Case Report

Maternal-Fetal Transfer of Anti–*N*-Methyl-D-Aspartate Receptor Antibodies

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Teaching Points

1. The constellation of neuropsychiatric symptoms, seizures, and autonomic instability is pathognomonic for anti–*N*-methyl-D-aspartate receptor encephalitis (NMDA) receptor encephalitis.
2. Maternal recovery often is accelerated with pregnancy interruption and oophorectomy.
3. NMDA antibodies are capable of maternal-fetal transfer.

BACKGROUND: Anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a neuroautoimmune disease commonly associated with ovarian teratomas. It is characterized by neuropsychiatric symptoms, seizures, and autonomic instability. Few cases are described in pregnancy, and little is known about potential fetal effects.

CASE: Anti-NMDA receptor encephalitis was diagnosed at 24 weeks of gestation. No improvement occurred with intravenous immunoglobulin, methylprednisolone, and plasmapheresis. Imaging was unremarkable. Cesarean delivery with concurrent bilateral oophorectomy resulted in prompt maternal improvement. Antibody titers were positive in cord blood.

CONCLUSION: Anti–*N*-methyl-D-aspartate receptor encephalitis in pregnancy can lead to NMDA receptor antibodies in the fetal circulation. Pregnancy interruption through early delivery with or without oophorectomy may accelerate maternal recovery.

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Anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a neuroautoimmune disease caused by antibodies that target synaptic proteins. It is becoming more commonly recognized as a cause of encephalitis in young adults. Antibodies develop against the NR1 subunit of the NMDA receptor, causing the distinct syndrome. This syndrome generally presents in five phases. The prodromal phase occurs in 70% of patients and is characterized by fever, malaise, headache, difficulty concentrating, and gastrointestinal or upper respiratory complaints. This is followed by the psychotic phase, seizure phase (or both), an unresponsive phase, and a hyperkinetic phase, characterized by autonomic instability.[1] The fifth and final stage is that of gradual recovery. About 80% of patients with anti-NMDA receptor encephalitis are women and 35–60% of patients have an underlying neoplasm, most commonly an ovarian teratoma.[2,3] Early surgical removal of the teratoma has been associated with faster recovery and improved outcome.[2,4] Additional reports have described recovery after oophorectomy in normal-appearing ovaries and accelerated recovery after delivery or termination of pregnancy.[2,5,6] Very few cases have been described in pregnancy,[6–10] and only one fetus has been extensively evaluated for antibodies, the results of which were negative.[6] One neonate had positive antibody titers when tested 2 days after birth.[8] These antibody subtypes are capable of crossing the placenta, and there remains concern for fetal effects. We present a case of maternal anti-NMDA receptor encephalitis during pregnancy with positive fetal antibody titers.

CASE

A 24-year-old woman, gravida 5 para 3, at 24 4/7 weeks of gestation was transferred to our facility for persistent catatonia. She initially presented at 20 weeks of gestation, disoriented and confused, with possible seizure-like activity. Laboratory evaluation and toxicology were unremarkable. She was diagnosed with psychogenic seizures, started on levetiracetam, and transferred to an inpatient psychiatric facility where she was treated with ziprasidone. She continued to decompensate and developed autonomic dysfunction and severe hypernatremia. Seizure-like activity continued. Antipsychotic medications were discontinued. She was given bromocriptine for suspected neuroleptic malignant syndrome and transferred to our tertiary care center 32 days after initial presentation.

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Past medical history included depression and anxiety. Obstetric history was significant for three uncomplicated term vaginal deliveries. Social history was significant for a remote history of intravenous drug use, including methamphetamines. She had received regular prenatal care.

On examination, she was tachypneic with oxygen saturation of 92% on 2 L per minute. She was somnolent and nonverbal and had no spontaneous eye opening. She withdrew to pain. Reflexes were 3+ with four beats of clonus. Heart, lung, and abdominal examinations were unremarkable. Continuous fetal monitoring was reassuring. Ultrasonogram demonstrated a normally growing fetus in the breech presentation.

She continued to have altered mental status and autonomic instability. Practitioners in psychiatry and neurology were consulted. Two days after admission, the patient had a grand mal seizure with acute respiratory decline requiring emergency intubation. Fetal status recovered with maternal resuscitation.

An extensive laboratory workup ensued. Testing was unremarkable for infections, autoimmune disorders, rheumatologic disorders, Wilson's disease, and heavy metal exposure. Initial electroencephalogram was significant for moderately diffuse background slowing with disorganization consistent with diffuse cerebral dysfunction, and right temporal epileptiform discharges. Lumbar puncture was significant for pleocytosis. Magnetic resonance imaging showed medial left temporal lobe T2 hyperintense signal and mild restricted diffusion. There was increased gyriform T2 hyperintense signal in the insula bilaterally along the anterior cingulate gyri. She was presumptively diagnosed with limbic encephalitis, and testing for NMDA receptor antibodies was performed on serum and cerebrospinal fluid. She was started on intravenous immunoglobulin (IVIG) 400 mg/kg and methylprednisolone 1 g daily.

