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Clinical Reasoning: Bacterial meningitis causing a neuromyelitis optica flare

Faysal Saab, MD*
Matthew Stutz, MD*
Lucas Restrepo, MD, PhD

Correspondence to Dr. Stutz: mstutz@mednet.ucla.edu

SECTION 1

A previously healthy 49-year-old woman experienced left arm paresthesias. Over the next few weeks, the paresthesias progressed to all extremities. Initial laboratory studies were unrevealing; the patient's progressive weakness and numbness continued. An MRI brain was consistent with an unspecified demyelinating disease affecting the cortical white matter and cervical spine. Lumbar puncture revealed normal cell count and differential, with negative culture, gram stain, and oligoclonal bands. She was then diagnosed clinically with multiple sclerosis (MS) and treated with teriflunomide. She soon developed skin and joint pain, intractable hiccups for 22 days, early satiety, and urinary incontinence. Repeat MRI again showed demyelinating lesions, this time in her thoracic spine. Her treatment was changed to glatiramer acetate.

Eight months later, the patient experienced bilateral vision loss and could see bright lights and vague object motion. A repeat MRI showed abnormal fluid-attenuated inversion recovery signal in the optic chiasm with postcontrast enhancement consistent with retro-orbital neuritis, and her serum aquaporin-4 antibody (AQP4)–immunoglobulin G (IgG) returned strongly positive at 24.3 units/mL (ref <1.6 units/mL).

Current diagnostic criteria for neuromyelitis optica spectrum disease (NMOSD) are divided into those who are AQP4-IgG-positive and those who are negative. Patients with the presence of AQP4-IgG require one of the following core clinical characteristics of NMOSD to be diagnosed: optic neuritis, acute myelitis, area postrema syndrome (uncontrolled hiccups/vomiting), acute brainstem syndrome, symptomatic narcolepsy, or a symptomatic cerebral syndrome with lesions typical of NMOSD.[1] This patient met these diagnostic criteria and received plasmapheresis, rituximab, and methylprednisolone. Afterward, her vision improved slightly, but she had chronic numbness in all extremities and could ambulate 10 feet with a walker. Neurologic examination at this time documented bilateral nonreactive pupils each measuring 6 mm, narrow-based gait, normal strength, and 1 + reflexes throughout.

The patient presented to the emergency department 12 weeks later complaining of worsening vision, weakness, and headache for the past 2 weeks. Her temperature was 35.9°C, blood pressure 172/95 mm Hg, heart rate 102 bpm, and respiratory rate 15, saturating 97% on room air. She was lethargic, arousable only to loud voice and painful stimuli. She moaned with neck flexion. Her pupils were sluggish. She had a right facial droop, was unable to track, 3/5 strength in the upper extremities, 0/5 in the lower extremities, and normal Babinski bilaterally.

MRI of the brain and spinal cord showed multiple enhancing lesions consistent with active demyelination in the internal capsule and cervical and thoracic spine (figure). Soon after, the patient experienced unstable supraventricular tachycardia necessitating synchronized cardioversion and returned to sinus rhythm.

Questions for consideration:

1. Based on the history and physical examination, what is in the differential diagnosis?
2. What further workup and management should be performed?

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*These authors contributed equally to this work.

From the Departments of Internal Medicine and Pediatrics (F.S., M.S.) and Neurology (L.R.), University of California at Los Angeles.

