Acute Disseminating Encephalomyelitis Following Legionnaires Disease

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Objective: To describe 2 patients presenting with severe neurological deficits and extensive lesions on brain magnetic resonance imaging after having experienced *Legionella* pneumonia.

Design: Case reports.

Setting: University hospital.

Patients: Two patients who developed severe neurological symptoms, including encephalopathic signs, following *Legionella* infection, with widespread lesions on magnetic resonance imaging compatible with demyelination.

Results: After extensive ancillary investigations, a diagnosis of acute disseminating encephalomyelitis was considered most likely. Steroid therapy was initiated in 1 of the patients, followed by plasmapheresis. In both patients, clinical and radiological signs gradually recovered, with only slight residual deficits.

Conclusion: In patients presenting with neurological symptoms after an episode of pneumonia, *Legionella* infection and a subsequent immune-mediated process such as acute disseminating encephalomyelitis should be considered.

**LEGIONELLA**, a gram-negative bacterium commonly found in aquatic environments, may cause pneumonia when infected aerosols are inhaled or contaminated water is aspirated. The majority of cases are caused by *Legionella pneumophila*, of which 16 different serogroups have been identified. Legionnaires disease is the systemic illness associated with *Legionella* infection, of which extrapulmonary manifestations include renal impairment, cardiac manifestations, and gastrointestinal symptoms. In addition, neurological symptoms have been described, in particular, encephalopathic signs. The diagnosis of legionnaires disease can be difficult, as clinical and radiological signs are nonspecific. Culture diagnosis is considered the gold standard but requires up to 7 to 10 days to obtain a positive result. The most commonly used laboratory test is detection of the *Legionella* urinary antigen, which is most sensitive for *L pneumophila* serogroup 1 and poorly sensitive for the other serogroups.

**REPORT OF CASES**

**CASE 1**

A 54-year-old man with a history of hypertension, chronic obstructive pulmonary disease, and myocardial infarction was admitted because of behavioral changes and unsteady gait. His medication consisted of antihypertensive drugs, acetylsalicylic acid, and inhalation therapy and he had smoked for 35 years. One month earlier he had been hospitalized with a bilateral pneumonia for which no causative organism had been identified. He had been treated with antibiotics, leading to good recovery and discharge home. However, 2 weeks after discharge the patient began to develop an unsteady gait, slurry speech, and difficulties performing daily tasks. His relatives also noticed behavioral changes, including aggression, that were slowly progressive. On readmission, body temperature, blood pressure, and auscultation of the heart and lungs were normal. Neurological assessment showed a disoriented patient with bradyphrenia, apraxia, atactic gait, tactile extinction of the left arm, and normal tendon reflexes with bilateral plantar response. During admission, he also developed choreatic movements of the head, arms, and legs, while his level of consciousness fluctuated.

Extensive laboratory investigations showed increased levels of C-reactive protein and leukocytes and mild hyponatremia. Serological test results for Epstein-Barr virus, cytomegalovirus, hepatitis B and C, *Borrelia*, *Treponema*, *Toxoplasma*, and human immunodeficiency virus were nega-
A 55-year-old man was admitted because of progressive respiratory complaints that had started after staying in several hotels during a business trip. His medical history was unremarkable, he did not use any medication, but he had smoked for 40 years. Physical examination on admission showed a normal body temperature and blood pressure, tachycardia, tachypnea, decreased arterial oxygen saturation, and diminished breath sounds in the left lung field. The patient was alert and oriented; neurological examination was completely normal. Laboratory investigations revealed increased levels of leukocytes and C-reactive protein. Chest radiography demonstrated extensive bilateral infiltrates suggestive of pneumonia. Because blood and sputum cultures were repeatedly negative, broad-spectrum antibiotic therapy (ciprofloxacin and cefuroxime) was initiated. Two days later, the patient had to be intubated and transferred to the intensive care unit because of severe respiratory distress. Temporary sedation was considered necessary to achieve adequate mechanical ventilation, and continuous veno-venous hemofiltration was initiated because of acute tubular necrosis with renal failure. In the intensive care unit, results of the *Legionella* urinary antigen test for serogroup 1 came out positive and cefuroxime administration was discontinued. Three weeks after admission, the patient's respiratory condition progressively improved. Hemofiltration could be discontinued, antibiotic medication was stopped, and he was successfully weaned from mechanical ventilation. Yet, while the patient was no longer sedated, he did not regain full consciousness. On the next day, he developed generalized tonic-clonic seizures, and neurological examination showed a mild paresis of the left arm and right leg. Brain MRI demonstrated extensive multifocal lesions, involving predominantly the white matter, without contrast enhancement. The lesions were hyperintense on the T2-weighted series, located in both hemispheres, the corpus callosum, basal ganglia, and brainstem, and compatible with demyelination. Stereotyped lesions were not initiated because of the relatively quick recovery. Eighteen months after admission, the lesions on MRI had evidently diminished (Figure 2) and the patient was living independently.

