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Resolution of Acute Disseminated Encephalomyelitis Following Termination of Pregnancy

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Acute disseminated encephalomyelitis (ADEM) is a rare autoimmune illness characterized by inflammation of central nervous system myelin with resultant white matter damage. ADEM includes a wide variety of clinical presentations, thus contributing to a complex differential diagnosis. It most frequently occurs in children during winter or spring months following an upper respiratory infection by viruses, such as Epstein Barr, coxsackie, coronavirus, cytomegalovirus, hepatitis A, human immunodeficiency virus, influenza, measles, rubella, varicella, and West Nile virus.1–3 Alternatively, it may result from a variety of bacterial or parasitic infections. Nearly 5% of cases are precipitated by immunization, with measles/mumps/rubella vaccine being the most frequent cause.4

Common clinical features of ADEM include fever, altered mental status, hemiparesis, ataxia, cranial neuropathies, and spinal cord dysfunction. Severe cases may be accompanied by seizures or coma, as neurological signs are referable to the location of the lesion burden.5,6,7 Although the exact pathophysiology remains unclear, a hypersensitivity reaction with demyelination is implicated.6 The prognosis varies and the outcome may be fatal. Surviving patients exhibit varying degrees of recovery and often do not return to their previous baseline functioning.7

Ms. A, a 23-year-old African-American woman was brought to the emergency room by her parents because she was socially withdrawn and was exhibiting strange behavior (such as bizarre posturing and aimless staring) for the previous 3 days. She was not speaking or responding to interviewer's questions, so history was obtained from relatives. They reported her as experiencing progressive difficulty in performing activities of daily living and not attending to personal hygiene. In addition, she was refusing oral intake. There was no recent history of fever, apparent infection, or vaccinations. She had become pregnant several weeks prior and had spoken to her family about planning to terminate the pregnancy. A previous pregnancy, labor, and delivery were uncomplicated. The medical history otherwise revealed no psychiatric diagnoses or medical illnesses, and her parents knew of no other current health concerns. She had no known allergies and was not taking any medications. The patient was a smoker and had been using marijuana and cocaine. There was a family history of schizophrenia in one relative.

On examination in the emergency department, Ms. A was 5 ft 8 in tall and weighed 150 pounds. Vital signs were within normal limits. She was awake but mute, did not respond to stimuli, had a flat affect, and appeared to be catatonic. Incontinence of urine was noted. She did not follow commands or visually track...
movement about the room. Cranial nerve examination was unremarkable, including a normal oculocephalic reflex with full nuclear eye movements. Assessment of the motor system was normal without waxy flexibility. Painful stimuli resulted in withdrawal of all extremities without focal weakness. Deep tendon reflexes were symmetrical and plantar responses were flexor. A complete blood count and comprehensive metabolic panel were within normal ranges. Her toxicology screen result was negative. An intrauterine pregnancy of 6 weeks gestation was confirmed by abdominal ultrasound. The patient was considered nondecisional. After a medical ethics consultant opined that her parents were appropriate decision-makers for her, they were included in clinical discussions and treatment planning.

The initial diagnosis was psychosis with catatonia, and she was admitted to the inpatient psychiatry unit. There, pharmacotherapy with olanzapine and lorazepam was initiated, but no improvement was noted. Given the bizarre nature of her presentation and the acute onset of her illness, a magnetic resonance imaging (MRI) scan of the brain was performed. It revealed several large, dense, deep white matter lesions in the frontal, parietal, and temporal lobes (Figure). These findings resulted in obstetrical and neurological consultations. The pregnancy was considered normal by the obstetrician, and a presumptive diagnosis of ADEM was made by the neurologist. The patient was transferred to the neurology service, and all aforementioned pharmacotherapies were discontinued.

On the neurology service, a lumbar puncture was performed and it revealed unremarkable results for cerebrospinal fluid glucose, protein, red blood cells, white blood cells, albumin, and an IgG synthesis rate. The evaluation of Lyme IgG and IgM, cytomegalovirus IgG, cryptococcus antibodies, Jakob-Creutzfeld virus, and oligoclonal bands showed negative results. Epstein Barr virus IgG was positive and IgM was negative; the herpes simplex virus IgM was positive. Serum herpes simplex virus 1 and 2 were negative, while IgG was positive, as determined by polymerase chain reaction. An electroencephalogram revealed normal brain activity without evidence of ictal activity or slowing.

Intravenous (IV) steroids and IV immunoglobulins (IVIg) were administered, a gastric tube was placed, and supportive care was initiated. Without clinical progress over the next 8 weeks, she received a second course of methylprednisolone, 5 plasma exchanges, and IV acyclovir. Despite these measures, no improvement in her neurological or mental status was observed. Three MRI scans over a 3-week period documented an increase in the size of the original lesions and central necrosis in 1 frontal lesion, without edema, shift, or hemorrhage.

