A 16-Year-Old Boy with Bilateral Hand and Foot Cramping and Numbness

Robert Listernick, MD

This 16-year-old boy’s symptoms started in August 2013, when he suddenly developed bilateral hand and foot cramping and numbness; these symptoms resolved after 5 seconds. Several days later, the symptoms recurred. He was seen at an outside emergency department, where a computed tomography (CT) scan of the head was normal. He was discharged to home.

After this episode, he experienced brief periods of double vision without eye pain. The paresthesias occurred with increasing frequency. He developed escalating lower extremity weakness and paresthesias, saying that he felt like “his legs were on fire.” Even a light touch would create severe pain to the extent that he could not put on pants or cover himself with bed sheets. He would also have episodes of severe retching and hiccups.

He was hospitalized at another hospital in September 2013, where he was found to have bilateral lower extremity weakness, diplopia, and difficulty with urination and defecation. He had an extensive evaluation that included neuroimaging. Magnetic resonance imaging (MRI) of the brain and spine showed non-enhancing regions in the medulla, the cervicomedullary junction, and from C2 to C5 and T12 to L2 in the spinal cord.

The diagnosis of acute disseminated encephalomyelitis was made and he was prescribed gabapentin for the pain. He received a 3-day course of high-dose methylprednisolone and 5 days of intravenous immunoglobulin. He had some resolution of his urinary function and gradual improvement of his lower extremity weakness and diplopia. He was discharged to an inpatient rehabilitation facility. At that point, he was able to walk with assistance; however, he still had double vision with left lateral gaze and persistent diminished left lower extremity sensation below the knee. His symptoms waxed and waned over the next 3 months until December 2013, when he had a recurrence and was hospitalized here.

His past medical history and family history were unremarkable.

His general physical examination was normal. On neurologic examination he had mild decreased visual acuity, left greater than right. The pupils were equal, round, and reactive to light. He was unable to abduct the right eye. Upward gaze was limited, left greater than right. He had decreased sensation to light touch of his forehead, cheeks, and around his mouth. His masseter muscle was symmetric to palpation and his chin opened against resistance. He had left-sided facial droop. Hearing was grossly normal. His palate elevated symmetrically. He had mild weakness of the left shoulder shrug. Head rotation was normal bilaterally. The tongue had mild deviation to the right. Strength was 5/5 in the upper and lower extremities. Tone, sensation, and cerebellar testing were normal. Reflexes were symmetrically 3+. Toes were up-going bilaterally with a few beats of clonus in his right foot. His gait was normal, although he said he felt unsteady.

On laboratory evaluation, cerebrospinal fluid (CSF) myelin basic protein was elevated. All remaining testing was normal: CSF cell count, CSF protein, CSF glucose, antinuclear antibody, anti–double-stranded DNA, antineutrophil cytoplasmic antibodies, complement levels, infectious titers, urine heavy metals, urine organic acids, plasma amino acids, lactic acid, ammonia, pyruvic acid, very long chain fatty acids, vitamin B12, folate, celiac antibody panel, serum, and CSF angiotensin-converting enzyme.

Robert Listernick, MD, moderator: Jen, can you walk us through the examination?

Jennifer Rubin, MD, pediatric neurologist: As neurologists, we tend to think about localization and time intensity curve, both of which may give clues to etiology. This illness sounds “relapsing,” with accumulation of new symptoms over days to weeks. As far as the examination goes, he had eye movement abnormalities, facial and extremity weakness, and sensory involvement. Conceivably, many of these abnormalities could localize to a single brain-
stem lesion; however, it is more likely that this is a multifocal process. Given these two findings, it sounds most like a patchy relapsing-remitting demyelinating process rather than something like a space-occupying lesion or infection. Another possibility would be one of any number of mitochondrial disorders.

Dr. Listernick: What about vasculitic processes?

Marisa Klein-Gitelman, MD, pediatric rheumatologist: Pretty unlikely. Central nervous system vasculitis is usually limited to the brain. We have seen transverse myelitis in systemic lupus erythematosus (SLE), but those children generally have other signs and symptoms.

