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Crisis in the Neuro-Muscular Junction: Anesthetic Implications

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Stem Case and Key Questions Content
At the conclusion of this educational activity, the participants will be able to:

1. Assess the perioperative risk stratification of patients with myasthenia gravis
2. Identify pharmacological challenges in the management of patients with myasthenia gravis
3. Review the intraoperative anesthetic management of myasthenia gravis
4. Recognize and manage postoperative complications of myasthenia gravis

60 years old male with a history of myasthenia gravis (MG) diagnosed seven years ago presents to the emergency room with one week of bilateral, progressive, lower extremity weakness accompanied on the day of admission by difficulty with urination. Further work-up shows a herniated disk in the lumbar area as the etiology of a cauda equina syndrome. The neurosurgical service is consulted and the decision is made to bring the patient to the operating room for lumbar decompression.

Patient's medical history includes hypertension, diabetes mellitus (DM), coronary artery disease status post coronary artery bypass grafting (CABG) 12 years ago and coronary stent placement in the last 18 months, automated implantable cardiac defibrillator (AICD) placement 12 months prior, obstructive sleep apnea (OSA) on home continuous positive airway pressure (CPAP) . Home medications include: prednisone 50 mg/day, carvedilol 20 mg/day, aspirin 81 mg/day, insulin 70/30, pyridostigmine bromide 90 mg every 8 hours, hydrocodone 2 tablets every 8 hours for back pain. He is allergic to penicillin.

On physical exam blood pressure (BP) is 120/60 mm Hg, heart rate (HR) 65 beats/minute, O2 sat 92 % on room air, height 5'6'' weight 230 lbs.
He has a beard, full dentition and a class II Mallampati examination.
Heart tones are distant, breath sounds are diminished and there is no peripheral edema. He has difficulty flexing his knees and performing plantar flexion and the ankle reflexes are absent.
Initial laboratory data included: blood urea nitrogen (BUN) 18 mg/dl, creatinine (Cr) 1.6 mg/dl, and normal complete blood count (CBC) and coagulation profile. Electrocardiogram (EKG) showed sinus bradycardia.

1. What elements in his medical history or details of his physical examination will help you identify the severity of his myasthenia gravis (MG)?

Upon further questioning the patient states that he has initially been diagnosed with "bulbar myasthenia". He underwent plasmapheresis several times in the past without any sustained

improvement of his symptoms. He has been taking 50 mg of prednisone daily for the past 5 years and has been on the same dose of pyridostigmine bromide for the past 6 months since he last saw his neurologist. He complains of generalized weakness, fatigues easily and has difficulty holding his head up at the end of the day. He also complains of increased pharyngeal secretions and difficulty swallowing.

2. Is this patient at risk for developing post-surgical respiratory failure? What are the risk factors?

3. What is this patient's peri-operative risk for cardiac complications? Should he receive a beta blocker pre-operatively?

4. What is the significance of OSA in patients with MG?

5. Are there any necessary pre-operative interventions? Should the pre-operative management be different for elective versus urgent or emergent surgery?
The patient was brought to the operating room and standard monitors were applied in preparation for induction.

6. What intubation technique and induction medications would you use?

7. How should general anesthesia be maintained?
Prior to incision the surgeon is requesting administration of intravenous clindamycin and gentamycin.

8. Is this regimen appropriate in this clinical scenario?
During the procedure, the surgeon asks for complete muscle relaxation

9. What pharmacologic agents would you choose?
The surgery is uneventful. At the end of surgery the patient is turned supine, inhalational agents turned off and he wakes up, follows commands but he is very weak. He cannot sustain a 5 sec head lift and his spontaneous tidal volume (TV) is less than 100cc and respiratory rate of 16 breaths/minute.

10. What is the differential diagnosis of this patient's weakness?

11. Are there any objective methods of quantifying his respiratory function intra-operatively?

12. Should you administer pyridostigmine and how much?
You decide to administer intravenous pyridostigmine. A couple minutes later patient develops bradycardia with a heart rate of 34 beats/minute.

