The implications of myasthenia gravis for the anaesthesiologist

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Myasthenia gravis is an autoimmune disease in which antibodies which are generated to the acetylcholine nicotinic receptors at the motor end plate cause skeletal muscle weakness.[1] There appears to be an association with the thymus gland, where T cells generate antibodies after being sensitised to a protein similar to the acetylcholine receptor.[1] Historically, myasthenia gravis was classified into five classes by Osserman, ranging from eye involvement alone, to mild, moderate or severe weakness, and the need for intubation and ventilation.[1] Patients with myasthenia gravis are commonly treated with the acetylcholinesterase inhibitor, pyrodistigmine, glucocorticosteroids, other immune suppressants, as well as plasma exchange and intravenous immunoglobulins. Patients with generalised disease may present for surgery to remove the thymus gland, after which approximately 75% of patients enter remission.[1] In the perioperative period, the nuances of the disease process must be appreciated in order to provide the most beneficent care. Neuromuscular blockade should be avoided unless absolutely necessary, and when non-depolarising agents are used, they must always be accompanied by monitoring of the neuromuscular junction and appropriately reduced doses, due to the increased sensitivity to these agents. Sugammadex should also be available. These patients are relatively resistant to succinylcholine, and an increased dose should be used with the knowledge that prolonged blockade may ensue.[1]

Keywords: myasthenia gravis, anaesthesia

Myasthenia gravis is a chronic, autoimmune disease, where acetylcholine receptors at the motor end plates are destroyed or inactivated by autoantibodies, resulting in fluctuating muscle weakness. Up to 80% of functional receptor loss can occur.[2] The hallmark of this condition is fatiguability. Repetitive use of muscles results in exhaustion, with some improvement after a period of rest.[2]

Myasthenia gravis can be classified as:[3]

1. Ocular: weakness of the eyelids and extraocular muscles (ptosis and diplopia).

2. Generalised: weakness affects ocular muscles, and a conglomerate of limb, respiratory and bulbar muscles.

Bulbar muscle involvement results in problems with speech, chewing and swallowing. The most distressing symptom is weakness of the respiratory muscles, resulting in shortness of breath and weak cough.[1]

The disease is commonly seen in females in the second and third decade and in males in the sixth to eighth decade of life.[3]

Confirming the diagnosis of myasthenia gravis can take the form of:

1. Clinical tests, i.e. history, examination, bedside testing (ice pack test)

2. Serological tests, i.e. antibody testing

3. Electrophysiology tests, i.e. repetitive nerve stimulation, single fibre electromyography[4]

The ice pack test can be performed in those patients who exhibit ptosis.[4] A bag filled with ice is placed on a closed eyelid for two minutes, after which improvement in ptosis is expected based on the principle that neuromuscular transmission improves at lower muscle temperature.[4] While this test is sensitive, it can yield false positive results and should not be relied upon as confirmatory of the diagnosis.[4]

Formal serological and electrophysiological testing can be used to confirm the diagnosis. Patients with seropositive myasthenia gravis exhibit positive acetylcholine receptor antibodies, muscle specific tyrosine kinase antibodies, or low density lipoprotein receptor related protein 4 antibodies.[4] Those that lack these antibodies have seronegative disease.[3]

Electrophysiological testing has a high diagnostic sensitivity, with repetitive nerve stimulation yielding 75–80%, and single fibre electromyography around 95%.[4]

For the anaesthesiologist, the knowledge that these patients are exquisitely sensitive to non-depolarising muscle relaxants, and relatively resistant to the depolarising neuromuscular blocker, succinylcholine, is only the tip of the iceberg. This disease requires a clear understanding of its pathophysiology, and treatment, to fully grasp the nuances from an anaesthetic perspective, that can dramatically alter an affected patient's perioperative course.

