Clinical Case Report

Medicine®

OPEN

Anesthesia for patient with anti-*N*-methyl-D-aspartate receptor encephalitis

A case report with a brief review of the literature

Nozomi Wada, MD, Kayoko Tashima, MD, Akira Motoyasu, MD, Harumasa Nakazawa, MD, PhD*,
Joho Tokumine, MD, PhD, Mieko Chinzei, MD, PhD, Tomoko Yorozu, MD, PhD

Abstract

Rationale: Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is an immune-mediated syndrome caused by the production of antibodies against NMDA receptors. As NMDA receptors are important targets of many anesthetic drugs, the perioperative management of patients with anti-NMDA receptor encephalitis is challenging for anesthesiologists.

Patient concerns: A 31-year-old woman presented with akinesia and aphasia, which worsened despite steroid therapy.

Diagnosis: Anti-NMDA receptor encephalitis associated with ovarian teratoma.

Interventions: Laparoscopic ovarian cystectomy was performed under total intravenous anesthesia (TIVA) with peripheral nerve block (PNB).

Outcomes: The patient recovered without postoperative complications or any adverse events after surgery.

Lessons: Ideal anesthesia for a patient with anti-NMDA receptor encephalitis is still under discussion. We decided to perform TIVA with PNB because the effect of propofol on NMDA receptors is considered less than that of volatile anesthetics; moreover, PNB may reduce the amount of propofol and opioids required for anesthesia. To conclude, TIVA with PNB may be the most appropriate method for anesthesia in a patient with anti-NMDA receptor encephalitis undergoing ovarian cystectomy.

Abbreviations: BIS = bispectral index, NMDA = *N*-methyl-D-aspartate, PNB = peripheral nerve block, QLB = quadratus lumborum block, RSB = rectus sheath block, TIVA = total intravenous anesthesia, TOF = Train of Four, VAP = ventilator-associated pneumonia.

Keywords: anesthesia, anti-NMDA receptor encephalitis, ovarian teratoma

1. Introduction

Anti-NMDA receptor antibody encephalitis is an autoimmune disorder associated with ovarian teratoma, and usually affects young women.[1–3] Prominent psychiatric symptoms, disturbance of memory and consciousness, and central hypoventilation are characteristic.[4–6] Anesthesiologists sometimes encounter these patients in the operating room because it has been reported that ovarian tumor resection with immunotherapy can facilitate earlier functional recovery.[7–9] A patient with anti-NMDA receptor encephalitis requires careful consideration of the anesthesia plan and drugs, because the NMDA receptor is a major target site of commonly-used anesthetic agents. However, standard anesthesia for such patients has not been established. We present a case of laparoscopic ovarian cystectomy who received intravenous propofol anesthesia with peripheral nerve block, and discuss appropriate anesthesia with a limited review of the literature.

2. Case report

A 31-year-old woman with no prior history presented with memory deficit, monologue, and loitering after common cold-like symptoms. Initially diagnosed by a psychiatrist as having an acute mental disorder, her symptoms subsequently worsened, with agitation, disorientation, and generalized seizures. Cerebrospinal fluid testing and head and abdominal magnetic resonance imaging suggested encephalitis and ovarian teratoma, and anti-NMDA receptor antibody was detected in cerebrospinal fluid. The psychiatrist diagnosed anti-NMDA receptor antibody encephalitis.

Her symptoms gradually worsened despite steroid therapy, and she developed akinesia and aphasia. She was transferred to our hospital and laparoscopic ovarian cystectomy was scheduled. At that time, her disease stage was considered unresponsive, as 9 months had passed since onset.

Medication was held on the operative day. Total intravenous anesthesia with peripheral nerve block was selected. Her bispectral index (BIS) was about 90 as she closed her eyes. General anesthesia was induced with bolus administration of 80 mg of propofol, with continuous infusion of remifentanil at 0.1 μg/kg/min. Train of Four (TOF) monitoring was calibrated and 40 mg of rocuronium was administered intravenously. Tracheal intubation was uneventful. Anesthesia was maintained with

Editor: N/A.

The authors have no funding and no conflicts of interest to disclose.

