Pregnancy Outcome in Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis

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BACKGROUND: Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune disorder resulting in neurologic and psychiatric symptoms. Treatment is challenging in pregnancy, because little data exist to guide management.

CASE: A 24-year-old woman with a known diagnosis of anti-NMDA receptor encephalitis using intravenous immunoglobulin therapy became pregnant. Her pregnancy was uncomplicated with no relapses. She delivered at 35 4/7 weeks of gestation after having preterm premature rupture of membranes. She had a relapse of symptoms after delivery.

CONCLUSION: This patient with anti-NMDA receptor encephalitis had an uneventful pregnancy with overall good outcome; however, she experienced relapse soon after delivery. This disease may mimic other autoimmune diseases, with improvement during pregnancy and risk for relapse postpartum.

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Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis was identified in 2007 by Josep Dalmau at the University of Pennsylvania.[1] It is caused by an autoimmune reaction to the NMDA receptor and is characterized by psychiatric and neurologic symptoms. Psychiatric manifestations include agitation, paranoia, and hallucinations. Neurologic manifestations include dystonia, dyskinesia, catatonia, and seizures.[2] Published reports to date include only patients with diagnoses during pregnancy[3,4] We report a case of a woman with known anti-NMDA receptor encephalitis who became pregnant.

CASE

The patient is a 24-year-old woman, gravida 1 para 0, who presented at 10 weeks of gestation. Five years before her pregnancy, acute onset of migratory choreoathetosis, bradykinesia, weakness, depression, and obsessive thoughts developed. She was admitted, and magnetic resonance imaging (MRI) revealed abnormal T2 signal hyperintensity within the bilateral caudate, globus pallidus, and putamen. Electroencephalogram (EEG) showed intermittent polymorphic bilateral frontal slowing. Cerebrospinal fluid evaluation showed lymphocytic pleocytosis and a muscle biopsy result was normal. Testing was unremarkable for viral infections, autoimmune disorders, rheumatologic disorders, Wilson disease, Huntington disease, multiple sclerosis, and heavy metal exposure. Based on these findings, autoimmune basal ganglia disease was diagnosed. During this time, she was treated with mirtazipine for depression and risperidone for obsessive thoughts and mood lability. She was administered high-dose intravenous steroids for choreoathetosis but psychosis resulting in discontinuation of therapy developed. She was then treated with plasmapheresis, with resolution of her choreoathetosis and improvement in her bradykinesia, and she was discharged.

Over the next 14 months, the patient had five flares requiring hospitalization. She received high-dose intravenous steroids or plasmapheresis for her flares, with symptomatic improvement. Diagnostic work-up included negative test results for Fahr disease, Hallervorden-Spatz disease, Creutzfeld-Jacob disease, kinesogenic dystonia, and neuroacanthocytosis. A brain biopsy showed microgliosis, perivascular lymphocytic infiltrates, and reactive astrocytosis. Despite treatment of her flares, she accumulated neurologic symptoms including ataxia, short-term memory loss, dysphagia, dysarthria, opsoclonus, spasticity, weakness, generalized dystonia, and bradykinesia. She started carbidopa and levodopa, with improvement in dystonia and bradykinesia. Dystonic hand posturing and spasticity was treated with trihexyphenidyl, baclofen, and botox injections. She required a temporary gastrostomy tube for dysphagia. She had recurrent psychiatric symptoms of depression, obsessive thoughts, and mood lability. There was no response to clonazepam, sertraline, or gabapentin, and haloperidol was discontinued because of tardive oral–buccal movements. She then received venlafaxine, resulting in significant improvement in her psychiatric symptoms.

The patient had a severe flare 15 months after initial presentation that was treated successfully with two doses of cyclophosphamide. Subsequent treatment included intravenous immunoglobulin (IVIG; Gammagard Liquid 10%) every 3 months and intravenous methylprednisolone monthly. This resulted in fewer flares and hospital admissions, and gradual improvement in neurologic symptoms. Further use of cyclophosphamide was minimized given the patient's desire to preserve her fertility.