Her family reported that Ms. A had told them that she did not want to remain pregnant and had planned to terminate this pregnancy. Expressing concern for potential congenital anomalies given the patient's substance abuse, the parents asked to terminate the pregnancy. Termination occurred

FIGURE. Frontal, Parietal, and Temporal Lobe Lesions.
1 month after admission, with normal histopathology reported.

Over the next 2 months, her condition gradually improved in modest proportions, as demonstrated by limited eye contact and facial gestures to family members. She began to visually track people in her room, but remained mute and unresponsive to commands. After 3 months of hospitalization, Ms. A was transferred to a long-term rehabilitation facility where she gradually recovered some language function and ambulation. A repeat MRI revealed interval improvement of inflammatory lesions with evidence of some deep tissue loss. At follow-up in the neurology clinic, she was slowly improving but still exhibited considerable cognitive impairment and depression. Referred to the psychiatry clinic, she showed some further improvement in speech and comprehension. Her neurological and psychiatric status remained stable 5 months later. She then declined future appointments and was lost to follow-up.

Discussion

Our case emphasizes the variable presentations of ADEM and highlights diagnostic and treatment dilemmas in the setting of pregnancy. Making a correct diagnosis and initiating proper treatment for ADEM are critical. Brain imaging is recommended in most new presentations of neurological dysfunction or psychiatric conditions or both. MRI and lumbar puncture may confirm the presence of demyelinating diseases, including ADEM. More invasive procedures, such as a brain biopsy or cerebral angiogram, are rarely necessary and pose additional risk. Vigorous treatment for a potential infectious process is recommended, whereas anti-inflammatory and immunomodulating pharmacotherapies are the primary interventions for ADEM. Corticosteroids and IVIg may shorten the duration and severity of illness or halt disease progression. Plasmapheresis may be offered with or without immunosuppressive agents, but usually in cases resistant to steroids. Supportive measures, including physical therapy and skin care, are provided on a routine basis. Surviving patients may exhibit slow, partial recoveries over several months, whereas others might retain permanent neurological deficits, persistent psychiatric symptoms, and residual cognitive impairments.

This case posed challenges to the usual treatment plan. Morbidity to both mother and fetus could escalate if immunomodulatory therapy was withheld. Alternatively, high-dose steroids can result in fetal hypoadrenalism, and methylprednisolone is a Category D pharmaceutical during the first trimester of pregnancy. In addition, there is a risk of stroke during IVIg infusions, and this could theoretically be increased owing to the hypercoagulable state of pregnancy. Conversely, there is some controversial evidence for IVIg being protective against repeated miscarriages.

Ms. A's neurological status began to improve after the pregnancy was terminated. This poses questions about whether pregnancy could have precipitated the illness and whether termination attenuated the disease process. The relationship between ADEM and pregnancy is uncertain. One case of ADEM in the third trimester responded favorably to plasmapheresis after treatment failure with high-dose corticosteroids. In contrast, other cases of fulminant demyelinating disease during pregnancy have resulted in coma. Another demyelinating illness, Marburg’s Disease, is similarly rapid and fulminant, but less likely during pregnancy; 1 case, resistant to steroids, IVIg, and plasmapheresis, resulted in death.

Pregnancy is associated with a reduced inflammatory response due to increased levels of anti-inflammatory and immunosuppressant cytokines which prevent fetal rejection and promote passive transfer of antibodies to the fetus. These hormonally-induced alterations are essential to support a successful full-term pregnancy. This may explain the decreased frequency of relapses in a related demyelinating disease, multiple sclerosis, during pregnancy. In a retrospective study of multiple sclerosis patients, higher parity was associated with a reduced risk of a first demyelinating event, with a 49% reduction in risk during each subsequent pregnancy. This stands in contrast to our case, in which a multiparous patient experienced her first demyelinating event. However, women with radiologically-identified, asymptomatic multiple sclerosis who then became pregnant were more likely to develop new MRI-documented pathology. This suggests that pregnancy may activate disease in presymptomatic individuals. It is possible that our patient had asymptomatic pathology that became evident during and exacerbated by pregnancy, but it is impossible to conclude this without premorbid brain imaging for comparison. Another explanation
includes her compromised immunity while being pregnant, which can lead to increasing severity of infectious diseases. For example, morbidity from influenza can increase during pregnancy, which might have predisposed her to a possible virally-induced ADEM. Alternatively, a direct immune-mediated response to the fetus may have triggered the ADEM; this is supported by the beginning of recovery after pregnancy termination in our vignette. Determining whether a causal relationship exists is not possible, because the natural course of this disease and its potential response to immunotherapies tend toward recovery over a similar time period.

This case emphasizes the variety of psychiatric and neurological signs and symptoms of ADEM as well as therapeutic options. Whether a relationship between pregnancy and ADEM exists remains uncertain. Research might discover why pregnant individuals with ADEM have demonstrated variable responses to steroids, plasmapheresis, and IVIg. Further investigation may determine whether an immune-mediated response to the fetus can precipitate ADEM. Given ethical concerns and the rarity of this condition, it is impossible to determine whether a causal relationship exists between termination of pregnancy and resolution of treatment-resistant ADEM.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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