Department of Anesthesiology, Kyorin University School of Medicine, Shinkawa, Mitaka-shi, Tokyo, Japan.

* Correspondence: Harumasa Nakazawa, Department of Anesthesiology, Kyorin University School of Medicine. 6-20-2 Shinkawa, Mitaka-shi, Tokyo 181-8611, Japan (e-mail: hal0413@ks.kyorin-u.ac.jp).

Medicine (2018) 97:50(e13651)

Received: 2 August 2018 / Accepted: 20 November 2018

http://dx.doi.org/10.1097/MD.0000000000013651

propofol using target-controlled infusion at 3.5 μg/mL and continuous infusion of remifentanil at 0.2 μg/kg/min. Rectus sheath block (RSB) and quadratus lumborum block (QLB, type 1) were performed using ultrasound guidance, and local anesthesia was achieved with a total of 60 ml of 0.25% levobupivacaine: 20 ml for RSB and 40 ml for QLB. Laparoscopic ovarian cystectomy was started. The BIS was about 60 during the operation, which was uneventful. The operative time was 35 minutes. Acetaminophen 700 mg was administered intravenously for postoperative analgesia. Sugammadex was administered to reverse the muscle relaxant. The patient was awake when her BIS increased to 90, and the TOF ratio was 90% at the time. Her tidal volume during spontaneous ventilation through the endotracheal tube was 400 mL/min and respiratory rate was 9 times per min. She could breathe spontaneously without snoring or apnea after extubation. Her vital signs were stable and she did not complain of pain.

One day after surgery, she had transient dyskinesia. Her aphasia was still not improved, but her facial expression and physical communication were improved during the 5 days after surgery. She was transferred back to the referring hospital.

3. Discussion

Three points should be considered for anesthesia in anti-NMDA receptor encephalitis: the choice of anesthetic and anesthesia type, appropriate anesthesia maintenance, and postoperative care. Ideally, anesthesiologists should choose the optimal anesthetic for a patient with anti-NMDA receptor encephalitis, because most anesthetics have some effect on the NMDA receptor. This means that the choice of anesthetic may influence the postoperative status. Anesthesia type is also important because it will affect the dose of anesthetic. Monitoring with BIS and TOF should be used to maintain appropriate anesthesia depth. These may effectively prevent deeper anesthesia. Unanticipated adverse effects of anesthesia can worsen postoperative status. These include delayed awakening from anesthesia, confusion, convulsions, apnea and hypoventilation after extubation, need for tracheal reintubation, aspiration and aspiration pneumonia, among others.

To manage these anesthesia-related adverse effects, understanding of the clinical entity of anti-NMDA receptor encephalitis is necessary.

3.1. Pathology

Anti-NMDA receptor encephalitis is considered an autoimmune disorder, in which autoantibodies produced by B-cells act against ion channels and synaptic receptors.[1,4] A recent theory has suggested a mechanism for the trigger. First, some ovarian teratomas contain neuronal tissue, in which NMDA receptors are expressed. Second, if these neurons are incidentally transported to regional lymph nodes, B-cells are exposed to the NMDA receptors. These B-cells migrate and reach the brain across the blood–brain barrier. Third, the B-cells differentiate into plasma cells in the brain, producing anti-NMDA receptor antibodies. The plasma cells continue to synthesize antibodies in the brain. These selectively combine with and internalize NMDA receptors, that is, NR1/NR2 heteromers, in both excitatory and inhibitory hippocampal neurons, and then induce synaptic current reduction. Finally, the antibodies disrupt NMDA receptor-related cognitive networks, and induce psychotic dysfunction. Involvement of the respiratory center in the brainstem causes breathing difficulty, and an impaired autonomic nervous system can cause arrhythmias, hypertension, and hypersalivation.

Anti-NMDA receptor encephalitis has the characteristics of a paraneoplastic syndrome. Other pathologic mechanisms may be involved, in which case, ovarian cystectomy will not promote recovery.

