OBSERVATION

Anti–*N*-methyl-D-aspartate Receptor Encephalitis During Pregnancy

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Objective: To report 3 patients who developed anti–*N*-methyl-D-aspartate receptor encephalitis during pregnancy.

Design: Case reports.

Setting: University hospitals.

Patients: Three young women developed at 14, 8, and 17 weeks of gestation acute change of behavior, prominent psychiatric symptoms, progressive decrease of consciousness, seizures, dyskinesias, and autonomic dysfunction.

Main Outcome Measures: Clinical, radiological, and immunological findings.

Results: The 3 patients had cerebrospinal fluid pleocytosis, normal magnetic resonance imaging, and electroencephalogram showing slow activity. All had higher antibody titers in cerebrospinal fluid than in serum and 2 had ovarian teratomas that were removed. The pregnancy was terminated in 1 patient with recurrent bilateral teratomas. All patients had substantial neurological recoveries, and the 2 newborns were normal. Results of extensive antibody testing in 1 of the babies were negative.

Conclusion: The current study shows that anti-NMDAR encephalitis during pregnancy can have a good outcome for the mother and newborn.

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Anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a synaptic autoimmune disorder that is likely mediated by antibodies against the NR1 subunit of the receptor.[1] Despite the severity of the disorder, most patients have substantial recoveries. Because the disease frequently affects women of childbearing age and the antibody subtypes (IgG1, IgG3) can cross the placenta, there is concern about the effects of the disorder during pregnancy.[2] We report 3 patients who developed the disorder during pregnancy.

REPORT OF CASES

Clinical features from the patients are described in this section and summarized in the **Table**. Antibodies to NMDAR were detected as reported elsewhere[1] and the titers were determined by serial dilution (starting at 1:10). The baby of patient 1 had antibody studies in the umbilical cord, serum, cerebrospinal fluid (CSF), and amniotic fluid.

CASE 1

A 19-year-old woman presented at 14 weeks of gestation with 2 weeks of headache and malaise followed by bizarre behavior and paranoid delusions resulting in hospitalization. Over the course of a week, her mental status worsened until she was minimally responsive. She had a generalized seizure that was treated with fosphenytoin and lorazepam, and she was intubated for airway protection. A bedside electroencephalogram (EEG) revealed generalized slowing but no epileptic activity. On examination, she was minimally responsive to noxious stimuli, had generalized hyperreflexia, and moved all limbs spontaneously. Results of magnetic resonance imaging (MRI) and CSF studies are described in the Table. Treatment with acyclovir was started for presumptive viral encephalitis.

On the third day in the intensive care unit, she developed repetitive pursing of the lips and furrowing of her brow without EEG correlates. These movements became more frequent and the dyskinesias spread to her limbs. By day 8, she developed diaphoresis, tachycardia, mydriasis, and hypertension. These symptoms were difficult to control despite treatment with fentanyl, lorazepam, propofol, bromocriptine, and β-blockers.

On day 5, a tracheostomy was performed. Treatment with intravenous immunoglobulin did not result in improvement. On day 23, an MRI of the abdomen and pelvis revealed a 2.5 × 3-cm left ovarian simple cyst. On day 43, NMDAR antibodies were identified in CSF. A second course of intravenous immunoglobulin treatment along with 1 g of methylprednisolone was given daily for 5 days. On day 50,

Table. Clinical Information and Antibody Titers

Patient	First Symptom of Encephalitis During Pregnancy	Other Symptoms	Teratoma	EEG	CSF WBC Count, /μL[a]	Week of Pregnancy, Antibody Titers in Serum and CSF	Outcome[b]
1	14th wk: Headache, malaise, bizarre behavior	Seizure, orofacial and limb dyskinesias, autonomic instability, minimally responsive	Left immature teratoma	Slow activity	244	14th wk: serum, ND; CSF, 1:80; 21st wk: serum, ND; CSF, 1:10; 32nd week: serum, ND; CSF, ND; baby at birth: serum, CSF, and umbilical cord blood, ND	Cesarean section at week 38; healthy baby; home on day 184; substantial recovery at 2-mo follow-up
2	8th wk: Abnormal, stereotyped behavior	Orofacial dyskinesias, autonomic dysfunction, seizures, minimally responsive, respiratory depression	Bilateral mature teratomas	1-Hz spikes, slow activity predominantly in frontal lobes	57	10th wk: serum, ND; CSF, 1:320; 13th week: serum, ND; CSF, 1:40	Bilateral tumor removal; pregnancy terminated; right ovary left to preserve fertility; home with minimal deficits on day 87
3	17th wk: Affective and behavioral change	Orofacial movements, tonic seizure without EEG correlate, episodes of agitation alternating with minimal response	No tumor or cyst	Generalized high-amplitude slow activity, 2 Hz	11	19th wk: serum, 1:320; CSF, 1:640; 5 mo postdelivery: serum, 1:80; CSF, NA	Spontaneous delivery at 37 wk of pregnancy; healthy baby; home 23 wk after symptom presentation; full recovery at last follow-up

