

# Potential Effect of Preoperative Immunotherapy on Anesthesia of Patients with Anti-N-methyl-D-aspartate Receptor Encephalitis

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Anti-N-methyl-D-aspartate receptor (anti-NMDA-R) encephalitis is a newly recognized neuro-autoimmune disease. Patients usually present with a series of neurological and psychiatric syndromes including memory impairment, seizures, dyskinesia, autonomic nervous system dysfunction, etc. Anti-NMDA-R encephalitis usually affects young women with teratoma being a common co-existing condition in nearly 47% of the diagnosed patients. Previous studies have shown that teratoma removal, being the current first-line therapy, may enhance the effectiveness of autoimmune therapy and decrease the incidence of relapse.<sup>[1]</sup> However, poorly controlled encephalitis poses as a perioperative anesthetic risk. Therefore, timing of the surgery is of great concern and is a question yet to be answered. Due to low incidence of anti-NMDA-R encephalitis in general population, literature of the perioperative management in these group of patients is scarce. Only few case reports were found yet, none has discussed the issue of surgery timing. In this study, 6 patients with anti-NMDA-R encephalitis undergoing teratoma removal were reviewed, and timing of surgery and anesthetic management for these patients were discussed.

A computerized search of the Medical Records Database was conducted from June 2011 to May 2014 to identify patients with anti-NMDA-R encephalitis and ovarian teratoma. Approval from Institutional Review Board of Peking Union Medical College Hospital (PUMCH) was obtained. Patients who underwent tumor removal under

general anesthesia were included. Data record include age, sex, clinical presentations, laboratory findings, diagnostic modalities (electroencephalogram [EEG], cranial magnetic resonance imaging [MRI], serum/cerebrospinal fluid [CSF] autoantibody test, and abdominal ultrasound), preoperation immunotherapy (drugs and dosage) and status of disease control, anesthesia course (anesthetic and emergence), and postoperative course (postoperative mechanical ventilation time, Intensive Care Unit [ICU] length of stay [LOS], and postoperative LOS). Diagnosis of anti-NMDA-R encephalitis as well as evaluating status of disease was double confirmed by a senior neurologist from PUMCH specializing in autoimmune encephalitis.

Six female patients with anti-NMDA-R encephalitis were identified from the electronic database. They were numbered as Patient 1 to Patient 6 randomly. The age of the six patients was 22, 26, 28, 32, 10, and 30 years, respectively. They were generally in good health otherwise from teratoma and encephalitis. All six patients were diagnosed with

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anti-NMDA-R encephalitis by the combination of clinical presentation, EEG, MRI, and serum/CSF anti-NMDA-R antibody test. All the patients present with psychiatric symptoms, seizures, and disturbances of consciousness during the course of disease; four (Patient 1, 3, 4, and 5) had autonomic instability including arrhythmia (sinus tachycardia or sinus bradycardia) and central hypoventilation.

Before the operation, three patients (Patient 1, 2, and 3) received intravenous immunoglobulin (IVIg), two patients (Patient 4, 5) received IVIg and corticosteroids. One patient (Patient 6) received IVIg, corticosteroids, plasma exchange therapy, as well as cyclophosphamide treatment. After immunotherapy, two patients (Patient 4, 6) experienced near-complete recovery and other four patients still have psychiatric symptoms and seizures. One patient was transferred to ICU with cardio-respiratory support due to respiratory insufficiency [Table 1].