3.2. Clinical course and treatment

Clinical manifestations are classified into 5 phases.[7,10,11] In the *prodromal phase*, symptoms of infection appear, and may resemble a common cold. In the *psychotic phase*, torpor, depression, schizophrenia-like symptoms, and abnormal behavior appear. Convulsions may occur in the phase. In the *unresponsive phase*, catatonic-like behavior appears, with akinesia and silence that disappear in response to verbal stimulation. In the *hyperkinetic phase*, orofacial dyskinesia and athetosis-like dystonia of the fingers appear. Almost all patients gradually recover (*Gradual recovery phase*).[7]

The clinical features vary. Severity may depend on the correct diagnosis and prompt treatment because impairment of NMDA receptors leads to functional deficits. Most patients (75%) who are diagnosed early and treated appropriately will recover, but some cases (7%) will ultimately be fatal.[10] Severity of symptoms tends to be related to the anti-NMDA receptor antibody titer, but despite appropriate treatment, there may be no significant difference in prognosis between those with and without severe symptoms.[11]

Early tumor resection and immune therapy are recommended in cases with ovarian teratoma. Steroid pulse therapy, plasma exchange, and intravenous immunoglobulin therapy are effective.

3.3. Influence of anesthetic drugs

The choice of anesthetic drugs for surgery can be difficult.[12] This disease interferes with NMDA receptors. Thus, encephalitis can worsen with administration of anesthetic drugs because they act on NMDA receptors.

3.4. Ketamine, nitrous oxide

These are NMDA receptor antagonists, and can influence the clinical manifestation of encephalitis. *Volatile anesthetics* (isoflurane, sevoflurane, desflurane): It is known that volatile anesthetics inhibit 50% of NMDA receptor-mediated currents at levels close to minimum alveolar anesthetic concentration. The density of the anesthetic affects the NMDA receptor. *Propofol*: Gamma-aminobutyric acid receptors play an important role in anesthesia with propofol. However, some studies reported that propofol indirectly affects NMDA receptors. *Opioids* (fentanyl, remifentanil, morphine): Recent studies revealed that the effect of opioids may be decreased in patients with anti-NMDA receptor antibody encephalitis because the NR1 subunit is conjugated with anti-NMDA receptor antibody. Hence, a relatively large amount of opioid may be necessary for analgesia. However, opioids should be carefully administered in these patients because of the risk of central hypoventilation.

3.5. Choice of anesthesia method

A previous report[24] described general anesthesia in combination with a peripheral nerve block (actually, more such cases were performed, but the reports did not describe the anesthesia method in detail). General anesthesia has been chosen predominantly for patients with anti-NMDA receptor antibody encephalitis. Among such cases, volatile inhalation anesthesia was used in

Table 1

Postoperative adverse events of patients with anti-NMDA receptor encephalitis.

Anesthesia	Clinical stage	Case	Postoperative adverse events
Inhalation anesthesia	Psychotic phase	6[5,13,14]	3 (pneumonia: 1[14], VAP: 2[14])
	Unresponsive phase	5[5,15–17]	2 (re-intubation: 1[5], hypoventilation: 1[15])
	Hyperkinetic phase	2[9,18]	0
	Gradual recovery phase	2[2,14]	0
TIVA	Psychotic phase	3[13,19,20]	0
	Unresponsive phase	1[21]	0
	Hyperkinetic phase	4[9,21–23]	0
	Gradual recovery phase	1[14]	0
	Unclassified	1[24]	0
TIVA+PNB	Unresponsive phase	1[21]	0
PNB	Psychotic phase	1[25]	0

NMDA = *N*-methyl-D-aspartate; PNB = peripheral nerve block; TIVA = total intravenous anesthesia; VAP = ventilator-associated pneumonia.

15 cases and total intravenous anesthesia (TIVA) in 10 cases. There have been no reports of spinal or epidural anesthesia, possibly because of potential worsening of encephalitis from local anesthetic toxicity.

The patients may have difficulty perceiving pain because NMDA receptors are inhibited. Hence, a peripheral nerve block, that is, a transabdominal plane block can be performed for open lower abdominal surgery for ovarian cystectomy. However, it may be difficult to achieve complete intraoperative analgesia using only a peripheral nerve block in laparoscopic surgery.