At the preoperative visit, the anaesthesiologist should review the patient's plan from their neurologist, to determine the appropriateness of the timing of surgery (ideally in the stable phase of the disease) and when their medication has been optimised.[5] A thorough history should involve noting whether

the patient undergoing thymectomy fulfils the four Leventhal criteria, which puts them at risk for requiring postoperative mechanical ventilation:[6]

1. A preoperative vital capacity of less than or equal to 2.9 L

2. A duration of myasthenia gravis of greater than or equal to six years

3. A dose of pyrodistigmine of greater than or equal to 750 mg/day

4. Chronic respiratory disease

These criteria have now been extrapolated, but still only apply to those patients undergoing thymectomy.[5] The additional risk factors are:

1. Preoperative bulbar symptoms (dysphagia, dysarthria, nasal/low intensity speech)

2. History of myasthenic crisis

3. Predicted intraoperative blood loss of greater than 1 000 ml

4. Serum antiacetylcholine receptor antibody titre > 100 nmol/ml

5. 18–20% decremental response on low frequency repetitive nerve stimulation[5]

The history should also include whether or not the patient has other autoimmune diseases.

A review of the patient's medical treatment is essential. Patients with myasthenia gravis are generally on anticholinesterases, glucocorticosteroids/other immune suppressants as well as immunomodulating agents.[5]

Pyrodistigmine is the commonest anticholinesterase used to treat myasthenia gravis. This drug's mechanism of action is to increase the level of acetylcholine at the neuromuscular junction, and thus reduce muscle weakness. It should be continued on the day of surgery for two main reasons: the first, to avoid patient discomfort associated with muscle weakness that can accompany omission of a dose, and secondly, to reduce postoperative muscle weakness.[5]

Glucocorticosteroids are used as an immune suppressant in the context of myasthenia gravis. Perioperatively, the essential concern is determining whether or not there has been hypothalamo-pituitary-adrenal axis suppression. This is evident in a patient who has been taking more than 20 mg/day of prednisone (or equivalent) for three or more weeks; or in someone who is Cushingoid in appearance.[7] In such patients, perioperative corticosteroid supplementation is essential to prevent an adrenal crisis. This is easily summarised as follows:

1. For minor procedures, the usual morning dose of corticosteroid should be taken. No supplementation is required.

2. For moderately stressful surgical procedures, the usual morning dose of corticosteroid should be taken. Fifty milligrams of hydrocortisone is given intravenously at induction, followed by 25 mg of hydrocortisone eight-hourly for 24 hours. The chronic steroid dose can be resumed thereafter.

3. For major surgical stress, the usual morning dose of corticosteroid should be taken. One hundred milligrams of hydrocortisone is given intravenously at induction, followed by 50 mg of hydrocortisone eight-hourly for 24 hours. This should be tapered by half the dose per day till the usual maintenance dose is arrived at.[7]

Patients who take long-term immune suppressants other than steroids, some examples of which are azathioprine, cyclophosphamide, methotrexate or tacrolimus, can safely omit these drugs on the morning of surgery.[5]

In some instances, patients may be undergoing plasmapheresis, or be given intravenous immunoglobulins to maintain remission in those who are not well-controlled on their chronic medications. They can also be used pre-thymectomy, and during a myasthenic crisis.[5]

In the lead up to surgery, it is prudent to avoid sedating premedication. These patients should always be in a monitored environment, and clear information should be conveyed regarding the anaesthetic plan to reassure them, rather than relying on pharmacological agents to allay anxiety. If pharmacological anxiolysis is required, small boluses of the chosen agent can be given.[5]

If a surgical procedure is amenable to being conducted under local, regional or neuraxial anaesthesia, this should be chosen. Amide-type local anaesthetics should be chosen over esters, as the amides do not rely on acetylcholinesterases for their breakdown, unlike esters.[5] One should be meticulous with one's technique, in order to spare the muscles of respiration as well as possible. This is especially important with supraclavicular and interscalene brachial plexus blocks, and inadvertent higher than expected neuraxial techniques.[5]

When a general anaesthetic is the required technique, the conduct of the anaesthetic is what is of utmost importance. Inhalational agents cause dose-dependent muscle relaxation, to an extent that endotracheal intubation and surgery can often be performed without the requirement for neuromuscular blockade.[5]

The combined use of other common intravenous agents: propofol, remifentanil, lignocaine, and fentanyl often also suffice in this regard.[5]

The avoidance of neuromuscular blockade is the first choice. If a muscle relaxant must be used, a steroidal non-depolarising agent can be used in conjunction with monitoring of the neuromuscular junction, with the dose adjusted to 0.1–0.2 x ED95, due to the reduced number of nicotinic acetylcholine receptors.[5] Reversal should be with sugammadex as neostigmine may result in a cholinergic crisis.[5]

