Acute Disseminated Encephalomyelitis

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Abstract

Introduction
Acute Disseminated Encephalomyelitis (ADEM) is a rare autoimmune demyelinating disorder of the central nervous system. Clinical manifestations include encephalopathy, motor deficits, ataxia, and meningeal signs. In most cases, ADEM is preceded by either vaccination or viral illness. Here, we present a case with neither of the two predisposing elements.

Discussion
A 28-year-old Hispanic female presenting with substance use and suicidal ideation was placed on an involuntary psychiatric hold, started on olanzapine and scheduled for a psychiatric facility transfer. The following day, she was noted to have neurological deficits when ambulating. Computed tomography of the brain showed a right frontal lesion. Magnetic resonance imaging of the brain was notable for multiple peripherally enhancing white matter lesions. Multiple sclerosis and other etiologies were ruled out through supporting tests and lumbar puncture. ADEM was suspected, and the patient was treated with both a five-day course of intravenous methylprednisolone as well as immune globulins. She continued to have mild expressive aphasia after treatment; however, the majority of her symptoms improved.

Conclusions
Diagnosis of ADEM versus multiple sclerosis can be difficult given there are no current diagnostic criteria for it in the adult population. In this case, we explain how we reached a diagnosis of ADEM and provide further discussion regarding the disease course and treatment.

Keywords
encephalomyelitis, acute disseminated; ADEM; demyelinating autoimmune diseases, CNS; autoimmune diseases of the nervous system, leukoencephalitis, acute hemorrhagic; immunoglobulins, intravenous
Her family noted that she had been exhibiting strange behavior for approximately one week. The behavior was first observed when her family was watching her play in a softball game. The patient, who was an avid softball player for the past fifteen years, did not know how to run around the bases properly. The family also stated that she was fired from her job two days prior to presentation, and it is believed this was due to odd behavior. Psychiatry was consulted by the emergency room physician for suicidal ideation. Urine drug screen was negative (Table 1). The initial examination revealed the patient to be responding to internal stimuli (talking to herself). She was placed on an involuntary psychiatric hold, started on olanzapine and planned to be transferred to an inpatient psychiatric facility.

The following day the patient was noted to be swaying in bed and having ataxic gait while walking with a nurse. A computed tomography (CT) of the brain without contrast was obtained (Figure 1A) which was notable for a right frontal lesion. The initial transfer to a psychiatric facility was cancelled, and the patient was admitted to an intermediate care bed (IMC) under the internal medicine service. Magnetic resonance imaging (MRI) of the brain with contrast (Figure 2A) was obtained and revealed multiple peripherally enhancing white matter lesions in the deep cortical matter with sparing of the corpus callosum. CT angiography of the head and neck, MR angiography of the brain, and MRI of the cervical spine and thoracic spine were all negative.

A lumbar puncture was performed, yielding an elevated cerebrospinal fluid (CSF) white blood cell count of 0.045 x 10^3 µL (normal 0-0.005 µL) with elevated lymphocytes (97%) and elevated myelin basic protein of 37.2 ng/mL (normal 0.0-1.2 ng/mL). Oligoclonal bands, JC virus and toxoplasma antibody were negative. Further lab testing was performed over the next few days and was negative (Table 1), except for Borrelia burgdorferi IgG, Epstein Barr Virus PCR and Varicella-Zoster Virus IgG.

