Anaesthesia TOTW

Anaesthesia and Myasthenia Gravis (122)

Richard Hughes All tutorials, General Anaesthesia

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Introduction

Myasthenia Gravis (MG) is an autoimmune disease characterized by weakness and fatigability of skeletal muscles, with improvement following rest. It may be localized to specific muscle groups or more generalized. MG is caused by a decrease in the numbers of postsynaptic acetylcholine receptors at the neuromuscular junction, which decreases the capacity of the neuromuscular end-plate to transmit the nerve signal. Initially, in response to a stimulus resulting in depolarization, acetylcholine is released presynaptically which results in a muscle action potential being generated. In MG, the number of activated postsynaptic receptors may be insufficient to trigger a muscle action potential. Further, with repeated stimulation, the decline in release of acetylcholine correlates with the characteristic fatigability.

Pathophysiology

Auto-antibodies develop against acetylcholine (ACh) nicotinic postsynaptic receptors. Cholinergic nerve conduction to striated muscle is impaired by a mechanical blockage of the binding site by antibodies and, ultimately, by destruction of the postsynaptic receptor. Patients become symptomatic once the number of ACh receptors is reduced to approximately 30% of normal. The antibodies to the acetylcholine receptor reduce the number of functional receptors by blocking the attachment of acetylcholine molecules, by increasing the rate of degradation of receptors and by complement induced damage to the neuromuscular junction. The cholinergic receptors of smooth and cardiac muscle have a different antigenicity than skeletal muscle and are not affected by the disease.

MG may be associated with other disorders of autoimmune origin such as thyroid hypofunction, rheumatoid arthritis and systemic lupus erythematosus. The role of the thymus in the pathogenesis of MG is not entirely clear, but 75% of patients with MG have some degree of thymus abnormality (eg, hyperplasia in 85% of cases, thymoma in 15% of cases). However, the stimulus that initiates the autoimmune process has not been identified.
An immunoregulatory defect has been postulated, and there is evidence of genetic predisposition. Using the most sensitive assays, AChR antibodies are detected in the sera of 85-90% of myasthenic patients. The great majority of AChR antibodies belong to the IgG class. Antibody-negative patients are those with mild or localized myasthenia, and may represent one end of the spectrum of myasthenia gravis.

Most of the antibodies bind to the main immunogenic region of the alpha subunit of the endplate receptors. Thus, MG is largely a post-junctional disorder characterized by a reduction of functional AChRs.

Epidemiology

The prevalence of MG is approximately 100 per 100 000 population with incidence of 2-4 per 100 000 per annum.

Mortality/Morbidity. In the past, untreated MG had a mortality rate of 30-70%, now most patients with MG have a near-normal life expectancy. Morbidity results from intermittent impairment of muscle strength, which may cause aspiration, increased incidence of pneumonia and falls. In addition, the medications used to control the disease may produce adverse effects. With prompt diagnosis and treatment, the mortality rate of myasthenic crisis is less than 5%.

Race. The onset of MG at a young age is slightly more common in Asians than in other races.

Sex. The male-to-female ratio in children and adults is 2:3. A female predominance exists in the young adult peak (ie, patients aged 20-30 y), and a slight male predominance exists in the older adult peak (ie, patients older than 50 y). The male-to-female ratio in children with MG and another autoimmune condition is 1:5.

Age. The onset peaks in neonates because of the transfer of maternal autoantibodies, in those aged 20-30 years, and in those older than 50 years.

Associated autoimmune conditions

Thyroid abnormalities (15%), systemic lupus erythematosis, rheumatoid disease, ulcerative colitis, pernicious anaemia, vitiligo, pemphigus, polymyositis/dermatomyositis

Classification of MG (Osserman)

• grade I – only eyes affected,
• grade IIa – mild generalised MG responding well to therapy,
• grade IIb – moderate generalised MG responding less well,
• grade III – severe generalised disease,
• grade IV – myasthenic crisis requiring mechanical ventilation
**Electrophysiological Studies**

Microelectrode studies indicate that the miniature endplate potential (MEPP) frequency is normal but the MEPP amplitude is reduced in myasthenia gravis, suggesting that the neuromuscular transmission defect is due to a reduction in the postsynaptic response. The presynaptic synthesis, packaging and release of ACh are normal. In MG, a large proportion of the EPPs are subthreshold, i.e., do not trigger an action potential, while the remainder are barely threshold. Repetitive nerve stimuli evoke successively smaller muscle action potentials indicating an increasing block of neuromuscular transmission. The most commonly used electrodiagnostic test of neuromuscular transmission is repetitive stimulation of a motor nerve while recording compound muscle action potentials (CMAPs) from an appropriate muscle. The amplitude of the initial CMAP is normal, though the average value of this measurement is less than the normal average. Repetitive stimulation at frequencies between one and five per second results in a decremental response. The decrement usually increases with increasing stimulation rate. The tested muscle must be warmed and the decrement must be measured after exhaustion to obtain the maximum diagnostic yield. However nerve conduction velocity measurements are normal.

**Clinical features**

The incidence is age and sex-related, with one peak in the second and third decades affecting mostly women and a peak in the sixth and seventh decades affecting mostly men.

The cardinal features are weakness and fatigability of skeletal muscles, usually occurring in a characteristic distribution. The weakness tends to increase with repeated activity and improve with rest. Ptosis and diplopia occur early in the majority of patients. Weakness remains localized to the extraocular and eyelid muscles in about 15 percent of patients.

When the facial and bulbar muscles are affected, there may be a characteristic flattened smile, "mushy" or nasal speech, and difficulty in chewing and swallowing.

Generalized weakness develops in approximately 85 percent of patients; it may affect the limb muscles, often in a proximal distribution, as well as the diaphragm and the neck extensors. If weakness of respiration becomes severe enough to require mechanical ventilation, the patient is said to be in crisis.

On physical examination, the findings are limited to the motor system, without loss of reflexes or alteration of sensation or coordination. The patient’s base-line strength should be documented quantitatively for later evaluation of the results of treatment. The most useful quantitative measures include timed forward-arm abduction, vital capacity, and dynamometry of selected muscles. The clinical severity of myasthenia gravis is usually graded functionally and regionally, as devised by Osserman.

Most patients who present to the A&E have an established diagnosis of myasthenia gravis (MG) and are already taking appropriate medications. The activity of the disease fluctuates, and adjustments in medication dosages must be made accordingly. Non-compliance with medications, infection, and other physiologic stressors may result in a fulminant exacerbation.
of the disease. Many other factors influence cholinergic transmission, including drugs, temperature, and emotional state.

