Anesthetic Management and Implications of Pediatric Patients With a Diagnosis of Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis: Two Case Reports

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This article discusses the anesthetic management and implications of 2 pediatric patients with a diagnosis of anti-N-methyl-D-aspartate (NMDA) receptor encephalitis. Anti-NMDA receptor encephalitis has been described as an immune-meditated syndrome that triggers the production of antibodies to the NMDA receptor: a site of action for many commonly used anesthetic agents. Symptoms of this disease can be autonomic, neurologic, and psychological in nature. This disease process can pose a challenge to the anesthesia provider during all stages of the anesthetic. Thus, the anesthesia provider must incorporate an understanding of the administered anesthetic agent's potential pharmacologic effect on the affected NMDA receptor when formulating the patient's anesthetic plan.

Keywords: Anesthesia, anti-NMDA receptor encephalitis, pediatric.

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis has been described as both an immune-mediated syndrome and a neurologic disorder seen primarily in females in conjunction with the presence of a mature ovarian teratoma.[1-3] Symptoms of this disorder were originally described in a 34-year-old woman with an underlying diagnosis of ovarian teratoma.[3] According to reports, her symptoms included neurologic, psychological, and autonomic involvement. Specific symptoms described included headache, anxiety, aggressive behavior, homicidal ideation, and seizures.[3] Autonomic instability was also documented and included hypotension, bradycardia, hypoventilation, hyperthermia and periods of asystole lasting up to 15 seconds.[3]

The first pediatric case was reported in 2007, and has since been deemed to be the most commonly reported cause of autoimmune-mediated encephalitis second only to acute demyelinating encephalitis.[4] Although symptoms of this disease in pediatric cases are similar to those in the adult population, the order of the onset of symptoms is different in the pediatric population because most reported cases occurring in patients under the age of 12 years occur in the absence of a tumor.[4] Cases have been reported in patients older than age 12 years; however, in those cases, tumors were detected either during the early stages of the disease or after symptoms of encephalitis resolved.[4]

There are very few case reports detailing the administration of anesthesia and its implications on the pediatric population with anti-NMDA receptor encephalitis. Therefore, the anesthetic implications in caring for the pediatric patient population with this disease process are not clearly defined. Presented here are 2 case reports detailing the administration of anesthesia to 2 separate pediatric patients with a diagnosis of anti-NMDA receptor encephalitis. Case 1 describes an 18-year-old female patient undergoing placement of a laparoscopic-assisted gastrostomy tube (G-tube). Case 2 describes a 13-year-old girl undergoing insertion of a double-lumen peripherally inserted central catheter, placement of a laparoscopically assisted G-tube, a microlaryngoscopy, and bronchoscopy as well as tracheostomy.

Case Summaries

• ***Case 1.*** Case 1 was an 18-year-old female patient with ASA class 4, a weight of 59 kg, and no known allergies, whose medical history contained nothing remarkable. While at a party to celebrate her high school graduation, she was witnessed by her family to have a tonic-clonic seizure. Following the seizure, the patient awoke with no memory of the event and was brought to the emergency room by her family. On her arrival to the emergency room, the patient's neurologic status had begun to deteriorate, leaving her expressively aphasic. The patient's medical history and family medical history included no seizures before this occurrence.

The patient was admitted to the pediatric intensive care unit (PICU), where she experienced blood pressure (BP) lability. In the course of a 10-minute period, her systolic BP was recorded as being less than 80 mm Hg twice and greater than 165 mm Hg 3 times. Blood and cerebrospinal fluid (CSF) cultures were obtained, and a magnetic resonance image (MRI) of the brain was ordered to rule out a brain tumor as the cause of

the seizure. The MRI showed no brain tumor, and the diagnosis of anti-NMDA receptor encephalitis was made based on the presence of NR1 antibodies in the CSF. All subsequent MRIs and computed tomographic (CT) scans of the chest, abdomen, and pelvis ordered showed no tumors present.