The electroencephalogram while the patient was awake showed a posterior dominant background rhythm consisting of low to normal amplitude (6-8 Hertz) theta slowing. Occasional sleep spindles were seen towards the end of

| Table 1. Negative and Normal Labs |
|----------------------------------|
| Acetaminophen level              |
| Ammonia level                    |
| Anti-neutrophil cytoplasmic antibodies (ANCA) |
| Anti-nuclear antibody (ANA)      |
| Ceruloplasmin                    |
| Complement C3 and C4             |
| Complete blood count (CBC)       |
| Comprehensive metabolic panel (CMP) |
| Corticotropin                    |
| C-reactive protein (CRP)         |
| Creatine kinase (CK)             |
| Cryoglobulin                     |
| Cyto megalovirus IgG             |
| Erythrocyte sedimentation rate (ESR) |
| Free T4                          |
| Haptoglobin                      |
| HCG                              |
| Hemoglobin A1C                   |
| Hepatitis A                      |
| Hepatitis B core                 |
| Hepatitis B surface              |
| Hepatitis C                      |
| HIV-2 Ab                         |
| HIV screen                       |
| HSV 1 & 2 PCR                    |
| Lactic acid dehydrogenase (LDH)  |
| Lipid panel                      |
| Lupus anticoagulant              |
| Paraneoplastic antibody profile  |
| Salicylate level                 |
| T-cell populations (CD3, CD4, CD8) |
| Thyroid-stimulating hormone (TSH) |
| Treponema pallidum antibody      |
| Troponin                         |
| Urine drug screen                |
| Urine analysis                   |
| VDRL                             |
| Vitamin B12 level                |
| West Nile                        |
the study. No electrographic seizures, focal/ lateralizing discharges, periodic discharges or epileptiform activity was seen. The EEG was consistent with mild background slowing, which is commonly seen in cases of mild encephalopathy.

These overall findings were most characteristic of acute disseminated encephalomyelitis (ADEM) although multiple sclerosis (MS) and other pathology needed to be ruled out. After reviewing the findings, ADEM best explained the findings. Intravenous (IV) methylprednisolone at a dosage of 1 gram every 24 hours was started. Over the next 48 hours the patient’s mentation worsened, and she became increasingly aphasic with associated hypotension. A repeat CT of the brain without contrast (Figure 1B) showed increasing hypo-density of the previous lesions, indicating a subacute phase. Intravenous immunoglobulin (IVIG) was then started in addition to the IV methylprednisolone. After 24 hours of IVIG the patient’s mental status, including her aphasia began to improve.

The patient received both a five-day course of IV methylprednisolone and IVIG. The IV methylprednisolone was started on day 2 of admission and the IVIG was started on day 5. Repeat MRI of the brain with contrast post-IVIG (Figure 2B) still showed multiple white matter lesions with increasing surrounding edema, but the enhancing components had resolved. The patient’s mentation improved, and she was speaking full sentences with mild expressive aphasia. The patient was then discharged to a skilled nursing and rehabilitation facility.

Discussion

The case demonstrates the importance of conducting a thorough history and physical exam, especially when determining whether a patient’s symptoms are the result of an acute psychiatric illness versus an underlying neurological disease. Initially, the patient was thought to have an acute psychiatric illness. However, the presence of a neurological abnormality on physical exam, noticed approximately twelve hours after her presentation, ultimately resulted in the discovery of an underlying neurological cause of the patient’s symptoms. Although new-onset schizophrenia can commonly present in young females (20-30 years old), there are several details within the history and physical itself that make the psychiatric illness less likely. The most important detail is the fact that the patient had motor deficits (i.e. not being able to run the bases at her softball game properly) and ataxic gait.

The ramifications of misdiagnosis can be fatal, as mortality rates in cases of ADEM have been reported to be as high as 20-25%. ADEM also has a hyperacute variant known as acute necrotizing hemorrhagic leukoencephalitis of Weston Hurst. This variant is a fulminant syndrome representing approximately 2% of ADEM cases and is characterized by abrupt onset of seizures, neck stiffness and fever with the finding of petechial hemorrhages on brain imaging. Acute necrotizing hemorrhagic leukoencephalitis has more than a 50% mortality rate.

