Acute Disseminated Encephalomyelitis in the Setting of Fever of Unknown Origin

Thomas Conway, DO[1] ▪ Asif Noor, MD[2]

A previously healthy 12-year-old boy presented with his parents to our emergency department (ED) with a 3-week history of daily fevers ranging from 38.0 °C to 38.9 °C. His fevers responded to ibuprofen and typically occurred in the evening hours.

The patient reported having a frontal headache with an intensity of 5 out of 10 one week prior to presentation, which responded to ibuprofen. Two weeks prior to presentation, he had visited his primary care pediatrician, who diagnosed otitis media and prescribed a course of amoxicillin. The patient completed the course without symptom improvement. One week prior to presentation, he had visited an infectious disease specialist. Results of an outpatient workup showed leukocytosis, but the results of a blood culture were negative for pathogens. An abdominal ultrasonography scan was also performed at that time, results of which were unremarkable.

The patient was born in Pakistan and immigrated with his family to United States 2 years prior to presentation. He denied new domestic travel and new animal or food exposures. He lives close to a wooded area on Long Island, New York, which is an endemic area for Lyme disease.

Physical examination

On presentation to the ED, the patient continued to have worsening headaches with new, mid-cervical neck pain. He had a fever of 38.3 °C, a heart rate of 93 beats/min, a blood pressure of 111/72 mm Hg, and a capillary refill of less than 2 s.

Diagnostic testing

Initial laboratory results were obtained in the ED 3 weeks after the patient's daily fever. The results of these tests on day 0 returned without a clear answer. His initial serum white blood cell count was elevated at 18.4 × 103/µL, with 88% neutrophils. Inflammatory markers revealed an erythrocyte sedimentation rate of 98 mm/h and a C-reactive protein level of 36 mg/dL. Serum chemistry tests returned results within normal limits for the patient's age.

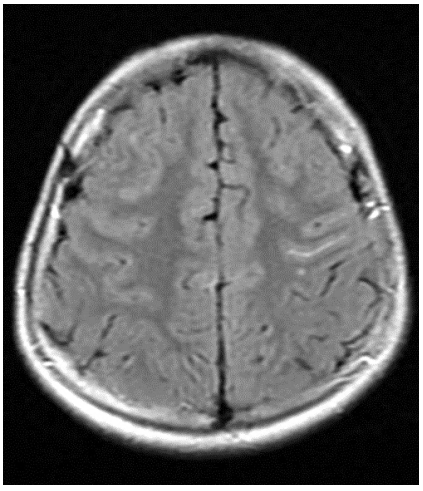

Figure 1. An initial brain MRI showed mild signal abnormality in some cerebral sulci.

Studies of the cerebrospinal fluid (CSF) obtained via lumbar puncture showed an elevated white blood cell count of 67 cells/µL, with 64% lymphocytes and 23% polymorphic cells, a red blood cell count of 300 × 10^6/µL, a glucose level of 56 mg/dL, and a protein level of 32 g/dL. Because of a cerebrospinal pleocytosis, aseptic meningitis rose to the top of the differential diagnosis list.

A chest radiograph showed no acute or focal pulmonary disease. A magnetic resonance imaging (MRI) scan of the brain showed mild signal abnormality in some cerebral sulci (**Figure 1**). Results of a urinalysis were unremarkable, and results of a malarial thick smear did not show any parasites.

AFFILIATIONS:
[1]Pediatric Emergency Medicine Department, Northwell Health, Astoria, New York
[2]Pediatric Infectious Diseases Department, New York University Winthrop Hospital, New York, New York

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CORRESPONDENCE:
Thomas Conway, DO, 2525 34th Street Astoria, NY 11103 (Tconway3@northwell.edu)

