Original Article

Anesthetic care for patients with anti-NMDA receptor encephalitis

ABSTRACT

Introduction: Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, an autoimmune disorder resulting from antibodies directed against the NMDA (glutamate) receptor, is the second most frequent cause of immune-mediated encephalitis. To date, the information related to the anesthetic care of children with this disorder is limited to anecdotal reports.

Methods: We reviewed the anesthetic care of six patients with anti-NMDA receptor encephalitis who underwent 21 procedures at our institution from 2014 through 2019.

Results: The study cohort included six patients, ranging in age from 2 to 18 years, who required anesthetic care during 21 procedures. Airway management included a laryngeal mask airway (n = 8), endotracheal intubation (n = 12), and native airway with spontaneous ventilation (n = 1). Intravenous (IV) induction with propofol was used in 17 procedures for five patients, including three that required rapid sequence intubation using rocuronium or succinylcholine. Inhalation induction with sevoflurane in nitrous oxide (N_2O)/oxygen (O_2) was chosen for two procedures in two patients. A combination of both induction techniques was used for two patients in two procedures. Maintenance anesthesia was accomplished with a volatile agent, predominantly sevoflurane, for 18 of the 21 procedures; propofol infusion for one procedure; and single dose of propofol was used for two short procedures. N_2O was not used for maintenance anesthesia in any of the encounters. None of the patients exhibited adverse events, including hemodynamic instability, thermoregulatory problems, or respiratory events perioperatively. Postoperatively, there was no observed deterioration in clinical status attributed to anesthetic care.

Discussion: Multisystem involvement in anti-NMDA receptor encephalitis includes memory loss, behavior irregularity, psychosis, arrhythmias, blood pressure (BP) instability, and hypoventilation. In our study cohort, we noted no intraoperative issues and deterioration in clinical status following the use of volatile anesthetic agents, opioids, dexmedetomidine, and propofol for general anesthesia (GA) or sedation. As ketamine, xenon, and N_2O mediate their anesthetic effects, primarily, through antagonism of NMDA receptors, theoretical concerns suggest that they should be avoided.

Key words: Anti-NMDA receptor encephalitis; autoimmune; encephalitis; NMDA receptor

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Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune disorder resulting from antibodies directed against the NMDA (glutamate) receptor. First reported in 2005 in a series of four women with ovarian teratomas, it is now recognized as the second most frequent cause of immune-mediated encephalitis.[1,2] The disorder has been most commonly reported in young African American women between 18 and 35 years of age.[2] However, cases in infants and the elderly have also been reported.[3-5] Clinical features include an initial presentation with psychosis, memory deficits, seizures, and language disintegration, which progresses to impaired consciousness, coma, and respiratory insufficiency.[6-8] Cardiovascular manifestations include arrhythmias, bradycardia progressing to cardiac arrest, hypotension, and autonomic instability. Prior to the characterization of the autoimmune nature of this disorder and its clinical features, patients were frequently erroneously diagnosed with schizophrenia and other mental health issues. The clinical symptomatology, cerebrospinal fluid (CSF) lymphocytosis, and an abnormal electroencephalogram (EEG) suggest the diagnosis with delta or theta activity. The diagnosis is confirmed by the presence of antibodies in the CSF against the NMDA receptor.[6,7]

Given its predominant neurologic presentation and the association with abdominal tumors (teratomas), patients with anti-NMDA receptor encephalitis often present for surgical or radiologic procedures that require anesthetic care. To date, there is limited evidence-based medicine regarding the anesthetic care of such patients, with information restricted to anecdotal reports including 1–2 patients.[9-13] The current report retrospectively reviews the anesthetic management of the largest series of pediatric cases of anti-NMDA receptor encephalitis.

Methods

This retrospective review was approved by the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). Patients with a diagnosis of anti-NMDA receptor encephalitis confirmed by clinical features of the disease and the presence of positive blood and CSF NMDA receptor antibody assays between 2014 and 2019 were identified from our electronic database. Patients who subsequently received anesthetic or procedural sedation care were included in the study cohort. Data retrieved included the patient demographic data; clinical presentation; type of procedure (radiological or surgical); and anesthetic management, including anesthetic agents used, type of induction, airway management technique, postoperative complications, and postanesthesia care unit (PACU) time. Specific postoperative complications included postoperative respiratory adverse events (PRAEs), including bronchospasm, laryngospasm, apnea/hypopnea, or hypoxemia/prolonged oxygen (O_2) requirement. The clinical significance of the event was then confirmed by the need for intervention or pharmacologic treatment. Bronchospasm was considered significant if treated with a bronchodilatory agent (albuterol, inhaled racemic epinephrine, intravenous (IV) epinephrine, ketamine). Laryngospasm was confirmed by the need for the application of positive pressure for O_2 saturation (SpO_2) <90% or the administration of propofol or succinylcholine. Apnea or hypopnea was defined as the need for bag-valve-mask ventilation. Hypoxemia/prolonged O_2 requirement was defined as the need for supplemental O_2 for >90 min to maintain O_2 saturation >90%. Hemodynamic adverse events were described as a heart rate less than the fifth percentile for age for bradycardia and systolic blood pressure (SBP) less than fifth percentile for age for hypotension. These events were judged clinically significant if the treatment with an anticholinergic agent, vasoactive agent, or fluid was administered.