3.6. Anesthesia monitoring

Patients with anti-NMDA receptor encephalitis may have altered sensitivity to general anesthesia, causing a problem with anesthesia depth. These patients have impaired nerve conduction through the NMDA receptors that are closely related to anesthesia depth. Balanced anesthesia may resolve this problem. However, it is unclear whether anesthesia monitoring using BIS and TOF can be performed and evaluated as usual. Evaluation of anesthesia depth with BIS in this disease is difficult because of the presence of epilepsy waves and generalized slow waves. It may important to assess BIS before anesthesia induction to determine appropriate anesthesia depth for each patient. Certainty of muscle relaxant reversal is necessary before tracheal extubation due to the risk of central hypoventilation. However, it is difficult to evaluate muscle relaxation with TOF because of reduced tone.

3.7. Adverse events during the postoperative period

Postoperative adverse events may induce psychological, circulatory, and respiratory complications (Table 1). We searched for previous reports of general anesthesia in patients with anti-NMDA receptor encephalitis using PubMed, and found 27 cases. These cases included ovarian cystectomy (laparoscopic surgery in 12, open surgery in 8), percutaneous endoscopic gastrostomy (4 cases), lumbar puncture for cerebrospinal fluid examination (2 cases), and emergent cesarean section (1 case).

Complications include delayed awakening, unconsciousness, and drowsiness, requiring artificial respiration (1 case); involuntary movement and ataxia (1 case); and seizures (1 case). Delayed awakening may be related to relatively deep anesthesia, but other complications were not clearly recognized as side effects, and were not listed in Table 1. Circulatory complications can occur postoperatively, but no cases were reported. Respiratory complications included hypoventilation, pneumonia (1 case), and ventilator-associated pneumonia (VAP, 2 cases). Hypoventilation was a major complication. Hence, artificial respiration was performed preoperatively in 3 cases, but reintubation in the intensive care unit was reported (1 case).

3.8. Appropriate anesthesia method

Inappropriate anesthesia may cause adverse events postoperatively. Review of previous reports suggests that postoperative adverse events were mostly respiratory-related complications. These included postoperative delayed awakening, need for reintubation, pneumonia, and VAP. All were reported in cases of inhalation anesthesia. Therefore, we recommend TIVA in preference to inhalation anesthesia.

In addition to our patient, 1 previous case underwent TIVA with PNB. Based on the pathology and pharmacology, addition of PNB should be recommended. Only 1 case reported successful anesthesia using a combination of PNB (transversus abdominis plane) and opiate (fentanyl, morphine) for laparoscopic ovarian cystectomy. However, whether regional anesthesia during laparoscopic surgery can prevent hypoventilation and aspiration is unclear.

Our case was successfully treated using TIVA with PNB. We believe that TIVA with PNB may be the most appropriate anesthesia method for ovarian cystectomy in a patient with anti-NMDA receptor encephalitis.

3.9. Informed consent

A written informed consent for publication of this case was obtained from the patient.

Author contributions

Conceptualization: Akira Motoyasu, Harumasa Nakazawa, Joho Tokumine.
Data curation: Nozomi Wada, Kayoko Tashima.
Supervision: Harumasa Nakazawa, Joho Tokumine, Mieko Chinzei, Tomoko Yorozu.
Writing – original draft: Nozomi Wada, Harumasa Nakazawa, Joho Tokumine.

References

[1] Dalmau J. NMDA receptor encephalitis and other antibody-mediated disorders of the synapse: the 2016 Cotzias Lecture. Neurology 2016;87:2471–82.

