Published in final edited form as:
Anesth Analg. 2011 November ; 113(5): 1188–1191. doi:10.1213/ANE.0b013e31822b8a7d.

Anti-N-Methyl-D-Aspartate Receptor Encephalitis and its Anesthetic Implications

Peter Gabriel Pryzbylkowski, M.D.,
Department of Anesthesiology and Critical Care, University of Pennsylvania Health System, Philadelphia, PA

William Jonathan Dunkman, M.D.,
Department of Anesthesiology and Critical Care, University of Pennsylvania Health System, Philadelphia, PA

Renyu Liu, M.D., Ph.D., and
Department of Anesthesiology and Critical Care, University of Pennsylvania Health System, Philadelphia, PA

Linda Chen, M.D.
Department of Anesthesiology and Critical Care, University of Pennsylvania Health System, Philadelphia, PA

Abstract

We describe the anesthetic management and implications of two patients with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis. Anti-NMDA receptor encephalitis is a neurological disorder caused by production of antibodies to the NMDA receptor. The NMDA receptor is the target of many drugs used in anesthesia. It is important to understand the pharmacologic interactions these anesthetics have with a disabled NMDA receptor while preparing an anesthetic plan for patients with anti-NMDA receptor encephalitis. Symptoms of the disease such as psychosis, paroxysmal sympathetic hyperactivity, and central hypoventilation pose risks to the induction and maintenance of anesthesia in these patients.

Corresponding Author: Linda Chen, M.D., University of Pennsylvania Health System, Hospital of the University of Pennsylvania, Dulles 772, 3400 Spruce St., Phila., PA 19104, Phone: 215 662 3548, FAX: 215 615 3898, Linda.Chen@uphs.upenn.edu.

The authors declare no conflicts of interest.

DISCLOSURES:
Name: Peter Gabriel Pryzbylkowski, M.D.
Contribution: This author helped conduct the study and write the manuscript.
Attestation: Peter Gabriel Pryzbylkowski approved the final manuscript.
Name: William Jonathan Dunkman, M.D.
Contribution: This author helped conduct the study and write the manuscript.
Attestation: William Jonathan Dunkman approved the final manuscript.
Name: Renyu Liu, M.D., Ph.D.
Contribution: This author helped design the study and write the manuscript.
Attestation: Renyu Liu approved the final manuscript.
Name: Linda Chen, M.D.
Contribution: This author helped design the study and write the manuscript.
Attestation: Linda Chen approved the final manuscript.

Introduction

N-Methyl-d-Aspartate (NMDA) receptor encephalitis is a recently identified neurological disorder. It was originally described in women with ovarian teratomas who presented with paroxysmal sympathetic hyperactivity (PSH), hypoventilation, psychosis and memory impairment that progressed to neurological deficits requiring intensive care unit (ICU) support. [1] The anesthetic implications of caring for these patients are not defined. Only one case of anesthesia for a pediatric patient with the disease has been reported. [2] We describe two patients in this report. The first case is that of a woman with anti-NMDA receptor encephalitis and a left cystic ovarian mass who presented for leftsided laparoscopic oopherectomy and salpingectomy. The second case is a man with anti-NMDA receptor encephalitis who presented for an open gastrostomy tube change and subsequent tracheostomy. The authors sought and received permission from the IRB of the Hospital of the University of Pennsylvania to publish this case report.

Case Report

A 20-year-old woman (ASA-PS IV, 165 cm, 91 kg) with anti-NMDA receptor encephalitis and a left ovarian cyst was scheduled for a left laparoscopic oopherectomy and salpingectomy under general anesthesia. Her medical history was significant for asthma, obesity and an ongoing prolonged ICU course secondary to her poor neurological status. The patient presented to an outside hospital two months before surgery when roommates found her home confused and disoriented. She was treated for aseptic meningitis and discharged home. After discharge, she became more somnolent, confused and began to show signs of seizure activity. Upon readmission, an indirect fluorescent antibody test, that detects antibodies against the NMDA receptor found in serum, confirmed the diagnosis of anti-NMDA receptor encephalitis and a CT scan of the abdomen showed a dominant follicle in the left ovary. The patient underwent tracheostomy and percutaneous endoscopic gastrostomy tube placement at the outside hospital before transfer to our institution for surgical management of her left ovary. In our ICU the patient remained severely encephalopathic, agitated requiring two point restraints with sedation, and ventilator dependent. The patient required hydromorphone 8mg/hr and lorazepam 10mg/hr during her ICU course for sedation.

