Anesthetic Considerations for the Patient with Anti-NMDA Receptor Encephalitis

Dr. Robert W. Simon, DNP, MS, CRNA
disclosures

• None
objectives

Review
• Review normal function of the glutamate receptors

Discuss
• Discuss disease process of anti NMDA receptor encephalitis

Review
• Review anesthetic agents effects on NMDA receptor

Discuss
• Discuss which meds to use/avoid in pts with anti NMDA receptor encephalitis
What is Glutamate?

The most abundant neurotransmitter in the brain and central nervous system.

It is involved in virtually every major excitatory brain function.

Glutamate is also a metabolic precursor for GABA (gamma-aminobutyric acid), the main inhibitory neurotransmitter in the CNS.

Principal mediator of cognition, emotions, sensory information, motor coordination, and pain response?
Glutamate’s Role

Glutamate plays a prominent role in synaptic plasticity
ability for strengthening or weakening of signaling between neurons over time to shape learning and memory.

Has great effect on long-term potentiation (LTP)
“The brain doesn’t grow new neurons to store memories. It strengthens connections between existing neurons. This process is called long-term potentiation (LTP).”
The Glutamate Receptors
The N-methyl-D-aspartate receptor (also known as the NMDA receptor or NMDAR), is a glutamate receptor and ion channel protein found in nerve cells.

Activated when glutamate and glycine (or D-serine) bind to it, and when activated it allows positively charged ions to flow through the cell membrane.
NMDA receptor factoids

- Implicated in the basic processes of memory formation.
- The NMDA receptor is one of the two main kinds of receptors activated by glutamate.
- Glutamate is a major excitatory synaptic transmitter found in all parts of the nervous system.
- NMDA receptor is especially sensitive to the glutamate agonist \( N\text{-}methyl-D\text{-}aspartate \).
The AMPA receptor - particularly sensitive to $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid.

AMPA receptors and NMDA receptors often work in conjunction to produce long-lasting changes in synaptic functioning.

This action is hypothesized to encode basic units of new memories.
AMPA receptors (AMPAR) are both glutamate receptors and cation channels that are integral to plasticity and synaptic transmission at many postsynaptic membranes.
Function

Glutamate binds to postsynaptic AMPARs and the NMDAR.

Ligand binding causes the AMPARs to open, and Na\(^{+}\) flows into the postsynaptic cell, resulting in a depolarization.

NMDARs do not open directly because their pores are occluded at resting membrane potential by Mg\(^{2+}\) ions.

- NMDARs can open only when a depolarization from the AMPAR activation leads to repulsion of the Mg\(^{2+}\) cation out into the extracellular space, allowing the pore to pass current.
Unlike AMPARs, however, NMDARs are permeable to both Na$^+$ and Ca$^{2+}$. The Ca$^{2+}$ that enters the cell triggers the upregulation of AMPARs to the membrane, resulting in a long-lasting increase in long term potentiation.
Molecules of glutamate bind to recognition sites of NMDA receptors as well as AMPA receptors. The ionotropic AMPA receptors admit sodium ions when activated, resulting in a moderate local depolarization...

...that dislodges the magnesium ions blocking the NMDA receptors. Large quantities of calcium ions may now enter the neuron through the NMDA receptors’ calcium channels. The NMDA receptor is thus both ligand and voltage gated. The calcium influx affects the metabolic machinery of the cell...

...resulting in the addition of more AMPA receptors to the postsynaptic membrane. The synapse has thus been strengthened—it will respond more rapidly and more strongly to future releases of glutamate.
NMDA

• The NMDA receptor is a ligand-gated ion channel where anions Ca\(^{2+}\) and Na\(^+\) are voltage dependent.
• L-glutamate, an amino acid and excitatory neurotransmitter, causes the opening of the ion channel.
• A rapid influx of Na\(^+\), Ca\(^{2+}\), and K\(^+\) results in the depolarization of the normally negative postsynaptic membrane that initiates the action potential.
NMDA Subunits

- NMDA receptor is an excitatory subtype of the glutamate receptor that contains two identified subunits classified as NR1 and NR2.
- NR1 AND NR2 are responsible for the binding of glycine and glutamate.
An increasing level of N-methyl-D-aspartate (NMDA) receptor hypofunction within the brain is associated with memory and learning impairments, with psychosis, and ultimately with excitotoxic brain injury.

As the brain ages, the NMDA receptor system becomes progressively hypofunctional, contributing to decreases in memory and learning performance.
In Summary

• The NMDA receptor contributes to the development of memory, learning, and cognitive function.

• The NMDA receptor may play a role in the mediation of the pain response.

• Impairment of the glutamate receptor and subsequently the NMDA receptor has been linked to multiple disease processes such as Alzheimer's and schizophrenia.
Anti-N-methyl-D-aspartate Receptor Encephalitis

Originally described as a neurological disorder primarily occurring in females with an average age of 23.

Can affect both children and adults.
Current research suggests that the disease process is more neuroautoimmune in nature as anti-NMDA receptor encephalitis has been associated with the formation of antibodies against the NR1 and NR2 subunits of the NMDA receptor.