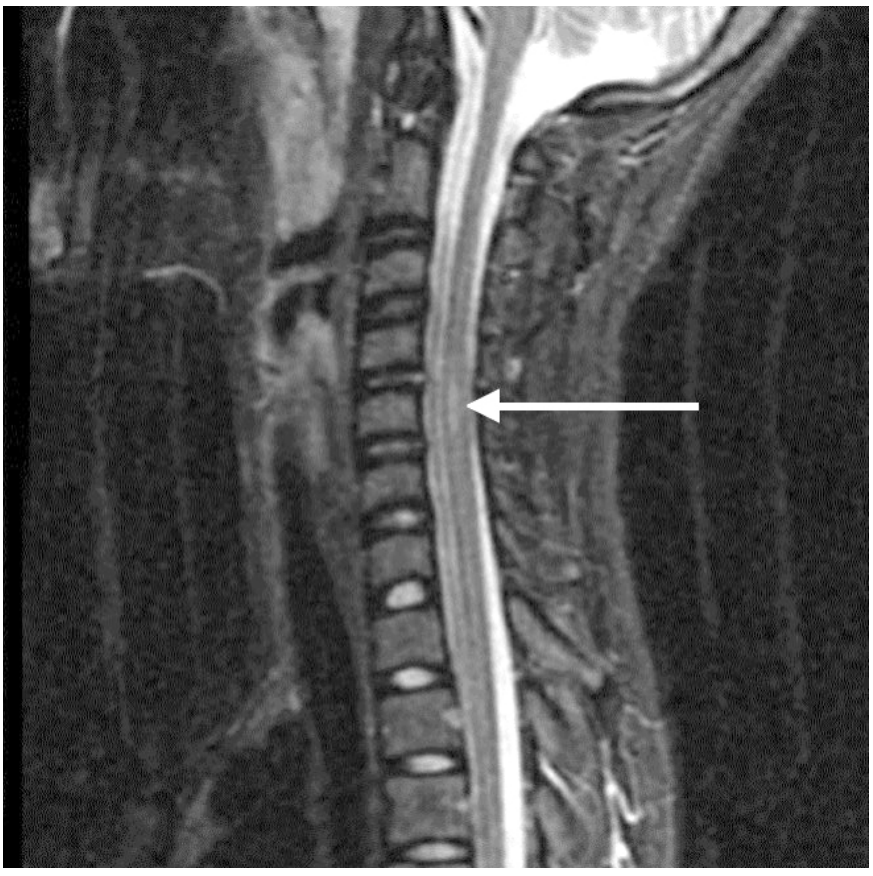

Figure 2. An MRI of the cervical spine conducted during the patient's hospital readmission showed a small focus of nonenhancing signal abnormality in the cord at the C5 level.

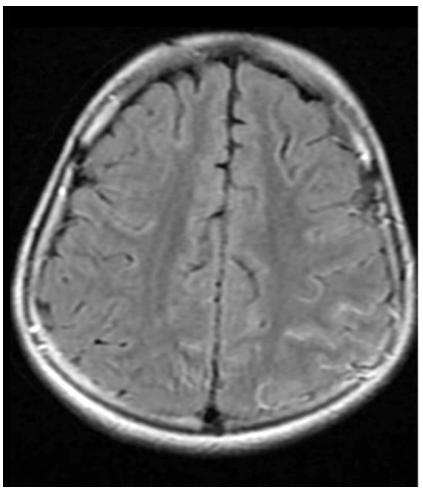

Figure 3. A brain MRI conducted during the patient's readmission showed enhancing signal abnormality in some of the cerebral sulci, more so on the left and greatest along the left parietal lobe; it was notably more prominent than on the previous scan.

Over his first 2 days on the general pediatric floor, the patient underwent various infectious disease workups, results of which remained unremarkable, and he was not given antibiotics. The initial CSF test and blood culture did not grow bacteria. A multiplex CSF meningitis panel was negative for *Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitides, Streptococcus agalactiae, Streptococcus pneumonia*, cytomegalovirus, enterovirus, herpes simplex virus 1 and 2, human herpesvirus 6, human parechovirus, varicella zoster virus, and *Cryptococcus gattii*. An enzyme-linked immunosorbent assay for Lyme disease and a polymerase chain reaction test for West Nile virus returned negative results as well. Since being admitted to the hospital, the patient had recurring nighttime fevers ranging from 38.9 °C to 39.4 °C, which were responsive to acetaminophen and ibuprofen.

