J Anesth (2017) 31:282–285
DOI 10.1007/s00540-016-2304-0

CLINICAL REPORT

# Anesthesia management of cesarean section in parturient with anti-*N*-methyl-D-aspartate receptor encephalitis: a case report

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Received: 21 September 2016 / Accepted: 23 December 2016 / Published online: 9 January 2017


**Abstract** A 24-year-old woman at 29 weeks' gestation, and with psychiatric symptoms, was admitted to hospital and diagnosed as having anti-*N*-methyl-D-aspartate receptor encephalitis. After 4 weeks of immunotherapy with little effect, an emergency cesarean section was performed at $33^{+4}$ weeks gestation under general anesthesia. The parturient was intubated after rapid sequence induction with etomidate, remifentanil and succinylcholine. Anesthesia was maintained with sevoflurane and remifentanil. Except for low weight, the infant was normal at birth. The surgery went uneventfully and teratoma or other masses were not found. The parturient was sent to ICU for further treatment without extubation after surgery. She was extubated on the 6th day after surgery and was transferred to the general ward of the neurology department to control her seizures. After the seizures were controlled, she was discharged home on the 80th postoperative day and her neurological symptoms had slowly improved half a year later. This case report presents the anesthetic considerations in patients with anti-NMDAR encephalitis undergoing cesarean section.

**Keywords** Anti-*N*-methyl-D-aspartate receptor encephalitis · Anesthesia management · Cesarean section

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## Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an immune-mediated syndrome characterized by psychosis and autonomic dysfunction, such as catatonia, agitation, visual and auditory hallucinations, seizure, hypotension, hypertension and hypoventilation [1, 2]. This disease was first reported by Dalmau et al. in 2007 [1]. Anti-NMDAR encephalitis is predominantly found in young women with ovarian teratoma (80%) [3], but has also been reported in pregnant women [4], men, and children without teratoma [5]. There have been a few reports about anesthesia management of ovarian tumor resection in patients with anti-NMDAR encephalitis [6–9], but no one has reported on the anesthesia management of cesarean section in those parturients, which should concern both mother and baby. In the current case, we discuss the anesthesia management of cesarean section in a parturient with anti-NMDAR encephalitis.

## Case report

A 24-year-old previously healthy woman (height 162 cm, weight 70 kg) with her first pregnancy was admitted to a psychiatric ward at 29 weeks gestational age. She was conscious but presenting psychiatric symptoms, including akamathesis, catatonia, agitation, delirium, and visual and auditory hallucination. Cerebrospinal fluid examination and brain magnetic resonance imaging were normal. The electroencephalogram revealed a paroxysmal middle-slow mixed wave. She was suspected of having intracranial infection and treated with acyclovir, but with little effect. On the 14th day after admission, repeated generalized

**Table 1** The different clinical syndromes of anti-NMDAR

| Clinical features |
|---|
| Prodromal symptoms Headache, fever, nausea, vomiting, diarrhea, upper respiratory-tract symptoms |
| Psychiatric symptoms Anxiety, insomnia, fear, grandiose delusions, hyper-religiosity, mania, paranoia, hallucinations, amnesiac, social withdrawal, stereotypical behavior |
| Autonomic instability Hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, erectile dysfunction |
| Seizures Dyskinesia, abnormal movement, epileptic seizure, status epilepticus |

seizure and intermittent conscious disturbance emerged. Testing was unremarkable for other diseases, such as autoimmune disorders, viral infection and heavy-metal poisoning. On the 18th day, the antibodies of NMDAR were detected in serum and cerebrospinal fluid, and anti-NMDAR encephalitis was confirmed. The parturient was transferred to the neurology department and was treated with high dose corticosteroid and immunoglobulins for 10 days but did not get better. On the 28th day, she was transferred to an obstetrics department at $33^{+2}$ weeks' gestation. On the 30th day, the fetal monitor showed no reactivity of the non-stress test (NST), and an emergency cesarean section was performed after dexamethasone was administered.

When arriving at the operation room, the Glasgow coma score of the parturient was 12 (3 + 4 + 5). Thirty milliliters of sodium citrate was administered. Her initial vital signs were: BP 120/80 mmHg, HR 98 beats/min, $SpO_2$ 94% (breathing 5l/min oxygen), RR 25 beats/min. The arterial blood gas analysis showed a pH of 7.35, a $PaO_2$ of 85 mmHg and a $PCO_2$ of 55 mmHg. The parturient lay in a supine position with left tilt of the uterus until baby delivery. General anesthesia was prepared. After rapid sequence induction with etomidate 14 mg, remifentanil 80 μg and succinylcholine 100 mg, a 7.0-mm ID tracheal tube was intubated. The infant was born 3 min later and weighed 2250 g. The parturient was administered 3 mg midazolam, 20 μg sufentanil and 10 mg cisatracurium. Anesthesia was maintained with 2% sevoflurane and 0.1 μg/kg/min remifentanil. The patient's vital signs were stable and BIS was 40–50 throughout surgery. The Apgar scores were 9, 10, 10 at 1, 5 and 10 min after delivery. The obstetrician explored the abdomen and the pelvis. Teratoma or other masses were not found. After the surgery, the patient had 4 switches in train-of-four testing with a 50-mA current. Nevertheless, the tidal volume was still less than 300 ml and pulse oxygen saturation was in the range of 85–90% while breathing room air. The patient was transferred into ICU without extubation. The duration of surgery and anesthesia were 66 min and 95 min, respectively. The intraoperative blood lose was approximately 340 ml, urine output was 400 ml, and administered crystalloid was 1000 ml. Intravenous infusion of sufentanil was administered for postoperative analgesia (0.5 μg/ml, 6 ml/h). After the operation, a nasogastric tube was given for nutrition support.