Over the next 3 weeks, the patient began to display signs and symptoms of autonomic dysregulation, and her condition continued to deteriorate. Her heart rate ranged from the mid-40s to low 100s per minute, and her systolic BP alternated from below 80 mm Hg to above 160 mm Hg. Neurologically, she became increasingly anxious but remained expressively aphasic. On PICU day 2, the patient experienced periods of apnea followed by desaturation, which necessitated intubation by the PICU team. She was placed on a regimen of high-dose corticosteroids, levetiracetam (Keppra), and rituximab, as well as midazolam (Versed) and fentanyl infusions for sedation. The patient's condition improved over the next month and approximately 1 week before her arrival in the operating room, the patient was extubated and received nasal cannulation.

The preanesthetic assessment in the preoperative holding area revealed the patient to be aphasic and extremely anxious. Increased drooling was noted along with difficulty swallowing. Vital signs taken in the preoperative area revealed a heart rate in the mid-50s and 60s per minute, a BP of 110/63 mm Hg, and a pulse oximeter reading of 98% on room air. The patient received 2 mg of midazolam intravenously (IV), and the decision was made to perform a rapid-sequence induction.

The patient was brought back to the operating room, and the full complement of monitors was placed. The patient was preoxygenated with 100% F_{IO_2}. Cricoid pressure was applied; then 60 mg of 2% lidocaine, 100 mg of propofol, 100 µg of fentanyl, and 100 mg of succinylcholine were administered IV. Also, 0.2 mg of glycopyrrolate was administered IV for antisialagogue effect. The patient was successfully intubated with a 7.0-mm cuffed endotracheal tube secured at 22 cm at the lip, and cricoid pressure was released. An esophageal temperature probe was then placed. A stress-dose regimen of corticosteroids (100 mg of hydrocortisone) was administered IV as well antibiotics given intraoperatively. Muscle relaxation was achieved via the administration of 7 mg of vecuronium before the start of the procedure. The patient was positioned supine, and an upper-body forced-air warming system (Bair Hugger, 3M) was placed and set to 43°C. Anesthesia was maintained with 6% to 7% desflurane for the duration of the operative case.

The case proceeded as planned, with the patient's vital signs remaining near their preoperative baseline throughout the case. Temperature and BP remained stable as well. The patient's heart rate increased to the low 100s per minute following administration of glycopyrrolate on induction but reverted back to a rate of 80/min before incision. Midway through the procedure the patient experienced a bradycardic episode in which her heart rate fluctuated between 40 and 45/min. This episode lasted approximately 5 seconds before returning to a rate of 76/min.

Reversal was achieved at the end of the case, with 0.6 mg of glycopyrrolate and 4 mg of neostigmine following the presence of 2 of 4 twitches on the train-of-four. Ondansetron (4 mg) was administered IV for antiemetic purposes approximately 30 minutes before completion of the case. The patient was successfully extubated and received 100% oxygen via "blow by," and was returned to the PICU postoperatively.

The patient continued to do well postoperatively and did not display any further signs of autonomic instability. She remained expressively aphasic but no longer appeared as anxious and was discharged from the PICU on postoperative day 4.

• ***Case 2.*** Case 2 was a 13-year-old girl with ASA class 4, weighing 54.5 kg, with no significant past medical history (except for an allergy to vancomycin). Her family reported that before attending cheerleader practice the patient demonstrated slurred speech and then experienced a seizure. Similar to case 1, the patient awoke with no memory of the event and was taken to the emergency room by her family. The patient's medical and family medical history also did not include seizures before this occurrence. She presented to the emergency room with elements of slurred speech, expressive aphasia, and mental slowing documented as having a pseudobulbar-like effect. The patient was admitted to the PICU and was placed on a regimen of divalproex sodium (Depakote) for seizure management.

Approximately 1 week following her admission, the patient began to experience left-sided weakness and posturing of the left arm. Blood samples and CSF cultures were obtained. An MRI of the brain was obtained as well as a pelvic ultrasound scan; both were normal, showing no signs of a mass or tumor. A CT scan of the abdomen and pelvis was performed and showed no tumor or mass but did reveal splenomegaly. Eventually the diagnosis of anti-NMDA receptor encephalitis was made based on the presence of NR1 antibodies along with lymphocytic pleocytosis (white blood cell count, 100×10^9/L per average high-power field; 93% lymphocytes) in the CSF; and the patient was placed on a regimen of high-dose prednisone and rituximab.