13. Any further interventions?

Model Discussion Content

• Diagnosis and mechanisms of disease

Myasthenia gravis is an autoimmune disease caused by antibodies against the post-synaptic nicotinic acetylcholine receptor (nAchR) at the neuromuscular junction resulting in a reduction in postsynaptic nAchR density (number of receptors drops to about 30 % of normal). 80-85 % of patients are antibody positive (1). The rest are antibody negative and of these a small fraction (40%) may have antibodies against muscle specific tyrosine kinase (MuSk). nAchR-antibody positive patients have a tendency to develop generalized muscle weakness whereas MuSk antibody positive patients more often develop oculobulbar muscle weakness.

Patients that are nAchR antibody positive respond to cholinesterase inhibitors and 15 % of them may have benign thymomas. Thymic follicular hyperplasia occurs in 70% of MG patients (1). Treatment includes thymectomy which may be associated with improvement and even remission of MG (2). MG patients with thymomas may have anti-ryanodine receptor antibodies and the titer correlates with clinical severity.

In contrast, in MuSk antibody positive patients cholinesterase inhibitors have no effect or may even worsen the symptoms, thymectomy is not indicated and patients may be resistant to intravenous immunoglobulins but respond to plasmapheresis.

• Clinical symptoms and treatment

Traditionally MG was considered a disease of young women but more recently there has been an increase in the prevalence of the disease particularly in older men (9, 10). Older age at onset brings with it other comorbidities, heart disease being just one of them.

MG patients present with fluctuating weakness of voluntary muscles that can be exacerbated by: ambient heat, pregnancy, systemic infections, surgery, certain antibiotics (aminoglycosides, quinolones), magnesium, iodinated contrast agents, calcium channel blockers, beta blockers, glucocorticoids, lithium, anticonvulsants, anti-arrhythmic medications, hypokalemia, and thyroid dysfunction (3).

Beta blockers regardless of their mode of administration have been shown to exacerbate MG (4, 5).

MG patients are at risk for two types of crises:

- Myasthenic crisis when patients exhibit increased muscle weakness and respiratory failure. Predictors for death in these patients are the patient's age, time to crisis recognition and the need for endotracheal intubation.
- Cholinergic crisis occurs when patient is overdosed with cholinesterase inhibitors and show symptoms such as salivation, sweating, cramps, urinary urgency, bradycardia, muscle fasciculations and muscle weakness.

Current therapies include plasmapheresis and intravenous immunoglobulins both equally effective for MG crisis and for optimization before surgery (6).

Prednisone is commonly started with cholinesterase inhibitors but may initially exacerbate symptoms if started at doses higher than 50 mg /day (7).

Other disease modifying agents include azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil. Of mention here is that azathioprine extends the effects of succinylcholine and antagonizes nondepolarizing blocking agents.

• Severity of illness classification

MG is classified by Osserman and Genkins based on the severity of the symptoms and distribution of skeletal muscles involved (8):

Class I Ocular signs and symptoms (limited to the extraocular muscles)
Class II Ocular signs and mild weakness of other muscles
Class IIA Generalized mild muscle weakness (slow and progressive skeletal muscle weakness that spares the muscles of respiration)
Class IIB Prominent bulbar and/or respiratory muscle weakness
Class III Eye muscle weakness of any severity and moderate weakness of other muscles
Class IIIA Predominant limb or axial muscle weakness
Class IIIB Predominant bulbar or respiratory muscles
Class IV ocular weakness and severe generalized muscle weakness
Class V Intubation needed to maintain airway

• Postoperative outcome predictors in patients with MG
In MG patients undergoing thymectomy, besides the presence of bulbar symptoms and history of myasthenic crisis Watanabe (17) found that serum level of antiAch receptor antibody higher than 100 nmol/l and intra-operative blood loss more than 1 liter were predictors of postoperative myasthenic crisis. Unfortunately there is currently no accepted grading system that applies to all patients.

A past history of respiratory pathology and ongoing bulbar symptoms are with certainty predictors of postoperative complications.

