8-2019

Myasthenia Gravis

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Pathophysiology of: AChR-MG Vs. MuSK-MG

- Acetylcholine Receptor Myasthenia gravis (AChR-MG) is an autoimmune disorder that is caused by antibody mediated degradation of somatic nicotinic acetylcholine receptors or muscle specific tyrosine kinase (Yokoyama & Hattori, 2017).
- MG can be immunogenic or caused by neoplasms of the thymus, known as thymoma (Melzer et al., 2016)
- Damage to acetylcholine receptors (AChR) limits the ability of that receptor to open a sufficient number of sodium channels in the muscle myocyte, reach threshold potential, propagate the nerve impulse, and cause muscle contraction (Koneczny, Cossins, & Vincent, 2014)
- Continued degradation of receptors leads to progressive weakness of the ocular muscles, skeletal muscles, bulbar muscles, and respiratory muscles (Phillips & Vinent 2016, Yokoyama & Hattori, 2017).
- The primary antibodies responsible for damage to the acetylcholine receptor are are IgG1 and IgG3 (Phillips & Vincent 2016)
- The antibody mediated destruction of the acetylcholine receptor comes in three different forms:
  1. Complement activated damage
  2. Antigenic modulation
  3. Functional blockage (Koneczny, Cossins, & Vincent, 2014)
- 85% of generalized myasthenia gravis patients and 50% of myasthenia gravis patients that experiencing ocular weakness test positive for cytotoxicity to the acetylcholine receptor (Yokoyama & Hattori, 2017).
- Thyoma-associated MG (TAMG) which is a tumor of the thymus accounts for 10-15% of MG cases and is frequently coupled with bulbar weakness, or weakness of the motor function of cranial nerves glossopharyngeal (IX), vagus (X), accessory (XI), and gypoglossal (XII) (Yokoyama & Hattori, 2017).

- Muscle Specific Tyrosine Kinase Myasthenia Gravis (MuSK-MG) is caused by antibody attack on a transmembrane kinase that is crucial for signaling for the location of AChRs accumulation in the neuromuscular junction (NMJ) during fetal development. MuSKs role in adult cells is unclear but appears to play a part in AChR maintenance and in creating AChR clusters in the NMJ. (Koneczny, Cossins, & Vincent, 2014)
- In MuSK-MG the IgG4 antibody is responsible for disease by degrading MuSK and limiting density of AChR on the post synaptic side of the neuromuscular junction (Koneczny, Cossins, & Vincent, 2014).
- Similar to AChR-MG, MuSK-MG leads to progressive muscle weakness.
- Interestingly, the decreased response at the neuromuscular junction in MuSK-MG does not lead to an increase in presynaptic acetylcholine release, indicating that MuSK antibodies, or decreased AChR clustering is somehow sensed by the presynaptic neuron and acetylcholine transmission is not upregulated (Koneczny, Cossins, & Vincent, 2014)
- The decrease in presynaptic acetylcholine also decreases a MuSK-MG patient's response to acetylcholinesterase inhibitors (Koneczny, Cossins, & Vincent, 2014)
- Approximately 10-15% of MG patients test positive for MuSK antibodies (Koneczny, Cossins, & Vincent, 2014)

Clinical Presentation

Generalized Myasthenia Gravis

- Weakness of the extraocular, bulbar, facial, limb, and extra axial muscles (Yokoyama & Hattori, 2017).
- Untreated generalized MG can lead to respiratory insufficiency and hypoventilation (Kołtuniuk et al., 2017).
- Initially weakness is noticed during periods of exercise or repetitive muscle usage (Yokoyama & Hattori, 2017).
- Some muscle strength is usually regained after periods of rest (Yokoyama & Hattori, 2017).
- Daily fluctuations of weakness are common (Yokoyama & Hattori, 2017).
- Like many chronic illnesses, patients with MG often show signs of depression, anxiety, and difficulty sleeping (Yokoyama & Hattori, 2017).

Ocular Myasthenia Gravis

- Highlighted by weakness specifically of the extraocular and intraocular muscles (Kołtuniuk, Rozensztrauch, Beniak, & Rosińczuk, 2017).
- Weakness of these muscles leads to ptosis and diplopia (Kołtuniuk, Rozensztrauch, Beniak, & Rosińczuk, 2017).
- Ocular myasthenia gravis patients will often have a characteristic squint (Kołtuniuk, Rozensztrauch, Beniak, & Rosińczuk, 2017).

Diagram of Normal Neuromuscular Junction Vs. MuSK Antibody Myasthenia Gravis

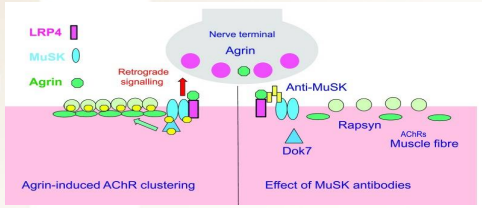

Figure 2. Left A normally functioning neuromuscular junction. Multiple acetylcholine receptors present on the post synaptic end plate. Retro-grade signaling is intact, creating a feedback loop to stop additional acetylcholine release. *Right* Few post synaptic acetylcholine receptors with limited clustering. Limited receptor clustering due to antibodies against MuSK which directs AChR location, making surpassing threshold potential unlikely leading to muscle weakness (Phillips & Vincent, 2016).

