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Case Report: Leptospirosis Complicated by Persistent, Bilateral Sensorineural Hearing Loss

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Abstract. The clinical manifestations of leptospirosis range from mild to life-threatening and can impact on multiple organ systems. A wide array of neurological manifestations of leptospirosis have been reported, although the pathophysiology of neuroleptospirosis remains incompletely understood. We present a case of leptospirosis complicated by bilateral sensorineural deafness, with nodular meningitis demonstrated in the internal auditory meatus on magnetic resonance imaging. The patient was treated with doxycycline, ceftriaxone, systemic and topical steroids, and hyperbaric oxygen therapy, with modest, but incomplete, improvement.

INTRODUCTION

Leptospirosis is a zoonotic infection that affects more than one million people annually. The pathogen is a spirochete bacterium of the *Leptospira* genus and has a global distribution, but it occurs more commonly in tropical regions.[1,2] Infection may be asymptomatic, but it can also present as life-threatening multiorgan failure.[3] Neurological sequelae occur in approximately 15% of cases, with aseptic meningitis the most common of these.[4] Many other neurological manifestations have been reported; however, their pathophysiology remains incompletely understood.[4,5]

PRESENTATION OF CASE

A previously well 45-year-old man presented to a regional hospital in Far North Queensland, tropical Australia with 2 days of fever, headache, myalgias, a nonproductive cough, and 1 day of new, bilateral hearing impairment. Two weeks earlier, he had spent 3 days performing forestry work, where he had significant exposure to freshwater creeks. There was no history of contact with rodents or other animals.

At presentation, he had a temperature of 36.9°C, blood pressure of 139/84 mm Hg, heart rate of 78 beats/minute, a respiratory rate of 18 breaths/minute, and his oxygen saturation, by pulse oximetry and breathing room air, was 95%. He had bilateral hearing loss to the point that his family had to speak slowly and loudly to enable him to participate in conversation. Otoscopic examination revealed an intact, normal appearing tympanic membrane. Rinne's and Weber's tests were consistent with bilateral sensorineural hearing loss, but there was no meningism, tinnitus, vertigo, or other cranial nerve abnormalities and the remainder of his physical examination was normal. Blood tests on day 3 of his illness revealed a mild thrombocytopenia but no other abnormality (Table 1). Blood cultures were negative, as were nucleic acid amplification tests (NAAT) for respiratory viruses, *Coxiella burnetii* and *Leptospira*. Serology for *Coxiella burnetii*, *Brucella*, and *Leptospira* were unreactive (Table 1). The evolving clinical symptoms in a previously well individual with recent significant environmental exposure in a region where zoonotic infections are endemic,[6,7] led local clinicians to commence oral doxycycline 100 mg twice daily.

However, his serum creatinine continued to increase (Table 1), and his hearing did not improve, so the patient was transferred to a tertiary hospital in Cairns for further evaluation; ceftriaxone 2 g intravenously once daily was commenced, and doxycycline was continued. Chest radiography and an abdominal ultrasound were unremarkable. However, repeat serology on day 7 of his illness detected *Leptospira* IgM, suggestive of a diagnosis of leptospirosis (Table 1) and magnetic resonance imaging (MRI) of the brain performed on day 8 demonstrated bilateral nodular T1 contrast enhancement within the internal auditory meatus (IAM), consistent with focal, nodular meningitis (Figure 1). By day 9 of his illness, the patient's fever, myalgia, and cough had resolved, and his serum creatinine started to decrease; however, a mild headache persisted, and his hearing had not improved.

A lumbar puncture was performed on day 9 of his illness. The opening pressure was 22 cm H_2O, the cerebrospinal fluid (CSF) protein, glucose and cell count were within normal limits and there was no growth after 5 days of incubation; serological and NAAT testing of the CSF for *Leptospira* was nonreactive and negative, respectively (Table 1). Audiometry on day 10 of his illness confirmed bilateral moderate to severe sensorineural hearing loss (Figure 2).