Demographic data are presented as the mean ± standard deviation (SD). Categorical variables are summarized as counts with percentages. Continuous variables are summarized as medians with interquartile ranges (IQRs) and compared using rank sum tests.

Results

The study cohort included 6 patients (2 male and 4 female)—in 2 to 18 years age range and weighing between 11.6 and 77.2 kg—who required anesthetic care during 21 imaging, invasive, or surgical procedures [Table 1]. In all the cases, the patients' initial clinical presentation consisted of the sudden onset of psychobehavioral abnormalities, agitation, memory deficits, language disintegration, movement disorders, and/or seizures. Due to a decreased level of conciseness, one of the six patients required intensive care unit (ICU) admission, endotracheal intubation, and mechanical ventilation.

Table 1: Demographic data of the study cohort

Age (years)	Gender	Weight (kg)
2	Female	11.6
10	Male	38.1
15	Female	69.1
13	Female	44.5
15	Male	67.8
18	Female	77.2

Anesthesia was provided in three different locations, including the operating room (OR), interventional radiology suite, and radiologic imaging centers. Procedures included surgical interventions; insertion or removal of central venous access devices or feeding tubes; and diagnostic procedures, such as a lumbar puncture or central nervous system (CNS) imaging. The duration of the procedures ranged from 18 to 166 min.

Airway management included a laryngeal mask airway ($n = 8$), endotracheal intubation ($n = 12$), and native airway with spontaneous ventilation ($n = 1$). IV induction with propofol was used in 17 procedures for 5 patients, including 3 patients that required rapid sequence intubation, 1 using succinylcholine and 1 using rocuronium. Inhalation induction with sevoflurane in nitrous oxide (N_2O)/O_2 was chosen for two procedures in two patients. A combination of both induction techniques was used for two patients in two procedures. Maintenance anesthesia was accomplished with a volatile agent, predominantly sevoflurane, for 18 of the 21 procedures; propofol infusion was used for one procedure (placement of an NJ feeding tube); and single propofol bolus for two brief procedures (computed tomography [CT] imaging and feeding tube placement). N_2O was not used for maintenance anesthesia in any of the encounters. Midazolam was administered during three procedures and dexmedetomidine during two. Opioids administered included fentanyl and hydromorphone. The anesthetic agents administered during the procedures are listed in Tables 2 and 3.

There were no documented perioperative respiratory or hemodynamic complications. One patient who had required ICU admission preoperatively had a history of profound bradycardia and cardiac arrest that had previously required resuscitation. After concluding the procedures, the airway device was removed in all, except one patient, and they were transported to the PACU. One patient, who was receiving mechanical ventilation preoperatively, was returned to the pediatric ICU (PICU) with the endotracheal tube (ETT) in place. The PACU stay ranged from 15 to 70 min. Postoperatively, there was no observed deterioration in the clinical status attributable to anesthetic care.

Table 2: Anesthetic agents used in the study cohort

Medication	Number of patients	Number of procedures
Sevoflurane	6	12
Isoflurane	2	3
Sevoflurane then isoflurane	1	1
Desflurane	1	3
N_2O (induction)	3	4
Propofol for induction	5	19
Propofol for maintenance	1	1
Fentanyl	5	12
Hydromorphone	2	3
Midazolam	2	3
Dexmedetomidine	2	2

N_2O=Nitrous oxide

Table 3: Airway devices used in the cohort

Airway management	Number of patients	Number of procedures
Laryngeal mask airway	5	8
ETT	3	12
Nasal cannula	1	1

ETT=Endotracheal tube

Discussion

The NMDA receptor is a ligand-gated cation channel that is one of the three types of ionotropic glutamate receptors (iGluRs). Its binds glutamate and glycine; controls the transmembrane movement of cations; and regulates synaptic transmission, synaptic plasticity, and memory function. In anti-NMDA receptor encephalitis, antibodies are formed against the NR1–NR2 heteromers of the NMDA receptor, which bind glycine and glutamate, respectively.[14] The autoimmune process accelerates the destruction of the NMDA receptor, resulting in a decrease in their surface density, leading to decreased synaptic NMDA receptor-mediated currents and decreased glutamatergic synaptic function.[15,16] This depressed function leads to memory loss, behavior irregularity, psychosis, arrhythmias, and hypoventilation.

