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Myasthenia Gravis

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Myasthenia Gravis

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Pathophysiological Processes

Topic

- Myasthenia Gravis (MG) – Chronic autoimmune neuromuscular disorder
- Caused by destruction or decreased availability of nicotinic acetylcholine receptors (AchR) (Collins et al., 2020).
- The Myasthenia Gravis Foundation of America (2022) reports that there are other similar but different conditions that affect the neuromuscular junction (NMJ)
  - Congenital myasthenic syndromes
  - Transient neonatal myasthenia
  - Lambert-Eaton myasthenic syndrome

Why Myasthenia Gravis?

- Rare but relevant disorder with a prevalence of 20 per 100,000 (Dontukurthy et al., 2020)
- Many anesthesia drugs specifically interface with the NMJ
- MG makes patients increasingly sensitive to most neuromuscular blocking agents (NMBAs) (Dontukurthy et al., 2020)
- MG patients are at a higher risk for respiratory failure or weakness following surgery (Dontukurthy et al., 2020)
- Education about the disorder may help providers with clinical decision making and improve outcomes

AChR-MG Pathophysiology

(Dresser et al., 2021)

- 80% of MG patients have AChR antibodies
  - Predominately IgG1 and IgG3
  - Fewer cases of IgG2 and IgG4
- AChR antibodies target specific subunits of the AChR
- α-subunits are targeted by at least 50% of antibodies
  - More pathogenic
- Pathogenic mechanisms vary but all impair receptor function
  - Binding (Primary)
  - Blocking
  - Modulating
- Complement cascade is activated and membrane attack complex causes damage to postsynaptic membrane, synaptic folds, AChRs, and AChR proteins
- Thymoma-Associated MG
  - 30% of patients with Thymoma develop MG

MuSK-MG Pathophysiology

(Rodolico et al., 2020)

- Muscle-specific tyrosine kinase antibodies (MuSK-Abs)
  - First identified in 2001
  - Confirmed as being pathogenic in 2019
  - Account for 5-8% of MG patients
  - IgG4 immunoglobulin
- A four-subunit complex on the post-synaptic membrane occurs because of the association between MuSK and low-density lipoprotein receptor-related protein 4 (LRP4)
- MuSK-Abs interfere with the MuSK-LRP4 complex
  - Grouping of AChRs is inhibited which decreases signal strength across the NMJ

Signs & Symptoms

- Muscle weakness that worsens with activity and improves with rest is a hallmark of MG (Collins et al., 2020)
- Eye Muscles
  - Drooping Eyelids (ptosis) (Johns Hopkins Medicine, 2022)
  - Double Vision (diplopia) (Johns Hopkins Medicine, 2022)
  - 80% of patients with ocular onset eventually develop generalized symptoms (Dresser et al., 2021
- Face and Throat
  - Difficulty speaking (Mayo Clinic, 2021)
  - Difficulty swallowing (Mayo Clinic, 2021)
  - Difficulty chewing (Mayo Clinic, 2021)
  - Difficulty changing facial expressions (Mayo Clinic, 2021)
- Neck and Limbs
  - Difficulty holding the head up (Mayo Clinic, 2021)
  - Weakness in the arms and legs (Mayo Clinic, 2021)
- Myasthenic Crisis
  - Severe muscle weakness (Collins et al., 2020)
  - Paralysis (Collins et al., 2020)
  - Respiratory failure (Collins et al., 2020)

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Significance of Pathophysiology

MG patients are at increased risk for postoperative complications such as respiratory failure, myasthenic crisis, pneumonia, intensive care unit admission, and septicemia. Even though Myasthenia Gravis is a rare disorder, MG patients are living longer, and are presenting to the hospital for surgery unrelated to MG at an increased rate. Therefore, is likely that anesthesia providers will encounter MG patients throughout their career and should be aware of the implications MG has on the anesthetic plan as well as potential outcomes.

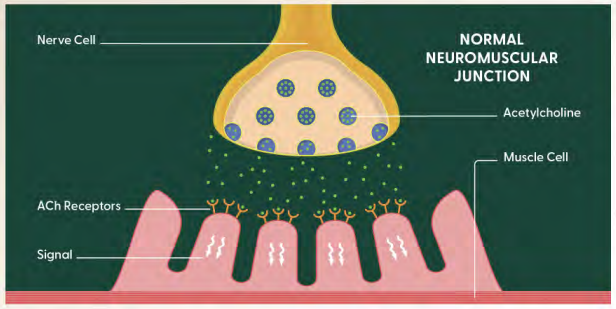

Figure 1: A normal functioning NMJ pictured above. Acetylcholine is released from the presynaptic terminal, crosses the synaptic cleft, and binds to the postsynaptic AChR to produce an action potential and subsequent muscle contraction (MG United, 2020)