Subclinical seizures worsened, as did episodes of autonomic instability. The remained in status epilepticus despite five antiepileptics, including levetiracetam, topiramate, midazolam, phenytoin, and clobazam. Propofol was required for further sedation. Cerebral spinal fluid NMDA receptor antibody testing returned positive, as did maternal serum, at a titer of 1:80. Imaging of the chest, abdomen, and pelvis did not show a teratoma or other suspicious mass.

There was no improvement on IVIG and methylprednisolone. Plasmapheresis was attempted. She continued to deteriorate, and autonomic instability led to frequent episodes of nonreassuring fetal heart rate testing. Therefore, the decision was made to proceed with delivery. To prevent further complications associated with prolonged ventilation and hospitalization, the patient's family chose concurrent bilateral oophorectomy, rather than interval delivery and subsequent oophorectomy if needed.

At 28 4/7 weeks of gestation, a primary low transverse cesarean delivery and bilateral salpingo-oophorectomy were performed. A male neonate weighing 1,275 g with 1-minute and 5-minute Apgar scores of 3 and 4, respectively, was delivered.

Pathologic evaluation of the fallopian tubes, ovaries, and placenta did not reveal any neoplastic process, including teratoma. The placental size was appropriate for gestational age, and no abnormalities were noted. Amniocentesis was performed before delivery. *N*-methyl-D-aspartate receptor antibody titers in the amniotic fluid were negative. Maternal serum and fetal cord blood were both collected at the time of delivery for NMDA receptor antibody testing. Both returned positive with 1:20 titers.

On postoperative day 3, the patient began to follow commands. Substantial improvement occurred daily, and by postoperative day 7 she had near normal mentation. She continued weekly plasmapheresis and was started on rituximab 12 days after delivery. Seizure activity was controlled on four antiepileptics. Seventeen days after delivery, she was discharged from the hospital to a rehabilitation facility. One year after delivery, she is doing well. She is seizure-free with only minimal residual effects, including slight disinhibition and memory deficits. She is on hormone replacement with 0.625 mg conjugated estrogen and 5 mg medroxyprogesterone.

The infant was discharged from the neonatal intensive care unit at a corrected gestational age of 38 2/7 weeks. He initially experienced respiratory and neuromuscular depression, likely related to maternal sedative and anti-epileptic drugs. Significant withdrawal-like symptoms required benzodiazepines followed by phenobarbital, which was continued for 30 days. Frequent supraventricular tachycardia required treatment with digoxin. At one year of age, he is doing well and is developmentally appropriate.

DISCUSSION

Anti-NMDA receptor encephalitis is a rarely diagnosed neuropsychiatric condition in pregnancy. Our patient demonstrated many of the commonly recognized phases of this illness, including psychosis, seizures, unresponsiveness, and autonomic instability. Her initial serum antibody titers were 1:80, and declined to 1:20 by the time of delivery, identical to the cord blood titers.

Placental transfer of maternal antibodies occurs through immunoglobulin G1 and G3 binding to the neonatal Fc receptor in synctiotrophoblasts.[6,11] This process starts slowly at the end of the first trimester and early second trimester and progressively increases until term. Additionally, by the end of the second trimester, the fetal blood-brain barrier is functional. However, there are no data available on short-term or long-term consequences of prenatal NMDA receptor antibody exposure. Prior case reports of NMDA receptor encephalitis in pregnancy resulted in clearance of maternal serum antibodies before delivery and negative fetal testing, including amniocentesis.[6,7,9,10] One neonate had positive antibody titers when tested two days after birth, consistent with transplacental transfer.[8] Our patient delivered with positive antibody titers during a period of fetal vulnerability, and we confirmed transfer of maternal antibodies to fetal circulation. Although the

neonate did show signs of autonomic instability, it was difficult to differentiate possible effects of the NMDA receptor antibody from those associated with extreme prematurity and medication exposure.

The majority of patients with anti-NMDA receptor encephalitis are women and there exists a frequent association with ovarian teratomas.[2,3,5] Faster recoveries and improved outcomes are associated with early surgical removal of teratomas.[2–5] However, there are reports of microteratomas only identified on histopathologic evaluation, and additional accounts of recovery after oophorectomy in normal ovaries.[5,12] Pelvic ultrasonogram and magnetic resonance imaging of our patient did not detect an ovarian teratoma, but the gravid uterus limited visualization of the ovaries. Therefore, after extensive counseling, the family decided to proceed with bilateral oophorectomy. Because of the concurrent plasmapheresis and delivery, the contribution of oophorectomy toward this patient's rapid recovery remains unknown. However, her sustained recovery suggests that the inciting process is no longer present.

As with previous reports of anti-NMDA receptor encephalitis in pregnancy, maternal and fetal outcomes can be excellent. Prompt recognition of the neuropsychiatric symptoms will hasten diagnosis and improve care. Standard treatments, including steroids, IVIG, and plasmapheresis are well-tolerated in pregnancy. A planned preterm birth may be considered to decrease fetal exposure to maternal antibodies and improve maternal outcome. Bilateral oophorectomy may also expedite recovery. Further study is needed to assess long-term neuropsychiatric outcomes of children exposed to NMDA receptor antibodies in utero and the role of pregnancy on the development, progression, and resolution of maternal NMDA receptor encephalitis.

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