The influence of the dose of pyridostigmine on the need for postoperative ventilation has not been established with certainty. However continuation of the daily dose of pyridostigmine pre-operatively is advised and may prevent post-operative respiratory distress (18).
The risk factors for prolonged post-operative ventilation are weighted according to their significance as predictors. In the 1980s it was thought that:

1. Duration of MG for longer than 6 years has the greatest value in predicting the need for post-operative ventilatory support (12 points).
2. A history of chronic respiratory disease other than dysfunction due to MG (10 points)
3. Dose of Pyridostigmine greater than 750 mg /day , 48 hours before the operation (8 points)
4. Pre-operative vital capacity less than 2.9 l (4 points)

Leventhal (14) found that a total of more than 10 points identifies patients at risk for post-operative ventilation for more than 3 hours. Later it was shown that this scoring system could not be used for all patients (15).
Other researchers in the late 1980's identified different positive predictors for prolonged post-operative ventilation (15):
- Osserman class III and IV
- History of respiratory failure due to MG
- Chronic steroid therapy

• Impact of comorbidities on the perioperative management of MG patients
According to the ACC/AHA 2007 guidelines this patient has two clinical risk factors (previous percutaneous coronary intervention-PCI and CABG and DM on Insulin) and is undergoing an intermediate risk procedure. His functional capacity is difficult to assess but he has no clinical evidence of decompensated heart failure or ischemia. He is currently on a beta blocker that

according to guidelines has to be continued in the perioperative period (11). Planned surgery with heart rate control carries a class IIa levelI recommendation and is supported by randomized trial results (11).

However it is established that beta blockers may exacerbate muscle weakness in an MG patient with preexistent muscle weakness (4, 5).
Also the prevalence of OSA and OSA syndrome is at least double in the MG population compared to the general population and may be underdiagnosed (13).

• Anesthetic management of MG patients
Anxiolytics, sedatives and opioids as pre-medications are rarely given to patients that have a limited respiratory reserve.
Induction of anesthesia can be done with inhalational agents only. Sevoflurane can be used as sole agent for induction, intubation and maintenance (19). A decrease in TOF is demonstrated when using inhalational agents. Both desflurane and sevoflurane produce a decrease in TOF when compared with propofol.
MG patients are resistant to depolarizing muscle relaxants due to the loss of receptors, since these agents produce the bock by agonistic action.
The ED95 in MG patients is 2.6 times that in non-myasthenic patients. The of succinylcholine dose of succinylcholine for rapid sequence induction is five times the ED95
in MG patients. Myasthenic patients are more likely to develop a phase II block with repeated doses of succinylcholine. Also cholinesterase depletion due to plasmapheresis or inhibition caused by pyridostigmine given pre-operatively may affect the metabolism of succinylcholine, remifentanil, ester local anesthetics and any other drugs metabolized by similar enzymes.
Nondepolarizing muscle relaxants (NDMR) interrupt the neuro-muscular transmission at the level of nicotinic Ach receptors and therefore myasthenic patients are extremely sensitive to very small doses including defasciculating doses. The ED 95 for vecuronium ranges from 40-55 %, atracurium 58% and rocuronium 50% of normal controls.
There is no difference in sensitivity to NDMR between the seropositive and seronegative patients with MG (20).
The site of neuro-muscular monitoring in myasthenia patients is recommended to be the forearm muscles because the ocular muscles are affected commonly and the neuromuscular blockade is deeper in orbicularis oculi compared with the adductor pollicis (20).

• Assessment of respiratory function/respiratory muscle strength on emergence from anesthesia
Muscular weakness on emergence from anesthesia could be multi-factorial. If myasthenic crisis is highly suspected, pyridostigmine should be administered intramuscularly at 1/20 of the oral dose or intravenously at 1/30 the oral dose. When administered parenteral, pyridostigmine may cause bradycardia due to increased acetylcholine effects on atrioventricular conduction or increase of the duration of ventricular repolarization. Steroid myopathy may be present pre-operatively and generalized weakness can be exacerbated by other multiple factors as mentioned above.

Respiratory muscle strength can be assessed bedside by several respiratory tests including negative inspiratory force (NIF) or maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), vital capacity (VC) and FEV1. Generally when MEP is more than 40 cm H2O, MIP is more than negative 40 cm H2O and VC is more than 20cc/kg patients are unlikely to

require mechanical ventilation. A decline of more than 30 % in the MIP predicts respiratory failure (21).

In conclusion, patients with myasthenia gravis present multiple challenges for the anesthesiologist. Key factors for a successful anesthetic management stem form: an accurate evaluation of the severity of their MG, recognition of a multitude of pharmacological interactions (22) in order to prevent worsening muscle weakness and timely diagnosis and treatment of postoperative myasthenic complications (23).

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