On arrival in the operating room general anesthesia with isoflurane was induced through the patient's 6.0 cuffed tracheostomy tube. Anesthesia was maintained with a minimum alveolar concentration (MAC) of isoflurane 1 to 1.5 % throughout the case and hydromorphone 3 mg IV was given intravenously for intraoperative pain control. Muscle relaxation was achieved with the use of vecuronium 26 mg. The case proceeded uneventfully and upon completion she was given midazolam 2mg for transport back to the ICU. Twenty-four hours postoperatively the patient was started on broad-spectrum antibiotics for a fever of 102° F. She remained encephalopathic in the ICU after surgery with no immediate improvement in her neurological status.

The second case was a 22-year-old man (ASA-PS IV, 168 cm, 59 kg) who was scheduled for an open gastrostomy tube change. His medical history was significant for varicella meningitis in 2005, asthma and anti-NMDA receptor encephalitis. He presented to an outside hospital after 3 weeks of decreased sleep, fast thoughts, agitation and paranoia. While in the hospital he experienced periods of waxing and waning consciousness, muscle spasms and PSH with periods of hypertension and tachycardia. He was diagnosed with anti-NMDA receptor encephalitis and was transferred to our institution. While in our ICU, he continued to have periods of PSH, tremors, and hypoventilation. A scrotal ultrasound excluded the presence of any testicular mass.

Upon arrival in the operating room general anesthesia was induced with propofol 50mg, fentanyl 225mcg and rocuronium 20mg to facilitate tracheal intubation with a 7.0 oral cuffed endotracheal tube. Anesthesia was maintained with inhaled desflurane. Fentanyl was given via IV bolus throughout the case with a total of 325 mcg provided. The procedure went smoothly and the patient remained intubated for transport back to the ICU after case conclusion. Although the patient was successfully tracheally extubated the morning after surgery, over the next 48 hours the patient continued to have PSH with periods of agitation and hypoventilation eventually requiring reintubation in the ICU. After reintubation the patient underwent tracheostomy two weeks later. During the tracheostomy procedure propofol 80 mcg/kg/min, fentanyl 100 mcg/hr along with a 0.5 MAC desflurane were well tolerated by the patient. Large doses of hydromorphone 6 mg/hr and lorazepam 7 mg/hr along with propofol 70 mcg/kg/min were needed to help sedate the patient during his ICU course.

Discussion

In this case report we describe the anesthetic management of two patients with a recently described neurological disorder. NMDA receptor encephalitis is a syndrome associated with antibodies to the NMDA receptor. First described in 2007, more than 400 patients have now been identified and some estimate this disease may account for up to 1-4% of cases of encephalitis. [3, 4] Early stages of the disease are characterized by symptoms of psychosis, memory deficits, seizures, and language disintegration which progresses to a state of decreased responsiveness and catatonia. This latter stage is often accompanied by PSH including hyperthermia, tachycardia, hypertension, bradycardia and hypotension, hypoventilation requiring respiratory support, orofacial dyskinesias and motor or complex seizures. According to Dalmau et al.[5] about 80% of patients diagnosed with the disease are women and it is most common between the ages of 19-24 years. The disorder is frequently associated with ovarian teratoma. About 75% of patients recover completely or have only mild sequelae, the remainder are severely disabled or die. There is an indirect fluorescent antibody test that detects antibodies against the NMDA receptor found in patient's serum or cerebrospinal fluid. Treatment modalities include chemotherapy, plasmapharesis, IV immunoglobulin, removal of teratoma if present, and supportive care. Some neurologists advocate the use of chemotherapy, regardless of tumor presence, due to their belief in the true paraneoplastic nature of the disease. Recovery may require 3-4 months of hospital care followed by several months of rehabilitation. [5] During the acute phase of their illness, most patients have either normal or atypical brain magnetic resonance imaging findings and only diffuse slowing or occasionally epileptiform abnormalities on surface electroencephalogram. [6]

