Clinical Reasoning: A 47-Year-Old Man With an Upper Respiratory Infection, Acute Confusion, Dysarthria, and Ataxia

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Neurology® 2023;100:978-983. doi:10.1212/WNL.0000000000206864

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Abstract

A patient presenting with acute confusion, dysarthria, and appendicular ataxia with gait instability warrants a broad differential including emergent consideration of acute ischemic or hemorrhagic stroke. Moreover, in acute to subacute presentations, a wide array of etiologies including infectious causes, toxins, or autoimmune conditions may be considered. This article features a 47-year-old man who presented acutely with confusion, severe dysarthria, left upper extremity dysmetria, and unsteady gait. In this case, these neurologic signs were preceded by symptoms of an upper respiratory infection. In addition, MRI brain without contrast demonstrated a small focus of hyperintensity on diffusion-weighted imaging in the splenium of the corpus callosum with apparent diffusion coefficient match. The article illustrates a diagnostic approach in evaluating a patient with this constellation of clinical and radiologic findings, as well as pertinent management considerations. A comprehensive overview of other potential causative factors of the imaging findings is described to augment the reader's differential diagnosis. Finally, a literature review pertaining to the revealed diagnosis highlights the epidemiologic relevance and important clinical pearls.

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Section 1

A 47-year-old man with a history of hypertension and remote pulmonary contusion presented to the emergency department with acute dysarthria and gait instability. After family recognized slurred speech during a phone call, he was immediately brought to the emergency department by an ambulance arriving 4 hours after his last-known-well. He exhibited symptoms of an upper respiratory infection including cough with fever over the last 5 days. He was tachycardic, tachypneic, hypertensive, hypoxic, febrile to 39.4°C, restless, and confused. His examination revealed severe dysarthria, limb ataxia in the left upper extremity with dysmetria on finger-to-nose, left lower extremity ankle clonus, and a markedly unstable gait with forward stumbling on taking a single step. No nystagmus or abnormal saccades were appreciated, tone was normal, his power was 5/5 in upper and lower extremities bilaterally, and deep tendon reflexes were 2+ throughout (except in left ankle). His NIH stroke scale score was 3. In addition, despite denying diplopia, he kept 1 eye closed while focusing on objects.

Questions for Consideration:

1. What is the localization for his presentation?
2. What is your working differential diagnosis?
3. What diagnostic testing would you obtain?

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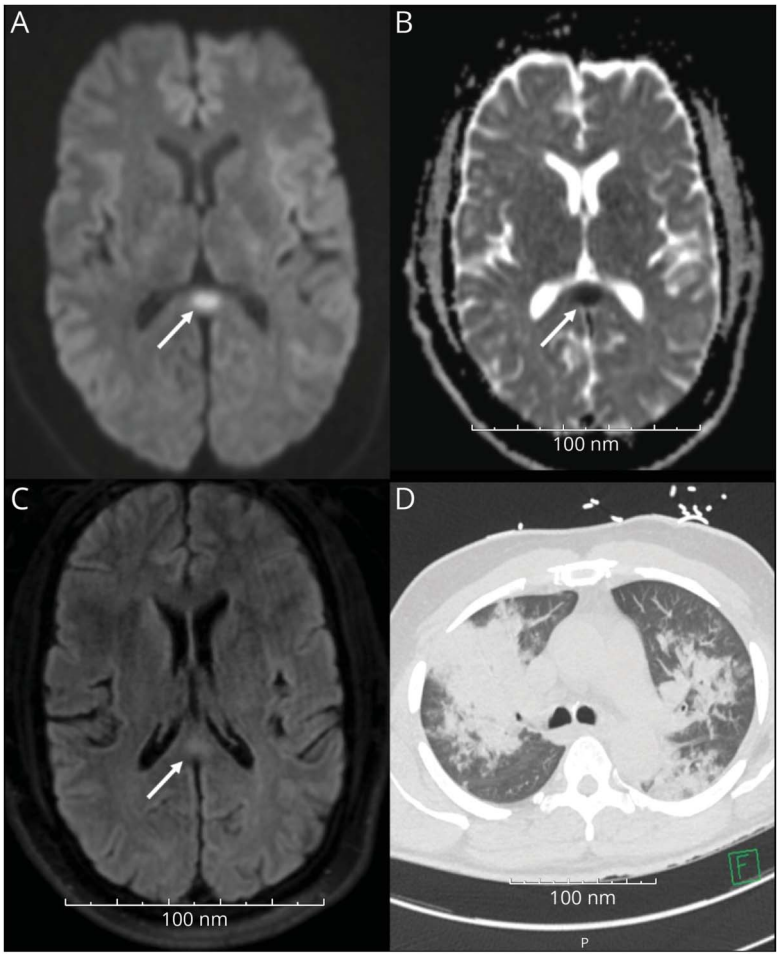
Section 2