The adverse effects of many medications may provoke exacerbations; therefore, obtaining a careful medication history is important.

Some of the medications reported to cause exacerbations of MG include the following:

Antibiotics – macrolides, fluoroquinolones, aminoglycosides, tetracycline, and chloroquine

Antidysrhythmic agents – beta-blockers, calcium channel blockers, quinidine, lidocaine, procainamide, and trimethaphan

Miscellaneous – diphenylhydantoin, lithium, chlorpromazine, muscle relaxants, levothyroxine, adrenocorticotropic hormone (ACTH), and, paradoxically, corticosteroids

Rarely, a patient may present with undiagnosed MG. Typical complaints are of generalized weakness and reduced exercise tolerance that improves with rest. Patients with MG do not present with primary complaints of sleepiness or muscle pain. The patient may also complain of a specific weakness of certain muscle groups (eg those used when climbing stairs).

In 20% of patients, MG affects the bulbar muscles alone.

Eighty-five percent of patients with bulbar weakness go on to develop generalized weakness involving the limbs.
**Transient neonatal myasthenia**

Fifteen to 20% of neonates born to myasthenic mothers have transient myasthenia, due to protective effects of alpha foetoprotein, which inhibits binding of anti-AChR antibody to AChPregnancy may produce either exacerbation or remission of the disease. Signs are usually present at birth, but occasionally may be delayed for 12-48 hr. Maternal anti-acetylcholine receptor antibody can cross via breast milk and accentuate neonatal myasthenia. Commonly associated features include difficulty in sucking and swallowing, difficulty with breathing, ptosis and facial weakness. The most likely explanation of neonatal myasthenia is the passage of AChR antibodies across the placenta, but no correlation has been found between the presence or degree of neonatal myasthenia and the concentration of the antibodies in the infant’s serum.

The condition has a tendency to spontaneous remission, usually within two to four weeks, and once therapy has been tapered and stopped there is no risk of relapse. In severely affected infants, treatment should be commenced immediately by oral neostigmine, depending on the severity of response.

**Severe exacerbations of myasthenia gravis**

Severe episodes may be caused by insufficient medication (myasthenic crisis) or excessive medication (cholinergic crisis) and are suggested by:

• Facial muscles may be slack, and the face may be expressionless

• Inability to support the head, which will fall onto the chest while the patient is seated

• Jaw is slack, voice has a nasal quality, body is limp

• Gag reflex is often absent, and such patients are at risk for aspiration of oral secretions

The patient’s ability to generate adequate ventilation and to clear bronchial secretions are of utmost concern with severe exacerbations of MG. An inability to cough leads to an accumulation of secretions; therefore, rales, rhonchi, and wheezes may be auscultated locally or diffusely. The patient may have evidence of pneumonia (ie fever, cough, dyspnea, consolidation).

**Cholinergic crisis**

One of the confusing factors in treating patients with MG is that insufficient medication (myasthenic crisis) and excessive medication (cholinergic crisis) can present in similar ways.

Cholinergic crisis results from an excess of cholinesterase inhibitors (neostigmine, pyridostigmine, physostigmine) and resembles organophosphate poisoning. In this case, excessive ACh stimulation of striated muscle at nicotinic junctions produces flaccid muscle paralysis that is clinically indistinguishable from weakness due to MG.
Myasthenic crisis or cholinergic crisis may cause bronchospasm with wheezing, bronchorrhea, respiratory failure, diaphoresis, and cyanosis.

Miosis and the SLUDGE syndrome (salivation, lacrimation, urinary incontinence, diarrhoea, GI upset and hypermotility, emesis) also may mark cholinergic crisis. However, these findings are not inevitably present.

Despite muscle weakness, deep tendon reflexes are preserved.

**Diagnosis**

**Laboratory tests.** None are available in a time frame that is useful to confirm the emergency diagnosis of myasthenia gravis (MG). An arterial blood gas determination can help guide respiratory management and should be obtained early in severe cases. An elevated PaCO2 suggests progressive respiratory failure and may indicate the need for emergency airway management.

Anti-AchR antibodies are detected in 80-85% of patients with MG and are pathognomonic for the disease. Other investigations exclude any associated autoimmune diseases.

**Imaging.** A chest Xray is indicated to determine the presence of aspiration or other pneumonias, which commonly occur in patients with MG. A CT scan or MRI of the chest is highly accurate in detecting thymoma and should be done in every new presentation. Chest radiography is relatively insensitive in screening for thymoma, as it does not detect up to 30% of cases.

**Tensilon (edrophonium) challenge test** is useful in diagnosing MG and in distinguishing myasthenic crisis from cholinergic crisis. A positive response is not completely specific for MG because several other conditions (eg amyotrophic lateral sclerosis) may also respond to edrophonium with increased strength.

Once the patient’s airway and ventilation are secured, an initial test dose of edrophonium is given. Some patients may respond noticeably to a small dose (1 mg). If no adverse reaction occurs following the test dose, another dose (3 mg) of edrophonium should produce noticeable improvement in muscle strength within 1 minute. If no improvement occurs, an additional dose of 5 mg can be administered to total no more than 10 mg.

Patients who respond generally show dramatic improvement in muscle strength, regaining facial expression, posture, and respiratory function within 1 minute.

During this procedure, the patient must be monitored carefully because edrophonium can cause significant bradycardia, heart block, and asystole. The return of muscle weakness after edrophonium wears off combined with residual increased oral secretions can exacerbate respiratory distress and the risk of aspiration.

Patients with a cholinergic crisis may respond to edrophonium challenge by increasing salivation and bronchopulmonary secretions, diaphoresis, and gastric motility (SLUDGE...
syndrome). These changes should be managed expectantly, as the half-life of edrophonium is short (approximately 10 min).

If muscle strength fails to improve following the maximum dose of edrophonium, the patient is having a cholinergic crisis, or has another cause of weakness that is unrelated to MG.

The effects of edrophonium are brief, and repeated doses may be required before oral anticholinesterase medication can take effect.

In patients with less severe exacerbations, the degree of improvement with edrophonium may be subtle. Many authors recommend having several blinded observers assess the patient’s response in these cases.

**Ice pack test.** Cooling may improve neuromuscular transmission. In a patient with MG who has ptosis, placing ice over an eyelid will lead to cooling of the lid, which leads to improvement of the ptosis. Lightly placing ice that is in a surgical glove or that is wrapped in a towel over the eyelid will cool it within 2 minutes. A positive test is clear resolution of the ptosis. The test is thought to be positive in about 80% of patients with ocular myasthenia.