Acute disseminated encephalomyelitis most often occurs 2-4 weeks after exposure to a viral illness or vaccination. Our patient did not
receive any vaccinations within the past six months; however, it is unconfirmed if she had suffered a recent viral illness, as she lived alone and was unable to give a history due to acute encephalopathy. Serum testing for Epstein Barr (EB) PCR, Varicella-Zoster IgG, and Borrelia burgdorferi IgG were positive. Positive EB can be explained by the reactivation of the virus post steroid treatment (transient viremia). The patient did not have signs of lymphoproliferative disorders, chronic active Epstein Barr virus infection or infectious mononucleosis.

There are currently no definitive diagnostic criteria for ADEM in the adult population (only suggested criteria); therefore, ADEM is considered a diagnosis of exclusion based on imaging findings, symptoms, serum studies and cerebrospinal fluid analysis. MRI of the brain with contrast is the study of choice as it provides optimal visualization of demyelinating CNS lesions and the soft tissue. Pathognomonic imaging findings on MRI for ADEM include lesions that are large in size, with irregular borders typically located in the white matter with sparing of the corpus callosum (although lesions can occur here). Spinal cord involvement with ADEM is variable, with some sources reporting as low as a 30% occurrence to as high as an 80% occurrence in adults. Cerebrospinal fluid analysis in patients with ADEM typically is absent for oligoclonal bands, whereas an elevated white blood cell count with a lymphocytic pleocytosis and elevated protein level are more common. Seze et al proposed that ADEM could be diagnosed based on the presence of 2 of the following 3 criteria: (1) Clinical symptoms atypical for MS, including 1 or more of the following: consciousness alteration, hypersomnia, seizures, cognitive impairment, hemiplegia, tetraplegia, aphasia or bilateral optic neuritis; (2) Absence of OCB (oligoclonal bands) in CSF; and (3) Gray matter involvement (basal ganglia or cortical lesions). Our patient met 2 of the 3 above criteria (atypical symptoms and absence of OCB) which is compatible with a diagnosis of ADEM.

Differentiation between ADEM and MS is difficult, as there can be an overlapping of symp-
toms. In this case, the diagnosis of ADEM was reached based on multiple factors, including the absence of oligoclonal bands in the CSF, the presence of acute encephalopathy, ataxic gait, imaging findings including bilateral lesions with variance in size and sparing of the corpus callosum, as well as the absence of old demyelinating lesions on the brain MRI. Of note, further imaging of the patient’s central nervous system, including MRI of the cervical and thoracic spine, were negative for demyelinating lesions.

Other neurological conditions such as anti-N-methyl-D-aspartic acid (NMDA) receptor encephalitis may also be considered in a young female patient. However, there were no clinical signs such as headache, fever or viral-like processes to suggest this entity. The absence of a Delta brush on the electroencephalogram and the presence of multiple demyelinating lesions on the brain MRI made this an unlikely diagnosis. MRI in patients with anti-NMDA receptor encephalitis is typically normal or occasionally shows enhanced T2 FLAIR signaling with non-specific white matter changes. CSF protein elevation is also less common.

We also cannot conclude if the patient’s symptoms were improved by glucocorticoids or IVIG. The patient received two days of intravenous glucocorticoids with no improvement in symptoms, and due to neurological worsening, the decision was made to start IVIG prior to completion of full steroid course. The patient’s symptoms improved remarkably with this combined treatment. However, we cannot conclude whether glucocorticoids or IVIG were more effective.

Conclusions
Acute disseminated encephalomyelitis can be difficult to diagnose, as the presentation of symptoms can be similar to both other demyelinating diseases and psychiatric disorders. After an extensive workup, we can conclude that this patient’s symptoms, imaging findings, and CSF testing are consistent with ADEM and that glucocorticoids and IVIG are an effective treatment.

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Conflicts of Interest
The authors declare they have no conflicts of interest.

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References

1. Yachnis A, Rivera-Zengotita M. Acute Disseminated Encephalomyelitis. In: Neuropathology. Saunders; 2014:285-286.

2. Bradshaw MJ, Bloch KC. Central Nervous System Infections. In: Textbook of Critical Care. 7th ed. Elsevier; 2017:862-876.e3.