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Then, 3 years after her presentation, the patient's initial cerebrospinal fluid (CSF) sample was analyzed by the California Encephalitis Project and was found to have antibodies reacting to NMDA receptor type 2A, consistent with anti-NMDA receptor encephalitis. Given its association with ovarian teratomas, a pelvic MRI scan and ultrasound examination were performed but yielded negative results. Rituximab was ordered but was denied by insurance. Intravenous methylprednisolone was discontinued and the patient was started on IVIG every 2 months. She gradually improved and was able to wean off of her symptomatic medications, except venlafaxine.

Two years after diagnosis of anti-NMDA receptor encephalitis, she became pregnant. At baseline, she had dysarthria, problems walking, and a flat affect, but she denied any new neurologic or psychiatric symptoms. Her IVIG treatments were to continue every 2 months. Plasmapheresis and steroids were reserved for worsening or refractory symptoms. Despite this plan, she received no further courses of IVIG because of insurance issues and poor compliance. However, her symptoms remained stable throughout her pregnancy.

At 35 3/7 weeks of gestation, the patient presented with preterm premature rupture of membranes. Given her gestational age, labor was induced; the patient received an epidural for analgesia, and, at 35 4/7 weeks of gestation, she delivered a viable newborn vaginally, weighing 2,345 g, with Apgar scores of 8 at 1 minute and 9 at 5 minutes. The newborn was observed in the neonatal intensive care unit for 4 hours for prematurity before being transferred to the newborn nursery. No specific testing was performed, and the newborn was discharged home with routine follow-up. The patient's immediate postpartum course was uneventful. Two months postpartum, the patient's spasticity in her right hand, dystonia while ambulating, and dysphonia were worsening. At this point, IVIG was resumed every 3 months. The newborn did well initially but was noted to have torticollis and strabismus at 4 months and 6 months of age. This was being monitored clinically, and no further testing has been performed yet.

COMMENT

Anti-NMDA receptor encephalitis is a recently discovered neuropsychiatric condition characterized by antibodies against subunits of the NMDA receptor that results in a synaptic autoimmune disorder.[1] It is theorized that these antibodies are produced after exposure to ectopic neural tissue contained within teratomas and small-cell lung cancer.[5]

In the largest case series to date, anti-NMDA receptor antibody encephalitis was found to be more frequent in women, with the median age of 23 years at the time of diagnosis.[2] It often starts with a prodromal viral-like illness for several weeks followed by either neurologic or psychiatric symptoms, or both.[2] From a large case series of patients with anti-NMDA receptor encephalitis, more than 75% of patients presented with psychiatric symptoms predominantly (agitation, bizarre behavior, paranoia, hallucinations).[1] The remaining patients had neurologic symptoms (decreased consciousness, dyskinesias, short-term memory loss, seizures, catatonia).[1] Autonomic instability (central hypoventilation, dysthermia, and cardiac dysrhythmias) was also common, occurring in 69% of patients.[1] Our patient presented with both neurologic and psychiatric symptoms, although neurologic symptoms were predominant.

Abnormalities are typically seen on EEG, MRI, CSF, and brain biopsy.[1] The EEG findings include bilateral frontal slowing, and MRI often shows increased signal on T2 or fluid-attenuated inversion recovery sequences in the temporal lobes, cortex, and other regions. The CSF findings often include lymphocytic pleocytosis, and a brain biopsy may show perivascular lymphocytic cuffing and microglial activation.[1] Our patient displayed the characteristic EEG, MRI, and CSF findings. Interestingly, her brain biopsy showed reactive astrocytosis in addition to the usual findings.

Anti-NMDA receptor encephalitis is associated with tumors in approximately 55% of patients.[1,5,6] Of these, 93% were mature cystic teratomas of the ovary. Of the pathologically examined teratomas, all contained neural tissue and were positive for NMDA receptor, highlighting the role of teratomas in this disease.[1] Available evidence suggests that surgical removal is associated with improved outcomes.[1,5] In one case series, 72% (n=36) had full recovery with removal compared with 36% (n=22) without removal.[1] Empiric surgical oophorectomy in the absence of a confirmed teratoma remains controversial.[6] Our patient had multiple imaging studies to evaluate for a teratoma (ultrasound scans, computed tomography scans, and an MRI), which were negative.