**Standard electromyography**, single-fiber electromyography, assays for acetylcholine receptor antibody [ARA]) are used to confirm the diagnosis of MG, but these tests usually are not available on an emergency basis.

EMG testing shows similar characteristics to a small dose of non depolarising relaxant given to normal subjects during anaesthesia – a reduced compound muscle action potentials (CMAP) to single supramaximal twitch and decrement (fade) of > 10% on tetanic stimulation. EMG findings not exclusive to MG.

**Treatment**

In general, four methods of treatment are currently in use: enhancement of neuromuscular transmission with anticholinesterase agents, surgical thymectomy, immunosuppression, and short-term immunotherapies, including plasma exchange and intravenous immune globulin.

Anticholinesterase agents continue to be used as the first line of treatment for myasthenia gravis. Pyridostigmine (Mestinon) is the most widely used anticholinesterase. Its effect begins within 30 minutes, peaks at about 2 hours, and gradually declines thereafter, with a half-life of 4 hours. The dosage and schedule of administration must be tailored to the patient’s needs. The maximal useful dosage of pyridostigmine rarely exceeds 120 mg every three hours. Higher doses may produce increased weakness. A sustained-release preparation is available but should be used only at bedtime if necessary to treat weakness occurring at night or in the early morning. Although anticholinesterase drugs benefit most patients, the improvement is usually incomplete and often wanes after weeks or months of treatment. Most patients therefore require further therapeutic measures.

Surgical thymectomy is indicated for its therapeutic effect in myasthenia gravis or to prevent the spread of a thymoma. The goal of thymectomy as a treatment for myasthenia gravis is to
induce remission, or at least improvement, permitting a reduction in immunosuppressive medication. There is now a broad consensus that patients with generalized myasthenia gravis who are between the ages of puberty and about 60 years should have surgical thymectomy. Although no adverse effects have been reported as a consequence of thymectomy in children, it is preferable to delay thymectomy until puberty if possible, because of the established role of the thymus in development of the immune system. Thymectomy has been advocated for elderly patients with myasthenia gravis, but there is uncertainty about the persistence of thymic tissue in such patients after the age of 60.

Thymectomy has also been carried out in patients with purely ocular manifestations, with good results reported. Thymic tumours must be removed surgically since they may spread locally and become invasive although rarely metastasize. The tumour and the remaining thymus gland should be removed as completely as possible.

Thymectomy should be performed in institutions that have extensive experience not only with the surgery but also with preoperative and postoperative management of myasthenia gravis. Thymectomy is not an emergency procedure. Preoperative preparation should optimize the patient’s strength and especially respiratory function, but immunosuppressive agents should be avoided if possible due to the increased risk of infection.

The requirement for anticholinesterase medication may be decreased for a few days after thymectomy; therefore, postoperative anticholinesterase medication is given intravenously at a dose equivalent at about 75% of the preoperative requirement. The benefits of thymectomy are usually delayed for months to years after surgery.

The mechanism by which thymectomy produces benefit in myasthenia gravis is still uncertain. In general, acetylcholine-receptor antibody levels fall after thymectomy, although there are conflicting reports. There are several possible mechanisms – removal may eliminate a source of continued antigenic stimulation, remove a reservoir of B cells secreting acetylcholine-receptor antibody or in some way correct a disturbance of immune regulation in myasthenia gravis.

Immunosuppressive therapy is indicated when weakness is not adequately controlled by anticholinesterase drugs and is sufficiently distressing to outweigh the risks of possible side effects of immunosuppressive drugs. Prednisone, azathioprine, and cyclosporin are the agents now used for long-term immunosuppression in myasthenia gravis. In general, treatment must be continued for a prolonged period, most often permanently. Because of the risks inherent in prolonged immunosuppressive treatment, conscientious medical follow-up and the patient’s compliance with therapy are essential for safe and effective management.

Table 1. Immunosuppressive agents used to treat MG

Steroids are the most commonly used and most consistently effective immunosuppressive agents for the treatment of myasthenia gravis. They also have significant side effects. Patients with moderate-to-severe generalized weakness are hospitalized for the initiation of steroid
therapy because of the risk of transient steroid-induced exacerbation of disease, which may occur during the first weeks of treatment.

The risk of exacerbation is minimized by increasing the dose gradually. The rate of increase must be guided by the patient’s clinical response, and the end point is either a satisfactory clinical response, or a dose of 50 to 60 mg per day. Improvement usually begins in 2 to 4 weeks, with maximal benefit realized after 6 to 12 months or more. Few patients are able to do without prednisone entirely.

In myasthenia gravis, steroid treatment may reduce acetylcholine-receptor antibody levels and diminish the anti-acetylcholine-receptor reactivity of peripheral-blood lymphocytes. In addition, corticosteroids are reported to have certain direct neuromuscular actions.

Experimentally, steroids increase the synthesis of acetylcholine receptors in cultured muscle cells and may enhance neuromuscular transmission, but the clinical relevance of such effects in myasthenia gravis has not been established.

Azathioprine is metabolized to the cytotoxic derivative 6-mercaptopurine. Its action is predominantly on T cells, and its effectiveness in myasthenia gravis may be due to the fact that the production of acetylcholine-receptor antibody is T-cell-dependent. It is most useful in patients with myasthenia gravis for whom corticosteroids are contraindicated, in those with an insufficient response to steroids, or as an adjunct to permit a reduction in the steroid dose. It is one of the easiest immunosuppressive agents to use, but it has two drawbacks.

First, up to 10 percent of patients have an idiosyncratic influenza-like reaction, consisting of fever, malaise, and myalgias, that precludes its use. Second, its therapeutic action in myasthenia gravis begins slowly, requiring many months to one year for an adequate therapeutic trial.

Cyclosporin, is a potent immunosuppressive agent increasingly used in the treatment of patients with the disease. Cyclosporine inhibits the production of interleukin-2 by helper T cells. Its efficacy is similar to that of azathioprine, but it works more quickly, usually within one to two months. The side effects of cyclosporin include nephrotoxicity and hypertension, which limit its use in patients with pre-existing renal disease or uncontrolled hypertension.