On hospital day 3, the patient's leukocytosis persisted with a white blood cell count of 16,000 cells/μL. On hospital day 4, a repeat blood culture was again negative for pathogens; the patient remained fatigued and reported lower back pain near the site of his initial lumbar puncture. A multidisciplinary team consisting of an infectious disease specialist, rheumatologist, immunologist, cardiologist, and ophthalmologist was convened. Bacterial meningitis was unlikely because of the patient's normal CSF glucose and protein levels, as well as negative results of his blood culture and Gram stain. With reassuring cell lines, normal lactate dehydrogenase levels on 2 separate occasions, and a normal chest radiograph, suspicion for lymphoma was low. The ophthalmologist conducted an eye examination, which ruled out anterior uveitis, and the cardiologist conducted an echocardiography scan, which ruled out endocarditis.

The patient's fever persisted through hospital day 5, and results of a rheumatology workup for antinuclear antibodies and double-stranded DNA were negative. While the prevailing initial diagnosis of aseptic meningitis was based on the CSF findings, results of all herpes simplex virus, CSF enterovirus, and viral panels were negative, as well as results of a serum CSF West Nile virus test. Results of serum Epstein-Barr virus titers suggested a past infection. The patient's mycoplasma immunoglobulin M level was slightly elevated, nonspecifically indicative of active infection. At the start of hospital day 6, the patient was afebrile and had improved back pain. He was discharged on hospital day 7 without fever and with improvement of his back pain and weakness.

Although he was afebrile for 4 days, the patient presented again to the ED 3 days after discharge with acute urinary reten-

tion. At that time, he reported suprapubic pain and expressed difficulty in creating a urinary stream. A renal ultrasonography scan was conducted in the ED, which showed no evidence of hydronephrosis. He did not report emesis, photophobia, headache, hand tingling, or gait instability/weakness.

An abdominal computed tomography scan was conducted on rehospitalization day 1, which ruled out a space-occupying mass. Because urinary retention was reported, a urologist was consulted. However, no abnormal findings were noted. On rehospitalization day 2, a spinal MRI was performed, results of which showed a small focus of nonenhancing signal abnormality in the cord at the C5 level (**Figure 2**). At this time, the patient again experienced low-grade nightly fevers ranging from 38.3 °C to 38.9 °C.

Because of the abnormal MRI scan, a repeat lumbar puncture was performed on rehospitalization day 3. Analysis of the patient's CSF showed a slightly higher white blood cell count of 94 cells/uL, compared with his first admission lumbar puncture, with an increased protein level of 48 g/dL and a glucose level in the normal range. His myelin basic protein level was elevated at 131 ng/mL.

With almost dermatome-like distribution of abdominal pain and waxing and waning mental status, including new-onset evening delirium, neurologic-related symptomatology was considered in the differential diagnosis, including transverse myelitis and acute disseminated encephalomyelitis (ADEM). Because of the positive mycoplasma titers obtained on rehospitalization day 3, the patient was started on a course of doxycycline for possible mycoplasma-induced transverse myelitis.

A repeat MRI scan of the brain was performed on rehospitalization day 4, results of which showed enhancing signal abnormality in some of the cerebral sulci, more so on the left and greatest along the left parietal lobe; it was notably more prominent than on the previous scan (**Figure 3**). Intravenous immunoglobin, 1 g/kg/dose was started on rehospitalization day 3 after the lumbar puncture was performed. The patient also completed a dose of intravenous immunoglobulin (IVIG) but had new-onset gait instability and motor weakness.

Suspicion for ADEM increased, and the neurologist recommended starting high-dose methylprednisolone for continued anti-inflammatory effects on the brain and spinal cord. The patient improved after taking corticosteroids and doxycycline and was discharged home on rehospitalization day 9 with a corticosteroid taper schedule.

