Anesthesia Management for a Boy with Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis

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Anti-*N*-methyl-D-aspartate receptor encephalitis is caused by autoantibodies to *N*-methyl-D-aspartate receptors. This disorder is poorly understood and occurs very rarely in children. We describe a total IV anesthetic for a 4-year-old boy with anti-*N*-methyl-D-aspartate receptor encephalitis and review the potential drug interactions with this autoimmune disease. (A&A Case Reports. 2015;5:182–4.)

Anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis was first described in 2007 in young women who developed prominent psychiatric symptoms, amnesia, seizures, frequent episodes of dyskinesia, autonomic dysfunction, and a decreased level of consciousness. This constellation of signs was associated with an ovarian teratoma and specific antibodies in the cerebrospinal fluid and blood.[1] Anti-NMDA receptor encephalitis has been recognized as one of the most common presentations of encephalitis in children, although rarely presenting for anesthesia.[2] We describe a 4-year-old boy with anti-NMDA receptor encephalitis who presented for gastric tube placement after complications from the encephalitis and review the interactions of anesthetic drugs with the NMDA receptors.

CONSENT FOR PUBLICATION

We attempted to contact the parents of our patient on multiple occasions to obtain their consent for publication of this report but were unsuccessful. We then sought approval from our local CYIRB that determined that approval is not required. The patient was deidentified by removing obvious demographic information without compromising the scientific validity of the case report.

CASE DESCRIPTION

A 4-year-old boy was scheduled for placement of a gastric tube for dysphagia. Seven weeks before the current hospital admission, he presented to our emergency department 3 times in 10 days. On the first visit, he presented with fever and emesis, was diagnosed with gastroenteritis, and was discharged home. A few days later, he presented with abdominal pain, poor oral intake, and constipation. He was prescribed polyethylene glycol (MiraLAX®) and discharged home again. The next day, he returned to our emergency department with the same complaints. On this occasion, he was given an enema and discharged home. Several days later, the boy presented yet again with abdominal pain, rhinorrhea, cough, and altered mental status. The parents also noted that his speech had changed since discharge and that he required diapers for bowel and bladder incontinence. A computerized axial tomography scan of his head revealed only sinusitis. A complete blood cell count showed an increased white blood cell count, mainly neutrophils. He was admitted to the hospital.

On the night of his admission, he became progressively more confused with hallucinations and unintelligible speech. His mother watched him lay awake at night staring off into "space." The next morning, he became agitated. This was followed by an episode of unresponsiveness, eye deviation, shivering movements, loss of consciousness, and recurrent agitation. At this point, he was transferred to the pediatric intensive care unit (PICU) for closer observation.

Magnetic resonance imaging of his brain was reported as normal. Ultrasound of the abdomen and scrotum failed to demonstrate any tumor. Laboratory investigations for bacterial and viral encephalitis were negative. An electroencephalogram showed diffuse slowing consistent with encephalopathy. A presumptive diagnosis of anti-NMDA receptor encephalitis was made and empirical treatment started with high-dose methylprednisolone and IV immunoglobulin. After identification of NMDA receptor antibodies in blood and cerebrospinal fluid, he was treated with plasmapheresis.

During his 2-week stay in the PICU, his mental status waxed and waned. He developed a self-mutilating behavior. His trachea was intubated for 1 day for status epilepticus. After tracheal extubation, his airway required temporary reintubation for episodes of bradypnea and apnea. His PICU course was also punctuated with several bouts of tachycardia and tachypnea. After psychiatric, hemodynamic, and respiratory improvement, he was discharged from the PICU to continue inpatient therapy.

On the inpatient ward, he remained unresponsive to verbal stimuli, socially isolated, and nonverbal with altered affect. After 7 weeks in the hospital, he had completed his plasmapheresis treatment and was completing his regimen of tapering steroids. However, as a consequence of the encephalitis, he was found to have severe oropharyngeal dysphagia necessitating placement of a gastric tube.

