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Neuraxial anesthesia in a patient with anti-N-methyl-D-aspartate receptor encephalitis in pregnancy: management for cesarean delivery and oophorectomy

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ABSTRACT
We describe the neuraxial anesthetic management of a 28-year-old primigravid patient with severe, treatment-refractory anti-N-methyl-D-aspartate receptor encephalitis undergoing cesarean delivery. The presence of an ovarian teratoma was suspected although not confirmed by imaging. The severity of symptoms, ineffective immunotherapy and the need for chemotherapy necessitated cesarean delivery and resection of a suspected teratoma at 28 weeks estimated gestational age. A combined spinal-epidural technique was used. Delivery was uneventful, and a right oophorectomy was performed for a visible lesion that was later confirmed to be a mature cystic teratoma.

Keywords: Anti-N-methyl-D-aspartate receptor encephalitis; Ovarian teratoma; Cesarean delivery; Anesthesia, combined spinal-epidural

Introduction

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is a neurological disorder caused by production of antibodies to the NMDA receptor (NMDAR) and is usually associated with ovarian teratomas in women of child-bearing age. It is characterized by major psychiatric and neurologic symptoms, which may worsen with pregnancy. It often starts with a prodromal viral-like illness, followed by predominantly psychiatric symptoms including agitation, paranoia, catatonia, and hallucinations. Neurologic symptoms, including decreased consciousness, dyskinesia, seizures, autonomic dysfunction, central hypoventilation and dysthermia, may develop. Cardiac dysrhythmias are also common.[1] Choice of appropriate anesthesia in patients with anti-NMDARE is challenging as many anesthetic agents interact with NMDARs and lead to unexpected clinical effects, and there is concern about neuraxial anesthesia in any patient with active encephalitis. We discuss the pathophysiology of anti-NMDARE and our rationale for the use of neuraxial anesthesia. To our knowledge, this is the first reported use of neuraxial anesthesia in a parturient with anti-NMDARE.

Case report

A 28-year-old primigravid patient was seen at a local hospital at an estimated 16 weeks of gestation. She had experienced two days of increased anxiety, insomnia, and hallucinations, which was initially thought to be a new-onset psychosis. She developed a fever and

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was started on empiric broad-spectrum antibiotic cover. Four days later, she had a tonic-clonic seizure, her trachea was intubated for airway protection and she was started on leviteracetam 500 mg 12-hourly. A computed tomography (CT) scan of the head was normal, and magnetic resonance imaging/angiogram (MRI/MRA) revealed only scattered white matter hyperdensities. Lumbar puncture was unremarkable. A paraneoplastic syndrome was suspected, and intravenous immunoglobulin and methylprednisolone 1000 mg daily were given for five days. Cerebrospinal fluid (CSF) was sent for anti-NMDAR antibody testing and the patient was transferred to our hospital for further evaluation.

The patient arrived at our intensive care unit (ICU) intubated and minimally responsive at 18 weeks of gestation. Cerebrospinal fluid immunology results indicated the presence of anti-NMDAR antibodies. Ovarian teratomas are known to coexist in most female patients with anti-NMDARE,[2] and an abdominopelvic MRI was performed but did not show any tumor. Her hospital course was complicated by the development of severe autonomic dysfunction, manifested as hypertension, tachycardia, and dysthermia. Clonidine 0.2 mg 12-hourly, bromocriptine 10 mg 8-hourly, methadone 15 mg 6-hourly, (an opioid agonist and NMDA antagonist which is known to reduce sympathetic outflow), and propranolol 50 mg 8-hourly, were started. She underwent a total of 11 plasma exchanges and started rituximab therapy (375 mg/m^2 for four doses) for management of deteriorating symptoms. Her clinical condition gradually improved over three weeks, she was weaned from ventilatory support and discharged to a rehabilitation facility while continuing multi-drug therapy.

