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Clinical Observations

An Infant Born to a Mother With Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis

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ABSTRACT

BACKGROUND: Anti–N-Methyl-D-Aspartate receptor (NMDAR) encephalitis is an autoimmune disorder that often affects women of childbearing age, and maternal-fetal transfer of anti-NMDAR antibodies during pregnancy has been documented in both symptomatic and asymptomatic women. The effects of these antibodies on the fetus, however, are incompletely understood. **PATIENT DESCRIPTION:** This term infant exhibited depressed respiratory effort, poor feeding, and abnormal movements after birth. Magnetic resonance imaging revealed diffuse cerebral edema with ischemic and hemorrhagic injury. Her mother had experienced anti-NMDAR encephalitis secondary to an ovarian teratoma 18 months earlier. The baby's serum NMDAR antibody titer was elevated at 1:320. Intravenous immunoglobulin did not result in clinical improvement, and care was withdrawn on day of life 20. Her mother had an elevated serum NMDAR antibodies (1:80), positive CSF antibody titers, and a new ovarian teratoma. **CONCLUSION:** Routine testing of NMDAR antibodies in pregnant women with a previous history of anti-NMDAR encephalitis may be warranted. Infants born to these mothers should be closely monitored throughout pregnancy and after birth.

Keywords: NMDA, anti-NMDA receptor encephalitis, ovarian teratoma, maternal-fetal NMDA receptor antibody transmission

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Introduction

Anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a synaptic autoimmune disorder that is mediated by antibodies against the NR1 subunit of the receptor.[1] Symptoms at presentation include neurological (decreased consciousness, dyskinesias, short-term memory loss, seizures, catatonia), psychiatric (agitation, bizarre behavior, paranoia, hallucinations), and autonomic instability (central hypoventilation, dysthermia, and cardiac dysrhythmias).[1-3] Children with anti-NMDA receptor encephalitis often exhibit more neurological symptoms than psychiatric manifestations when compared with the adults.[4] Anti-NMDA receptor encephalitis has also been described during pregnancy, and recently, transplacental transfer of NMDA receptor antibodies in neonates acquired from mothers has been reported.[5,6] Short-term or long-term consequences of prenatal NMDA receptor antibody exposure are not well documented.[7] We present an infant with fatal anti-NMDA receptor encephalitis acquired via transplacental transfer of antibodies and expand the clinical spectrum of infants with acquired anti-NMDA receptor encephalitis.

Patient Description

A 32-year-old woman with history of anti-NMDA receptor encephalitis presented to the emergency department with

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headache and seizures. She had been previously diagnosed with anti-NMDA receptor encephalitis one and half years before this admission after presenting with psychosis with positive cerebrospinal fluid (CSF) and serum NMDA receptor antibodies. She received treatment with intravenous methylprednisone and intravenous immunoglobulins and underwent unilateral oophorectomy after she was found to have a cystic ovarian teratoma of the left ovary.

She underwent intense inpatient rehabilitation and returned to her normal mental state until her current admission to the emergency department. She had three separate seizures lasting five minutes each for which she received lorazepam and loading dose of levetiracetam. She did not require additional anti-epileptics and remained stable on room air. Her urine pregnancy test was positive and a 37-week gestation was confirmed by ultrasound. The mother was unaware of her pregnancy and had not perceived prior fetal movements. She had a body mass index of 35.3 kg/m^2, consistent with severe obesity at baseline along with a history of polycystic ovarian syndrome and irregular menstrual cycles. It was also her understanding that she was unable to become pregnant after the diagnosis of ovarian teratoma. She had hypertension and elevated liver function tests concerning for eclampsia on admission and was placed on magnesium drip.

A Caesarean section was performed on the same day due to a non-reassuring fetal heart rate. A girl with Apgar scores of 1, 2, and 5 at one, five, and ten minutes, respectively, was delivered. She exhibited hypotonia and poor respiratory effort requiring intubation and mechanical ventilation. In the neonatal intensive care unit, the baby was noted to have stiffening of all extremities along with abnormal movements concerning for seizures. Intravenous fosphenytoin was administered.