His preoperative physical examination was normal, except that he was unresponsive to verbal stimuli and interacted poorly with parents and personnel. His vital signs

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and routine laboratory tests were normal. His weight was 14.4 kg.

On the day of surgery, he displayed dyskinetic motion of the wrists. He was premedicated with 1 mg IV midazolam. After standard monitors were applied in the operating room, he received a second dose of midazolam (1 mg IV). Anesthesia was induced with 40 mg of IV propofol followed by 30 mg IV because he did not lose consciousness. Anesthesia was maintained with morphine, rocuronium, and a propofol infusion. His vital signs remained stable throughout, except for a transient increase in heart rate from 98 to 140 beats per minute. His arterial blood pressure remained stable within 20% variation of baseline (120/65 mm Hg) throughout the anesthetic. At the conclusion of surgery, local anesthesia was infiltrated into the wound and muscle paralysis was antagonized using neostigmine and glycopyrrolate. His trachea was extubated, and the recovery was uneventful. On the day after surgery, his mental status was unchanged. He displayed no subsequent dyskinetic wrist movements. Four days postoperatively, he was discharged home.

DISCUSSION

Anti-NMDA receptor encephalitis is a rare autoimmune disorder of young adults, primarily affecting females, and associated with antibody-secreting tumors, most commonly ovarian teratomas.[1] Two large case series demonstrated that this disorder primarily affected women, because only 10% to 15% of afflicted patients were male.[2,3] Anti-NMDA receptor encephalitis is increasingly recognized in children, who now comprise 40% to 65% of all cases.[2,4] The youngest child diagnosed with anti-NMDA receptor encephalitis was 8 months old.[5] The majority of children who are diagnosed with the disorder develop seizures, stereotyped movement, autonomic instability, and hypoventilation.[2,5] Anti-NMDA receptor encephalitis is less commonly associated with tumors in children than in adults, 31% vs 56%, respectively, and it has not been associated with tumors in young boys.[2] Nonetheless, it is one of the most common forms of encephalitis in children, accounting for >4% of pediatric cases.[4,6,7]

Anti-NMDA receptor encephalitis is caused by autoantibodies against NMDA receptors. Although the presence of a tumor that expresses NMDA receptors likely contributes to breaking immune tolerance, other unknown immunological triggers may be involved because 45% of patients have no detectable tumor.[2,3] Viral illness-like prodromal symptoms are very common. Whether the prodromal symptoms form part of an early immune activation or result from a nonspecific infection that facilitates crossing of the blood–brain barrier by the immune response is unknown.[3]

NMDA receptors are formed from heteromers of NR1 and NR2 subunits.[8,9] Both subunits are required to create a functional receptor. The autoantibodies react with both subunits, although the primary target is the NR1 subunit.[3] The antibodies decrease the numbers of cell-surface NMDA receptors and NMDA receptor clusters in postsynaptic dendrites. This decrease can be reversed by removing the antibodies.[1,3] The decrease in NMDA receptors leads to characteristic symptoms in 5 relative phases: prodrome (fever, headache, upper respiratory symptoms, vomiting, or diarrhea in 48% of patients), psychosis (temper tantrums, behavioral change, agitation, aggression, progressive speech deterioration, hallucinations), unresponsiveness (no response to pain, no eye contact, no visual tracking, catatonia-like state, seizures), hyperkinesia (dystonia, dyskinesia), and a slow recovery characterized by persisting amnesia of the disease.[2,3] Autonomic dysfunction is less frequent and less severe in children than in adults. Hypertension, tachycardia, and hyperthermia occur frequently and often correlate with agitation, reminiscent of an autonomic storm.[2] Other signs of autonomic dysfunction that might occur include hypersalivation and urinary incontinence.[10] The frequency of hypoventilation in affected children is 23% compared with 66% reported in a mixed population of adults and children.[2,3]

First-line treatment of anti-NMDA receptor encephalitis consists of removing the source of the anti-NMDA receptor antibodies. This treatment is curative in adults because most females have anti-NMDA–secreting tumors that can be removed without the risk of recurrence. In contrast, because tumors occur far less frequently in children, medical therapy becomes the primary strategy to eliminate these antibodies from affected children: high-dose IV steroids, IV immunoglobulins, and plasmapheresis. Second-line treatment comprises cyclophosphamide and/or rituximab. Recovery after medical therapy is protracted. Fortunately, most children recover with either no sequelae or only minor deficits.