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; NA, not applicable; ND, not detectable (<1:10); NMDAR, *N*-methyl-D-aspartate receptor; WBC, white blood cell.

[a] Normal, ≤4/μL. All 3 patients had normal CSF protein and glucose concentrations.

[b] Days relate to duration of stay in the hospital.

a left oophorectomy was performed, revealing an immature teratoma. On day 52, plasmapheresis was initiated, with a total of 7 treatments over 2 weeks. On day 72, she became more alert, responded to voice, and tracked objects. Throughout the hospitalization, the fetus was monitored weekly by Doppler ultrasonography, showing normal heart tones. Obstetric ultrasonography performed at weeks 20 and 26 revealed normal fetal anatomy and appropriate growth for gestational age.

The patient remained in the intensive care unit because of persistence of sympathetic storms. By day 107, she was following simple commands and the sedation was slowly weaned. On day 127, she began mouthing words. A cesarean section and concomitant surgical staging was performed on day 166 (at 37 weeks of gestation, following amniocentesis confirming fetal lung maturity). The infant weighted 6 lb 3 oz and Apgar scores were 3 at 1 minute and 6 at 5 minutes. All pathological specimens (left adnexa, pelvic lymph nodes, and peritoneal samples) were negative for tumor. Over the next 3 days, the patient was weaned from the ventilator and she made steady gains in physical therapy. By day 184, she was able to ambulate with a walker and her speech was fluent, but she was only oriented to self. Her progress was hampered by impulsivity, short-term memory loss, and physical deconditioning. Two months after discharge, she was functioning independently at home, although she was persistently impulsive and complained of somnolence. The infant has met all developmental milestones to date.

CASE 2

A 20-year-old woman developed change of behavior during the eighth week of pregnancy. She became argumentative, refused to talk and eat, and developed stereotyped behaviors, such as walking endlessly around a room or filling and emptying a glass with water. Two days before hospital admission, semirhythmic movements including blinking, licking, and tongue protrusion were noted. One day before admission, she developed hyperthermia and decreased level of consciousness and had a seizure. She had a history of bilateral ovarian teratomas that were removed when she was 16 years of age.

At admission, she had neck stiffness, without fever, and showed repetitive orofacial movements. She was poorly responsive to verbal and painful stimuli and had generalized hyperreflexia. Ancillary test results are described in the Table. Intravenous acyclovir and methylprednisolone administration were started. On day 3, cardiac pauses up to 5 seconds were noted (**Figure**, A). Over the next few days, she developed hypersalivation and generalized tonic convulsions. On day 13, status epilepticus and respiratory depression led to intubation and mechanical ventilation. On day 15, a pelvic computed tomographic scan revealed bilateral ovarian tumors (Figure, B, arrows); 2 days later, a left salpingo-oophorectomy and removal of both tumors was performed, and the pregnancy was terminated. Pathological studies confirmed bilateral mature teratomas.

From days 23 to 27, she received intravenous immunoglobulin and sedation with midazolam was discontinued. She gradually started tracking objects and following commands but continued having partial seizures that were treated with carbamazepine and gabapentin. On days 32 to 36, intravenous immunoglobulin administration was repeated, and by day 43, she was able to breathe spontaneously. By day 52, she was able to drink; the last seizure was observed on day 53. On day 64, she was eating regularly, and a few days later, she was able to walk. Her Mini-Mental State Examination score was 27 of 30 on day 85 and she was discharged home with minimal deficits on day 87.

