 serogroups.4 Mammalian proximal convoluted tubules, primarily those of rodents, serve as the primary reservoir for leptospirosis. Human infections result from contact with contaminated soil or freshwater through cuts, abrasions, mucous membranes, and conjunctivae.

Leptospirosis encompasses a diverse spectrum of clinical manifestations, spanning from mild to severe. It is characterized by a biphasic illness, beginning with a leptospiraemic phase and transitioning into an immune phase.3 Neurological manifestations of leptospirosis are more pronounced in the immune phase and the hallmark is aseptic meningitis.2 It is rare for leptospirosis to present as a primary neurological disease. Those affected may exhibit involvement of both the central nervous system, including aseptic meningitis, encephalitis, seizures, and intracranial bleeding, and the peripheral nervous system, including Guillain-Barre syndrome-like presentation, mononeuritis, and autonomic lability.2

Aseptic meningitis causes headache, neck pain, nuchal rigidity, and rarely papilledema. CSF findings include lymphocytic pleocytosis, slightly elevated proteins, and normal glucose. *Leptospira* PCR is typically negative, indicating the host’s immune response and not direct central nervous system infection.

Our patient’s CSF analysis showed a mixed neutrophilic-lymphocytic pattern, elevated protein, and normal glucose levels. Real-time PCRs were positive for *Leptospira* DNA in both CSF and serum and were confirmed by repeated samples. His presentation was more suggestive of direct *Leptospira* invasion to the central nervous system causing meningitis rather than an immune reaction. Microscopic Agglutination Test (MAT) conducted on day 7 and day 14 yielded insignificant results, reaching a maximum titer of 1:20. It could potentially be due to the absence of the specific strain in the MAT panel.

Neuroleptospirosis complicated with cerebral venous sinus thrombosis (CVST) is a rare clinical presentation with only a handful of cases reported worldwide.5 The proposed pathophysiological mechanisms that govern CVST in primary neuroleptospirosis involve cerebral vasculitis, and cerebral vascular endothelial injury leading to thrombotic thrombocytopenic purpura (TTP).5

Diagnosis of leptospirosis is established by PCR, serology, and culture conducted on blood, urine, and CSF samples. Follow-up serological studies may be performed after 14 days of the initial test. In patients with suspected meningitis CSF for PCR is more
sensitive in the leptospiraemic phase, as in our patient, where the CSF samples for PCR were obtained on the third day of the illness.

Molecular diagnostic tests, such as PCR confirm the diagnosis of leptospirosis with a single positive test. Due to the transience of *Leptospira* in body fluids, the sensitivity of the PCR testing depends on the timing of collection of the sample relative to the onset of the symptoms. The overall sensitivity of the PCR remains typically in the range of 40-60% and specificity above 95%.

**Conclusion**

This case highlights the need for heightened suspicion of unusual presentations of common diseases in endemic areas and emphasizes the importance of comprehensive history to identify potential causes.

**Author declarations**

**Consent**

The corresponding author obtained informed written consent of the patient to publish the patient’s details.

**Competing interests**

The authors declare that they have no conflicts of interest.

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**Author contributions**

All authors contributed to the conceptualization and writing of the manuscript. History taking, examination, necessary investigations, follow-up of the patient, and writing of the manuscript were done by CTWM. AHNF supervised the management of this case and contributed to writing the manuscript. All authors read and approved the final manuscript.

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