Ten hours after surgery, a generalized tonic–clonic seizure occurred which gradually developed to 3–5 times a day. Levetiracetam and sodium valproate were administered to control her seizures; midazolam and sufentanil were intravenously infused for sedation and analgesia until extubation. Multi-treatments were continued in ICU including administration of immunoglobulin, corticosteroids, plasmapheresis, rituximab and cyclophosphamide and supportive mechanical ventilation. She was weaned from the ventilator and was extubated on the 6th day after surgery. On the next day, she was transferred to the general ward of the neurology department. Antiepileptic and sedation drugs were administered to control the seizures, which gradually reduced to 1–2 times a week. On the 80th day after surgery, the seizures were finally controlled and the patient was discharged home. At the 6-month follow-up, the patient's neurological symptoms had been slowly improving, but antibodies of NMDA receptors in serum and cerebrospinal fluid were still weakly positive. The baby grew normally without obvious adverse effects.

## Discussion

Anti-NMDAR antibodies selectively combine to NR1 subunits of NMDAR, and cause a reversible decrease of post-synaptic NMDAR density at the glutamatergic synapse which correlates with antibody titers [10]. An increase of anti-NMDAR antibodies could result in anti-NMDAR encephalitis, whose clinical syndrome is similar to the behavioral effects of NMDA antagonists such as ketamine. This disease mainly occurs in young females with or without ovarian teratoma [2, 3]. Its diagnosis depends on testing for special antibodies in serum and cerebrospinal fluid. Four different syndromes have been identified in anti-NMDAR encephalitis patients, including atypical prodromal symptom, psychiatric and neurological symptoms, autonomic instability, and seizures (Table 1) [11]. Currently, corticosteroids, immunoglobulin, plasmapheresis, immunosuppressants, removal of presented teratoma, and supportive care are recommended to treat anti-NMDAR encephalitis [12].

As this parturient was in a state of unstable consciousness and epileptic seizures, general anesthesia was chosen. GABA receptors and NMDA receptors are the two main target sites of anesthetics. Ketamine, nitrous oxide, tramadol, magnesium, and xenon are well-known NMDAR antagonists. They inhibit NMDAR mediated excitatory neurotransmission in the nervous system [13]. Since the density of NMDAR was changed, the pharmacodynamics of those drugs on patients with anti-NMDAR encephalitis is unclear. Therefore, NMDAR antagonism should be avoided in this kind of patient.

Propofol and etomidate are GABA agonists, which have also been reported to act on NMDARs. These drugs were tolerated well by anti-NMDAR encephalitis patients [6–9]. Propofol has vasodilative and cardiodepressive effects, which might be magnified in patients in comas. Etomidate can provide as deep a sedation as propofol, but without hemodynamic fluctuation. In this long-term bedridden comatose parturient, who also had autonomic dysfunction, the abnormality of circulation capacity and sympathetic activity had to be considered, so we chose a regular dosage of etomidate for anesthesia induction.

Inhaled anesthetics primarily act on GABA receptors, but also inhibit NMDA receptors in the central nervous system [14]. Several cases [6, 7, 9] have reported that inhaled anesthetics are not harmful for anti-NMDAR encephalitis patients. Sevoflurane has been widely used in obstetrics anesthesia without harm for newborns [15]. In this patient, 2% sevoflurane was used to maintain BIS at 40–50 throughout the whole procedure. Lapébie et al. [16] suspected that sevoflurane and propofol might worsen the clinical presentation of anti-NMDAR encephalitis because a tonic–clonic generalized seizure occurred after surgery. As described in our case, and mentioned in most cases, motor and complex seizures are common symptoms of anti-NMDAR encephalitis which could develop at early stages of the disease [11]. Therefore, the occurrence of a seizure may be more due to the natural course of the disease than a side effect of anesthetics.

NMDAR antagonists can increase the analgesia effect of opioids and suppress symptoms of withdrawal [7, 9]. But, it does not appear that anti-NMDAR encephalitis patients require fewer hypnotics and opioids. In this case, we applied opioids for intraoperative and postoperative analgesia, at the normal dose. The protective laryngeal reflex and swallowing function is weakened in comatose patients. To prevent gastroesophageal reflux and aspiration, rapid sequence induction and endotracheal intubation with a visual laryngoscope were chosen.

Except for low weight, the infant was normal at birth. The antibodies of NMDAR were not detected in the newborn, and in the half-year follow-up, the baby grew and developed normally. Mathis et al. [4] summarized the current reports about anti-NMDAR encephalitis during pregnancy and found that most babies in those cases grew normally in the short-term but it was not clear what happened in the long term. The good outcome of these neonates might be due to the low level of blood IgG transfer after 14–16 weeks, and the fetal blood–brain barrier becomes functional at the end of the second trimester [17]. Further investigations and research on the long-term influences on the baby are expected.

In this case, the parturient had almost 4 months' hospitalization, and developed slight neurological sequelae. Mathis et al. [4] summarized 10 cases of anti-NMDAR encephalitis in pregnancy, and found that 3 cases were left with sequelae out of 5 parturients who had surgery; and 2 cases out of 5 parturients who did not have surgery. In the current literature, there is no evidence showing whether the anesthetics and anesthetic management influence the prognosis of anti-NMDAR encephalitis. Further observational study is needed.

In conclusion, this report describes the presenting symptoms and the specific anesthetic issues relevant to newborns and parturients with anti-NMDAR encephalitis. The controversial anesthetics that act on NMDARs should be avoided, and those which could potentially cause harm to parturients or newborns should be used at the right time and at the appropriate dosage.

#### Compliance with ethical standards

**Conflict of interest** This work was supported by grants from the Support Program of Sichuan Science and Technology Agency (2013FZ0005, Chengdu, China). The authors report no conflicts of interest.

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