CASE 3

A 19-year-old pregnant woman presented at 17 weeks of gestation with acute-onset behavioral change, including increas-

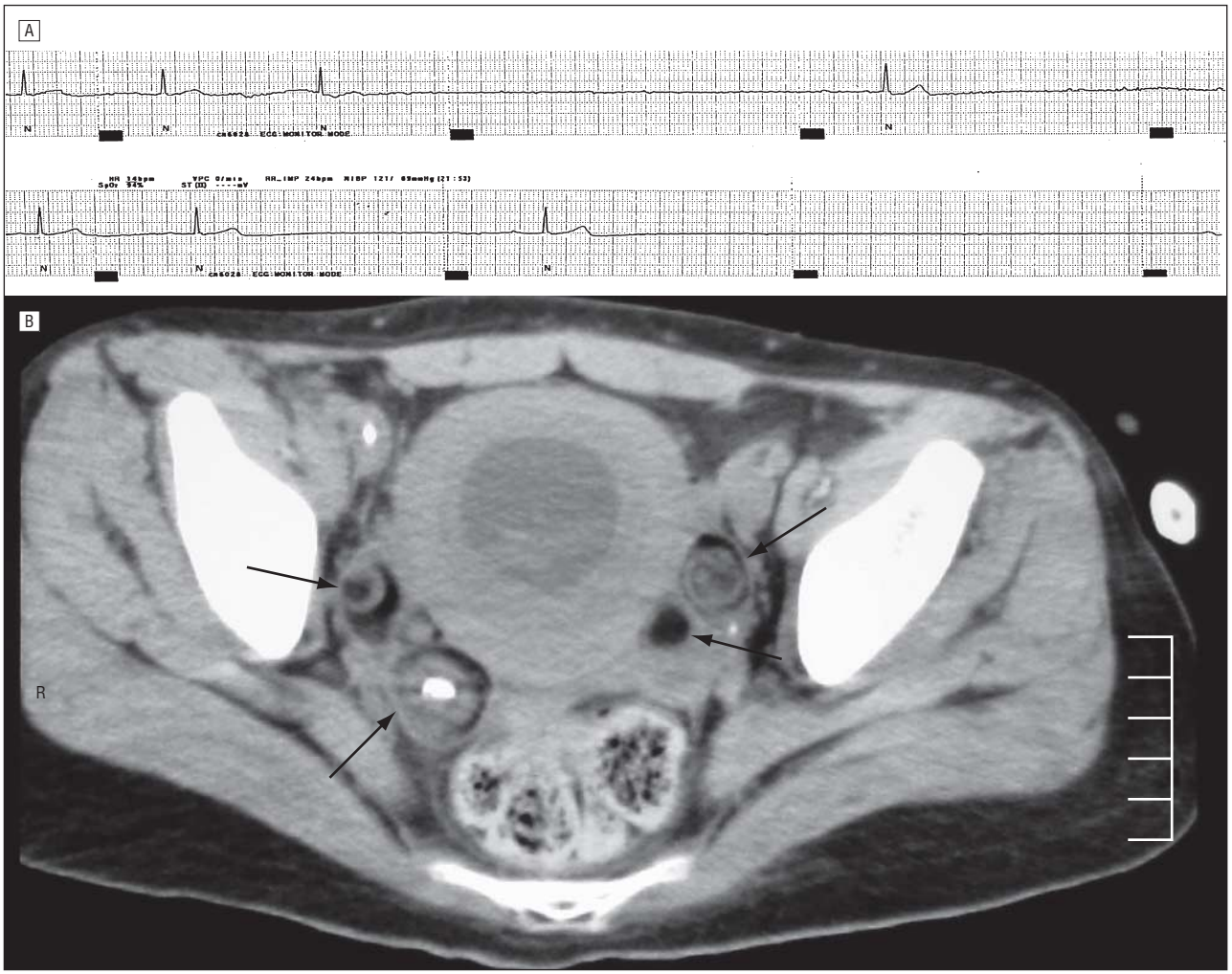

Figure. Cardiac pauses and bilateral teratomas in patient 2. A, Cardiac pauses up to 5 seconds were noted on day 3 of hospital admission. B, A pelvic computed tomographic scan revealed bilateral recurrent teratomas (arrows).