Patient outcome

The patient was prescribed a 4-week taper of oral prednisone at the time of hospital discharge, with the only adverse effect being weight gain, and was followed as an outpatient by the infectious disease specialist and neurologist. He maintained gastric prophylaxis with pantoprazole daily while taking the corticosteroids. He remained afebrile with improved strength and sensation. A repeat MRI scan of the brain and spinal cord 5 months after discharge was normal.

Discussion

With an insidious onset of neurologic signs and symptoms, ADEM is often a diagnostic dilemma. However, it is often discovered to have an identifiable cause in 70% to 75% of cases.[1] Although it is a rare illness, ADEM affects an estimated 1 in 125,000 to 250,000 individuals each year.[1] Although most cases occur in children (the majority is younger than age 10 years, and the remainder is between the ages 10 and 20 years), ADEM has been documented in adults ranging from ages 18 to 82 years as well.[2] It presents with a sudden onset, and the disease process is usually limited to a monophasic course. While irritability and lethargy are common presenting symptoms, about half of patients with ADEM also report fever and headache.[3] Studies have found infection to be an antecedent trigger in 67% of cases; however, there have been instances without recognition of a preceding event.[4] While infection may cause prolonged fevers, etiology may also include autoimmune, oncologic, neurologic, factitious, and iatrogenic causes.[3] Fever of unknown origin is defined as a temperature higher than 38.0 °C that lasts longer than 8 days without a clear source.[5] Herein, we described an uncommon diagnosis: ADEM presenting as fever of unknown origin.

Our patient had waxing and waning fevers for 3 weeks with headache and initially underwent workup for fever of unknown origin. However, with development of acute neurologic symptoms including urinary retention, hyperreflexia, and right-sided clonus, as well as with MRI brain signal abnormalities, the clinical picture was suggestive of ADEM. Fever of unknown origin in children can be caused by infections, rheumatologic causes, or oncologic causes.6 On average, no cause is identified in 23% of cases.[6] In children, the presence of prolonged fevers, headache, and CSF pleocytosis without a source should prompt consideration of ADEM and early consultation with a neurologist. Our patient met the International Pediatric MS Study Group's 2013 criteria, including:[7]

- Being the first monoclonal clinical central nervous system event with presumed inflammatory demyelinating cause
- Having encephalopathy
- Havin brain MRI abnormalities
- Having no new clinical findings 3 months or more after onset

The incidence of ADEM has been found to be 0.3 to 0.6 per 100,000 annually.8 Men are more common than women to present with ADEM symptoms, and the mean age at presentation is 5 to 8 years.[8] Our patient's clinical picture matches the neurologic manifestations of progressive muscle weakness and altered mental status. Spinal cord lesions are often present, seen as multilevel, segmental hyperdense foci, unlike in our patient who had a single cervical lesion.[8]

In our patient, CSF studies lacked results that confirmed a diagnosis. CSF

pleocytosis is typically mild, with a high percentage of lymphocytes and monocytes. CSF protein is increased in 23% to 62% of pediatric patients with ADEM.[9] The diagnostic process for ADEM is one of elimination, aiming to rule out an infectious cause. Many cases are believed to be "postinfectious" or "parainfectious," with the pathogenesis thought to be myelin-reactive T-cell activation through molecular mimicry.[10] While we had initial suspicion of aseptic meningitis in our patient, the results of all the cultures of the patient's CSF and blood were negative.

Undiagnosed fevers of unknown origin possibly consist of prolonged viral syndromes or difficult-to-confirm atypical bacterial infections.[11] The categorical workup of our patient included a system-based approach for infectious, oncologic, autoimmune, and immunodeficient causes. With zoonoses and travel-related illnesses ruled out via the patient's history, CSF and blood cultures were conducted in hopes a pathogen would be identified. The only positive results returned, though, were a mycoplasma immunoglobulin M titer and an Epstein-Barr virus titer, which suggested a prior infection. Oncologic causes were less likely, with uric acid and lactate dehydrogenase levels in the normal range. Autoimmune processes were ruled out, since the patient's complement and antinuclear antibody levels were within the normal ranges.