3. Ketelslegers J, Visser I, Neuteboom R, Boon M, Catsman-Berrevoets C, Hintzen R. Disease course and outcome of acute disseminated encephalomyelitis is more severe in adults than in children. Mult Scler. 2011;17(4):441–448. https://doi.org/10.1177/1352458510390068

4. Cross AH. Demyelinating and Inflammatory Disorders. In: Andreoli and Carpenter’s Cecil Essentials of Medicine. 9th ed. Philadelphia, PA: Elsevier/Saunders; 2016:1069-1076.

5. Noorbakhsh F, Johnson RT, Emery D, Power C. Acute Disseminated Encephalomyelitis: Clinical and Pathogenesis Features. Neurol Clin. 2008;26(3):759-ix. https://doi.org/10.1016/j.ncl.2008.03.009

6. Freudenreich O, Brown HE, Holt DJ. Psychosis and Schizophrenia. In: Massachusetts General Hospital Comprehensive Clinical Psychiatry. 2nd ed. Elsevier; 2016:307-323.e7.

7. Miller BJ, Buckley PF. Schizophrenia. In: Conn’s Current Therapy 2020. Elsevier; 2020:806-809.

8. Sonnevile R, Demeret S, Klein I, et al. Acute disseminated encephalomyelitis in the intensive care unit: clinical features and outcome of 20 adults. Intensive Care Med. 2008;34(3):528–532. https://doi.org/10.1007/s00134-007-0926-2

9. Frosch MP, Anthony DC, Girolami UD. The Central Nervous System. In: Robbins and Cotran Pathologic Basis of Disease. 9th ed. Elsevier/Saunders; 2015:1251-1318.

10. Kleinschmidt-DeMasters BK, Simon JH. Dysmyelinating and Demyelinating Disorders. In: Neuropathology. Saunders; 2012:183-239.

11. Yildiz Ö, Pul R, Raab P, Hartmann C, Skripuletz T and Stangel M. Acute hemorrhagic leukoencephalitis (Weston-Hurst syndrome) in a patient with relapse-remitting multiple sclerosis. J Neuroinflammation. 2015; 12(1):175. https://doi.org/10.1186/s12974-015-0398-1

12. Greenlee JH. Nervous System Complications of Systemic Viral Infections. In: Aminoff’s Neurology and General Medicine. 5th ed. Elsevier; 2014:857-883. https://doi.org/10.1016/B978-0-12-407710-2.00043-6

13. Bathla G, Policeni B. Acute Disseminated Encephalomyelitis. In: Neuroradiology: Spectrum and Evolution of Disease. Elsevier; 2019:80-96.

14. Alobeidi F, Thurnher MM, Jager HR. Non-Tumoral Spinal Cord Lesions. In: Grainger & Allison’s Diagnostic Radiology. 6th ed. Elsevier; 2015:1345-1363.

15. de Seze J, Debuverie M, Zephir H, et al. Acute Fulminant Demyelinating Disease. Arch Neurol. 2007;64(10):1426–1432. https://doi.org/10.1001/archneur.64.10.1426

16. Kaufman DM, Geyer HL, Milstein MJ. Brain Tumors, Metastatic Cancer, and Paraneoplastic Syndromes. In: Kaufman’s Clinical Neurology for Psychiatrists. 8th ed. Elsevier; 2017:449-470. https://doi.org/10.1016/B978-0-323-41559-0.00019-8

17. Rosenfeld MR, Dalmau J. Autoimmune Encephalitis with Antibodies to Cell Surface Antigens. In: Bradley’s Neurology in Clinical Practice. 7th ed. Elsevier; 2016:1196-1200.

18. Fazekas F, Strasser-Fuchs S, Hommes OR. Intravenous immunoglobulin in MS: Promise or failure? J Neurol Sci. 2007; 259(1-2):61-66. https://doi.org/10.1016/j.jns.2006.12.018