Short term immunotherapies – plasma exchange and intravenous immune globulin

Plasmapheresis removes antibodies from the circulation and produces short-term clinical improvement in patients with myasthenia gravis. It is used primarily to stabilize the condition of patients in myasthenic crisis or for the short-term treatment of patients undergoing thymectomy. Typically, five exchange treatments of 3 to 4 liters each are carried out over a two-week period. The effect of plasmapheresis is rapid, with improvement occurring within days of treatment. Improvement correlates roughly with a reduction in the anti-acetylcholine-receptor antibody titres, but even patients with antibody-negative myasthenia gravis may improve after plasmapheresis. The beneficial effects of plasmapheresis are temporary, lasting only weeks. Repeated plasmapheresis as long-term therapy is occasionally helpful in the rare patient who does not respond to the other methods outlined above. The drawbacks of
plasmapheresis include problems with venous access, the risk of infection of the indwelling catheter, hypotension, and pulmonary embolism. The benefit must be weighed against these problems and the high cost of the procedure.

The indications for the use of intravenous immune globulin are the same as those for plasma exchange: to produce rapid improvement to help the patient through a difficult period of myasthenic weakness. It has the advantages of not requiring special equipment or large-bore vascular access. In responsive patients improvement begins within four to five days.

The mechanism of action of immune globulin is unknown, but it has no consistent effect on the measurable amount of acetylcholine-receptor antibody. Adverse reactions include headache, fluid overload, and rarely, renal failure. Immune globulin is very expensive.

**Anaesthetic Management**

The anaesthetic management of the myasthenic patient must be individualized to the severity of the disease and the type of surgery. The use of regional or local anaesthesia seems warranted whenever possible. Whenever local or regional anaesthesia is used, the dose of the local anaesthetic may be reduced in patients to decrease the possible effects of anaesthetics on neuromuscular transmission. This may be particularly important when ester local anaesthetics are administered to patients receiving anticholinesterase therapy (inhibit plasma cholinesterase). General anaesthesia can be performed safely, provided the patient is optimally prepared and neuromuscular transmission is adequately monitored during and after surgery.

Preoperative preparation. Adequate preoperative evaluation of the myasthenic patient must be carried out carefully. Age, sex, onset and duration of the disease as well as the presence of thymoma may determine the response to thymectomy. Also, the severity of myasthenia and the involvement of bulbar or respiratory muscles must be evaluated. Patients should be admitted 24-48h before surgery to allow detailed assessment of respiratory muscle and bulbar function and review of anticholinesterase and corticosteroid therapy. Respiratory reserve is best monitored by serial forced vital capacity (FVC) measurement.

Preoperative factors associated with need for prolonged postoperative IPPV include: FVC < 2.9l, history of MG > 6 years, major surgery, co-existing lung disease and grades III and IV MG. Other autoimmune diseases need to be elicited and appropriate preoperative investigations initiated.

Optimization of the condition of the myasthenic patients can markedly decrease the risk of surgery and improve the outcome. Many regimens have been recommended for preoperative treatment. It is controversial whether anticholinesterase therapy should be maintained or discontinued before and after surgery. Anticholinesterases potentiate the vagal responses and hence adequate atropinization must be ensured. Also, anticholinesterases can inhibit plasma cholinesterase activity with a subsequent decrease in the metabolism of ester local anaesthetics, and the hydrolysis of suxamethonium will be decreased.
As in non-myasthenic patients, the duration of suxamethonium block in myasthenic patients is inversely related to the plasma cholinesterase activity. In contrast with suxamethonium, the inhibition of acetylcholinesterase by anticholinesterases may increase the need for nondepolarizing muscle relaxants in the myasthenic patient, although this has not been documented. Recently, plasmapheresis alone without immunosuppression has been used to optimize the medical status of the myasthenic patient prior to major surgery. Anticholinesterase agents are discontinued, while corticosteroid medications are maintained to be tapered and discontinued postoperatively.

Premedication. Myasthenic patients may have little respiratory reserve and hence depressant drugs for preoperative premedication should be used with caution, and avoided in patients with bulbar symptoms, but an anticholinergic may be useful. Hydrocortisone ‘cover’ should be given to those on long-term corticosteroid therapy.

Anaesthetic techniques. Two techniques have been recommended for general anaesthesia in the myasthenic patient, although none is superior. Because of the unpredictable response to suxamethonium and the marked sensitivity to non-depolarizing muscle relaxants, some anaesthetists avoid muscle relaxants and depend on deep inhalational anaesthesia, for tracheal intubation and maintenance of anaesthesia. These agents allow neuromuscular transmission to recover, with rapid elimination of these agents at the end of surgery. In theory, desflurane and sevoflurane may offer some advantages, due to their low blood solubility. Sevoflurane is probably superior to desflurane, due to its lower incidence of excitatory airway reflexes during inhalational induction.

However, others utilize a balanced technique which includes the use of muscle relaxants, without the need for deep inhalational anaesthesia, titrating small doses (10–25% of the ED95) of intermediate-acting relaxants monitoring with a peripheral nerve stimulator for both intubation and surgical relaxation, if required. The decision as to whether to reverse residual neuromuscular blockade at the end of surgery is controversial. Some argue that the presence of anticholinesterases and antimuscarinics will confuse efforts to differentiate weakness due to inadequate neuromuscular transmission from cholinergic crisis in the recovery room. Some prefer spontaneous recovery and extubation when the patient has demonstrated adequate parameters for extubation (head-lift, tongue protrusion).

Similarly, the presence of fade (T4/T1 < 0.9) in the preanaesthetic period predicts decreased atracurium requirements in patients with MG. This technique, along with preoperative pulmonary function testing, may be useful in determining preoperative baseline function.

Total intravenous anesthesia (TIVA) for the management of myasthenics has been reported. Haemodynamic instability in older patients makes this approach more difficult, whereas younger patients usually tolerate it. The use of remifentanil as part of TIVA may alleviate some of the hemodynamic instability.

When possible, many clinicians prefer to utilize regional or local anesthetic techniques. Regional techniques may reduce or eliminate the need for muscle relaxants in abdominal
surgery. Epidural techniques offer the advantage of postoperative pain control with minimal or no opioid use.

Postoperative management. Ventilatory function must be monitored carefully after surgery. There are few tests of neuromuscular function which correlate with adequate ventilation. It has been shown recently in normal patients that many of the recommended tests such as maintained response to tetanic stimulation of a peripheral nerve can return to normal, while the pharyngeal and neck muscles necessary to protect the airway can still be partially paralysed. The different response of peripheral versus bulbar muscles may be more evident in myasthenic patients, particularly those suffering from bulbar and/or respiratory muscle weakness. It is essential that sustained respiratory muscle strength be confirmed before extubation of the trachea and resumption of spontaneous ventilation. Myasthenic patients may be at increased risk of developing postoperative respiratory failure – following transsternal thymectomy, up to 50% of patients require prolonged postoperative ventilation.