A Rare But Clinically Important Neuromuscular Disease

Introduction

- Myasthenia Gravis (MG) is an autoimmune disease of the neuromuscular junction that causes muscle weakness, fatigability, and in severe untreated cases respiratory failure (Kołtuniuk, Rozensztrauch, Beniak, & Rosińczuk, 2017).
  - First Described by Thomas Willis in 1672 (Santos et al., 2016)
- Women are most commonly diagnosed in their 20th to 30th year of life, while diagnosis in males is generally occurs in the 50th to 60th year of life. (Kołtuniuk et al., 2017).
- MG has a prevalence rate of 8-20 per 100,000 people globally and diagnosis rate may be increasing (Guptill et al., 2018, Muckler et al., 2019)
- Multiple forms of MG exist. The primary mechanism is due to antibody degredation of acetylcholine receptors and muscle specific tyrosine kinase in the neuromuscular junction causing muscle weakness. Other MG causing antibodies are still being discovered (Guptill et al., 2018).
- MG is of particular interest to the nurse anesthetist because of the associated complications when administering neuromuscular blockers during anesthesia (Muckler et al., 2019)

Diagram of Normal Neuromuscular Junction Vs. AChR Antibody Myasthenia Gravis

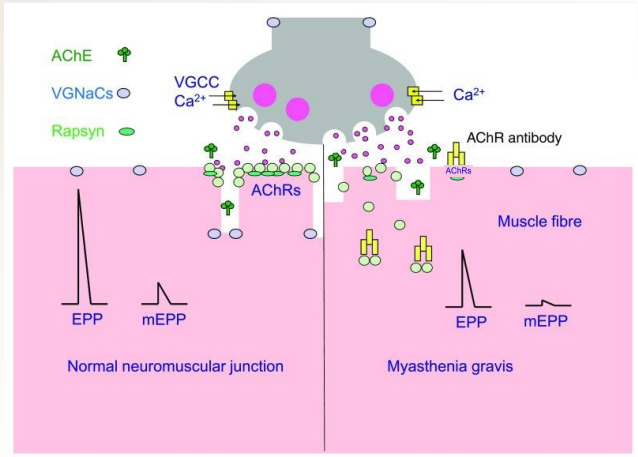

Figure 1. Left shows a physiologically normal neuromuscular junction. Acetylcholine released from the presynaptic neuron stimulates additional acetylcholine release through activation of the presynaptic Miniature End Plate Potential (mEPP). The additional acetylcholine then crosses the synapse and stimulates the post synaptic acetylcholine receptor and creates an End Plate Potential (EPP) large enough to surpass threshold and cause muscle contraction. *Right* shows a myasthenia gravis degraded neuromuscular junction with fewer acetylcholine receptors and antibody blockade of the remaining receptor. Stimulation of this single receptor creates a far lower EPP, unable to reach threshold potential and cause muscular contraction despite increased acetylcholine released into the synapse (Phillips & Vincent, 2016).

Treatment

- Symptom management is generally the first line treatment for MG with use of acetylcholinesterase inhibitors (AChEI) which increase levels of acetylcholine in the neuromuscular junction, improving strength. (Muckler et al., 2019).
- These same drugs are used in the diagnosis of MG. Increased strength with use of AChEIs is a strong indicator of AChR-MG. (Muckler et al., 2019).
- AChEIs used for MG treatment include Pyridostigmine (Mestinon), Edrophonium (Tensilon), and Neostigmine (Prostigmine) (Muckler et al., 2019).
- If AChEIs are ineffective, the second line treatment is immunosuppression using corticosteroids (Muckler et al., 2019).
- While steroid therapy is relatively effective, the side effects of chronic steroid use are often poorly tolerated (Muckler et al., 2019).
- Plasmapheresis has provided approximately 45% of patients with significant but transient benefit by removing circulating AChR antibodies from the blood stream (Muckler et al., 2019).
- While very effective for a significant portion of MG patients, plasmapheresis also has significant side effects of potential pulmonary embolism, infection and hypotension (Muckler et al., 2019).
- Recently however, Okusanya et al. (2016) have suggested that thymectomy for all myasthenia gravis patients may be an effective treatment reducing immunosuppression use, steroid use, postoperative hospitalization due to MG exacerbations.
- More work will need to be done to determine best surgical approach to thymectomy including open procedure, Video assisted thoracic surgery and robotic assisted. (Okusanya et al., 2016)

Risk Factors

- People with a first degree relative with MG have a 4.5% likelihood of developing MG (Melzer et al., 2016).
- Approximately 5% of MG patients experience another autoimmune disease concurrently such as lupus erythematosus, pernicious anemia, or rheumatoid arthritis (Muckler et al., 2019).
- 55% of patients who originally present with ocular MG converted to generalized MG with a mean conversion time of 13 months (Hendricks, Bhatti, Hodge & Chen, 2019)
- Some studies suggest that incidence remains steady while prevalence is increasing which may mean diagnosis is getting better, environmental factors may be worsening, but treatment is effective (Santos et al., 2016).
- Men are most susceptible to late onset myasthenia gravis (LOMG) with a ratio of .95:1 (Santos et al., 2016).
- Women are more susceptible to early onset myasthenia graves (EOMG) with a ratio of 2.73:1 (Santos et al., 2016).

Anesthesia Considerations

- No clearly defined consensus on anesthesia technique for MG patients (Muckler et al., 2019).
- Practitioners may utilize 1/10th of standard dose for non-depolarizing neuromuscular blocking agents (NNBA) or 1-1.5 mg/kg of succinylcholine for rapid sequence intubation. (Muckler et al., 2019).
- Suggamadex has been successfully used for reversal of NNBAs in MG patients (Muckler et al., 2019).
- Close monitoring of neuromuscular activity is also imperative with the use of antibiotics, beta-blockers, calcium channel blockers, and statins (Muckler et al., 2019).

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