NMDA receptors are excitatory, tetrameric receptors with two classes of subunits: NR1 and NR2 that bind glycine or glutamate. Dysregulation of NMDA receptors has been linked to schizophrenia, Alzheimer's and Parkinson's. [7] In NMDA receptor encephalitis, NMDA receptor antibodies decrease NMDA receptor surface density and synaptic localization via selective antibody-mediated capping and internalization of surface NMDA receptors. [8] Hence, drugs such as ketamine, methadone, and the inhaled drug nitrous oxide (N_2O), which act at the NMDA receptor, may behave unpredictably.

NMDA receptors are one of two receptors (along with gamma-aminobutyric acid [$GABA_A$] most associated with the actions of anesthetics. [9] Halogenated anesthetics act on the NMDA receptor, reducing NMDA-activated currents; however, their effects on $GABA_A$ receptors may be dominant. [10,11,12] NMDA receptors likely mediate the anesthetic effects of both xenon[13] and N_2O.[14] Xenon has been shown to reduce the NMDA-activated currents in hippocampal [15] neurons. N_2O reduces NMDA receptor-mediated excitatory currents in the

basolateral amygdala, an area associated with anesthesia-induced amnesia, formation of aversive memories, fear, and addictive behavior. [16]

Phencyclidine and ketamine are well known NMDA receptor antagonists. Ketamine provides analgesic and anesthetic effects without respiratory and cardiac depression. Ketamine binds to the phencyclidine binding site in the ion channel of the NMDA receptor, inhibiting glutamate triggered calcium influx. [17] NR2 knockout mice have been shown to be resistant to the anesthetic effects of numerous drugs, including those known to act at the NMDA receptor such as ketamine and N_2O, but also (to a lesser extent) to those with primary action at the $GABA_A$ receptor including pentobarbital, propofol, diazepam and midazolam. This finding was unexpected and suggests that the NMDA receptor may play some indirect role in these drugs actions in vivo. [1819], The resemblance of these patients to those who are taking ketamine is strikingly similar (hallucinations, psychosis, tachycardia) and this disease may serve as a natural human model for much of the physiology of ketamine. Alternatively, there is the possibility exists that we might learn more about anti-NMDA receptor encephalitis based upon our current knowledge of ketamine.

NMDA receptors are also involved in regulation of chronic pain and antagonists have been shown to augment analgesia from opioids in acute and chronic settings, block development of tolerance, and suppress symptoms of withdrawal. Although NMDA receptor antagonists LY235959, R(+)-HA-966 and ifenprodil did not have an analgesic effect when given alone, they were shown to enhance the acute antinociceptive effects of opioids. [20] NMDA receptor antagonists ketamine and dextromethorphan improve postoperative pain control and reduce opioid requirements when given before painful stimulus, a concept known as preventive [21] analgesia. It does not appear that these patients had any reduction in their requirements for hypnotics or opioids.

Methadone also acts as an NMDA receptor antagonist. Intrathecal methadone has been shown to block morphine tolerance and NMDA-induced hyperalgesia in rats. [22] This antagonism of NMDA receptors is thought to explain methadone's usefulness in chronic pain patients tolerant to other opioids. Researchers were also able to block development of tolerance to the hypnotic effects of dexmedetomidine with NMDA receptor antagonists MK-801 and ketamine. Interestingly, this effect was not seen once tolerance had developed, indicating that the antagonists block the synaptic plasticity involved in the development of tolerance. [23]