Over the next 2 weeks, the patient's condition continued to deteriorate. In the PICU, she displayed signs and symptoms of dysautonomia, which included episodes of profound bradycardia (heart rate in the 30s per minute) alternating with periods of tachycardia (heart rate > 150/min), as well as episodes of hypertension (systolic BP > 150 mm Hg). She also experienced periods of central apnea accompanied by desaturation and was intubated by

the PICU team on PICU day 16. Following intubation, an arterial line was placed, and the patient was started on a regimen of fentanyl and midazolam infusions for sedation. The patient remained ventilator dependent over the next 2.5 weeks on SIMV mode with a set rate of 12, positive end-expiratory pressure of 5 cm H_2O, tidal volume of 500 mL, and 30% fraction of inspired oxygen (F_{IO_2}).

During the initial preanesthetic assessment and evaluation in the PICU, the patient was found to be extremely anxious despite current treatment modalities. Approximately 2 hours before the preanesthetic visit, the patient's heart rate decreased from 84 to 43/min. This event lasted 2 minutes. An episode of hypertension (163/92 mm Hg) also occurred before the change in the patient's heart rate. No medication was administered before these vital sign changes; nor was any procedure being performed that could be attributable to the sudden change in vital signs. The patient's family was present at the bedside and was able to give a detailed account of the patient's PICU course. The family reported that the patient would often wake from a sleeping state appearing extremely anxious and confused, which sometimes precipitated a hypertensive event but never a bradycardic event. However, the family stated that the patient appeared to have been sleeping during both recorded events.

Preoperative vital signs at the time of the anesthesia assessment revealed a heart rate of 70/min, BP of 90/45 mm Hg, and a pulse oximetry reading of 98% on a F_{IO_2} of 30%. A 2-mg IV bolus of midazolam was administered before the patient was transported to the operating room. The patient was escorted intubated to the operating room by anesthesia staff and was hand-ventilated with 100% F_{IO_2} via a Mapleson D system with a full complement of monitors, including an arterial line cable and transducer. On her arrival in the operating room, anesthesia was induced IV with 100 µg of fentanyl and 100 mg of propofol. Muscle relaxation was maintained throughout the course of the 4-hour procedure with IV vecuronium totaling 10 mg. A stress-dose regimen of corticosteroids and intraoperative antibiotics were also administered. The patient was positioned supine, and an esophageal temperature probe was placed. A lower-body forced-air warming system (Bair Hugger) was also placed and set to 43°C.

Anesthesia was maintained with 2% to 2.5% sevoflurane for the duration of the case, and a total of 5 mg of morphine was administered IV over the course of the procedure for intraoperative pain control. The case proceeded uneventfully with the patient's vital signs remaining stable. No signs and symptoms of cardiac or hemodynamic instability were noted and the patient's temperature remained 36.5°C to 37°C during the course of the procedure. The decision was made by the surgical team to keep the patient paralyzed and sedated over the next 24 hours; thus, no reversal agents were administered.

At conclusion of the case, the patient was transported back to the PICU sedated and fully monitored while being hand-ventilated with 100% F_{IO_2} via a Mapleson D system through the patient's newly established surgical airway. During the postoperative anesthesia assessment 3 days later, no change in the patient's condition was noted, and she continued to remain ventilator dependent while still occasionally experiencing symptoms of bradycardia and tachycardia as well as hypotension and hypertension.