Theorized that these antibodies are formed in response to a particular type of stimuli such as a tumor or viral infection.

Majority of adult cases reported are frequently associated with the presence of ovarian teratoma.
Devil or Disease?

• In adults, classic presentation of this disease 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.

• In fact, many researchers now believe that most cases of reported “possession,” were actually the result of anti-NMDA receptor encephalitis
The First Reported Case

Symptoms of this disorder were originally described in a 34 year old female patient with an underlying diagnosis of ovarian teratoma in 2007.

According to the literature, her symptoms included neurological, psychological, and autonomic involvement. Symptoms reported included headache, anxiety, aggressive behavior, homicidal ideation, as well as seizures.

Autonomic instability was also documented and included hypotension, bradycardia, hypoventilation, hyperthermia and periods of asystole lasting up to fifteen seconds.
• Anti-NMDA receptor encephalitis has also been reported in the pediatric population and has been deemed to be the most commonly reported cause of autoimmune mediated encephalitis second only to acute demyelinating encephalitis.

• While symptoms of this disease are similar in nature to the adult population, the order of the onset of symptoms is different in the pediatric population.
Most reported pediatric cases under the age of 12 the presence of an underlying tumor has not been identified.

In cases involving patients over the age of 12, tumors have been detected either during the early stages of the disease or after symptoms of encephalitis have resolved.
Adult presentation

• In adults, classic presentation of this disease usually begins with symptoms of a psychiatric nature, such as psychosis, personality change, memory loss, and hallucinations.

• New research suggests that there is a preliminary phase that occurs five days to two weeks prior to the onset of psychiatric symptoms.
Preliminary phase

- Symptoms reported during this phase are nonspecific in nature and include:
  - Fever
  - Nausea
  - Vomiting
  - Headache
  - Lethargic feeling
  - Inability to concentrate
Disease Progression

- Neurological symptoms are exhibited and include:
  - Depression
  - Anxiety
  - Decreased cognitive skills
  - Aphasia
  - Tonic clonic seizures
  - Ataxia
  - An unresponsive stage wherein patients appear as if they are in a catatonic state.
The Final Phase

- The final and most severe phase of symptoms incorporates autonomic involvement wherein autonomic instability occurs manifesting as:
  - Cardiac arrhythmias
  - Hyper- and hypotension
  - Hyper-and hypothermia
  - Dyskinesias
Symptomatology remains relatively similar between the adult and pediatric populations

- Initial symptoms first displayed by the pediatric population seems to differ from that of the adult population.

Majority of reported pediatric cases occurring in children under age 12

- First and most commonly experienced symptom reported is usually seizures or inappropriate movement of the body.
• Speech dysfunction has been documented as being more prevalent among the pediatric population

• Autonomic instability has been reported as being less likely to occur
  • Still can occur, especially in older teens
Prior to the development of a symptom complex that is specific to anti-NMDA receptor encephalitis, people may experience prodromal symptoms:

- Headaches
- Flu-like illness
- Upper respiratory infection like symptoms.

These symptoms may be present for weeks or months prior to disease onset.
Symptom Summary

Disease progresses at varying rates

Patients may present with a variety of neurologic symptoms.

- Initial stage of the disease, symptoms vary slightly between children and adults.
- Behavior changes are a common first symptom within both groups.
- Agitation
  - Paranoia
  - Psychosis
  - Violent behaviors
Other common first manifestations

- Seizures and bizarre movements, mostly of the lips and mouth, but also including pedaling motions with the legs or hand movements resembling playing a piano.
- Impaired cognition
- Memory deficits
- Speech problems (including aphasia and mutism).
## Later Symptoms

<table>
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<tr>
<th>Autonomic dysfunction</th>
<th>Hypoventilation</th>
<th>Cerebellar ataxia</th>
<th>Hemiparesis</th>
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<td>Loss of consciousness</td>
<td>Catatonia</td>
<td>The majority of patients experience at least four symptoms, with many experiencing six or seven over the course of the disease.</td>
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Diagnosis

Currently the only definitive form of diagnosis is the presence of nmda antibodies in the csf.

Once this has been confirmed, the next step would be to assess for the presence of abdominal/ovarian tumors.
Food for thought

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.

This may help to explain some of the hallmark symptoms associated with this disease process.
Anesthesia and the NMDA Receptor
NMDA receptor is the site of action for many commonly administered anesthetic drugs in both the adult and pediatric population.

- These medications include known NMDA receptor antagonists such as nitrous oxide and ketamine.
Schematic representation of the NMDA (N-Methyl-D-Aspartate) receptor complex

- Extracellular side
- Cytoplasmic side
- Glutamate recognition site
- Polyamine site
- Zn$^{2+}$ site
- Glycine site
- PCP site
- Mg$^{2+}$ site
- Na$^+$
- Ca$^{2+}$
ANESTHESIA AND THE NMDA RECEPTOR

• The NMDA receptor may be responsible for mediating the effects of other commonly administered anesthetic agents such as propofol, fentanyl, and sevoflurane.