[2] Kawano H, Hamaguchi E, Kawahito S, et al. Anaesthesia for a patient with paraneoplastic limbic encephalitis with ovarian teratoma: relationship to anti-*N*-methyl-D-aspartate receptor antibodies. Anaesthesia 2011;66:515–8.
[3] Kamei S, Kuzuhara S, Ishihara M, et al. Nationwide survey of acute juvenile female non-herpetic encephalitis in Japan: relationship to anti-*N*-methyl-D-aspartate receptor encephalitis. Intern Med 2009;48:673–9.
[4] Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8.
[5] Pryzbylkowski PG, Dunkman WJ, Liu R, et al. Case report: anti-*N*-methyl-D-aspartate receptor encephalitis and its anesthetic implications. Anesth Analg 2011;113:1188–91.
[6] Sansing LH, Tuzun E, Ko MW, et al. A patient with encephalitis associated with NMDA receptor antibodies. Nat Clin Pract Neurol 2007;3:291–6.
[7] Iizuka T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. Neurology 2008;70:504–11.
[8] Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25–36.
[9] Pascual-Ramirez J, Munoz-Torrero JJ, Bacci L, et al. Anesthetic management of ovarian teratoma excision associated with anti-*N*-methyl-D-aspartate receptor encephalitis. Int J Gynaecol Obstet 2011;115:291–2.
[10] Wojtowicz R, Krawiec M, Orlicz P. Autoimmune anti-*N*-methyl-D-aspartate receptor encephalitis—the current state of knowledge based on a clinical case. Anaesthesiol Intensive Ther 2018;50:34–9.
[11] Zhang Y, Liu G, Jiang M, et al. Clinical characteristics and prognosis of severe anti-*N*-methyl-D-aspartate receptor encephalitis patients. Neurocrit Care 2018;29:264–72.
[12] Kingston S, Mao L, Yang L, et al. Propofol inhibits phosphorylation of *N*-methyl-D-aspartate receptor NR1 subunits in neurons. Anesthesiology 2006;104:763–9.
[13] Splinter WM, Eipe N. Anti-NMDA receptor antibodies encephalitis. Paediatr Anaesth 2009;19:911–3.
[14] Gong YH, Zhang MZ, Zhang XH, et al. Potential effect of preoperative immunotherapy on anesthesia of patients with anti-*N*-methyl-D-aspartate receptor encephalitis. Chin Med J (Engl) 2015;128:2972–5.
[15] Liao Z, Jiang X, Ni J. Anesthesia management of cesarean section in parturient with anti-*N*-methyl-D-aspartate receptor encephalitis: a case report. J Anesth 2017;31:282–5.
[16] Simon RW. Anesthetic management and implications of pediatric patients with a diagnosis of anti-*N*-methyl-D-aspartate receptor encephalitis: two case reports. AANA J 2014;82:431–6.
[17] Yamanaka D, Kawano T, Tateiwa H, et al. Successful management of dexmedetomidine for postoperative intensive care sedation in a patient with anti-NMDA receptor encephalitis: a case report and animal experiment. Springerplus 2016;5:1380.
[18] Lapebie FX, Kennel C, Magy L, et al. Potential side effect of propofol and sevoflurane for anesthesia of anti-NMDA-R encephalitis. BMC Anesthesiol 2014;14:5.
[19] Liu H, Jian M, Liang F, et al. Anti-*N*-methyl-D-aspartate receptor encephalitis associated with an ovarian teratoma: two cases report and anesthesia considerations. BMC Anesthesiol 2015;15:150.
[20] Sato M, Yasumoto H, Arai T. General anesthesia with propofol for ovarian teratoma excision associated with anti-*N*-methyl-D-aspartate receptor encephalitis. JA Clin Rep 2018;4:14.
[21] Broderick DK, Raines DE, Nanji KC. Total intravenous anesthesia using *N*-methyl-D-aspartate (NMDA) receptor-sparing drugs in a patient with anti-NMDA receptor encephalitis. A A Case Rep 2014;2:83–5.
[22] Arteche Andres MA, Zugasti Echarte O, de Carlos Errea J, et al. Anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma: Description of a case and anesthetic implications. Rev Esp Anestesiol Reanim 2015;62:468–71.
[23] Lang Y, Wang T, Lan F, et al. Anesthesia management for a patient with anti-NMDA receptor encephalitis undergoing ovarian tumor resection. Chin Med J (Engl) 2014;127:2197–8.
[24] Senbruna B, Lerman J. Anesthesia management for a boy with anti-*N*-methyl-D-aspartate receptor rncephalitis. A A Case Rep 2015;5:182–4.
[25] Chaw SH, Foo LL, Chan L, et al. Anesthesia in anti-*N*-methyl-D-aspartate receptor encephalitis—is general anesthesia a requisite? A case report]. Rev Bras Anestesiol 2017;67:647–50.