This patient's presentation includes acute confusion, dysarthria, and appendicular ataxia with gait instability. There is no paresis, sensory abnormality, or specific bulbar involvement. Attempting to localize to the cerebellum is a reasonable initial consideration–but there is a lack of other supporting findings given his normal extraocular movements and no lateropulsion. Moreover, the most common clinical findings associated with the splenium of corpus callosum (CC) lesions are confusion, ataxia, and dysarthria, which would account for his presentation.[1] His acute symptom onset prompts emergent consideration of acute ischemic or hemorrhagic stroke. An initial workup included a CT head without hemorrhage, and CT angiography head and neck without large vessel occlusion or stenosis. Acute to subacute presentations with these findings potentially prompt consideration of infectious causes, toxins, vitamin deficiencies, neoplasm, paraneoplastic syndromes, or an autoimmune process.

Arterial blood gas revealed an anion gap acidosis secondary to lactic acidosis. He had leukocytosis to 15.7 and evidence of renal and hepatic dysfunction. A CT chest was completed which demonstrated dense bilateral consolidations (Figure). His rapid coronavirus disease 2019 (COVID-19) test was negative. MRI brain without contrast demonstrated a small focus of restricted diffusion in the CC midline splenium with apparent diffusion coefficient match (Figure)—consistent with a cytotoxic lesion. No other abnormalities were found on the noncontrast axial diffusion-weighted, gradient echo, and T2 fluid-attenuated inversion recovery (FLAIR) images. Owing to the atypical location for a vascular event, this presumed reversible cytotoxic lesion of the CC prompted further infectious workup in the setting of sepsis. Studies included blood cultures, HIV, legionella, parvovirus B19, cytomegalovirus, Epstein-Barr virus, and respiratory panel testing for influenza A and B, adenovirus, parainfluenza, and mycoplasma pneumoniae.

On arrival, he was started on broad-spectrum antibiotics. However, he developed mixed septic and cardiogenic shock requiring intubation and inotropic support in the medical intensive care unit (ICU). An infectious workup resulted positive for urinary legionella pneumophila serogroup 1 antigen. The

Figure MRI Brain and CT Chest



(A) Axial orientation of a diffusion-weighted MRI series. Arrow pointing to a focus of hyperintensity in the midline splenium of the corpus callosum. (B) Axial orientation with apparent diffusion coefficient correlates at the CC midline splenium as indicated by the arrow. (C) T2 fluid-attenuated inversion recovery MRI showing hyperintensity at the same location of the CC. (D) CT chest without IV contrast demonstrating dense consolidative bilateral lung opacities.

antibiotic regimen was narrowed to daily 500 mg IV azithromycin with plan for continuation until he remained afebrile with resolution of infectious signs and symptoms.

He was extubated 3 days after admission. His severe legionella pneumonia with concomitant encephalopathy, cardiomyopathy, rhabdomyolysis, acute renal failure, and hepatic shock involved a 16-day ICU stay. His acute kidney injury necessitated continuous renal replacement therapy. Besides underlying Legionnaires disease (LD) with neurologic manifestations, metabolic derangements—including hypoxemia, hepatic dysfunction, and uremia—may have been a contributing factor to the confusion with agitation. Nonetheless, despite medical interventions treating these processes, his neurologic symptoms persisted. For ongoing agitation, dexmedetomidine was continued for 1 week. Of note, he lacked pertinent symptoms or associated risk factors to suggest neuropathy as the cause of his ataxia.