• It is theorized that medications acting 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 the patient with anti-NMDA receptor encephalitis.
Nitrous oxide
Nitrous oxide

- Nitrous oxide (N2O) has been shown to achieve its anesthetic effect through antagonization of the NMDA receptor when administered at anesthetically significant levels.

- Effect is achieved due to an N2O initiated up regulated binding of the NMDA radioligand which causes the dose dependent inhibition of NMDA activated currents in the amygdala and cerebral cortex.
n2o

- It is hypothesized that because of their very similar pharmacological profiles, ketamine and N2O may share a similar mechanism of NMDA receptor antagonization.

- Antagonism of the NMDA receptor via the administration of N2O or ketamine has been shown to cause a decrease in the hyperalgesic effects associated with fentanyl administration.
Ketamine
Ketamine

- 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.
Ketamine

Interacts with the mu, delta, and kappa opioid receptors as well as voltage sensitive calcium channels, muscarinic receptors, and monoaminergic receptors to achieve its effects.

The side effects of ketamine administration have been well documented and include psychosis, memory impairment, and hallucinations.
Special k

- These side effects often mimic some of the symptoms associated with anti-NMDA receptor encephalitis as well as schizophrenia.

- Studies have shown a worsening in positive, negative, and cognitive symptoms in patients with schizophrenia following the administration of ketamine.
Propofol
Propofol

- Propofol is a short acting intravenous phenolic sedative-hypnotic derivative that causes global central nervous depression via direct activation of the γ-aminobutyric acid (GABA) receptors.

- Propofol also inhibits the NMDA receptor.
Propofol

• 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.

• This decrease of intracellular calcium influx lends itself to the theory that propofol possesses an organ protective capacity as increased intracellular concentrations have been thought to be responsible for tissue injury as well as cellular dysfunction.
Propofol

• Neuroprotective as it inhibits NMDA activated dilation of the cerebral parenchymal arterioles through activation of neuronal nitric oxide synthase in rats.

• 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.
Propofol

• Due to the inhibitory effects of propofol on the NMDA receptor it is unknown as to how its administration will affect the symptomatology 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 propofol bolus.

• Further research is needed to determine what effects, if any, propofol administration may have on the symptomatology of anti-NMDA receptor encephalitis.
Fentanyl
Fentanyl

• a rapid acting synthetic mu opioid agonist activates the mu opioid receptors in conditions where persistent pain is present.

• Fentanyl has 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.
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 mu opioid agonists.

Opioids such as remifentanil, fentanyl, and to a lesser extent morphine, have been shown to cause hyperalgesia following abrupt termination or long term administration.
Fentanyl

- 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.

- Administration of select NMDA receptor antagonists such as methadone and ketamine, have been used to mediate the hyperalgesia associated with opioid administration, manage the symptoms associated with opioid withdrawal, and in the treatment of chronic pain patients.
Recent study involving genetically altered mice with a decreased NR1 subunit determined that the exhibited potency of fentanyl, morphine, and methadone was three times less than the potency of the same drugs observed in mice with normal functioning NR1 subunits.

These findings may suggest the theoretical need for an increased dosage of opioids in patients with anti-NMDA receptor encephalitis as the function of the NR1 subunit is impaired.
Fentanyl

Study also showed no difference between the genetically altered mice and the control group in regards to the development of opioid tolerance and dependence, suggesting that the NR1 subunit may play a more minor role in the development of mu opioid tolerance.

These findings may also help to explain why there hasn't been any reported reductions in the opioid requirements for patients suffering from anti-NMDA receptor encephalitis.
Sevoflurane
Sevoflurane

- Sevoflurane is an isopropyl ether inhaled anesthetic that has been shown to intensify transmission of GABA.
- 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.
Sevoflurane

at minimum alveolar concentration (MAC), Sevoflurane has been shown to exhibit an increased potentiation of the glycine receptor but only a moderate antagonism of the NMDA receptor.

This finding suggests that the immobility caused by the volatile anesthetic sevoflurane may be more a byproduct of its effects on the glycine and GABA receptors as opposed to its effect on the NMDA receptor.
sevoflurane

- Additionally, it has been suggested that Sevoflurane may display a synergistic antagonism of the NMDA receptor when administered along with a known NMDA receptor antagonist.

- Currently, only one case report to date has been published suggesting that the administration of Sevoflurane in conjunction with propofol, to a patient suffering from ant-NMDA receptor encephalitis, may have caused a worsening of the patient’s clinical presentation.
In conclusion
Conclusion

• In summary, anti-NMDA receptor encephalitis can present a challenge to the anesthesia provider in all phases of the anesthetic.

• 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.
Conclusion

Comparatively speaking, little literature describing the anesthetic management of this disease in the adult and pediatric population.

May be prudent to avoid known NMDA receptor antagonists, such as ketamine and N2O in this population.

Also, until further research is conducted, it may be wise to use decreased dosages of medications that act indirectly on the NMDA receptor or just avoid those medications as well if at all possible.
Questions?

Thank you!!


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