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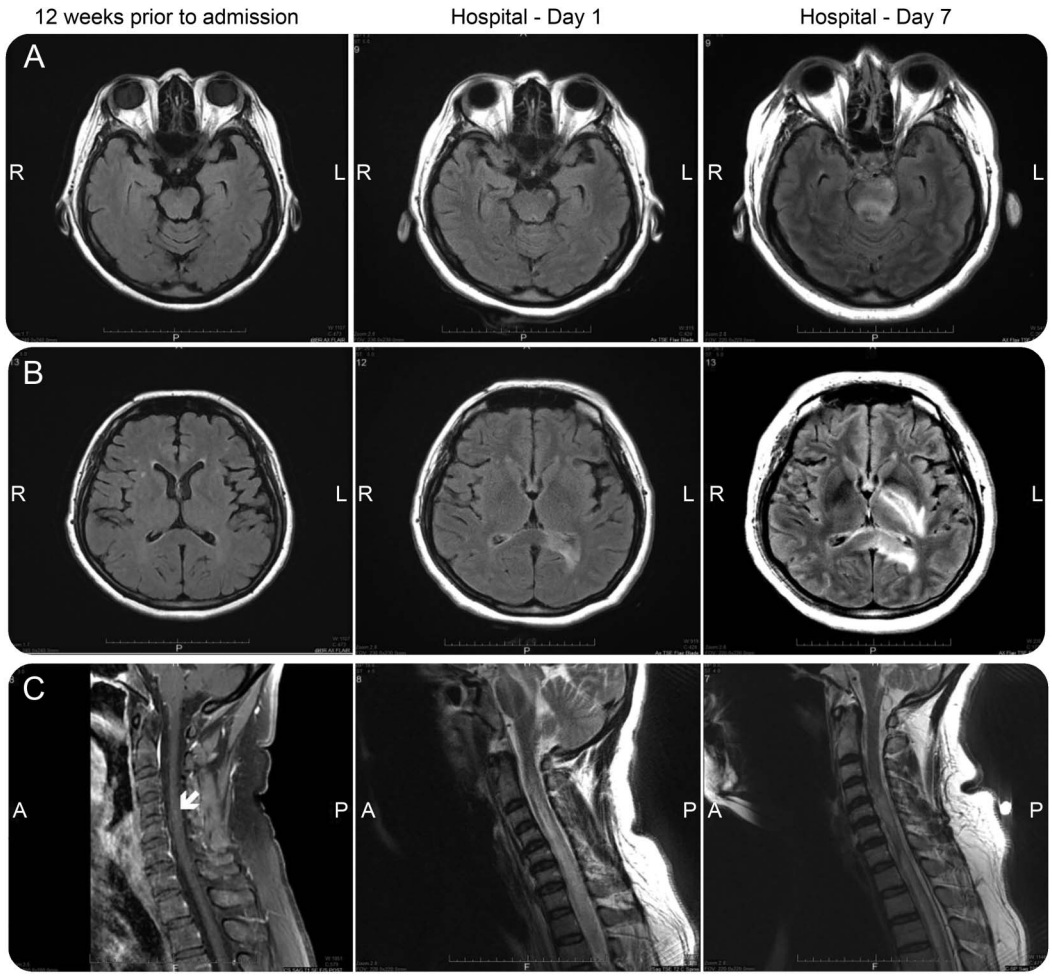
Figure MRI of the brain and spinal cord



(A) Axial fluid-attenuated inversion recovery (FLAIR) sequence 12 weeks prior to admission after steroids and plasmapheresis, compared to hospitalization imaging showing FLAIR hyperintensity into the left tegmentum and left pons, consistent with active demyelination. (B) Axial FLAIR sequence shows progression of demyelination in splenium and corpus callosum. (C) Sagittal T1 with contrast 12 weeks prior to admission and sagittal T2 turbo spin echo at hospital days 1 and 7 show multifocal enhancement of the cervical cord and diffuse enhancement of the thoracic cord, with interval increase in abnormal expansion and T2 signal hyperintensity of the spinal cord during hospitalization.

SECTION 2

The differential diagnosis for this patient's presentation is broad and includes infectious, metabolic, neurologic, traumatic, and immunologic etiologies. NMOSD is a rare, severe, inflammatory, demyelinating autoimmune disease of the CNS characterized by recurrent optic neuritis and myelitis.[2] Clinically, NMOSD differs from MS on several points. First, it is mediated by anti-AQP4. Second, NMOSD flares are generally more severe.[3] Third, NMOSD has specific abnormalities seen on MRI. Magnetic resonance findings alone are not diagnostic of NMOSD; however, they play a key role in diagnosis. Cerebral, optic, and spinal cord lesions can be seen in NMOSD. Cerebral lesions include increased T2 signal in the dorsal medulla, internal capsule, thalamus, hypothalamus, deep white matter, and the periependymal tissue of the third and fourth ventricle. Optic lesions can be unilateral or bilateral and include optic nerve or chiasm and show increased T2 signal or increased T1 signal with gadolinium. Acute spinal cord abnormalities are notable for increased sagittal T2 lesions extending continuously over 3 vertebral segments with over 70% in the central gray matter. Chronic spinal cord changes show longitudinal atrophy in ≥3 vertebral segments.

Given the patient's altered mental status, high clinical suspicion for infection, and history of immunosuppression, a lumbar puncture was performed, and suggested severe bacterial meningitis (table). Interestingly, 65.9% of patients with NMOSD have at least one CSF abnormality during the acute phase. The most common finding is a polymorphonuclear pleocytosis, followed by increased protein concentration.[4] However, our literature search lacked reports of NMOSD causing such severe pleocytosis and hypoglycorrhachia in an NMOSD flare.