The anesthetic management of children with this disorder requires an understanding of the pathogenesis of the disease as well as the pharmacodynamics of anesthetics. Only 1 case of a 14-year-old girl with this disease who required anesthesia has been published.[11] The goals of anesthesia are to prevent a deterioration in the child's mental status, to maintain stable hemodynamics, and to manage central apnea and hypoventilation.

The effects of drugs that interact with NMDA receptors are unpredictable and may worsen the symptoms. Therefore, it is prudent to avoid ketamine, nitrous oxide, xenon, tramadol, and methadone. Ketamine can replicate the symptoms of early-stage anti-NMDA receptor encephalitis: hallucinations, delusions, disorganized and impoverished thought, speech dysfunction, agitation, and emotional lability. Larger doses of NMDA receptor antagonists can decrease responsiveness and cause dissociative amnesia, catatonic symptoms, autonomic dysregulation, and coma.[12]

NMDA receptors are major target sites of anesthetics.[13] Inhaled anesthetics inhibit NMDA receptor function in a reversible, concentration-dependent, and noncompetitive manner. The half-maximal NMDA receptor inhibitory concentration for sevoflurane, isoflurane, and desflurane is approximately 1.2 MAC.[14] It is possible that inhaled anesthetics are unsafe in patients with this disease,[15] although there are several reports of inhaled anesthetics being used successfully in critically ill patients.[11,16] In the presence of the NMDA antagonists, ketamine and magnesium, the partial pressures of inhaled anesthetics that inhibit NMDA receptors are reduced by 30%.[14] Differences in NMDA receptor inhibition among volatile anesthetics at 1 MAC range from 12% to 39%.[17] This differential inhibition of NMDA receptors may explain, in part, the conflicting case reports about the safety of inhaled anesthetics in these patients.

The effects of propofol in patients with anti-NMDA receptor encephalitis are conflicting.[11,14,15,18] Propofol acts primarily on γ-aminobutyric acid type A receptors with minimal effects on NMDA receptors. In supraclinical concentrations, propofol inhibits NMDA receptors only by 10% to 20%.[19,20] In the presence of autonomic dysfunction, the dose should be titrated and limited to avoid hemodynamic instability.[11,18] Total IV anesthesia with propofol has been successfully used in 2 adults with this disease.[18,21] For induction of anesthesia, 2 consecutive doses of propofol, 2.7 and 2 mg/kg, were used because the first dose failed to induce hypnosis. For the maintenance of anesthesia, a propofol infusion was used without adverse events. Our patient remained hemodynamically stable throughout the anesthetic.

The following medications are presumed safe for patients with anti-NMDA receptor encephalitis based on their pharmacodynamics: muscle relaxants, benzodiazepines, α-2 agonists, etomidate, and opioids. However, opioids might enhance central apnea and should be titrated carefully.

Acidosis inhibits NMDA receptors at glutamate (noncompetitive antagonist) and at glycine (mixed antagonist) binding sites.[22,23] The inhibitory effects of acidosis are additive with the inhibitory effects of isoflurane and synergistic with the inhibitory effects ketamine.[22] It is likely that hydrogen ion modulation of the NMDA receptors is the mechanism by which carbon dioxide exerts its anesthetic action during hyper- and hypocarbia. Therefore, it is important to carefully control the carbon dioxide tension in children with anti-NMDA receptor encephalitis to avoid negatively impacting both their neurologic status and the depth of anesthesia.

In summary, we used IV propofol and morphine to provide anesthesia for a child who was recovering from anti-NMDA receptor encephalitis. Avoiding drugs that interact with NMDA receptors may have contributed to the unremarkable course.

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