Electroencephalogram reflected diffuse encephalopathy without epileptiform activity. A detailed diagnostic evaluation included liver function, kidney function, thyroid panel, and infection parameters (blood and urine culture, herpes simplex virus polymerase chain reaction of blood). Multiple attempts to obtain CSF were unsuccessful. Except for mild elevation in liver function tests which normalized over the next few days, her test results were normal.

Empiric treatment with broad-spectrum antibiotics was discontinued after 48 hours because of negative cultures. The baby exhibited profound hypotonia, absent Moro and swallow reflexes, and minimal response to stimulation. Magnetic resonance imaging of the brain (Figure) showed diffuse cerebral edema with extensive areas of ischemic and hemorrhagic injury. Because of the maternal history of anti-NMDA receptor encephalitis, serum NMDA receptor antibodies were tested and elevated to 1:320 in infant. The diagnosis of anti-NMDA receptor encephalitis was considered and intravenous immunoglobulin 400 mg/kg was administered daily for five days. There was no clinical improvement (absent brainstem reflexes, minimal spontaneous movements) and care was withdrawn on day of life 20.

The mother was subsequently evaluated and found to have elevated titers of NMDA receptor antibodies in serum (1:80) and positive CSF titers. On follow-up, she was diagnosed with a new ovarian teratoma of the right ovary.

Discussion

NMDA receptor encephalitis is an autoimmune disorder that frequently affects women of childbearing age, but the effects of the antibody on the fetus are yet to be completely understood. Maternal-fetal transfer of NMDA receptor antibodies during pregnancy has been documented in both symptomatic and asymptomatic pregnant women.[5,6] Maternal antibodies of subtype IgG1 and IgG3 can cross the placenta from week 14 to week 16 of pregnancy and have been known to cause autoimmune newborn diseases.[8] Additionally, the fetal blood-brain barrier becomes functional only by the end of the second trimester, leading to susceptibility for exposure of the fetal brain to potentially harmful maternal antibodies.[9] Previously, five infants born to mothers with acute anti-NMDA receptor encephalitis during pregnancy were not noted to have any neurological symptoms.[6,10] Jagota et al. reported a symptomatic newborn whose mother developed NMDA receptor encephalitis during second trimester.[5] The baby had abnormal movements at birth along with elevated NMDA receptor antibodies (1:450) and, in a three-year follow-up, found to have developmental delay, generalized seizures, and cortical dysplasia on magnetic resonance imaging. Our patient had elevated NMDA receptor antibodies (1:320) associated initially with abnormal movements followed by progressive worsening neurological function. Hilderink et al. described a second symptomatic newborn born to a mother who was asymptomatic during pregnancy, 2.5 years since her last relapse of NMDA receptor encephalitis.[6] The infant was noted to have poor respiratory effort, poor feeding, and lethargy at birth, which significantly improved over ten days. Symptom resolution correlated with transient nature of NMDA receptor antibody levels in the infant. Our patient had similar features at birth but progressed to a fatal outcome in the setting of elevated NMDA receptor antibodies, thereby expanding the clinical spectrum of infants with NMDA receptor encephalitis.

Based on the previous reports, pregnancy risk assessment and routine NMDA receptor antibody surveillance in asymptomatic pregnant women with history of anti-NMDA receptor encephalitis must be strongly considered. The majority of patients with anti-NMDA receptor encephalitis are women of childbearing age and there is a strong association with ovarian teratomas.[11] Patients in whom tumors were identified and excised within four months of symptom onset showed the highest cure rate and the lowest risk of relapse.[12] The mother of our patient was diagnosed with a new ovarian teratoma in the setting of elevated CSF titers of NMDA receptor antibodies after a previous oophorectomy, further emphasizing the need for routine NMDA receptor antibody surveillance in this subset of women of childbearing age. Similar to the various autoimmune diseases such as myasthenia gravis and systemic lupus erythematosus, the effect of maternal autoantibodies on the fetus can be variable.[9] Pregnant women with a previous history of anti-NMDA receptor encephalitis should be encouraged to have regular prenatal care and institutionalized delivery with close monitoring of infant after birth. Our report documents poor fetal