Questions for Consideration:

1. What is on the differential for lesions to the splenium of the CC?
2. What therapeutic approach may be considered?

GO TO SECTION 3

Section 3

It is crucial to recognize that various causative factors produce lesions to the splenium of the CC. Transient splenial CC lesions typically demonstrate hyperintensity on T2-weighted and FLAIR images, with changes in diffusion-weighted imaging occurring earlier. T1-weighted images tend to be isointense or hypointense without enhancement.[1] Among infectious causes, there are numerous pathogens found to cause reversible cytotoxic lesions. A host of noninfectious causes have also been attributed to these lesions (Table).[1-3]

The use of IV immunoglobulins (IVIgs) or corticosteroids has only been cited in 2 of 9 legionellosis cases with the associated T2 hyperintensity at the splenium of the CC—clinical improvement was reported in these limited cases.[4,5] The potential role of these adjunctive modalities in treating patients with splenial CC lesions remains unclear. As such, they were not initiated in this case because of the lack of sufficient evidence supporting efficacy and associated risk in context of his acute renal failure. He completed a 14-day course of azithromycin, and his fevers resolved. Dysarthria had resolved; however, assessment with physical therapy 1.5 months after his hospitalization showed limited tolerance of activities of daily life, inability to work, fatigue, and decreased balance.

Discussion

Over the last decade, there has been a reemergence of legionella pneumophila infection. In the United States, there was nearly a 3.5-fold increase between 2000 and 2011.[6] Similarly, there was an increase of 30% in the number of reported cases in the European Union in 2017 compared with the year prior.[7] Legionellosis severity ranges from mild febrile illness, termed Pontiac fever, to severe pneumonia known as LD.[8] Among severe cases, clinical manifestations typically include fever (often with relative bradycardia), cough (productive in about half of patients), dyspnea, diarrhea, nausea/vomiting, myalgias, pleuritic chest pain, and neurologic symptoms.[9] Gastrointestinal and neurologic manifestations in patients with pneumonia prompt consideration of LD—approximately half may have headache, altered mentation, cerebellar-like signs, seizure, and other focal findings.[9] Mortality rates depend, in part, on the time to initiate therapy (macrolide or fluoroquinolone antibiotics) and whether the infection is sporadic or nosocomial. The average fatality rate of sporadic LD is between 10% and 15%. Untreated nosocomial cases in patients with severe underlying comorbidities may have mortality rates as high as 80%.[10]

A number of reported LD cases have reversible splenial CC lesions associated with dysarthria and/or gait instability.[2] This patient provides further evidence for this unusual clinical and radiologic constellation of findings (unfortunately, a follow-up MRI is unavailable for comment on lesion resolution). Although diverse etiologies produce cytotoxic splenial CC lesions (Table), there are discrete reported neurologic findings—including this patient's presenting signs and symptoms. Other less frequently associated neurologic manifestations of splenial CC lesions include seizure, headache, hemiparesis, tremor, and hypertonia.[1,3] It has been

Table Differential Diagnosis of Transient Lesions to the Splenium of the CC

Category	Examples
Infection	Viral: influenza A and B, Epstein-Barr virus, rotavirus, measles, parvovirus B19, cytomegalovirus, varicella-zoster, adenovirus, rubella, HHV-6, HHV-7, HIV, mumps, parainfluenza, enterovirus, and tick-borne encephalitis
	Bacterial: *Legionella pneumophila*, *Streptococcus pneumoniae*, *Salmonella enteritidis*, *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Campylobacter jejuni*
Drug-related	Antiseizure medications (e.g., carbamazepine, phenytoin, and valproate)
	Chemotherapeutic agents (e.g., 5-fluorouracil, cisplatin, and carboplatin)
	Antimicrobials (e.g., metronidazole and tetracycline)
Metabolic derangements	Hypoglycemia, hyponatremia, hypernatremia, vitamin B12 deficiency, Wernicke encephalopathy, hemolytic-uremic syndrome, and thyroid storm
Cerebrovascular disorders	Vasculitides, subarachnoid hemorrhage, posterior reversible encephalopathy syndrome
Traumatic brain injury; diffuse axonal injury	
Autoimmune disorders	Autoimmune encephalitis, multiple sclerosis, autoimmune thyroid disease, systemic lupus erythematosus
Malignancy	Glioblastoma, lymphocytic leukemia, spinal meningeal melanocytoma
Other neurologic conditions	Epilepsy, Marchiafava-Bignami disease, high-altitude disease, status migrainosus, transient global amnesia
Miscellaneous conditions	Radiation therapy, preeclampsia, toxins (e.g., carbon monoxide, methyl bromide)