NMDA receptor encephalitis presents many interesting management challenges to the anesthesiologist. Understanding of the disease process may guide the theoretical considerations in development of the anesthetic plan. Given the severe dysregulation of NMDA receptor-mediated pathways in this disease, it is probably wise to avoid use of drugs which act through these receptors, including ketamine, N_2O, and methadone. Medications with indirect interaction with NMDA receptors could still be considered for use. Several important medications including propofol, isoflurane, desflurane, vecuronium, rocuronium, fentanyl, and hydromorphone were well tolerated in the cases we present. Anesthesiologists should also be prepared for the PSH that is frequently seen with this disorder and might not otherwise be expected in a young patient. It would be prudent to have vasopressors, beta-blockers, antihypertensives, and anticholinergics readily available during the case, so that any autonomic instability can be dealt with in a timely fashion. PSH has recently been described in patients suffering from severe traumatic brain injury and as we learn to take care of these patients, management principles learned in traumatic brain injury patients may be usefully applied to NMDA patients. [24,25] Although the second patient had PSH in the ICU postoperatively, the two patients presented here had no PSH intraoperatively, hence

there is the possibility that volatile anesthetics could blunt the autonomic hyperactivity seen in this patient population.

In conclusion, this case report explained the presenting symptoms and the specific anesthetic issues for patients diagnosed with anti-NMDA receptor encephalitis. There is currently no literature describing the anesthetic management of this patient population. Hence, it would be prudent to avoid drugs that antagonize or act indirectly at the NMDA receptor (Table 1) until further research is conducted.

Acknowledgments

The authors would like to thank Mary Hammond for her help in obtaining IRB approval for this case report.

Funding: None

References

1. Dalmau J, Tuzun E, We H, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR. Paraneoplastic anti-N-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma. Ann Neurol. 2007; 61:25–36. [PubMed: 17262855]
2. Splinter WM, Eipe N. Anti-NMDA receptor antibodies encephalitis. Pediatr Anaesth. 2009; 19:911–913.
3. Pruss H, Dalmau J, Harms L, Holtje M, Ahnert-Hilger G, Borowski K, Stoecker W, Wandinger KP. Retrospective analysis of anti-glutamate receptor (type NMDA) antibodies in patients with encephalitis of unknown origin. Neurology. 2010; 75:1735–39. [PubMed: 21060097]
4. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, Cunningham R, Zuckerman M, Mutton KJ, Solomon T, Ward KN, Lunn MP, Irani SR, Vincent A, Brown DW, Crowcroft NS. UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010; 10(12):835–44. [PubMed: 20952256]
5. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011; 10:63–74. [PubMed: 21163445]
6. Nasky KM, Knittel DR, Manos GM. Psychosis associated with Anti-N-methyl-D-aspartate receptor antibodies. CNS Spectr. 2008; 13(8):699–702. [PubMed: 18704025]
7. Mony L, Kew JNC, Gunthorpe MJ. Paoletti Pierre. Allosteric modulators of NR2B-containing NMDA receptors: molecular mechanisms and therapeutic potential. British Journal of Pharmacology. 2009; 157:1301–1317. [PubMed: 19594762]
8. Hughes EG, Peng Z, Gleichman AJ, Lai M, Zhou L, Tsou R, Parsons TD, Lunch DR, Dalmau J, Balice-Gordon RJ. Cellular and Synaptic Mechanisms of Anti-NMDA Receptor Encephalitis. J Neurosci. 2010; 30(17):5866–5875. [PubMed: 20427647]
9. Chau PL. New insights into the molecular mechanisms of general anesthetics. British Journal of Pharmacology. 2010; 161:288–307. [PubMed: 20735416]
10. Martin DC, Plagenhoef M, Abraham J, Dennison RL, Aronstam RS. Volatile Anesthetics and glutamate activation of N-methyl-D-aspartate receptors. Biochem Pharmacol. 2010; 49:809–817. [PubMed: 7702639]
11. Hollman MW, Liu H-T, Hoenemann CW, Liu W-H, Durieux ME. Modulation of NMDA receptor function by ketamine and magnesium. Part II: interactions with volatile anesthetics. Anesth Analg. 2001; 92:1182–1191. [PubMed: 11323344]
12. Solt K, Eger EI, Raines DE. Differential modulation of human N-methyl-D-aspartate receptors by structurally diverse general anesthetics. Anesth Analg. 2006; 102:1407–1411. [PubMed: 16632818]
13. de Sousa SLM, Dickinson R, Lieb WR, Franks NP. Contrasting synaptic actions of the inhalational general anesthetics isoflurane and xenon. Anesthesiology. 2000; 106:107–113.