After discussion of the risks and benefits of different therapies in the context of the potential lifelong sequelae of significant hearing impairment, otolaryngology specialists recommended oral prednisolone 60 mg daily, intratympanic (IT) dexamethasone (2 mg weekly), and hyperbaric oxygen therapy (HBOT; delivered with 100% oxygen at a pressure of 243 kPa); these therapies were commenced on days 10, 12, and 13 of the illness, respectively. In total, the patient received 14 days of doxycycline, 7 days of ceftriaxone, 10 days of oral prednisolone, 13 treatments of HBOT, and three doses of bilateral IT dexamethasone. Fourteen days after his initial presentation, his hearing impairment persisted, but all other symptoms had resolved completely. Leptospira microagglutination titers repeated 10 weeks after the patient's presentation and performed in parallel with his previous serology, confirmed the diagnosis of leptospirosis with *Leptospira* interrogans serovar Copenhageni titers rising from undetectable to 800 (Table 1).[8]

The patient reported some hearing improvement during his intratympanic dexamethasone and HBOT therapy, although this plateaued, and repeat audiometry at 6 months demonstrated only modest recovery across all frequencies (Figure 2). The patient was able to return to work, but hearing aids were

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TABLE 1
Laboratory data over the course of the patient's illness

Variable	Ref. range	Laboratory data							
Day of illness	–	3*	5†	6	7	9	11	22	76
Laboratory test									
Hemoglobin (g/L)	135–180	146	136	136	–	–	138	145	–
WBC ($\times 10^9$/L)	4–11	4.2	4.9	4.7	–	–	10.1	9.2	–
Platelets ($\times 10^9$/L)	140–400	121	115	134	–	–	460	252	–
Neutrophils ($\times 10^9$/L)	2–8	3.8	4.27	3.91	–	–	7.42	7.85	–
Lymphocytes ($\times 10^9$/L)	1–4	0.21	0.36	0.54	–	–	1.82	1	–
C-reactive protein (mg/L)	<5	49	84	102	–	–	–	–	–
Sodium (mmol/L)	135–145	134	130	134	–	–	139	138	–
Potassium (mmol/L)	3.5–4.2	4.4	4.2	4.3	–	–	4.7	4.7	–
Chloride (mmol/L)	95–110	110	98	102	–	–	105	102	–
Bicarbonate (mmol/L)	22–32	28	25	26	–	–	25	28	–
Urea (mmol/L)	2.1–7.1	4.8	7.8	8.6	–	–	6.8	6.9	–
Creatinine (μmol/L)	60–110	88	154	194	–	–	90	92	–
Bilirubin (μmol/L)	<20	8	27	23	–	–	7	10	–
Alkaline phosphatase (IU/L)	30–110	53	229	218	–	–	230	92	–
Gamma-glutamyl transferase (IU/L)	< 55	35	512	448	–	–	379	155	–
Alanine aminotransaminase (IU/L)	< 45	27	205	203	–	–	315	54	–
Aspartate aminotransferase (IU/L)	< 35	20	155	143	–	–	131	23	–
Blood cultures	NA	NG	NG	NG	–	–	–	–	–
Urine WBC	< 10	20	20	–	–	–	–	–	–
Urine RBC	< 10	20	< 10	–	–	–	–	–	–
Urine protein	< 100 mg/L	480	–	–	–	–	–	–	–
Urine culture	NA	NG	NG	–	–	–	–	–	–
Leptospirosis NAAT	NA	ND	–	–	ND	–	–	–	–
Leptospira antibodies IgM	NA	NR	–	–	R	–	–	–	R
Leptospira interrogans serovar Copenhageni titer	NA	–	–	–	< 50	–	–	–	800
CSF opening pressure (cm H_2O)	5–25 cm H_2O	–	–	–	–	22	–	–	–
CSF protein (mg/L)	150–500	–	–	–	–	230	–	–	–
CSFglucose (mmol/L)	2.2–3.9	–	–	–	–	3.4	–	–	–
CSF WBC ($\times 10^6$ cells/L)	< 5	–	–	–	–	3	–	–	–
CSF RBC ($\times 10^6$)	< 5	–	–	–	–	2	–	–	–
CSF bacterial culture	NA	–	–	–	–	NG	–	–	–
CSF leptospirosis NAAT	NA	–	–	–	–	ND	–	–	–

CSF = cerebrospinal fluid; NA = not available; NAAT = nucleic acid amplification; ND = not detected; NG = no growth; NR = nonreactive; R = reactive; RBC = red blood cell; Ref. = reference; WBC = white blood cell.

*Other negative tests on day 3: Q fever serology, *Rickettsia rickettsii* serology, *Orientia tsutsugamushi* serology, *Brucella* serology, EBV IgM, CMV IgM, *Burkholderia pseudomallei* serology, Flavivirus IgM, Dengue NS1 antigen, Ross River IgM, Barmah Forest IgM, HIV serology, hepatitis B surface antigen, hepatitis C antibody, syphilis serology, antinuclear antibody, extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies.

† Other negative tests on day 5: Spotted fever group and scrub typhus PCR, Q fever serology, serum cryptococcal antigen.

recommended to allow a return to his premorbid level of function.