Four risk factors have been identified: (Anesthesiology 1980; 53: 26-30)

- Duration of myasthenia gravis for longer than six years (12 points). (Duration of MG proved to have the greatest value in predicting the need for ventilatory support).
- A history of chronic respiratory disease other than respiratory dysfunction directly due to MG (10 points).
- A dose of pyridostigmine greater than 750 mg per day, 48 hr before operation (8 points).
- A preoperative vital capacity < 2.9 L (4 points)

These risk factors were weighted according to their significance as predictors; a total score of ≥ 10 points identified those patients likely to need postoperative pulmonary ventilation for more than three hours.

**ZF Comments:** A useful review. When answering a question pick the method of anaesthesia you are well versed in. For example to me it is sevoflurane anaesthesia with atracurium top ups starting at 25% of normal dose and titrating to nerve stimulator. Reversal with neo/glycin usual doses at end. Rapid sequence is accomplished with suxamethonium in a “strong” myasthenic and propofol/remi or propofol alfentanil in a “weak” myasthenic.
Pharmacology of Neuromuscular Blocking Drugs and Anticholinesterases

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Tutorial Questions

After reading the tutorial you should try to answer the following questions

1. How are neuromuscular blocking drugs classified?
2. How do neuromuscular blocking drugs work?
3. What are the adverse effects of suxamethonium?
4. Which non-depolarizing neuromuscular blocking drugs affect the cardiovascular system?
5. How does neostigmine work?
6. What are the adverse effects of anticholinesterases and how are they prevented?

Introduction

Neuromuscular blocking drugs (NMBDs) are used in anaesthesia to impair neuromuscular transmission and provide skeletal muscle relaxation. These drugs enable the anaesthetist to perform tracheal intubation, facilitate ventilation and to provide optimal surgical operating conditions, for example during laparotomy. NMBDs are quaternary ammonium compounds structurally similar to acetylcholine (ACh); they act mostly at the post-junctional nicotinic receptor of the neuromuscular junction. NMBDs may be agonists (“depolarising” NMBDs) or antagonists (“non-depolarizing” NMBDs) at the nicotinic receptor.

Anticholinesterase drugs (also known as acetylcholinesterase inhibitors) are used to reverse the effects of non-depolarizing NMBDs. These drugs increase the concentration of ACh at the neuromuscular junction by inhibiting the enzyme acetylcholinesterase.

If you are uncertain about some of the terms used so far, now is a good point to review the tutorial on “physiology of the neuromuscular junction.”
Depolarizing NMBDs

Suxamethonium (succinylcholine) is the only depolarizing NMBD in clinical use. Structurally it is two ACh molecules joined together and it acts as an agonist at the nicotinic receptor. Suxamethonium binds with the two alpha sub-units of the receptor mimicking ACh resulting in membrane depolarization. When depolarization occurs it causes muscle contraction, which occurs rapidly and is observed clinically as muscle fasciculation. After depolarization the membrane potential must be reset before further depolarization can occur and skeletal muscle remains in a state of flaccid relaxation until this occurs.

An intravenous dose of suxamethonium of 1.0-1.5 mg/kg produces profound neuromuscular block within 60 seconds, this is faster than with any other NMBD. The blockade typically resolves spontaneously after approximately 10 minutes. Suxamethonium results in a Phase I block, characterised by absence of fade and post-tetanic facilitation on peripheral nerve stimulation. Suxamethonium is hydrolysed rapidly by plasma cholinesterase to succinyl monocholine and choline. Prior to use it is stored at 4 degrees Celsius to prevent hydrolysis.

Although not commonly used, an infusion of suxamethonium can be used to produce prolonged neuromuscular blockade. 500mg of suxamethonium are put in a 500ml bag of saline (0.1% solution). The rate of infusion is adjusted to achieve the desired degree of relaxation, usually 5-15mg/kg/hour (5-15ml/kg/hour). Pre-treatment with atropine is required if this technique is used.

Suxamethonium can be given intramuscularly at a dose of 3-5mg/kg. The onset is considerably slower than when given intravenously. This route is usually used only in infants where venous access is not possible.

Suxamethonium; Indications and Side Effects

Suxamethonium is the NMBD with the most rapid and predictable onset of action. This and the fact that it has a short duration of action mean that it is the drug of choice for anaesthesia when a rapid sequence induction (RSI) is used for patients at risk of aspiration, or when rapid tracheal intubation is required in an emergency situation. It is also indicated when rapid recovery of neuromuscular function may be required.

Suxamethonium has numerous unwanted side effects:

*Bradycardia.* Occurs due to stimulation of muscarinic receptors in the sino-atrial node. Bradycardia is more common in children and after repeated doses of the drug.
Increased intra-ocular pressure. There is a theoretical risk of expulsion of vitreal contents with the use of suxamethonium in patients with a penetrating eye injury. This risk must be balanced with the risk of aspiration of gastric contents in emergency surgery.

Muscle pain. Occurs commonly, especially in young, fit adults with early ambulation. Strategies such as precurarization exist to reduce the incidence but no strategy is fully preventative.

Hyperkalaemia. Average serum potassium levels increase by 0.5 mmol/L on administration of suxamethonium. Patients with pre-existing hyperkalaemia are at risk of cardiac arrhythmias and death. Fatal hyperkalaemia can occur in burns patients, patients with muscular dystrophies and paraplegic patients. This may be due to proliferation of extra-junctional receptors in these patients. Maximal risk of hyperkalaemia in burn patients occurs during days 9-60 after the burn. The use of suxamethonium within the first 2-3 days after a severe burn injury is regarded as safe.

Increased intragastric pressure. This is offset by an increase in oesophageal barrier pressure.

Phase II block. This may occur after large or repeated doses of suxamethonium. Neuromuscular block is prolonged and peripheral nerve stimulation results in fade of the train-of-four twitch height response and post tetanic facilitation.

Anaphylaxis. Suxamethonium is responsible for over 50% of anaphylactic reactions to NMBDs.

Prolonged block due to reduced plasma cholinesterase activity. This may be due to congenital or acquired causes. Acquired causes include reduced enzyme synthesis, which may occur in liver disease, carcinomatosis, pregnancy or starvation (hypoproteinaemic states), cardiac failure, renal failure, and burns. The co-administration of other drugs such as etomidate, ester local anaesthetics, methotrexate, remifentanil and esmolol can result in a reduction in plasma cholinesterase activity.