**CASE 2**

![Figure 1](Image 66x603 to 293x747)

**Figure 1.** Case 1. Magnetic resonance imaging (T1 weighted with gadolinium and fluid-attenuated inversion recovery) on day of hospital admission showing multiple disseminated lesions with contrast enhancement.

![Figure 2](Image 66x603 to 293x747)

**Figure 2.** Case 1. Magnetic resonance imaging (T1 weighted with gadolinium and fluid-attenuated inversion recovery) 18 months after hospital admission showing a decline in size and number of lesions.
cell count and glucose concentration, elevated total protein concentration (1.13 g/L), and elevated IgG level (0.320 g/L) with a normal IgG index (0.7). Routine aerobic and anaerobic bacterial culture results of CSF were negative. Given the lesions in the corpus callosum and brainstem, vasculitis was considered unlikely. A diagnosis of hemorrhagic ADEM was made and treatment with high-dose methylprednisolone was started, followed by 9 sessions of plasmapheresis, after which the patient’s neurological condition gradually improved. Three weeks later, he was alert and without focal neurological deficits except for a moderate receptive aphasia. He was transferred to the Neurological Department and discharged home after several weeks. A follow-up MRI 1 month after admission showed considerable attenuation of the lesions and microbleeds (Figure 4).

### COMMENT

Several older case reports have described the occurrence of neurological symptoms in patients with legionnaires disease. Most of these involve encephalopathic signs like alterations of mental status, confusion, hallucinations, and personality changes.2-4 Focal neurological dysfunction has also been reported, in particular ataxia or other cerebellar signs.5-7 In a case series comprising 16 persons with legionnaires disease, neurological symptoms were found in the majority of patients. Encephalopathy was the most common finding, with patients displaying impaired consciousness, disorientation, or confusion.3 In another series, neurological abnormalities were found in 9 of 21 patients, with encephalopathy again being the most frequent symptom.4 More recent case reports have also described neurological dysfunction associated with Legionella infection, consisting of either generalized central nervous system involvement, focal signs, or peripheral neuropathy.8-10

The pathogenetic mechanisms that underlie the occurrence of neurological manifestations in patients with legionnaires disease are unclear. Postmortem brain examinations of 40 patients with Legionella pneumonia, 16 of whom had neurological symptoms that were not explained by preexisting disease, did not demonstrate evidence of infectious lesions attributable to Legionella in any of the cases. The CSF findings were normal in the vast majority of these patients, suggesting that Legionella does not directly affect the central nervous system.11 Presence of Legionella bacteria in the central nervous system has only sporadically been described.6,12 Therefore, in the absence of convincing evidence of direct cerebral invasion, it seems plausible that other mechanisms account for the occurrence of neurological manifestations in legionnaires disease. It has been hypothesized that neurotoxins might be involved,3,5 as there is some evidence that Legionella species may produce a weak endotoxin-like substance.13

Alternatively, a role of immunological mechanisms has been suggested.5,14 Indirect support for this theory comes from 2 recently reported cases of patients who developed ADEM after infection with Legionella.14,15 In our patients, an immune-mediated etiology rather than a direct infectious process was also deemed very likely, given the interval between the episode of pneumonia and the onset of neurological symptoms. Although the duration of this interval is unknown for case 2 because of sedation, neurological examination on admission was completely normal. In both cases, the nature of the extensive MRI lesions and the neurological manifestations with prominent encephalopathic signs strongly support a diagnosis of ADEM.

Acute disseminating encephalomyelitis is an acute immune-mediated demyelinating disorder of the brain and spinal cord, often occurring within 2 to 30 days after an antigenic challenge. The characteristic clinical presentation includes a rapid-onset encephalopathy in combination with multiple focal neurological deficits and may be preceded by a prodromal phase with fever, malaise, and headache. In general, the disease course is progressive, developing over hours to days. Brain computed tomography is often normal, but MRI usually demonstrates multiple large, asymmetric, patchy lesions with increased signal.
intensity on T2-weighted and fluid-attenuated inversion recovery sequences, involving the white matter and cortical gray-white junction of both cerebral hemispheres, the cerebellum, brainstem, and spinal cord. Acute hemorrhagic encephalomyelitis, as seen in case 2, is an acute, rapidly progressive, and frequently fulminant subform of ADEM that is often triggered by respiratory tract infections. Demyelinating lesions are usually large with perilesional edema and evidence of hemorrhage.

Disturbed consciousness, confusion, and cerebellar signs are prominent features of the condition that in the past has occasionally been termed Legionella encephalopathy. Although in many of the earlier-described patients no abnormalities were found on neuroimaging, radiological tests often merely comprised computed tomographic scans, as more sophisticated methods were not widely available yet. However, several recent reports describe abnormalities on cerebral MRI from patients with neurological symptoms and Legionella infection, suggesting that brain lesions in legionnaires disease are more common than previously thought. We hypothesize that a proportion of the cases formerly diagnosed as Legionella encephalopathy may actually have been due to an immune-mediated process such as ADEM following legionnaires disease. In patients presenting with neurological symptoms—in particular encephalopathic signs—after an episode of pneumonia, Legionella infection and subsequent immune-mediated demyelination should be considered.

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REFERENCES


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