Given the patient's severe clinical status, vancomycin, piperacillin-tazobactam, and acyclovir were initiated before a successful lumbar puncture was performed and the CSF culture was ultimately negative. A novel test to identify noncultured bacteria is the 16s rRNA gene sequence, a highly conserved region specific to each species of bacteria. PCR is used to amplify the 16S rRNA gene sequence and identify bacterial pathogens. In our patient, the 16s rRNA sequencing was unable to identify the causative organism. However, it has been shown to have clinical utility in larger studies.[5]

We posit that concurrent bacterial meningitis triggered the neuromyelitis optica (NMO) flare in our patient, as her pleocytosis and hypoglycorrhachia improved after broad-spectrum antibiotics (table 1). Her presenting symptoms were similar to her prior flares, which had previously improved with immunosuppression. Furthermore, despite improvement of her CSF indices with antibiotics, she continued to deteriorate clinically, suggesting a noninfectious etiology. Although CNS infections can cause MRI abnormalities involving the white matter tracts, the predilection for the spinal cord seen in this case and the progressive demyelinating lesions seen on MRI also suggest NMO exacerbation. Finally, her serum anti-AQP4 was 78.6 units/mL, up from 24.3 units/mL at the time of initial diagnosis, although whether this correlates with disease activity continues to be debated.[6]

As MRI suggested NMO flare, debate ensued regarding the use of plasmapheresis and corticosteroids given the concomitant presumptive diagnosis of meningitis. Ultimately, plasmapheresis was administered for 3 days, but was subsequently discontinued given the unknown effect it could have on the antibiotic concentrations and their ability to reach therapeutic levels in the CSF. Corticosteroids were not given, in order to avoid further immunosuppression in the setting of bacterial meningitis, which was thought to be the inciting factor.

Over the next few days, the patient's clinical status continued to deteriorate despite antibiotic therapy and improvement in her CSF indices on serial lumbar punctures. She developed Mobitz 1 atrioventricular block, was noted to become persistently hypothermic, and developed a highly sensitive dependence on 0.01 mcg/kg/min drip of norepinephrine for pressor support. During a repeat MRI, she developed pulseless electrical activity and a code blue was initiated. She regained a pulse and returned to the unit intubated and sedated. Plasmapheresis was reinitiated, but a few days later she died after developing cerebral edema and intracerebral hemorrhage.

Table CSF results during hospitalization

	Day 1	Day 4	Day 6	Day 8
Hematology, CSF				
Erythrocyte count/mm^3	2,000	8,000	125	2
Leukocyte count/mm^3	12,565	30,973	1,582	2
Seg neutrophils, %	92	97	96	51
Lymphocytes, %	2	1	2	34
Monocytes, %	6	2	2	15
Chemistry, CSF				
Glucose, mg/dL	<10	<10	12	74
Protein, mg/dL	296	600	374	123

Questions for consideration:

1. What are common triggers of NMOSD flares?
2. What is the role of corticosteroids in patients with meningitis and coexisting NMO flare?

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When evaluating patients with NMOSD, one must keep the differential broad and be proficient in identifying triggers of disease attacks. In addition, patients with NMOSD are often immunosuppressed, increasing the risk of rapidly progressing infection. Known antecedent events leading to NMO flares are viral illness, immunization, and other autoimmune disease flares.[2] Although bacterial infections have not been previously described as triggers for NMO flares, this case demonstrates there should be concern that a bacterial infection could be the inciting event that led to an NMO flare and that these processes can be coexistent. Infection is likely an underrecognized cause of NMOSD flares, thus a complete infectious workup including a lumbar puncture is indicated in patients with NMOSD and altered mental status.

DISCUSSION The presentation of NMOSD can be variable; however, it classically presents with symptoms of optic neuritis (unilateral or bilateral vision loss) and myelitis. Less commonly, patients may develop the Lhermitte sign, radicular pain, tonic spasms, facial numbness, vertigo, or cerebellar tremor.[2] Fulminant NMOSD flares can also lead to respiratory depression and autonomic instability, as observed in this case.[7] Respiratory depression in NMOSD is likely due to demyelinating lesions in the brainstem. There are 3 neural mechanisms responsible for respiratory drive: central command, chemoreflexes, and neurofeedback from muscles. The retrotrapezoid nucleus is responsible for sensing changes in pH and subsequently innervates 4 structures in the brainstem essential for respiration: the ventral respiratory column, Kölliker-Fuse nucleus, lateral parabrachial nucleus, and nucleus of the solitary tract. A demyelinating lesion in any of these areas or in the tracts between them could explain the respiratory depression exhibited in NMOSD.[6–8]

The treatment of fulminant NMOSD is immunosuppression followed by plasmapheresis for refractory or progressive symptoms.[9] High-dose corticosteroids are the standard of care for NMOSD flares; however, their role in the treatment of meningitis is more limited. When given prior to or with the first dose of antibiotics, studies suggest a morbidity and mortality benefit in adult patients with pneumococcal meningitis. However, multiple studies have failed to show that steroids worsen the prognosis of bacterial meningitis, regardless of when the first dose is given.[10] Thus, when there is suspicion for concurrent NMO and bacterial meningitis, corticosteroids should be considered in addition to broad-spectrum antibiotics.

AUTHOR CONTRIBUTIONS

Dr. Saab: case writeup, structure, and edits. Dr. Stutz: academic discussion, structure, and edits. Dr. Restrepo: edited manuscript and critical revision of manuscript for intellectual content.

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