Inherited causes of prolonged block after suxamethonium occur due to production of atypical plasma cholinesterase. The structure of the cholinesterase enzyme is determined genetically by a gene on chromosome 3, this gene is described as the usual gene (94% of the population homozygotes). Three variants from the usual gene exist and are known as the atypical, silent and fluoride resistant genes. Individuals with these variant genes have atypical cholinesterase enzyme, and have a prolonged neuromuscular block after suxamethonium. Duration of prolonged block varies from 30 minutes (eg. people
heterozygous for the atypical gene) to several hours (eg. homozygotes for the silent gene.)

*Malgnant hyperthermia*. This condition may be triggered by suxamethonium and therefore its use is absolutely contraindicated in susceptible patients.

**Non-depolarizing NMBDs**

Non-depolarizing drugs are competitive antagonists of ACh at the postsynaptic nicotinic receptor. They bind to one or both alpha subunits of the receptor and prevent depolarization due to ACh. The binding of antagonists to the receptor is reversible and repeated association and dissociation occurs. Neuromuscular blockade starts to occur when 70-80% of receptors are antagonised, to produce a complete block over 90% of receptors must be occupied. Non-depolarizing NMBDs are also believed to have an action at pre-junctional receptors at the neuromuscular junction. Stimulation of pre-junctional receptors by ACh normally results in further mobilisation of ACh to cope with increasing stimulation frequency. Non-depolarizing NMBDs antagonise these receptors and inhibit this process.

When assessing the block caused by non-depolarizing NMBDs with a peripheral nerve stimulator a characteristic response is observed. Fade of twitch height response occurs during a train of four or tetanic pattern of stimulation. Fade is due to the action of these drugs at the presynaptic receptor resulting in reduced availability of ACh with repeated nerve stimulation. Post tetanic facilitation of neuromuscular transmission is another feature of non-depolarizing neuromuscular blockade and is due to increased quantities of ACh in the synapse of the junction after tetanic stimulation. Non-depolarizing NMBDs are not metabolised at the neuromuscular junction and resolution of block is due to a dilutional effect of the drug with time. They are highly ionised, water-soluble drugs and their volume of distribution approximates to that of plasma and extracellular fluid. There are two groups of non-depolarizing NMBDs, benzylisoquinolinium compounds and aminosteroid compounds.

**Benzylisoquinolinium Compounds**

These drugs consist of two quaternary ammonium groups joined by a chain of methyl groups. They are more liable to break down in the plasma and often cause release of histamine; examples include tubocurarine, atracurium, cisatracurium and mivacurium.
**Tubocurarine.** A drug with a long onset and prolonged duration of action (see Table 1). It causes marked histamine release, with hypotension and tachycardia. Ganglion blockade may occur with large doses. Tubocurarine is excreted unchanged mostly in the urine but also in bile. Its effects are prolonged in renal failure. It has been superseded by agents with better side effect profiles and is no longer available in the UK.

**Atracurium.** A racemic mixture of 10 stereoisomers and geometric isomers. Atracurium has an intermediate onset and duration of action. It causes release of histamine but has no direct cardiovascular effects. Metabolism is by Hofmann degradation and ester hydrolysis in the plasma, hence its duration of action is independent of renal and hepatic function.

**Cisatracurium.** The R-cis R′-cis isomer of atracurium. It constitutes 15% of the parent compound and is four times more potent with a longer duration of action. Unlike atracurium it does not release histamine. It is metabolised by Hofmann degradation and does not accumulate in renal failure.

**Mivacurium.** Mivacurium is a drug with a short duration of action of approximately 15 minutes, making it potentially useful for short procedures. It is a racemic mixture of three isomers that is hydrolysed by plasma cholinesterase. Mivacurium is associated with histamine release causing significant hypotension with doses greater than 0.2mg/Kg. Like suxamethonium its duration of action is increased in patients with atypical plasma cholinesterase.

**Aminosteroid compounds**

All aminosteroid NMBDs posses at least one quaternary ammonium group attached to a steroid nucleus. They tend not to cause histamine release and most are metabolised in an end organ before excretion.

**Pancuronium.** The first steroid NMBD in clinical use has a slow onset and long duration of action. It does not cause histamine release but has weak sympathomimetic properties and causes tachycardia. It is partly de-acylated in the liver to a metabolite with neuromuscular blocking properties, and partly excreted unchanged in the urine. Its action is prolonged in renal and hepatic impairment.

**Vecuronium.** Vecuronium is structurally similar to pancuronium but has a slightly faster onset and shorter (intermediate) duration of action. It does not release histamine or have any cardiovascular effects. Metabolism in the liver occurs to
active metabolites before being excreted in the bile and urine. Vecuronium is unstable in solution and is stored as powder and requires mixing with water prior to administration.

**Rocuronium.** This monoquaternary amine has the most rapid onset of the clinically available non-depolarizing NMBDs. Intubating conditions can be achieved in 60-90 seconds after an induction dose of 0.6 mg/Kg. Rocuronium has an intermediate duration of action and is metabolised in the liver and excreted in the bile. Rocuronium has minimal cardiovascular effects and does not release histamine, however, it has a higher incidence of anaphylactic reactions than other aminosteroid NMBDs.

### Table 1. Dose, speed of onset and duration of neuromuscular blocking drugs.

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg/Kg)</th>
<th>Onset time (min)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>1.0-1.5</td>
<td>&lt;1</td>
<td>5-10</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.5</td>
<td>3-5</td>
<td>30-50</td>
</tr>
<tr>
<td>Atracurium</td>
<td>0.5</td>
<td>2-3</td>
<td>20-30</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.1</td>
<td>2-3</td>
<td>30-40</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>0.15-0.20</td>
<td>2-3</td>
<td>10-20</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.1</td>
<td>3-5</td>
<td>40-60</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.1</td>
<td>2-3</td>
<td>20-30</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6</td>
<td>1-2</td>
<td>30-40</td>
</tr>
</tbody>
</table>

**Anticholinesterases**

Anticholinesterases (also known as acetylcholinesterase inhibitors) are agents that inhibit the action of the acetylcholinesterase enzyme at the neuromuscular junction. Enzyme inhibition leads to a reduction in the breakdown of ACh and potentiates its action.

Anticholinesterases are used in anaesthesia to reverse the effects of non-depolarizing NMBDs. Reversal of non-depolarizing neuromuscular blockade usually occurs at the end of surgery, and should not take place before some resolution of the block has already occurred. Early administration of anticholinesterase may be ineffective due to high receptor occupancy by the NMBD. Reversal of *intermediate* acting NMBDs with anticholinesterase should be at least 20 minutes after giving the drug. If peripheral nerve stimulation is used, at least 3 twitches on a train of four should be detected before attempting reversal. The most reliable sign that a block is fully reversed by anticholinesterase is a sustained response to tetanic stimulation with a peripheral
nerve stimulator (i.e. no fade). Clinical tests of adequate resolution of neuromuscular block include the ability to lift the head from the bed for 5 seconds, although this is a much less reliable assessment. 