Treatment for anti-NMDA receptor antibody encephalitis involves a multidisciplinary approach. Given that most patients present with psychiatric symptoms, this is often an initial therapeutic target.[7] Antipsychotic medications have improved symptoms but can worsen the dyskinesia, whereas mood stabilizers and antidepressants have not been reported to be effective.[7] Our patient was started on risperidone, with improvement in mood lability. However, she was started on immunotherapy simultaneously, making it unclear which therapy resulted in improvement. In subsequent hospitalizations, her mood lability and obsessive thoughts worsened despite drug treatment; ultimately, venlafaxine showed the best response. We agree that because psychiatric symptoms improve

with immunotherapy and because there is a lack of data supporting medication therapy, immunotherapy should remain the mainstay of treatment for both neurologic and psychiatric symptoms.[7] The role of serotonin–norepinephrine reuptake inhibitors, such as venlafaxine, for the management of psychiatric symptoms associated with this disease warrants further study.

Treatment for neurologic symptoms consists of tumor resection, immunotherapy, and rehabilitation.[1,2] Patients in whom tumors were identified and excised within 4 months of symptom onset showed the highest cure rates and lowest risk of relapse.[2,6] The mainstays of immunotherapy are steroids, IVIG, and plasmapheresis. Cyclophosphamide and rituximab also have been used for more aggressive cases. Future fertility is an important consideration when using cyclophosphamide. Immune therapy can be monitored with serial CSF titers to determine length of treatment.[2] Although evidence for carbidopa and levodopa is lacking, our patient primarily had basal ganglia involvement and her dystonia, dysarthria, and dysphagia improved with this therapy.

To date, the only published cases evaluate patients with diagnoses during pregnancy. In these reports, immunotherapy (steroids, IVIG, and plasmapheresis) was used with good results.[3,4] For treatment of refractory symptoms, immunomodulators such as rituximab may be considered in pregnancy, whereas azathioprine and cyclophosphamide should be avoided. Carbidopa and levodopa were not used in any previous reports; however, they were used successfully in our patient. For seizure management, phosphenytoin, lorazepam, carbamazepine, and phenobarbital were successfully used in the case reports of pregnant patients.[3,4] If teratomas are present, then they should be removed.[1,2,6]

Literature on pregnancy course or outcomes in patients with anti-NMDA receptor antibody encephalitis is limited. In one case series of three patients with diagnoses during pregnancy, two had diagnoses in the first trimester, and the other had diagnosis in the second trimester. One patient terminated her pregnancy, whereas the other two delivered at term, one vaginally and one by cesarean delivery.[3] In all three cases, behavioral change was noted first, followed by neurologic deficits. All three patients had positive antibody titers in their CSF and frontal slowing on EEG. Two patients were found to have teratomas, one of whom had hers removed along with the termination of the pregnancy. Her recovery was lengthy. The two other patients were hospitalized for the remainder of their pregnancies and for several weeks postpartum, with clinical improvement noted postpartum. The newborn outcomes were reassuring early on.[3] In another case report, a patient at 17 weeks of gestation presented with behavioral changes and seizures. A work-up showed EEG slowing and CSF pleocytosis. After diagnosis, she was treated with intravenous steroids and phenobarbital for her seizures. She delivered vaginally at term without complication.[4]

Our patient's symptoms did not worsen during the pregnancy. This is in contrast to the case series of three patients with diagnoses during pregnancy. They each had prolonged hospitalizations, as did our patient at the time of her initial presentation.[3] These findings suggest that although the initial presentation is challenging diagnostically and therapeutically, pregnancy itself may not worsen or cause disease relapse. However, postpartum, our patient had gradually worsening symptoms over the course of 2 months, requiring reinitiation of IVIG treatment. Previously published reports have documented substantial improvements in symptoms postpartum, and further study is needed to characterize the disease response postpartum.

The newborn course was unremarkable until 4 months of age, when torticollis and strabismus were noted. These persisted at the 6-month well-visit examination and were being followed-up clinically. The newborn had not been tested for NMDA receptor antibodies. Given the patient's prominent dystonia, it was felt that the newborn's torticollis might be related to antibodies crossing the placenta. Studies have shown that NR1 antibodies of subtype IgG1 and IgG3 decrease NMDA receptor clusters in vitro, and that these antibody subtypes are known to cause other autoimmune newborn diseases.[3] No other studies have demonstrated adverse outcomes in the neonate, and further studies are needed to characterize the potential effect of transplacental transfer of antibodies to the newborn.