Discussion

In adults, classic presentation of anti-NMDA receptor encephalitis usually begins with symptoms of a psychiatric nature, such as psychosis, personality change, memory loss, and hallucinations, leading some to describe the changes as almost being of a demonic nature.[1-6] New research suggests that there is a preliminary phase that occurs 5 days to 2 weeks before the onset of psychiatric symptoms.[5] Symptoms reported during this phase are nonspecific in nature and include fever, nausea, vomiting, headache, a lethargic feeling, and an inability to concentrate.[5] As the disease continues to progress, neurologic symptoms are exhibited and include depression, anxiety, decreased cognitive skills, aphasia, tonic-clonic seizures, ataxia, and an unresponsive stage wherein patients appear as if they are in a catatonic state.[5] The final and most severe phase of symptoms incorporates autonomic involvement wherein autonomic instability occurs, manifesting as cardiac arrhythmias, hypertension and hypotension, hyperthermia and hypothermia, and dyskinesias.[5-7]

Although the symptoms remain relatively similar between the adult and pediatric populations, the initial symptoms first displayed by the pediatric population seem to differ from those of the adult population.[4-6] In most reported pediatric cases of anti-NMDA receptor encephalitis occurring in children under age 12, the first and most commonly experienced symptom reported is usually seizures or inappropriate movement of the body.[4] Speech dysfunction has also been documented as being more prevalent among the pediatric population, whereas autonomic instability has been reported as being less likely to occur.[5]

The NMDA receptor is an excitatory subtype of the glutamate receptor that contains 2 identified subunits classified as NR1 and NR2, which are responsible for the binding of glycine and glutamate.[7,8] Additionally, the NMDA receptor along with the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor have been theorized to play a cardinal role in synaptic plasticity. The NMDA receptor may also contribute to the development of memory, learning, and cognitive function.[9] Current research findings suggest that the NMDA receptor may play a role in the mediation of the pain response.[10,11] Impairment of the glutamate receptor

and subsequently the NMDA receptor has been linked to multiple disease processes such as Alzheimer disease and schizophrenia.[1,9] However, the antibodies formed as a result of anti-NMDA receptor encephalitis, specifically the NR1 antibody, have been shown to cause a reversible loss of the NMDA receptor as well as the abolishment of NMDA receptor and glutamate-mediated synaptic currents, with no effect noted on the AMPA receptor.[9] This may help to explain some of the hallmark symptoms associated with this disease process.

The NMDA receptor is the site of action for many commonly administered anesthetic drugs in the pediatric population. These medications include known NMDA receptor antagonists such as nitrous oxide (N_2O) and ketamine.[1,10-12] The NMDA receptor may also be responsible for mediating the effects of other commonly administered anesthetic agents such as propofol, fentanyl, and sevoflurane.[11,13] Thus, it can be theorized that medications that act on the NMDA receptor to achieve their desired effect, especially known NMDA receptor antagonists, may behave unpredictably and could potentially aggravate the symptoms of the disease if administered to a patient with anti-NMDA receptor encephalitis.

Nitrous oxide has been shown to achieve its anesthetic effect through antagonization of the NMDA receptor when administered at anesthetically significant levels.[10-12] This effect is achieved via an N_2O initiated upregulated binding of the NMDA radioligand, which causes the dose-dependent inhibition of NMDA-activated currents in the amygdala and cerebral cortex.[1,12] It has been hypothesized that because of their very similar pharmacologic profiles, ketamine and N_2O may share a similar mechanism of NMDA receptor antagonization.[12] Antagonism of the NMDA receptor via the administration of N_2O or ketamine has been shown to cause a decrease in the hyperalgesic effects associated with fentanyl administration.[12] Further research is needed, however, to determine if the underlying mechanisms associated with anti-NMDA receptor encephalitis will allow the patient to experience this same decrease in fentanyl-induced hyperalgesia without N_2O or ketamine administration.

Ketamine is a noncompetitive antagonist of the NMDA receptor that achieves its desired effects at clinically significant concentrations by interacting with the phencyclidine binding site, resulting in the inhibition of the calcium channels of the NMDA receptor.[14] In addition to the NMDA receptor, ketamine interacts with the μ-, δ-, and κ-opioid receptors as well as voltage-sensitive calcium channels, muscarinic receptors, and monoaminergic receptors to achieve its effects.[14] The side effects of ketamine administration have been well documented and include psychosis, memory impairment, and hallucinations.[1,14,15] These side effects often mimic some of the symptoms associated with anti-NMDA receptor encephalitis as well as schizophrenia.[15] Consequently, studies have shown a worsening in positive, negative, and cognitive symptoms in patients with schizophrenia following the administration of ketamine.[15,16] Further research is needed to determine whether this also occurs in patients with anti-NMDA receptor encephalitis following ketamine administration.