ing nervousness, irritability, and anxiety. She stopped walking and communicating but would say the same word repetitively and was transferred to a psychiatric facility. Her bizarre behavior continued; for example, she was frequently hitting the walls, taking cold baths, and accusing the physicians of "being murderers." She had fluctuating periods of decreased level of consciousness and agitation. She had a partial tonic seizure involving the left arm without EEG correlate; this showed generalized high-amplitude slow activity (2 Hz). Because of progressive deterioration and the presumptive diagnosis of viral encephalitis, she was transferred 1 week later to a neurology unit. On physical examination, her temperature was 37.1°C, and she had no neck stiffness. She developed hyperhidrosis and repetitive semirhythmic oral movements, like automatisms. Brain computed tomography and MRI were normal. The CSF showed lymphocytic pleocytosis (white blood cell count, 11/μL) with normal protein and glucose concentrations. Results of extensive viral studies and autoimmune and paraneoplastic markers were negative. Anti-NMDAR antibodies were identified in her serum and CSF. A second EEG showed no changes compared with the previous study. Magnetic resonance imaging of the abdomen and pelvis and abdominal ultrasonography were normal.

From day 19, the patient was treated with intravenous methylprednisolone (500 mg/d for 5 days) without clinical improvement, and a similar course of methylprednisolone treatment was started on day 35. After this second treatment, the orofacial dyskinesias subsided, but she continued with a decreased level of consciousness. On day 54, she had a generalized tonic-clonic seizure and treatment with phenobarbital was started. One month later, her level of consciousness started to progressively improve. Throughout the hospitalization, she did not develop hypoventilation. The fetus was monitored regularly by Doppler ultrasonography, showing normal heart tones. At 37 weeks of pregnancy, she spontaneously delivered a healthy 2892-g baby with Apgar scores of 8 at 1 minute and 9 at 5 minutes. Her Mini-Mental State Examination score was 24 of 30, and she was discharged 3 weeks later. At the last follow-up, she was fully functional and had returned to work. The child remains healthy with no obvious adverse effects.

DETECTION OF NMDAR ANTIBODIES

All 3 patients had higher NMDAR antibody titers in CSF than serum (Table). No antibodies were identified in the amniotic fluid, umbilical cord blood, serum, or CSF from the baby of patient 1. The baby of the other patient was not examined for antibodies.

COMMENT

To our knowledge, these are the first reported patients with anti-NMDAR encephalitis diagnosed during pregnancy. The 3 patients had substantial neurological recoveries, although in 1 case the pregnancy was terminated because of the severity of neurological symptoms, presence of recurrent bilateral teratomas, and early stage of pregnancy. The newborns of the other 2 patients were healthy and their physical and cognitive milestones are being closely followed up. Concern for the fetus and newborns is warranted in this disorder as studies indicate that NR1 antibodies from patients decrease NMDAR clusters in vitro and in animal models.[1,3] Moreover, the antibodies are IgG1 and IgG3, which are the subtypes involved in autoimmune newborn illnesses, such as congenital lupus.[4]

The good outcome of the 2 neonates of our study is likely due to several factors, including the variable effects of autoimmune disorders on the fetus. For example, despite experimental models showing that Ro/SSA antibodies cause congenital heart block, only 2% to 5% of neonates from patients with these antibodies have congenital heart block.[5] Two additional factors relate to the levels of serum maternal antibodies and the timing of transplacental transfer of IgG. IgG1 and IgG3 cross the placenta by binding to an Fc neonatal receptor present in syncytiotrophoblasts.[6] This mechanism of placental transfer develops around weeks 14 to 16, resulting initially in very low levels of fetal blood IgG that gradually increase until the time of delivery.[4] Additionally, the fetal blood-brain barrier becomes functional by the end of the second trimester. Our patients developed symptoms between 8 and 17 weeks of pregnancy when the IgG placental transfer is absent or limited, and assuming the immune response was triggered systemically, the levels of serum NMDAR antibodies decreased rapidly. In fact, 2 patients had negative serum but positive CSF antibody titers (both tested at initial dilution 1:10) by the time they were diagnosed with anti-NMDAR encephalitis, explaining the absence of NMDAR antibodies in the baby who was tested.

With a sharp increase in the number of cases with anti-NMDAR encephalitis, more patients will be identified during pregnancy. This study suggests that these patients and the newborns can do well. The concern should be the search (and removal) of a teratoma along with supportive care of the mother and fetus. Treatment with corticosteroids, intravenous immunoglobulin, and plasmapheresis was well tolerated but the effects could not be assessed because of the close temporal association with tumor removal in 2 patients. The third patient only received corticosteroids, with questionable improvement of the dyskinesias. The recovery seemed to accelerate after giving birth; this and the predominance of the disorder in young women bring into consideration a possible role of hormonal factors that needs further study.

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