One week later, increased agitation, catatonic episodes, autonomic dysfunction, intrauterine growth restriction and maternal malnutrition (her weight on admission was 55.5 kg, down 21.3 kg from two months previously; height 152 cm) prompted readmission to our institution. As the current literature shows a response rate of 65% to rituximab and cyclophosphamide combination therapy after other treatments have failed in tumor-negative patients, cyclophosphamide (750 mg/m^2) and additional intravenous rituximab (600 mg every 7 days) were given. Anti-NMDAR antibody titers before the treatment were 1:160 (normal <1:10), and two weeks later were 1:10. Despite this robust immunologic response, her symptoms improved only mildly.

Elective cesarean delivery (CD) at 28 weeks of gestation was planned, in combination with laparotomy to look for ovarian masses. The surgical plan was to perform single-sided oophorectomy if an ovarian teratoma was shown using frozen section techniques, or bilateral oophorectomy if teratoma was not shown on frozen section. Betamethasone was given for fetal lung maturity, but magnesium sulfate was withheld for fetal neuroprotection because of its known antagonism of NMDA.[3]

A combined spinal-epidural (CSE) anesthetic was performed to provide a dense initial block with the ability to prolong anesthesia with epidural drug administration. Non-invasive blood pressure, heart rate, pulse oximetry, and five-lead electrocardiography were monitored; invasive hemodynamic monitoring was considered unnecessary as autonomic dysfunction was well-controlled. Subarachnoid block was performed with 0.75% hyperbaric bupivacaine 1.2 mL, fentanyl 10 μg, and preservative-free morphine 300 μg. Despite the apparent return of CSF in the spinal needle (clear free-flowing fluid demonstrating a swirl when aspirated), there was no appreciable sensory level after 10 min. Subsequently, 0.5% bupivacaine 20 mL was administered in divided doses via the epidural catheter to achieve surgical anesthesia. She had been taking methadone daily for several weeks, and intravenous methadone 2.5 mg was given to mitigate severe insomnia, autonomic dysfunction (personal communication with psychiatry service) and reduce the potential for opioid withdrawal. Perioperative hemodynamic variables did not vary by more than 15% from baseline, no vasopressor therapy was required, and no hypoventilation was observed. Delivery of a male infant (Apgar scores 1 at 1 min, 8 at 5 min, 9 at 10 min) occurred without incident. She underwent right oophorectomy for a grossly visible mass that was pathologically confirmed as a mature cystic teratoma. The left ovary had no visible lesions and was not removed. Estimated blood loss was 400 mL. Epidural morphine 4 mg was administered at the end of surgery, and a subfascial wound infusion of 0.5% bupivacaine was started at 5 mL/h. Additional epidural morphine 2 mg was administered before epidural catheter removal 24 h later. This provided excellent postoperative analgesia (verbal numeric pain score 1/10).

The patient continued to experience cognitive impairment and elevated blood pressure. She remained on anticonvulsant therapy (leviteracetam 1500 mg 12-hourly and lacosamide 200 mg 12-hourly), but was gradually weaned from methadone and bromocriptine. Two weeks post-delivery, she experienced recurrent status epilepticus. Brain MRI (Fig. 1) showed subcortical and periventricular white matter intensities consistent with limbic encephalitis. Seizures were ultimately controlled with high-dose anticonvulsants (leviteracetam 1500 mg, lacosamide 200 mg 12-hourly, fosphenytoin 100 mg 8-hourly). She was discharged home with persistent cognitive impairment 10 days later.

Discussion

Eighty percent of patients with anti-NMDARE are female, and the condition was initially classified as a paraneoplastic syndrome associated with mature cystic teratomas of the ovary,[2] in which pathologically con-