Anticholinesterases will augment the Phase I block due to depolarizing NMBDs and there is no role for anticholinesterases in reversing the effects of suxamethonium.

**Side effects of anticholinesterase agents**

Anticholinesterases cause a build up of ACh that results in potentiation of its effects at muscarinic receptors. This can cause bradycardia, miosis, GI upset, nausea, bronchospasm, increased bronchial secretions, sweating and salivation. For this reason an antimuscarinic such as glycopyrronium or atropine must be administered along with the anticholinesterase to minimise these effects.

**Anticholinesterase drugs**

*Neostigmine.* By far the most commonly used anticholinesterase in anaesthesia is neostigmine. This is a water-soluble quaternary ammonium compound that combines reversibly with the esteratic site of the acetylcholinesterase enzyme rendering it inactive for about 30 minutes. Neostigmine is given as an intravenous injection at a dose of 0.05 mg/kg (maximum 5mg), and should be administered with glycopyrronium 0.01 mg/kg or atropine 0.02 mg/kg. Neostigmine starts to take effect after approximately 2 minutes but has its maximal effect at 5-7 minutes. It is excreted unchanged by the kidney and has a half-life of about 45 minutes.

*Edrophonium.* This anticholinesterase forms an ionic bond at the anionic site of the enzyme. Bonding is reversible and short lived in the order of a few minutes. Edrophonium is used as a diagnostic test for the neuromuscular disease myasthenia gravis. ACh potentiation by the drug results in a transient increase in muscle power in the myasthenic patient. Edrophonium is rarely used to reverse the effects of NMBDs as its effects are short lived and neuromuscular block may increase after an initial recovery.

*Pyridostigmine.* This agent has a longer onset than neostigmine and lasts for several hours. It is used more frequently as a therapy for myasthenia gravis.

*Physostigmine.* Like neostigmine and pyridostigmine, physostigmine acts reversibly at the esteratic site of the acetylcholinesterase enzyme. As it is more lipid soluble than the other agents it can be absorbed from the GI tract and crosses the blood brain barrier.
Organophosphorous compounds. These substances are found in some pesticides and agents used in chemical warfare. Organophosphorous compounds form an irreversible bond with the enzyme and recovery only occurs after generation of new enzyme, which takes weeks. Poisoning results in salivation, sweating, bradycardia, bronchospasm and muscle weakness. Treatment is with atropine and supportive measures.

Further reading


Critical Illness Polyneuropathy

Dr John Griffiths DICM MRCP FRCA MA

CriticalCareUK Editor

Focus on critical illness polyneuropathy

Critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) are acquired during the course of critical illness, and cause weakness and paralysis. The incidence of these neuromuscular diseases in ICU patients with sepsis or multi-organ dysfunction is estimated at 70 to 80%. Risk factors for CIP and CIM include sepsis and multi-organ dysfunction, prolonged duration of stay on the ICU and hyperglycaemia. Weakness associated with CIP and CIM may be exacerbated by muscle wasting secondary to catabolism and immobility. It is proposed that CIP and CIM are caused primarily by the use of glucocorticoids or neuromuscular blocking agents or by nutritional deficiencies. However, conclusive evidence regarding the true aetiology of CIP and CIM is currently lacking and the exact pathophysiological mechanisms remain to be determined. Cytokines such as interleukin-1 and tumour necrosis factor, which are released during sepsis, have been identified as mediators of skeletal muscle proteolysis in animal models and may therefore play a pivotal aetiological role. CIP and CIM are important disorders because they might prolong the duration of mechanical ventilation and both ICU and hospital length of stay. The need for intensive physiotherapy and extended rehabilitation add considerably to the cost of care. Although muscle strength generally seems to recover well, some patients report weakness for a prolonged period of time, sometimes even up to 4 years after ICU discharge. In one study of survivors of at least 28 days of ICU treatment, nearly all patients displayed electrophysiological evidence of chronic partial denervation (indicative of either a previous CIP or pure motor neuropathy) 5 years after ICU discharge.

Focus on histopathological features of CIP and CIM

CIP is a primary axonal degeneration of motor and sensory fibres. It is commonly accompanied by myopathic changes with scattered atrophic and occasional necrotic muscle fibres, but no evidence of inflammation. Acute motor neuropathy is a variant of CIP in which the axonal degeneration affects primarily motor fibres.

Critical illness myopathy (CIM) is usually a mild myopathy. Features seen on biopsy include fibre atrophy and angulated fibres, fatty degeneration and fibrosis with minimal necrosis. It may be present simultaneously with CIP. Plasma creatinine kinase levels are mostly normal.

A different type of myopathy has been described in patients who have received high-dose corticosteroids for acute severe asthma, in recipients of organ transplantation and in patients with myasthenia gravis. A thick filament myopathy has been described, characterised by selective loss of myosin filaments. There are usually no neuropathic changes. However, plasma creatinine kinase levels are often elevated, and progression to diffuse myonecrosis (rhabdomyolysis) is possible. Experimentally, thick filament myopathy can be produced by surgical denervation of muscle followed by exposure of the muscle to corticosteroids. This causes an upregulation in the number of steroid receptors and a resultant steroid hypersensitivity. It follows that denervation of neuromuscular transmission by either pharmacological (e.g. neuromuscular blocking agents) or
immunological (e.g. myasthenia gravis) means could render muscle susceptible to the myopathic effects of corticosteroids. However, the fact that thick filament myopathy has been described in patients who have not received muscle relaxants or steroids suggests that other factors are involved in its aetiology.

In acute necrotising ICU myopathy, myonecrosis with vacuolisation and phagocytosis of muscle fibres is prominent. Plasma creatinine kinase levels are frequently raised, and in a minority of patients frank rhabdomyolysis may ensue. Necrotising myopathy has also been described in patients admitted to ICU with status asthmaticus. These patients were generally non-septic and received high-dose corticosteroids, either alone or in combination with muscle relaxants. Myonecrosis has also been reported in other critically ill patients, some of which had received very high doses of neuromuscular blocking agents alone.