In our retrospective review of anesthetic care at our institution with patients having anti-NMDA receptor encephalitis, sedation or general anesthesia (GA) was provided for 21 procedures for diagnostic or therapeutic procedures. End organ involvement with anti-NMDA receptor encephalitis may include the CNS, cardiac system, and respiratory system. Autonomic nervous system involvement may include dysrhythmias (tachycardia), bradycardia progressing to cardiac arrest, and BP instability (hypotension or hypertension) because of autonomic dysfunction.[7,8] These episodes have been labeled "paroxysmal sympathetic hyperactivity or PSH". Although one of our patients manifested abrupt episodes of bradycardia and asystole during the early phase of her disease process within the ICU, no intraoperative problems were noted in our study cohort. However, based on the patient's clinical status, invasive hemodynamic monitoring may be indicated for patients and treatment with vasoactive agents required.

The primary involvement of the CNS is generally the presenting sign and may include the CNS excitability, including behavioral symptoms, abnormal movement, agitation, and seizures. In some patients, it may lead to a diminished response to verbal or tactile stimuli, central hypoventilation, bulbar abnormalities with risk of aspiration, obtundation, and coma requiring intubation and mechanical ventilation, as noted in one of our patients. In selected patients, as was encountered in our study cohort, rapid sequence intubation may be indicated based on the clinical scenario. For these patients, the neuromuscular blocking agent used included either rocuronium or succinylcholine. Alternatively, in patients with limited upper airway involvement, sedation with a native airway or supraglottic device may be appropriate. Anticonvulsant therapy should be optimized preoperatively and medications continued during the perioperative period.[17]

Although uncommon in the pediatric-aged patient, the disorder may be associated with abdominal teratomas, thereby requiring surgical intervention. Given the limited evidence-based medicine available regarding the effect of anesthetic agents on patients with this novel disorder, extrapolation from receptor pharmacology and animal data may be needed. The NMDA receptor and the gamma-aminobutyric acid (GABA) receptors are the two main receptors responsible for the actions of general anesthetic agents.[18] Reversible inhibition of the NMDA receptor by volatile anesthetic agents is concertation-dependent with the half-maximal inhibitory effect produced by isoflurane, sevoflurane, and desflurane at approximately 1.2 minimum alveolar concentration (MAC).[19] Propofol acts primarily on GABA receptors with 10–20% inhibition of NMDA receptors occurring at supraclinical dose.[20,21] Although the majority of anecdotal experience has reported the safe administration of propofol, the inhaled anesthetic agents, neuromuscular blocking agents (vecuronium and rocuronium), and opioids (fentanyl, remifentanil, and hydromorphone), Lapebie *et al*. reported worsening of their patient's neurologic status after GA with sevoflurane and propofol.[22] As this may have been merely a result of the primary disease process, it is not feasible to discern a causal relationship with the anesthetic agents used.

The anesthetic agents, ketamine, xenon, and N2O mediate their anesthetic effects directly through modulating NMDA receptor activity in the hippocampus and basolateral amygdala.[23-27] The predominant antagonism of the NR1 and NR2A-D subtype of the NMDA receptor by these anesthetic agents, especially ketamine, may mimic the primary presenting clinical features of the disorder, including psychosis, hallucinations, and delirium.[27] Given these pharmacologic interactions, theoretical concerns would suggest that these medications should be avoided during anesthetic care to prevent further decline in the NMDA receptor function.

In summary, anti-NMDA receptor encephalitis is an autoimmune disorder resulting from antibodies directed against the NMDA (glutamate) receptor. Antibodies to the NMDA receptor result in multisystem involvement that includes memory loss, behavior irregularity, psychosis, and hypoventilation. Autonomic nervous system involvement may include dysrhythmias, bradycardia progressing to asystole, and BP instability. The volatile anesthetic agents, propofol, dexmedetomidine, and opioids did not result in a further decline in our patients' status. Anecdotal experience has suggested the potential for an exaggerated effect of propofol on BP resulting in hypotension.[9,13] It has also been suggested that there may be decreased anesthetic requirements related to the effects of the disease process on the NMDA system.[28] Anesthetic care may be further impacted by therapeutic interventions, including the administration of immunosuppressive agents, corticosteroids, and plasmapheresis.

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Conflicts of interest
There are no conflicts of interest.

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