Dr. Listernick: Let’s look at the imaging.

Mariam Kappil, MD, pediatric radiologist: On the MRI, there are multiple regions of abnormal signal within the right side of the midbrain, the dorsal pons, and near the cervicomedullary junction. There was no significant enhancement. These same signal abnormalities are throughout the posterior spinal cord in a patchy distribution. Demyelinating diseases are certainly at the top of the list. Given the prominent spinal cord and brain stem involvement, neuromyelitis optica (NMO) is the most likely diagnosis.

Dr. Listernick: Can you explain NMO?

Dr. Rubin: NMO is an immune-mediated demyelinating disease that predominantly affects the optic nerves and spinal cord. It differs from multiple sclerosis (MS) in that we see longitudinally extensive lesions in the spinal cord as opposed to the more discrete plaques seen in MS. NMO is characterized by antibodies against the aquaporin channels, which are concentrated around the ventricles, the optic nerves, the spinal cord, and in the brain stem, particularly around the fourth ventricle.

Dr. Listernick: What about the retching and hiccups?

Dr. Rubin: That’s classic for NMO, with involvement of the area postrema in the posterior medulla. This small region has a more permeable blood–brain barrier so as to alert the individual to the presence of noxious substances. Hypothalamic involvement is also common and may lead to hypersomnolence, hyperphagia, or diabetes insipidus.

Dr. Listernick: How is it diagnosed?

Dr. Rubin: NMO should be suspected in any child who has the combination of optic neuritis and longitudinally extensive transverse myelitis. In addition, the presence of antibodies against aquaporin 4 antigen is highly specific for NMO. However, the sensitivity for detection of these antibodies is around 75%.

Dr. Listernick: Unfortunately, this child’s antibodies against aquaporin 4 were negative in both the serum and CSF. What does that mean?

Dr. Rubin: That’s why we were aggressive in looking for alternate diagnoses. However, they may become positive later in the course of the illness.

Dr. Listernick: I’ve also heard the term “NMO spectrum disorder.”

Dr. Rubin: These are patients who are suspected of having NMO but don’t meet the classic case definition. They have positive antibodies and have atypical presentations, such as recurrent optic neuritis or transverse myelitis in isolation. In addition, a small minority of these patients have been found to have systemic inflammatory diseases such as SLE.

Dr. Listernick: Treatment?

Dr. Rubin: Corticosteroids are the first-line treatment, followed by plasmapheresis. He didn’t respond to steroids but responded well to plasmapheresis and had return of function.

Dr. Klein-Gitelman: The fact that he responded to plasmapheresis suggests that there is an etiologic antibody present that can be removed; we just don’t know which one.

Dr. Rubin: He also received long-term immunosuppression, first with rituximab followed by azathioprine.

Dr. Listernick: Moving forward, his neurologic symptoms improved and he remained symptom-free for the next 13 months. One year after discharge, he presented with a 2-week history of cough and left-sided pleuritic chest pain. He had no shortness of breath, palpitations, or fever. There were no recent illnesses or sick contacts. He denied any neurologic symptoms. On examination, he had decreased breath sounds at the left base. His neurologic examination was entirely normal. Can we see the imaging please?

Dr. Kappil: The lung parenchyma is normal. He has a moderate left pleural effusion. This was followed by CT of the chest that once again identified the pleural effusion. However, in addition, there’s definite nodularity along the pleural surface. It was called “nonspecific.”

Dr. Listernick: At this point, he had a diagnostic thoracentesis. The pleural fluid had a white blood cell count of 2300/mm³, of which 66% were eosinophils. All bacterial, fungal, and tuberculosis stains were negative. Complete blood
count was normal without eosinophilia, erythrocyte sedimentation rate (ESR) was 24 mm/h, and C-reactive protein (CRP) was 4 mg/dL. Comprehensive metabolic profile was normal. Pleural fluid eosinophilia? Sounds unusual.