DISCUSSION

Leptospirosis infects a variety of wild and domestic mammals that pass the spirochetes into the environment in their urine. Human infection develops when the pathogen enters the host through cut or abraded skin, the conjunctivae, or mucous membranes. The disease is traditionally considered to have an incubation period of between 2 and 30 days before manifesting as a biphasic illness. The first, "leptospiremic," phase begins after the organism gains entry to the bloodstream, and the second develops after immune recognition and response to the infection. However, in clinical practice there is often little delineation between these two phases.[9]

The clinical course of leptospirosis is highly variable. Most cases are subclinical or mild and self-limiting, although severe disease also occurs.[10,11] Patients typically present with abrupt onset of fever, headache, rigors, and myalgias, which can evolve to life-threatening manifestations including renal failure, hepatic failure, acute respiratory distress syndrome, and pulmonary hemorrhage.[3,10] Neurological manifestations present in up to 15% of patients, although they are probably underrecognized.[4,5] The most common neurological manifestation of leptospirosis is aseptic meningitis. However, other neurological sequelae including Guillain-Barré–like syndromes,[12] seizures,[4] encephalitis with cortical blindness,[13] cerebellar dysfunction,[14] and transverse myelitis have been reported.[15] Cranial nerve deficits including optic neuritis,[15] bilateral abducens palsy,[16] and both unilateral and bilateral facial nerve palsies have also been documented.[17,18] The pathophysiology of these neurological manifestations is incompletely understood.

Leptospira disseminate rapidly throughout the body, from the site of the inoculum to the bloodstream. *Leptospira* virulence factors include proteins that are adapted for cell adhesion, survival in phagosomes, and resisting the complement system, while others trigger the breakdown of the extracellular matrix.[9] Invasion of the endothelial cell leading to loss of vascular integrity, ischemia, and necrosis appears central to the pathophysiology of leptospirosis[19]; however, dysregulated inflammatory responses induced by the organism also appear to contribute to the wide spectrum of severity and clinical manifestations.[20] *Leptospira* also invade the CSF, although some authors have noted that the focal neurological manifestations of leptospirosis are seen more commonly later in the disease course during the immunological phase of the disease, rather than the acute leptospiremic phase, and have highlighted that histologically, the neuropathological findings typically appear immune mediated.[4]

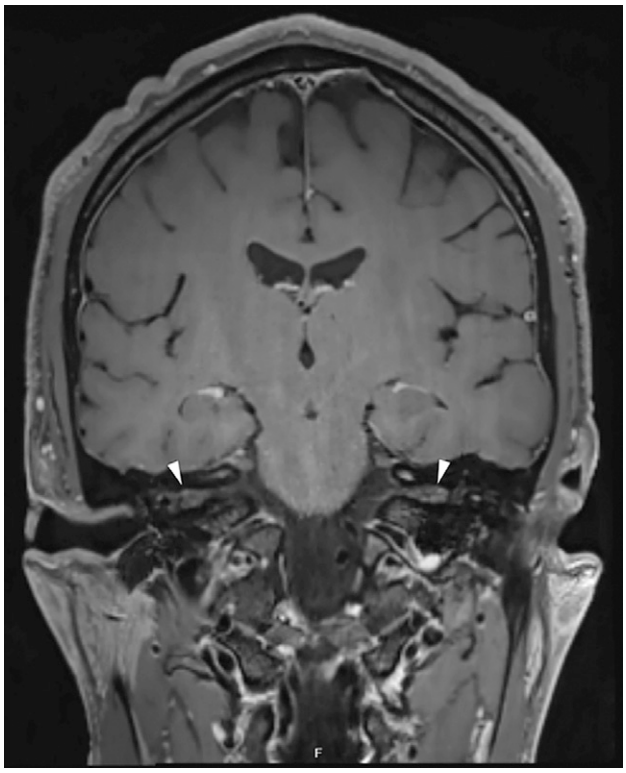

FIGURE 1. Coronal slice of a T1 fat saturated magnetic resonance imaging. White arrows demonstrate bilateral nodularity of the internal acoustic meatus (a canal within the petrous portion of the temporal bone, which contains the facial nerve, the vestibulocochlear nerve, the vestibular ganglion, and the labyrinthine artery).