All six patients underwent laparoscopic ovarian cystectomy under general anesthesia. For the two near-complete-recovery patients, induction was carried out with propofol, morphine, and cisatracurium for Patient 4 and propofol, midazolam, fentanyl, and rocuronium for Patient 6. Anesthesia was maintained with targeted controlled infusion of propofol (effect-site concentration of 3–4 µg/ml) + 1:1 air in oxygen for Patient 4, and sevoflurane + 1:1 N<sub>2</sub>O in oxygen for Patient 6. Both of the patients emerged from anesthesia uneventfully and were extubated right after the operation. They were sent back to general ward. No anesthesia-related complications or exacerbation of neurological symptoms were noted after the surgery. For the rest four patients whose symptoms were not well-controlled, anesthesia induction was with propofol, fentanyl, and rocuronium. Anesthesia maintenance was with sevoflurane + 1:1 air in oxygen for Patient 3, 5 and with sevoflurane + 1:1 N<sub>2</sub>O in oxygen for Patient 1, 2. All of them were transferred to ICU with tracheal intubation. Patient 3 was extubated 1-day after surgery without anesthesia-related complications. Patient 1, 2, and 5 were kept intubated after surgery for 46, 4, and 21 days, respectively, and all of them developed ventilator-associated pneumonia or pulmonary infection due to prolonged intubation. Two patients (Patient 1, 5) received tracheotomy and Patient 1 underwent unexpected tube prolapse due to dysphoria. Patients who got pneumonia recovered after treatment with antibiotics and the tracheostoma healed up before discharge [Table 2].

Postoperative ventilation time, ICU LOS, and postoperative LOS were longer in the patients whose symptoms were poorly controlled after autoimmune therapy (Patient 1, 2, and 5) than well-controlled ones (Patient 4, 6).

Management of anti-NMDA-R encephalitis mainly involves immunotherapy and removal of the teratoma if present together. Early tumor removal was strongly advocated for patients with anti-NMDA-R encephalitis by some authors,<sup>[1]</sup> but the appropriate timing for surgery is still unknown. This study highlights the importance of adequate immunotherapy

before surgery. Patients with poor disease control had longer postoperative invasive ventilation time, ICU LOS, postoperative LOS, or higher incidence of pulmonary complications while patients with better disease control had a smoother recovery. Therefore, it is assumed that although tumor removal may enhance the effectiveness of drug therapy, inadequate preoperative therapy may prolong postoperative ventilation time and result in unwanted pulmonary complications. This suggests that it may be appropriate to provide adequate immunotherapy for patients with anti-NMDA-R encephalitis before the surgery. Patient 1 and Patient 5 share similar status of preoperative disease control, but Patient 5 who received both IVIg and methylprednisolone led a relatively better recovery than Patient 1 who received only IVIg. This suggested that intensive combined treatment might be beneficial to patients with severe anti-NMDA-R encephalitis.

Many anesthetic drugs can inhibit NMDA-R, and may induce the same symptoms as those observed in anti-NMDA-R encephalitis. NMDA-R can be strongly inhibited by nitrous oxide and ketamine. Therefore, it is presumed that patients with anti-NMDA-R encephalitis may be more sensitive to ketamine and nitrous oxide, which may aggravate the symptoms of encephalitis transiently during or after the operation. As a consequence, most authors suggested that ketamine and nitrous oxide should be avoided during the anesthesia.<sup>[2]</sup> But in our cases, nitrous oxide had been used in three patients. The effect of nitrous oxide on encephalitis could not be accessed due to continued sedation in ICU. In one patient whose symptom had been well-controlled before surgery thus was transferred to general ward without further sedation, no symptom deterioration was noted after anesthesia.

Inhalational anesthetics are strong inhibitors of NMDA-R but not specific. They can also act on other ligand-gated ion channels such as GABAA and glycine receptors. Propofol seems to produce general anesthesia mainly by enhancing GABA pathway.<sup>[2]</sup> But a recent *in vitro* study showed that propofol may also block NMDA-R at the concentrations routinely used in general anesthesia<sup>[3]</sup> although the clinical relevance of this inhibition is not established. Therefore, the clinical effect of inhalational anesthetics and propofol on anti-NMDA-R encephalitis is still eluding. However, Lapébie *et al.*<sup>[4]</sup> did report a case of symptom deterioration after general anesthesia with propofol and sevoflurane. Splinter and Eipe<sup>[5]</sup> reported pronounced hypotension secondary to propofol injection at induction of anesthesia for diagnostic lumbar puncture. These suggest that patients with anti-NMDA-R antibody may be sensitive to propofol and sevoflurane. Interestingly, Splinter and Eipe<sup>[5]</sup> also reported that another lumbar puncture was performed several months later for the same patient with propofol and no hypotension happened. In this study, propofol and sevoflurane were separately used for two patients whose symptoms had been well-controlled. Both of them were extubated immediately and emerged uneventfully after the surgery. Neither hypotension nor

