Case Report

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

Introduction
Acute disseminated encephalomyelitis (ADEM) is an uncommon autoimmune demyelinating disorder of the central nervous system.[1,2] It is more common in the pediatric population but can occur in adults.[3] In most cases, ADEM is preceded by an acute viral illness and in extremely rare cases by vaccination.[4,5,6] Clinical manifestations include encephalopathy, motor deficits, ataxia and meningeal signs. The combination of these non-specific symptoms, its low incidence and lack of universally accepted diagnostic criteria make it challenging to diagnose. Here we present a case of ADEM with no known prior vaccination or preceding acute viral illness, and discuss how we reached the diagnosis.

Case Report
A 28-year-old Hispanic female was brought to the emergency department with a chief complaint of suicidal ideation. The patient, who lived by herself, was on the phone with her mother, when she reported snorting an unknown substance and verbalized suicidal ideation. Her mother then called emergency medical services, who transported the patient to our facility. The patient had no previous history of mental illness but had a history of domestic abuse and two spontaneous abortions.

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
Cytomegalovirus 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

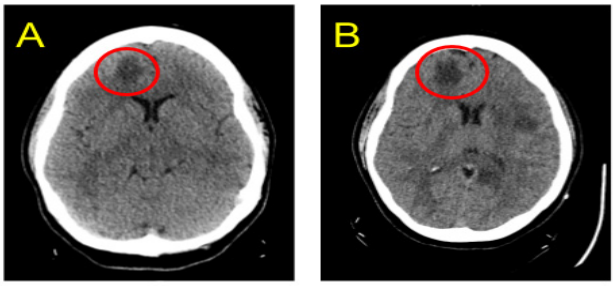

Figure 1.
A) Computed tomography (CT) of the brain without contrast showing a 2 x 1.9 x 1.7 cm low-density area in the right frontal lobe in the axial plane. Differential included encephalomalacia, subacute infarct or mass.
B) A repeat CT of brain without contrast 3 days after the first CT showing increasing hypo-density to the lesion, which is suggestive of a subacute phase.

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.[7,8] 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.[9]

The ramifications of misdiagnosis can be fatal, as mortality rates in cases of ADEM have been reported to be as high as 20-25%.[10,11] 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.[12, 13] Acute necrotizing hemorrhagic leukoencephalitis has more than a 50% mortality rate.[14]

Acute disseminated encephalomyelitis most often occurs 2-4 weeks after exposure to a viral illness or vaccination. Our patient did not

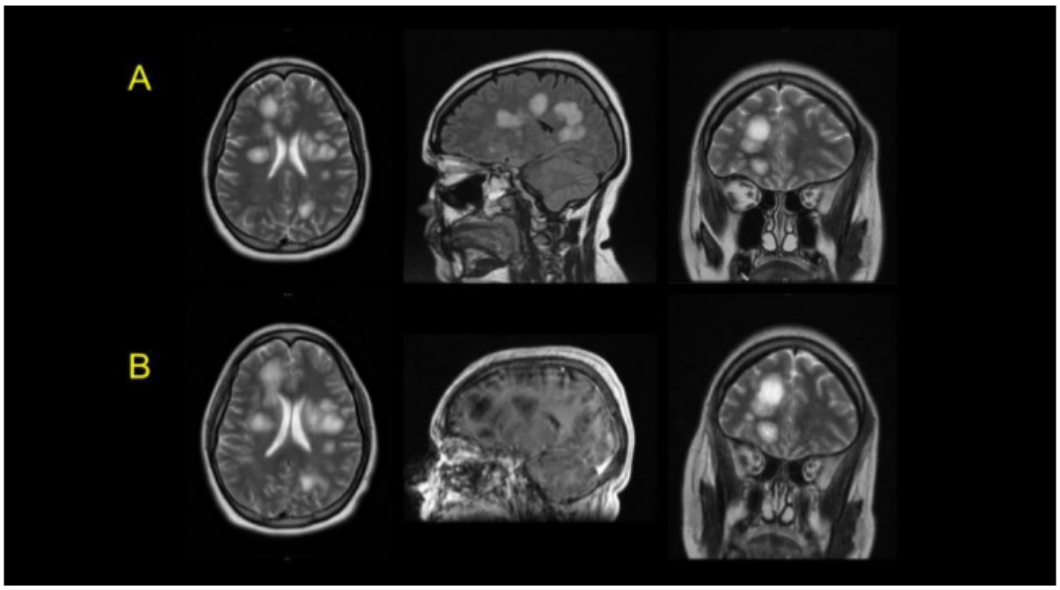

Figure 2.
A) Magnetic resonance imaging (MRI) of the brain with contrast. Shown from left to right are T2 weighted axial, sagittal and coronal planes showing innumerable peripherally enhancing white matter lesions distributed throughout the periventricular, deep and juxtacortical white matter of the supratentorial brain with sparing of the posterior fossa and corpus callosum.
B) Repeat MRI of the brain with contrast 8 days after the above MRI. Shown from left to right are a T2 weighted image in the axial plane, a reformatted post-gadolinium BRAVO image in the sagittal plane and a T2 weighted image in the coronal plane. The MRI is notable for a large number of white matter lesions that persist and demonstrate a mild increase in surrounding edema. However, the enhancing components have resolved. Of note, the study was limited due to the motion artifact.

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).[13] 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.[15,16] 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.[6] 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).[17] 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.[16] CSF protein elevation is also less common.[18]

Treatment for ADEM includes glucocorticoids, IVIG and plasmapheresis. Intravenous methylprednisolone at a dosage of 1 gram every 24 hours for a course of 3 to 5 days is typically recommended.[2] IVIG and plasmapheresis are treatment options if symptoms are refractory to glucocorticoids. Currently, there are no randomized clinical trials for either of these therapies, and the majority of data stems from observational studies.[19] In contrast to multiple sclerosis, IVIG is not considered a standard of treatment for acute episodes and has not been shown to provide additional clinical benefit.[20] Further treatment options for ADEM not used in this case include plasmapheresis and cyclophosphamide. ADEM typically does not recur, unlike MS; therefore, chronic immuno-suppressive therapy is not indicated.[4]

Limitations

In this case, an anti-glu N1 antibody which is diagnostic for anti-NMDA receptor encephalitis was ordered but never resulted. However, as discussed previously, the MRI and EEG results make this diagnosis less likely.

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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