Due to the destruction of acetylcholine receptors, these patients are relatively resistant to succinylcholine, with the ED95 being 2.6 times that of unaffected patients.[5] However, when used, it may have a prolonged duration of action due to its metabolism

by pseudocholinesterase, which may be inhibited by treatment with anticholinesterases.[5]

It is always important to keep in mind that certain medications can worsen the muscle weakness of myasthenia gravis. The list is potentially exhaustive, however, notable ones include the aminoglycoside and polymyxin class of antibiotics, calcium-channel blockers, beta blockers, certain anti-epileptics, diuretics, magnesium, glucocorticosteroids, procainamide and opioids.[5]

At the end of surgery, if appropriate, the patient should be extubated, when muscle strength has been confirmed clinically, after full reversal of neuromuscular blockade, and with appropriate train-of-four monitoring (TOF > 0.9).

No discussion on myasthenia gravis is complete without a glance at the two crises these patients may experience: myasthenic and cholinergic.

A myasthenic crisis is respiratory and/or bulbar muscle weakness that requires intubation, or delays extubation.[5] It can be caused by surgical stress, infection, residual anaesthetic, withholding or reduced dosage of myasthenia gravis treatment, or medications that worsen muscle weakness.[5] It presents as profound muscle weakness, including that of the bulbar muscles. As central control of breathing should be intact, rapid, shallow breathing may be one of the first signs noted. Accessory muscle use and paradoxical breathing may also be seen. A rise in the partial pressure of carbon dioxide indicates impending respiratory failure.[5]

Treatment involves intubation and ventilation, optimisation of treatment and potentially plasma exchange and/or intravenous immunoglobulins.[5]

A cholinergic crisis occurs, in the context of myasthenia gravis, in those patients who are overtreated with the anticoholinesterase pyrodistigmine, or perioperatively with the administration of neostigmine. An excess of anticholinesterase results in a similar clinical picture to organophosphate poisoning. These patients have muscle weakness, and the symptoms of an excess of acetylcholine at muscarinic receptors – as described by the SLUDGE mnemonic[5] – **S**alivation, **L**acrimation, **U**rination, **D**efaecation, **G**astrointestinal distress and **E**mesis. Treatment involves the use of 0.4–2 mg of intravenous atropine or 0.2–1 mg of intravenous glycopyrrolate.[5]

Clinically, the weakness of a myasthenic and cholinergic crisis can be difficult to differentiate.

Differentiating a myasthenic crisis from a cholinergic crisis is conducted using the historically described Tensilon test. A test dose of edrophonium, an ultra short-acting acetylcholinesterase inhibitor, is given. If the patient presents with a cholinergic crisis, their clinical condition will worsen, whereas the edrophonium

will improve the symptoms of a myasthenic crisis transiently. Caution should be exercised in those with asthma and heart disease.[4]

A specific subclass of patient must be mentioned: the parturient with myasthenia gravis. These patients are likely to require an assisted delivery or caesarean section, due to muscle weakness. The second stage of labour is dependent on skeletal muscle (the bearing down of delivery), and assistance may be required.[5] In the patient who requires a caesarean section, while neuraxial anaesthesia is ideal in that it avoids muscle relaxation and the need for opioid-based systemic analgesia, the level of block required may reduce accessory respiratory muscle function in an already weak patient, and this must be weighed up against the benefits of a general anaesthetic (especially given the likelihood of a concurrent bulbar palsy).[5]

When discussing myasthenia gravis, mention should also be made of Lambert Eaton Myasthenic Syndrome (LEMS). LEMS occurs due to destruction of the presynaptic voltage-gated calcium ion channels, and is associated commonly with small cell cancer of the lung.[5] Reduced release of acetylcholine is accompanied by autonomic dysfunction, seen clinically as an exaggerated decline in blood pressure post induction of anaesthesia.[5] Classically, these patients' clinical conditions improve with exercise. For the anaesthesiologist, it is important to be aware that these patients are sensitive to both depolarising and non-depolarising neuromuscular blockers, and these agents should be avoided if possible.[5] Treatment involves using drugs such as guanidine, aminopyridines and acetylcholinesterase inhibitors. Immune suppressants and intravenous immunoglobulins also have a role in the management of this disease.[5]

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