Propofol is a short-acting, IV phenolic sedative-hypnotic derivative that causes global central nervous system depression via direct activation of the γ-aminobutyric acid (GABA) receptors.[13,17] Propofol also inhibits the NMDA receptor.[17] Specifically, it affects the NR1 subunit via activation of protein phosphatase 2A, which results in an inhibition of NR1 phosphorylation, leading to a dose-dependent decrease in the ability of the NMDA receptor to modulate calcium influx through slow calcium ion channels.[17,18] This decrease of intracellular calcium influx lends itself to the theory that propofol possesses an organ-protective capacity because increased intracellular calcium concentrations are thought to be responsible for tissue injury as well as cellular dysfunction.[17] Newer studies have determined that propofol is neuroprotective because it inhibits NMDA-activated dilation of the cerebral parenchymal arterioles through activation of neuronal nitric oxide synthase in rats.[19] In humans, it is theorized that propofol prevents the excessive glutamate accumulation in the extracellular space, which is thought to be responsible for triggering mechanisms resulting in irreversible brain damage.[17] Because of the inhibitory effects of propofol on the NMDA receptor, it is unknown as to how its administration will affect the symptoms of patients with anti-NMDA receptor encephalitis. One case report describes a worsening of symptoms after administration of a propofol infusion for sedation purposes following resection of the teratoma but does not report any adverse reactions following an intraoperatively administered bolus of propofol.[13]

Both cases 1 and 2 were placed on a regimen of fentanyl and midazolam infusions for sedation in the PICU, and both patients received propofol intraoperatively. However, only case 1 had a change in hemodynamics intraoperatively as she experienced a decrease in heart rate. It is unknown whether the administration of propofol was responsible for this decrease in heart rate. Further research is needed to determine what effects, if any, propofol administration may have on the symptoms of anti-NMDA receptor encephalitis.

It has been documented that opioids such as fentanyl, a rapid-acting synthetic μ-opioid agonist, and morphine—another μ-opioid agonist—activate the μ-opioid receptors in conditions where persistent pain is present.[20] These opioids have been shown to provide only partial relief of the painful symptoms associated with a multitude of conditions, including cancer, nerve injury–induced neuropathy, and chronic inflammatory pain.[20] Studies have revealed that continued activation of the NMDA receptor,

especially in conditions associated with different types of neuropathic pain, is responsible for certain neuronal alterations in the periaqueductal gray matter leading to an altered response to μ-opioid agonists.[20] Opioids such as remifentanil, fentanyl, and, to a lesser extent, morphine have been shown to cause hyperalgesia following abrupt termination or long-term administration.[21] This response has been attributed to the postsynaptic activation of the NMDA receptor, as well as an increase in G-protein coupling and calcium postsynaptically.[21] As a result of these findings, the administration of select NMDA receptor antagonists such as methadone and ketamine have been used to mediate the hyperalgesia associated with opioid administration, as well as to manage the symptoms associated with opioid withdrawal, and in the treatment of patients with chronic pain.[18-22]

A recent study involving genetically altered mice with a decreased NR1 subunit determined that the exhibited potency of fentanyl, morphine, and methadone was 3 times less than the potency of the same drugs observed in mice with normal functioning NR1 subunits.[23] These findings suggest the theoretical need for an increased dose of opioids in patients with anti-NMDA receptor encephalitis as the function of the NR1 subunit is impaired. This study also showed no difference between the genetically altered mice and the control group regarding the development of opioid tolerance and dependence, suggesting that the NR1 subunit may play a more minor role in the development of μ-opioid tolerance.[23] These findings may also help to explain why there has not been any reported reductions in the opioid requirements for patients with anti-NMDA receptor encephalitis.