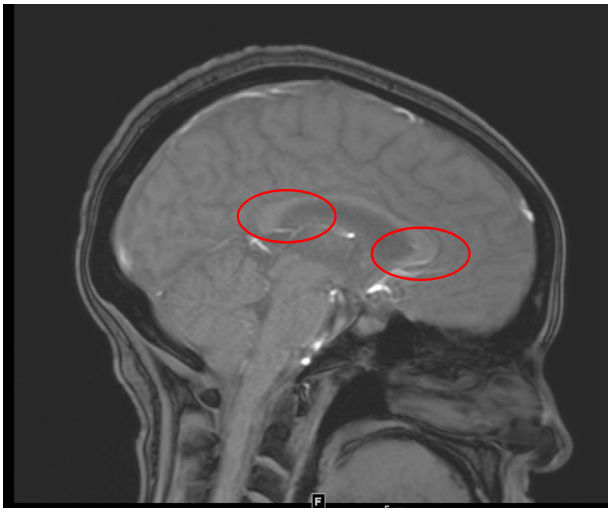

Fig. 1 Postpartum sagittal MRI. Contrast demonstrates slight, cortical signal abnormality without abnormal enhancement involving the cingulate gyri (indicated by ovals). Concurrent coronal images confirmed a symmetrical, bilateral signal abnormality in this region. This finding is nonspecific, but is seen in the setting of various limbic encephalitides

firmed teratomas contain neural tissue positive for NMDARs.[1] Surgical removal of tumors is associated with improved outcome.[1] In pregnant women with anti-NMDARE improvement in maternal condition after fetal delivery has been reported.[4]

General anesthesia with volatile agents or total intravenous anesthesia for patients with anti-NMDARE has been described.[5–10] The NMDAR is the site of action for many commonly administered anesthetic drugs, including known NMDA antagonists such as nitrous oxide and ketamine and the NMDAR may also be responsible for mediating the effects of other commonly administered anesthetic agents such as propofol, fentanyl, and sevoflurane.[7,11–14] Propofol has inhibitory effects on the NMDAR, and one case report describes worsening symptoms in a patient with anti-NMDARE following propofol infusion and sevoflurane.[7]

Neuraxial anesthesia was chosen to meet the following goals: to avoid further NMDAR antagonism with symptomatic deterioration, afford airway protection, avoid central hypoventilation, maintain stable hemodynamics in the face of paroxysmal sympathetic hyperactivity, avoid increased postoperative confusion, and provide postoperative pain control with epidural morphine. The risks of neuraxial anesthesia including sympathectomy, post-dural puncture headache and intolerance to the procedure were thought be outweighed by the potential benefits, and by the avoidance of the potential risks of general anesthesia.

The apparent failure of the spinal component of the CSE was unexpected, although spinal anesthetics fail for a variety of technical and patient reasons. It is thought unlikely that failure was due to impaired interaction of bupivacaine with the NMDAR. First, since part of the effect of an epidurally administered local anesthetic is mediated at the spinal cord level, an impairment of the epidural limb of the CSE might also be expected; an effect which was not observed. Second, the predominant effect of spinal bupivacaine is mediated via neuronal sodium channel antagonism, a mechanism which should still occur in patients with anti-NMDARE. Finally, as bupivacaine acts to inhibit excitatory NMDA effects in the spinal cord, it might be expected to be more potent in anti-NMDARE, as suggested by general anesthesia case reports.[5–10] Therefore, we believe that either the intrathecal portion of the CSE was fully misplaced or that a mistake in drug formulation occurred.

The patient was assumed to be opioid tolerant, and because it was felt most likely that the intrathecal morphine dose was not delivered, a further epidural dose of morphine was given intraoperatively. Over the first 72 h postoperatively, she did not have clinical signs of respiratory depression as evidenced by decreased respiratory rate, increasing somnolence or oxygen desaturation. The combination of a continuous subfascial wound infusion of 0.5% bupivacaine, multiple doses of epidural morphine, and non-steroidal anti-inflammatory drugs provided excellent pain control.

In conclusion, patients with anti-NMDARE undergoing anesthesia are at risk for perioperative complications and worsening of symptoms due to the known and theoretical interactions of anesthetic agents and the NMDAR. This case report is the first to describe neuraxial anesthesia in an affected patient undergoing CD. Although the intrathecal portion of the CSE was unsuccessful, epidural supplementation worked well, allowing successful CD, oophorectomy and postoperative pain control without worsening the symptoms of anti-NMDARE.

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