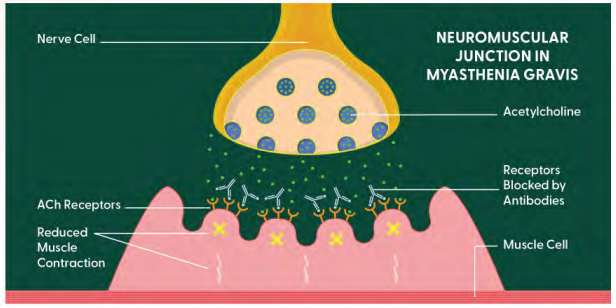

Figure 2: An NMJ affected by MG. Acetylcholine is released from the presynaptic terminal, crosses the synaptic cleft, but has limited AChR binding sites available due to destruction by AChR antibodies or prevention of clustering as seen in MuSK-MG patients. As a result, a weaker action potential and muscle contraction is produced (MG United, 2020)

Nursing Considerations

(Collins et al., 2020)

- Preoperative
  - Informing the patient that surgical stress will likely worsen the disease process temporarily, but a full recovery is expected
  - Elective surgeries should be performed when the patient is in a stable phase
  - Immunosuppressants generally don't interact with anesthesia. Azathioprine is an exception
  - Azathioprine prolongs effects of Succinylcholine and inhibits effects of nondepolarizing NMBAs
  - If having an acute exacerbation or crisis but needs emergent surgery, the provider should try to optimize the patient first
    - Plasmapheresis
    - Immunosuppressants
  - Avoid premedicating with respiratory depressing agents
- Anesthesia Management
  - Peripheral nerve blocks preferred. MG patients are more likely to develop respiratory failure when regional techniques are used for the upper extremities
  - Induction should be performed with short-acting intravenous drugs
    - Respiratory depressant effects will be increased
  - Volatile anesthetics are used to maintain anesthesia
    - With or without nitrous oxide
    - Volatile anesthetics may decrease or eliminate need for muscle relaxants
  - If paralysis is required nondepolarizing NMBAs are preferred
    - NMBA dose should be reduced by at least 50%
    - Depolarizing NMBAs have unpredictable effects in MG patients
    - MG patients are at increased risk for residual neuromuscular blockade
      - Acceleromyography is the preferred method of monitoring blockade
  - Acetylcholinesterase inhibitors (AChEI) are not preferred for NMBA reversal with MG patients
    - Underdosing AChEI can result in myasthenic crisis
    - Overdosing can result in cholinergic crisis
  - Sugammadex has been shown to rapidly, completely, and safely reverse NMBAs
    - Postoperative risks such as reintubation, pneumonia, residual block, myasthenic crisis, cholinergic crisis are greatly diminished
- Postoperative
  - MG patients have higher risk of postop complications
    - Pneumonia
    - Septicemia
    - Intensive care unit (ICU) admission
  - Myasthenic crisis risk is higher with myasthenic crisis history, long surgical time, high blood loss, and presence of thymoma
  - Specific extubation criteria include normal level of consciousness, tidal volume ≥ 5 mL/kg, respiratory rate <30/minute
  - Ensure adequate spontaneous breathing and no residual block
  - Avoid ICU admission
    - If ICU admission is necessary, consult neurology
  - Optimize pain management
    - Opioids with rapid onset and short half-life
    - Nonsteroidal anti-inflammatory drugs

Treatment

(Farmakidis et al., 2019)

- Acetylcholinesterase inhibitors – Inhibit hydrolysis of acetylcholine in the synaptic cleft by acetylcholinesterase
  - Pyridostigmine
  - Edrophonium
- Corticosteroids – Exact mechanism of action is unknown but may affect cell-mediated immunity.
  - Prednisone
- Thymectomy – Standard first line treatment despite a lack of evidence
  - No trials comparing surgical techniques
- Other immunosuppressants – See (Farmakidis et al., 2019) for mechanism of action of each agent.
  - Azathiorpine
  - Mycophenolate Mofetil
  - Cyclosporine
  - Methotrexate
  - Cyclophosphamide
  - Rituximab
- Rapid acting immunotherapies
  - Plasma exchange – Removes pathogenic autoantibodies
  - Intravenous immunoglobulins (IVIG) – Complex modulation of the immune system
- Eculizumab – Inhibits complement and formation of a membrane attack complex
- Emerging therapies
  - Belumimab
  - Tirasemtiv

Conclusions

Myasthenia Gravis is a rare, complex, and potentially debilitating and life-threatening disease. Many treatment options exist and are emerging, but more research is needed to maximize data and optimize outcomes. Understanding the pathophysiology and its implications is imperative for anesthesia providers if adverse outcomes and complications are to be avoided.

References