The diagnosis of anti-NMDA receptor encephalitis will no doubt continue to increase as awareness and testing for this disease increase. It will then be possible to determine if its course in pregnancy is similar to that of other autoimmune diseases that improve in pregnancy, with relapses occurring postpartum. Further study also can be performed to evaluate therapeutic options that may improve symptoms during pregnancy.

REFERENCES

1. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and

analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8.
2. Rosenfeld MR, Dalmau J. Anti-NMDA-receptor encephalitis and other synaptic autoimmune disorders. Curr Treat Options Neurol 2011;13:324–32.
3. Kumar MA, Jain A, Dechant VE, Saito T, Rafael T, Aizawi H, et al. Anti-N-methyl-D-aspartate receptor encephalitis during pregnancy. Arch Neurol 2010;67:884–7.
4. Ito Y, Abe T, Tomioka R, Komori T, Araki N. Anti-NMDA receptor encephalitis during pregnancy. Rinsho Shinkeigaku 2010;50:103–7.
5. Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25–36.
6. Kort DH, Vallerie AM, DeMarco EF, Lobo RA. Paraneoplastic anti-N-methyl-D-aspartate-receptor encephalitis from mature cystic teratoma. Obstet Gynecol 2009;114:373–6.
7. Chapman MR, Vause HE. Anti-NMDA receptor encephalitis: diagnosis, psychiatric presentation, and treatment. Am J Psychiatry 2011;168:245–51.

Uterine Clostridial Myonecrosis After Thermal Balloon Endometrial Ablation

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BACKGROUND: We present a case of a patient who had development of uterine clostridial myonecrosis after elective thermal balloon endometrial ablation in the absence of identifiable risk factors.

CASE: A 51-year-old woman underwent uneventful thermal balloon endometrial ablation for the treatment of menorrhagia. The next day, she presented with acute inflammatory syndrome, severe intravascular hemolysis, and acute kidney injury. The blood cultures and the high vaginal swab showed moderate growth of *Clostridium* species. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. Her postoperative course was uneventful, and renal function gradually recovered.

CONCLUSION: Clostridial myonecrosis after uncomplicated surgery, although rare, should be considered in the differential diagnosis of the acutely septic patient with massive hemolysis, regardless of the presence of patient's risk factors.

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Clostridial myonecrosis (gas gangrene) of the uterus is a severe infection that is characterized by rapid evolution and considerable mortality. Despite the common presence of anaerobic bacteria in the female genital tract, the manifestations of infection, which may vary from endometritis to gas gangrene, occur infrequently. Underlying malignancy,[1,2] immunocompromised status,[1] and septic abortion[3] may contribute to the development of the infection. In this case report, we present a patient who had development of uterine gas gangrene after elective thermal balloon endometrial ablation of the uterus in the absence of identifiable risk factors.

CASE

A 51-year-old woman, classified as American Society of Anesthesiologists physical status 2, underwent elective thermal balloon endometrial ablation for the treatment of menorrhagia. Significant medical history included iron deficiency anemia and obesity, with a body mass index (calculated as weight (kg)/[height (m)]^2) of 35. Physical findings on examination were unremarkable. All preoperative investigations were normal. On the day of the surgery, a routine urine dipstick test was performed preoperatively that showed 1+ protein, 1+ leukocytes, and no evidence of nitrates. The patient had no symptoms of urinary tract infection. Hence, no treatment for this was commenced, but urine specimen was sent for culture and sensitivity. The next day the report was received, showing growth of Coliform species.

The endometrial ablation was conducted uneventfully under general anesthesia. The choice of anesthesia was based on the patient's preference. Surgical site asepsis was performed using surgical iodine on the perineum and intravaginally. No prophylactic antibiotic was administered. Intraoperatively, the cervix, vulva, and vagina showed no obvious abnormality or pathologic process. The operative procedure and immediate postoperative recovery also were noted as uneventful. The patient was discharged from hospital the same day.

The next day, the patient presented to the emergency department with nausea, vomiting, and jaundice. Her abdomen was slightly distended and diffusely tender but