Marielle Fricchione, MD, pediatric infectious diseases physician: We don’t typically see eosinophils in pleural fluid. It has been described with Aspergillus infections, especially in allergic bronchopulmonary aspergillosis. Still, we felt that the most likely cause was infectious, particularly in an immunocompromised patient.

Dr. Klein-Gitelman: Pleural eosinophils are not specific for any rheumatologic disease. I agree that in an immunocompromised patient one should think about infection first, particularly fungal disease.

Dr. Rubin: I don’t necessarily disagree but I think it’s important to continually rethink initial diagnoses when unusual complications arise. I definitely had brief second thoughts. For instance, given the pulmonary involvement, could this child’s original diagnosis have been neurosarcoid? Although it generally doesn’t involve the spinal cord, neurosarcoid definitely can affect the brain stem and different parts of the brain. The other consideration was whether the pleural involvement could be a direct side effect of his medication.

Dr. Listernick: How did you go about trying to diagnose the possible infection?

Dr. Fricchione: We suggested staining the fluid for fungi as well as bacteria. We recommended sending urine for detection of histoplasma and blastomyces antigen.

Dr. Listernick: Urine antigen detection was negative for both organisms. As was discussed, evidence for an overarching systemic vasculitis was sought. He had negative antinuclear antibodies and antineutrophil cytoplasmic antibodies. His symptoms abated and he was discharged with diagnosis of “viral” pleural effusion, without any direct evidence of viral infection. How reliable are the urine fungal antigen detection tests?

Dr. Fricchione: They have a sensitivity of approximately 93% and specificity of 78%. There are some studies that show a higher degree of false negativity early on in patients who have localized pulmonary disease.

Dr. Listernick: Six weeks later, he had recrudescence of similar chest pain and was readmitted. The physical examination was similar with decreased breath sounds at the left base. Complete blood count showed a white blood cell count of 12,000/mm³ with 85% neutrophils and 2% eosinophils, ESR of 102 mm/h, and CRP of 17 mg/dL. He had a second CT scan performed.

Dr. Kappil: The pleural effusion was present, and it was somewhat larger than on the previous scan. In addition, the previously seen pleural nodules were larger with some associated pleural thickening. One of the nodules can be seen eroding one of the left posterior ribs. The differential diagnosis of pleural nodules includes fungal diseases, tuberculosis, lymphoma, and metastatic tumors.

Dr. Listernick: He had a second thoracentesis with placement of a chest tube. The pleural fluid had a white blood cell count of 485/mm³ with 23% neutrophils, 62% lymphocytes, 14% monocytes, and only 1% eosinophils. Core biopsies of the pleural nodules were obtained by the interventional radiologist.

Jonathan Bush, MD, pediatric pathologist: The core biopsy revealed a mix of acute and chronic inflammation. There are a number of neutrophils and eosinophils with focal areas of necrosis, in addition to some multinucleated histiocytes. This is not the caseous necrosis we’d see in a mycobacterial infection. On the silver stain, we identified fungal forms consistent with blastomyces.

Dr. Listernick: When he was admitted, upon hearing the story, pleural nodularity, the bony destruction, and the fact that he lived near the Illinois-Wisconsin border, I felt pretty sure that he had blastomycosis. This time, the urine tests for both histoplasma and blastomyces antigens were positive.

Dr. Fricchione: There’s a high degree of cross reactivity between the histoplasma and blastomyces antigens. By the way, the classic triad of blastomycosis is pulmonary, bone, and skin disease.

Dr. Listernick: Treatment?

Dr. Fricchione: There’s a spectrum of treatment options. Immunocompetent patients who have localized pulmonary disease may require no treatment at all. There are numerous individuals in endemic areas who have evidence of prior asymptomatic infections, such as old pulmonary granulomas. Patients with mild to moderate disease generally are treated with oral itraconazole for 6 to 9 months. For those with moderate to severe disease (eg, patients with bony involvement or who are immune-compromised), we will start intravenous amphotericin for at least several weeks followed by oral itraconazole for 6 to 12 months.

Dr. Rubin: He had very severe neurologic disease so I feel compelled to continue his immunosuppression for a long time.

Dr. Listernick: Thanks everyone.