**Table 1: Autoimmune therapy, status of preoperative symptom control and postoperative recovery of the six patients**

Patient number	Autoimmune therapy			Preoperative symptoms				Postoperative recovery	
	IVIg	Methylprednisolone	Second-line therapy	Psychiatric symptoms	Seizures	Disturbances of consciousness	Autonomic instability	Postoperative ventilation time (d)	ICU LOS/postoperative LOS (d)
1	20 g/d × 5 d × 4 periods	N/A	N/A	+	+	+	+	46	5/90
2	25 g/d × 5 d × 2 periods	N/A	N/A	+	—	+	—	4	3/28
3	20 g/d × 5 d × 2 periods	N/A	N/A	+	—	+	+	1	1/2
4	20 g/d × 3 d (withdrawn due to allergic reaction)	1 g × 5 d	Plasmapheresis CTX	—	—	—	—	0	0/1
5	20 g/d × 5 d	240 mg × 5 d 40 mg × 15 d 20 mg × 13 d	N/A	+	+	+	+	21	28/30
6	2 g/kg × 5 d	1 g × 3 d 500 mg × 3 d 240 mg × 7 d 80 mg × 14 d	N/A	—	—	—	—	0	0/1

+: Symptom is uncontrolled; —: Symptom is well-controlled; IVIg: Intravenous immunoglobulin; ICU: Intensive Care Unit; LOS: Length of stay; CTX: Cyclophosphamide; N/A: Not available.

**Table 2: Anesthetic management for the six patients with anti-NMDA-R encephalitis**

Patient number	Induction	Maintenance	Duration of surgery (min)	Postoperative care	Postoperative complications
1	Propofol 130 mg Midazolam 2 mg Fentanyl 50 µg Rocuronium 30 mg	50% O <sub>2</sub> 50% N <sub>2</sub> O 1.5–2.0% sevoflurane	50	ICU	Ventilator-associated pneumonia, left atelectasis, tube prolapsed, tracheotomy
2	Propofol 90 mg Midazolam 2 mg Fentanyl 100 µg Rocuronium 40 mg	50% O <sub>2</sub> 50% N <sub>2</sub> O 1.5–2.0% sevoflurane	70	ICU	Pulmonary infection
3	Propofol 100 mg Midazolam 1 mg Fentanyl 100 µg Rocuronium 50 mg	50% O <sub>2</sub> 50% air 1.5–2.0% sevoflurane	90	ICU	—
4	Propofol 4 µg/ml (TCI, Marsh) Morphine 6 mg Cisatracurium 8 mg	Propofol (TCI) (effect-site concentration 3–4 µg/ml) 50% air	30	General ward	—
5	Propofol 120 mg Fentanyl 50 µg Rocuronium 30 mg	50% O <sub>2</sub> 50% air 1.5–2.0% sevoflurane	30	ICU	Ventilator-associated pneumonia, tracheotomy
6	Propofol 150 mg Midazolam 1 mg Fentanyl 100 µg Rocuronium 40 mg	50% O <sub>2</sub> 50% N <sub>2</sub> O 1.5–2.0% sevoflurane	30	General ward	—

ICU: Intensive Care Unit.

symptom deterioration had been found. So, we hypothesize that patients without disease control may be sensitive to anesthesia agents such as sevoflurane and propofol. While in patients whose preoperative symptom is under control, it may be safer to use sevoflurane, propofol, and nitrous oxide. But further investigation with more cases is needed to validate our findings.

Our study shows that adequate preoperative immunotherapy and good disease control may be critical to anesthetic and postoperative management of patients with anti-NMDA-R encephalitis. Limited data show that commonly used anesthetics such as propofol, sevoflurane, and N<sub>2</sub>O may be safe for patients whose encephalitis had been well-controlled with immunotherapy.

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## Conflicts of interest

There are no conflicts of interest.

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