Abbreviations: CC = corpus callosum; HHV = human herpesvirus.

postulated that the dysarthria and gait abnormalities of CC lesions may be related to interhemispheric disconnection with subsequent incoordination.[11] This patient's profound encephalopathy limited evaluating for signs such as alexia without agraphia, unilateral agraphia, or a unilateral tactile anomia. Alien hand and left-right confusion are other disconnection or callosal syndrome findings and were not observed in this case.

With overlap between clinical manifestations of LD and COVID-19, it is prudent to use diagnostic testing when clinical suspicion for these pathogens is high. Indeed, coinfection has been reported.[12] Since the bacterium is ubiquitous in aquatic habitats,[8] it is theoretically plausible that cooling towers and plumbing systems of closed buildings during lockdowns become fertile grounds for legionella replication—particularly during humid months.[12,13]

Pathophysiology of neurologic involvement in legionellosis remains unknown, with direct invasion of the CNS seeming less likely. A review including 16 cases with CSF studies revealed normal CSF in 13 patients. Cultures/stains were negative in all cases[14]—as such, CSF in this case was not obtained to confirm legionella. Given bland CSF findings and possible lack of imaging findings in affected patients, more plausible theories include a toxin-mediated process. The bacterium is known to produce a host of exotoxins and cytotoxins, which may explain associated injury to other organs.[10] Another consideration is an immune-mediated process.[4,14] Lesions to the CC may be attributed to a higher density of cytokine receptors, increasing susceptibility to cytotoxic edema in instances of cytokine release (e.g., tumor necrosis factor α, interleukin [IL]-1, and IL-6). Moreover, the splenium of the CC has hypothesized susceptibility to cytokine release given blood supply from both anterior and posterior circulation—unlike the rest of the CC.[3]

Furthermore, a persisting left-sided unilateral balance deficit posthospitalization provides some pause regarding the transitory course of deficits after legionellosis. At least 3 other reported cases with a reversible cytotoxic splenial lesion described mild deficits several weeks later—specifically, involving dysarthria and ataxia.[2] Another literature review, including patients with LD and cerebellar-like deficits (with or without the splenium hyperintensity), found that in 13 of 24 cases, the deficits of gait or speech persisted after 3 months.[15] A longer neurologic follow-up and the evaluation of more cases are needed in determining the natural history of these associated neurologic symptoms. Finally, although this patient did not receive corticosteroids or IVIg, management of such patients with these treatment modalities is an important consideration. This especially may be the case in trying to hasten recovery in patients who lack immediate resolution of neurologic signs and symptoms.

Acknowledgment

A special acknowledgement is made to Dr. Andrew Dorsch and Dr. Caitlin Radnis (both affiliated with Rush University Medical Center) for their care of the patient. Their encouragement in completing this article was greatly appreciated.

Author Contributions

Konrad Kubicki: drafting/revision of the manuscript for content, including medical writing for content. Alejandro Vargas: drafting/revision of the manuscript for content, including medical writing for content. Rebecca O'Dwyer: drafting/revision of the manuscript for content, including medical writing for content; study concept or design.

Study Funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* June 29, 2022. Accepted in final form December 12, 2022. Submitted and externally peer reviewed. The handling editor was Resident and Fellow Section Editor Whitley Aamodt, MD, MPH.

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Neurology 2023;100;978-983 Published Online before print January 25, 2023
DOI 10.1212/WNL.0000000000206864