We present the case of a previously well, immunocompetent man with laboratory-confirmed leptospirosis, presenting with typical symptoms of the disease. However, he also had new, bilateral sensorineural hearing impairment that developed early in the course of the illness, before the receipt of antibiotics, at a time when leptospirosis serology was unreactive. This may suggest that vascular injury during the leptospiremic phase of the disease is more likely to be responsible for our patient's symptoms rather than an immune-mediated phenomenon.[19] Bilateral IAM nodular meningitis was identified on MRI imaging, suggesting that this was the mechanism for the patient's hearing loss. However, it was notable that CSF analysis revealed no pleocytosis, identified no *Leptospira* DNA and was serologically nonreactive, with the caveat that CSF analysis was delayed until day 9 of his illness, 6 days after initiation of doxycycline. It is important to highlight this because although the pooled sensitivity of polymerase chain reaction testing for a diagnosis of leptospirosis is 70%, this figure is strongly influenced by the specimen tested, the timing of the testing, and whether a patient has already received antibiotic therapy.[21]

Steroids have been used in the treatment of leptospirosis-associated focal neurological symptoms and have been associated with both positive and negative outcomes.[12,22] However, management with antibiotics alone has also resulted in symptomatic improvement,[16] and in other neurological conditions, the success of therapy is highly time sensitive.[23] Although our patient had some hearing improvement in the weeks after the administration of local and systemic steroids it is uncertain—particularly in the absence of any definite evidence of immune-mediated pathology—if any of these therapies contributed to the partial recovery of his hearing.

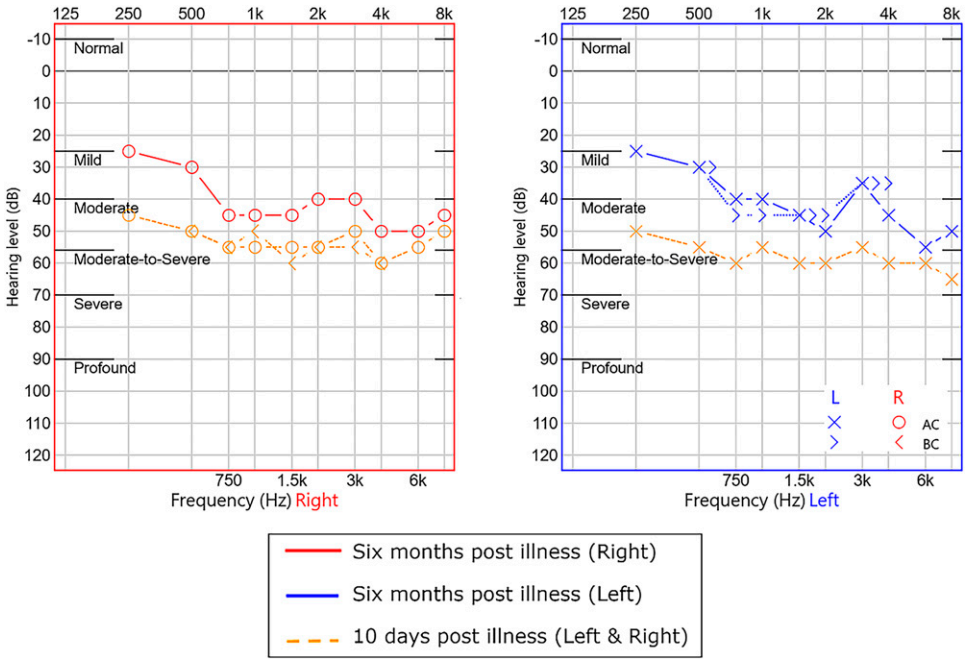

FIGURE 2. Audiometry performed on day 10 post–illness onset (yellow dashed line) and 6 months post–illness onset in both the right (solid red line) and left (solid blue line) ear. AC = air conduction; BC = bone conduction.

It is also uncertain if earlier steroid therapy, at the time of presentation and given concurrently with antibiotics, may have resulted in greater improvement, although it should be emphasized that the role of steroids in the therapy of leptospirosis is controversial, and there is insufficient evidence for their prescription for any clinical manifestation of the illness. Finally, the ability of different antibiotics to penetrate the blood–brain barrier is always a consideration when treating central nervous system infections, and although both doxycycline and ceftriaxone are used to treat these infections, it is unclear whether the prescription of higher doses may have additional utility in patients with neuroleptospirosis.[24]

CONCLUSION

The pathophysiology of neuroleptospirosis is incompletely understood, and its presentation is highly variable. We present a case of bilateral, isolated sensorineural hearing impairment in an otherwise well individual that developed during the early phase of laboratory-confirmed leptospirosis and in whom imaging demonstrated focal nodular meningitis. His hearing loss improved with antibiotics, systemic and local steroid therapy, and HBOT, although the relative contributions of these therapies to the patient's partial recovery are uncertain. Indeed, we hypothesize that the nerve damage occurred early in the disease course and was most likely related to vascular injury during the leptospiremic phase of the infection. It is hoped that this case will facilitate earlier recognition of hearing impairment as a complication of leptospirosis, particularly in rural, remote, and resource-limited settings where the disease is most commonly seen.

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