Sevoflurane is an isopropyl ether, inhaled anesthetic that has been shown to intensify transmission of GABA.[13,24,25] Sevoflurane has been shown to cause a dose-dependent decrease in NMDA-induced cell damage via inhibition of NMDA-induced mitochondrial membrane depolarization as well as an inhibition of NMDA-gated receptor channels.[24] At minimum alveolar concentration, sevoflurane exhibits an increased potentiation of the glycine receptor but only a moderate antagonism of the NMDA receptor.[25] This finding suggests that the immobility caused by sevoflurane to be more a byproduct of its effects on the glycine and GABA receptors as opposed to its effect on the NMDA receptor.[25] Sevoflurane may also display a synergistic antagonism of the NMDA receptor when administered along with a known NMDA receptor antagonist.[24,25] To date, only one case report has been published suggesting that the administration of sevoflurane in conjunction with propofol, to a patient with anti-NMDA receptor encephalitis, may have caused a worsening of the patient's clinical presentation.[13] Further research is needed to determine if this hypothesis is indeed correct because other case reports, including this one, have not reported a worsening in the clinical presentation of the disease following administration of the same anesthetic agents.

Many similarities existed between the 2 cases presented here. Both patients were female and previously healthy teenagers. Both experienced a sudden onset of seizures without having a prior history of seizures, and both patients became expressively aphasic following their seizures. No tumors were discovered in either case. Last, both patients displayed symptoms of dysautonomia, which required intubation in the PICU and mechanical respiratory support.

However, the progression and severity of each patient's symptoms varied greatly between the 2 cases. The patient in case 1 did not display any slurring of speech before or after the onset of her seizures, which was the first symptom observed in case 2. The second patient demonstrated weakness and dyskinesia of her upper extremities, specifically her left arm, whereas no such occurrence was observed in case 1. Management of the hemodynamic and autonomic instability of patient 2 required placement of an arterial line as well as surgery to establish a tracheostomy, whereas patient 1 did not require placement of an arterial line and was able to be successfully extubated in the PICU.

Preoperatively on the day of surgery, patient 2 demonstrated some cardiovascular instability but intraoperatively remained hemodynamically stable. In contrast, patient 1 had a sudden decrease in heart rate of unknown cause during the intraoperative period, but preoperatively on the day of surgery no such symptoms were noted. Both patients underwent a laparoscopic-assisted G-tube placement, although patient 2 also underwent multiple procedures during the course of the same anesthetic. One could theorize that with a longer procedure, the likelihood of experiencing hemodynamic and autonomic instability would be greater. However, this did not appear to be true because patient 2 remained hemodynamically stable during the 4-hour case.

In both cases, fentanyl, midazolam, propofol, ondansetron, vecuronium, glycopyrrolate, and neostigmine were administered. Between the 2 patients, only patient 1 received succinylcholine and desflurane, whereas case 2 received morphine and sevoflurane. The administration of succinylcholine and desflurane in conjunction with the other aforementioned medications may have predisposed the patient to a greater likelihood of hemodynamic instability, although further research would be needed to support this theory.

Conclusion

Anti-NMDA receptor encephalitis can present a challenge to the anesthesia provider in all phases of anesthesia. Understanding the disease process and anticipating the potential complications associated with administration of anesthesia to patients with this disease is key to the

development of a successful anesthetic plan. Because of the increased likelihood of hemodynamic instability associated with this disease, it may be wise to have vasopressors, antihypertensive agents, and anticholinergic medications readily available. For longer, more complex surgical procedures, one should consider the placement of an arterial line to monitor BP throughout the case as well a central line in case vasopressor and/or antihypertensive infusions are required.

As there is very little literature describing the anesthetic management of this disease in the pediatric population, it may be prudent to avoid known NMDA receptor antagonists, such as ketamine and N_2O, in this population. Also, until further research is conducted, it may be wise to use decreased doses of medications that act indirectly on the NMDA receptor, although they should still be considered for use because medications such as sevoflurane, propofol, fentanyl, morphine, vecuronium, midazolam, and ondansetron were well tolerated in case 2.

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