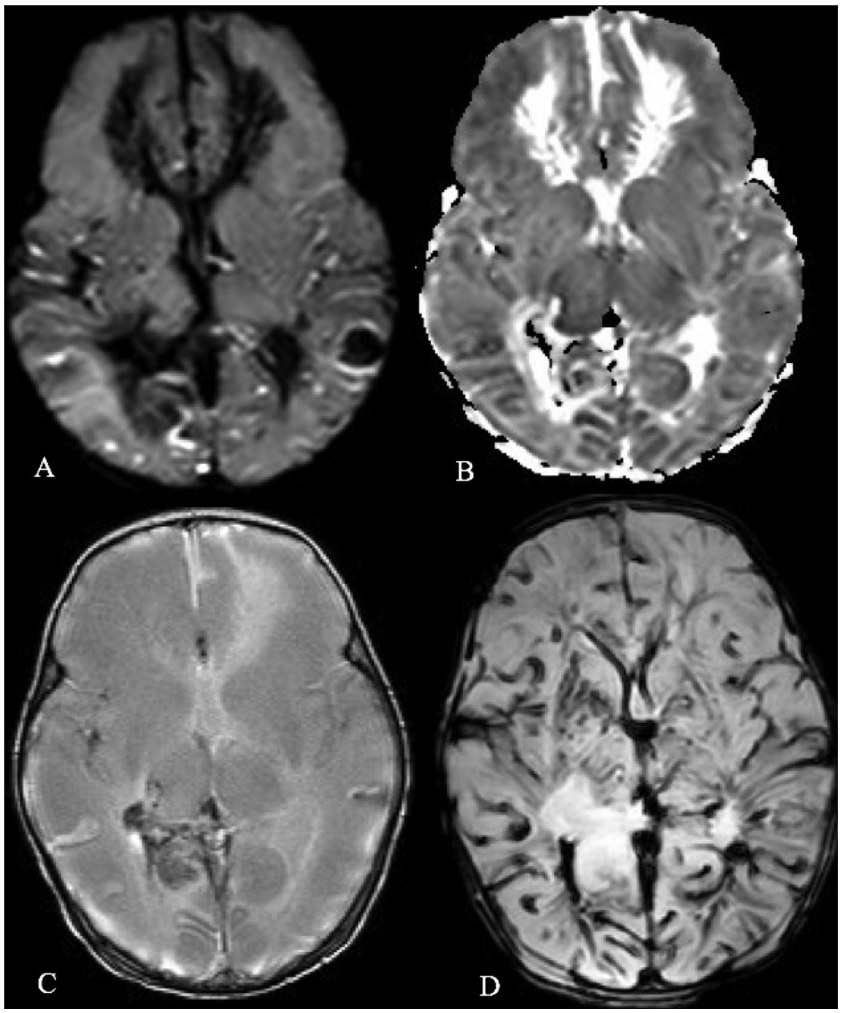

FIGURE.
Magnetic resonance imaging of the brain: (A, B) Bilateral areas of hyperintensity on diffusion-weighted imaging and hypointensity on apparent diffusion coefficient sequence consistent with infarction. (C) T2 Flair showing diffuse cerebral edema. (D) Gradient-restricted echo sequence showing hypointensities along the right lateral ventricle and right frontal lobe consistent with petechial hemorrhages.

outcome secondary to intrauterine exposure to NMDA receptor antibodies.

Conclusion

We describe a neonate with fatal anti-NMDA receptor encephalitis acquired through transplacental transfer of maternal antibodies. This patient highlights the need for routine testing of NMDA receptor antibodies in pregnant women with a previous history of anti-NMDA receptor encephalitis. Similar to the other autoimmune diseases such as Graves disease, systemic lupus erythematosus, and myasthenia gravis, mothers with history of anti-NMDA receptor encephalitis should be closely monitored throughout pregnancy along with the infant after birth.[8] If the infant is symptomatic and NMDA receptor antibodies are present in the infant at birth, close clinical monitoring with respiratory, cardiac, and renal support should be maintained.

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Within your heart, keep one still, secret spot where dreams may go.

Louise Driscoll