14. Jevtovic-Todorovic V, Todorovic SM, Mennerick S, Powell S, Dirkranian K, Benshoff N, Zorumski CF, Olney JW. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med. 1995; 4:460–463. [PubMed: 9546794]
15. Franks NP, Dickinson R, de Sousa SLM, Hall AC, Lieb WR. How does xenon produce anesthesia? Nature. 1998; 396:324. [PubMed: 9845069]
16. Ranft A, Kurz J, Becker K, Dodt HU, Zieglgansberger W, Rammes G, Kochs E, Eder M.
17. Weiner AL, Vieira L, McKay CA, Bayer MJ. Ketamine Abusers Presenting to the Emergency Department: A Case Series. The Journal of Emergency Medicine. 2000; 18(4):447–451. [PubMed: 10802423]
18. Petrenko AB, Tamakura T, Fujiwara, Askalany AR, Baba H, Sakimura K. Reduced.
19. Sato Y, Kobayashi E, Murayma T, Mishina M, Seo N. Effect of N-methyl-D-aspartate Receptor ε1 Subunit Gene Disruption of the Action of General Anesthetic Drugs in Mice. Anesthesiology. 2005; 102:557–61. [PubMed: 15731593]
20. Fischer BD, Carrigan KA, Dykstra LA. Effects of N-Methyl-D-Aspartate Receptor Antagonists on AcuteMorphine-Induced and I-Methadone-Induced Antinociception in Mice. The Journal of Pain. 2005; 6:7–425.
21. McCartney CJL, Sinha A, Katz J. A Qualitiative Systematic Review of the Role of N-Methyl-D-Aspartate Receptor Antagonists in Preventive Analgesia. Anesth Analg. 2004; 98:1385–400. [PubMed: 15105220]
22. Inturrisi CE. Pharmacology of methadone and its isomers. Minerva Anestesiologica. 2005; 71:435–7. [PubMed: 16012416]
23. Davies MF, Reid K, Guo TZ, Agashe GS, Amin YK, Maze M. Sedative but not Analgesic α2 Agonist Tolerance Is Blocked by NMDA Receptor and Nitric Oxide Synthase Inhibitors. Anesthesiology. 2001; 95:184–91. [PubMed: 11465557]
24. Perkes I, Baguley IJ, Nott MT, Menon DK. A Review of Paroxysmal Sympathetic Hyperactivity after Acquired Brain Injury. Ann Neurol. 2010; 68:126–135. [PubMed: 20695005]
25. Bower RS, Sunnarborg R, Rabinstein AA, Wijdicks EFM. Paroxysmal Sympathetic Hyperactivity after Traumatic Brain Injury. Neurocrit Care. 2010; 13:233–234. [PubMed: 20517713]

Table 1

Direct and indirect acting N-Methyl-d-Aspartate (NMDA) receptor antagonists. Drugs known to antagonize the NMDA receptor by binding to the NR1 or NR2 subunit are considered to be direct acting. Whereas, drugs that antagonize the NMDA receptor through an alternative method are considered indirect acting.

Drug	NMDA receptor antagonist Citations	
	Direct Acting	Indirect Acting
Dextromethorphan	21	
Ketamine	17, 18, 21	
Methadone	22	
N_2O	14, 16, 19	
PCP	17	
Pentobarbital		18, 19
Propofol		19

PCP = phencyclidine

N_2O = nitrous oxide