There appears to be a scant number of published cases of ADEM presenting as fever of unknown origin. In a similar study in Italy, a patient had similar acute-onset neurologic symptoms, with CSF studies revealing an elevated protein level, a normal glucose level, and lymphocytic leukocytosis.[3] This patient's neuroimaging showed demyelinated areas typical of an autoimmune inflammatory process. The patient was immediately started on high-dose methylprednisolone with resolution of symptoms. The major difference between this case and our case is that our patient was administered both intravenous immunoglobulin and corticosteroids, compared with corticosteroids alone. The patient in Italy took several months to recover because of ophthalmologic involvement; therefore, there may be a role for intravenous immunoglobulin plus corticosteroids in the treatment of ADEM.[12] Our patient showed treatment response within 48 hours of initiating intravenous immunoglobulin and high-dose corticosteroids and demonstrated the typical course of recovery within weeks rather than months.[13,14]

References

1. Tenembaum S, Chitnis T, Ness J, Hahn JS; International Pediatric MS Study Group. Acute disseminated encephalomyelitis. *Neurology*. 2007;68(16 Suppl 2):S23-S36. https://doi.org/10.1212/01.wnl.0000259404.51352.7f
2. Pohl D, Hennemuth I, von Kries R, Hanefeld F. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. *Eur J Pediatr.* 2007;166(5):405-412. https://doi.org/10.1007/s00431-006-0249-2
3. Costanzo MD, Camarca ME, Colella MG, Buttaro G, Elefante A, Canani RB. Acute disseminated encephalomyelitis presenting as fever of unknown origin: case report. *BMC Pediatr.* 2011;11:103. https://doi.org/10.1186/1471-2431-11-103
4. Pavone P, Pettoello-Mantovano M, Le Pira A, et al. Acute disseminated encephalomyelitis: a long-term prospective study and meta-analysis. *Neuropediatrics.* 2010;41(6):246-255. https://doi.org/10.1055/s-0031-1271656
5. McCarthy PL. Fever. *Pediatr Rev.* 1998;19(12):401-408. https://doi.org/10.1542/pir.19-12-401
6. Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. *World J Pediatr*. 2011;7(1):5-10. https://doi.org/10.1007/s12519-011-0240-5
7. Krupp LB, Banwell B, Tenembaum S; International Pediatric MS Study Group. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology*. 2007;68(16 Suppl 2):S7-S12. https://doi.org/10.1212/01.wnl.0000259422.44235.a8
8. Pohl D, Alper G, Van Haren K, et al. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. *Neurology*. 2016;87(9 Suppl 2):S38-S45. https://doi.org/10.1212/wnl.0000000000002825
9. Torisu H, Kira R, Ishizaki Y, et al. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. *Brain Dev*. 2010;32(6):454-462. https://doi.org/10.1016/j.braindev.2009.10.006
10. Koelman DL, Mateen FJ. Acute disseminated encephalomyelitis: current controversies in diagnosis and outcome. *J Neurol*. 2015;262(9):2013-2024. https://doi.org/10.1007/s00415-015-7694-7
11. Antoon JW, Potisek NM, Lohr JA. Pediatric fever of unknown origin. *Pediatr Rev.* 2015;36(9):380-391. https://doi.org/10.1542/pir.36-9-380
12. Nishikawa M, Ichiyama T, Hayashi T, Ouchi K, Furukawa S. Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. *Pediatr Neurol.* 1999;21(2):583-586. https://doi.org/10.1016/s0887-8994(99)00042-9
13. Tenembaum SN. Acute disseminated encephalomyelitis. *Handb Clin Neurol.* 2013;112:1253-1262. https://doi.org/10.1016/b978-0-444-52910-7.00048-9
14. emram SK, Ghosh A, Annigeri S. Rare and atypical presentations of acute disseminated encephalomyelitis in children: a case series. *J Trop Pediatr.* 2021;67(2):fmab045. https://doi.org/10.1093/tropej/fmab045