**Focus on the diagnosis of CIP and CIM**

The diagnosis of CIP and CIM is based on the triad of clinical examination, electrophysiological studies and muscle biopsy. However, in order to make a confident diagnosis of CIP and CIM, it is important to exclude any existing conditions associated with neuromuscular weakness. These conditions include spinal cord disorders, Guillain-Barré syndrome and chronic inflammatory demyelinating neuropathy, diabetic polyneuropathy, myasthenia gravis and Lambert-Eaton syndrome, and muscular dystrophy. Low electrolyte states (hypokalaemia, hyponatraemia, hypophosphataemia) are recognised causes of muscle weakness and rhabdomyolysis and need to be excluded. Other recognised causes of myonecrosis and rhabdomyolysis are trauma, prolonged immobility with muscle compression, status epilepticus, toxins and drugs, hypothermia and heat stroke.

**Electrophysiological studies and muscle biopsy**

Electroneurography (ENG) and needle electromyography (EMG) show reduced amplitude of nerve action potentials but normal conduction velocities in >90% of patients with either CIP or CIM, or both. However, ENG and EMG seem to be of little use to distinguish between CIP and CIM. This requires muscle biopsy. Myopathy appears to be more common than neuropathy. In one series of ICU patients with generalised weakness, myopathy was diagnosed on biopsy in 23 out of 24 patients, whereas only eight out 24 had histological evidence of axonal degeneration. Five patients had mixed changes.

**Focus on the prevention of CIP and CIM**

Prevention of both CIP and CIM involves the prompt and effective treatment of sepsis and multi-organ dysfunction. It is prudent to use neuromuscular blocking agents and corticosteroids as cautiously as possible. The need for neuromuscular blocking agents should be reviewed frequently and overdosing should be avoided by the use of a peripheral nerve stimulator. Patients that are prescribed neuromuscular blocking agents and/or steroids should be monitored for the development of neuropathy and myopathy, including serial serum creatinine kinase measurements and repeated electrophysiological testing. Recent evidence suggests that tight glycaemic control reduces the incidence of CIP and CIM. In one study, tight glycaemic control lowered the incidence of CIP from 52% to 29%.
Key learning points

- CIP and CIM are a source of considerable ICU-related morbidity
- CIP and CIM can result in weakness that persists beyond ICU and hospital discharge, ultimately to affect a patient’s quality of life
- Any patient who develops a CIP or CIM needs adequate long-term follow-up to ensure adequate recovery and rehabilitation
- The exact aetiology of CIP and CIM remains to be determined
- Prevention of CIP and CIM involves early and effective treatment of sepsis, tight glycaemic control and cautious use of muscle relaxants and corticosteroids on the ICU

Key references

Hund E. Myopathy in critically ill patients.

Fletcher SN, Kennedy DD, Ghosh IR et al.
Persistent neuromuscular and neurophysiological abnormalities in long-term survivors of prolonged critical illness.
Crit Care Med 2003; 31: 1012-1016.

Latronico N, Fenzi F, Recupero D et al.
Critical illness myopathy and neuropathy.
Curr Opin Crit Care 2005; 11(2):126-32

Intensive insulin therapy in critically ill patients.

ZF Comments:

Perhaps make a little more of hypophosphatemia and refeeding syndrome
Perhaps a little more on role of nutrition
Emphasise role of physiotherapy and OT in preventing contractures and maintaining joint mobility
Also positioning and avoiding nerve injury esp. foot drop
**Guidelines for the management of a malignant hyperthermia (MH) crisis**

**Association of Anaesthetists of Great Britain and Ireland 1998**

**Diagnosis**

Consider MH if:

- masseter spasm after suxamethonium
- unexplained, unexpected tachycardia, together with
- unexplained, unexpected increase in end-tidal CO2

**Early management**

1. Withdraw all trigger agents (i.e. all anaesthetic vapours)
2. Install clean anaesthetic breathing system and hyperventilate
3. Abandon surgery if feasible
4. Give dantrolene IV 1 mg/kg initially and repeat prn up to 10 mg/kg
5. Measure arterial blood gases, K+ and creatine phosphokinase (CPK)
6. Measure core temperature
7. Surface cooling, avoiding vasoconstriction

**Intermediate management**

1. Control serious arrhythmias with beta-blockers etc.
2. Control hyperkalaemia and metabolic acidosis

**Later management**

1. Clotting screen to detect disseminated intravascular coagulation
2. Take first voided urine sample for myoglobin estimation
3. Observe urine output for developing renal failure
4. Promote diuresis with fluids/mannitol (20 mg dantrolene contains 3 mg mannitol)
5. Repeat CPK at 24 h.

**Late management**

1. Consider other diagnoses and perform appropriate investigations, e.g. vanillyl mandelic acid, thyroid function tests, white cell count, chest X-ray
2. Consider possibility of myopathy, neurological opinion, EMG
3. Consider possibility of recreational drug ingestion (Ecstasy)

4. Consider possibility of neuroleptic malignant syndrome

5. Counsel patient and/or the family regarding implications of MH

6. Refer patient to MH unit.

Reference

[i] Dantrolene in pregnancy: lack of adverse effects on the fetus and newborn infant.

Shime J, Gare D, Andrews J, Britt B.


Related examination questions

1. In the treatment of established malignant hyperthermia, the following are recognised as part of the treatment:

   (a) Chlorpromazine
   (b) EDTA sodium
   (c) Sodium bicarbonate
   (d) Magnesium sulphate
   (e) Glucose and insulin

Answers

FFTFT

Comments:

I would rewrite early management as:

1. Instruct a named person to fetch all available dantrolene and to summon the pharmacy staff to obtain more
2. Call for help
3. Withdraw all trigger agents (i.e. all anaesthetic vapours)
4. Hyperventilate with 100% oxygen at highest flow machine can deliver
5. Initiate core temperature monitoring if not already in situ
6. Give dantrolene IV 2 mg/kg initially and repeat 1mg/kg every 15 minutes prn up to 10 mg/kg (exceptional cases require 20mg/kg)
7. Install clean anaesthetic breathing system
8. Abandon surgery if feasible
9. Measure arterial blood gases, K+ and creatine phosphokinase (CPK)
10. Insert urinary catheter if not already in situ
11. Surface cooling, avoiding vasoconstriction
12. Consider cold water lavage of:
   a. Surgical field
   b. Stomach via nasogastric tube
   c. Bladder via urinary catheter
13. Maintain anaesthesia with ivi opiates and an hypnotic eg propofol
14. Be prepared to provide inotropic support
A Clinical Grading Scale to Predict Malignant Hyperthermia Susceptibility


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§§ Associate Professor, Department of Anesthesiology, Herlev University Hospital, Herlev, Denmark.
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Address reprint requests to Dr. Larach: Department of Anesthesia, Pennsylvania State University College of Medicine, P.O. Box 850, Hershey, Pennsylvania 17033.
MALIGNANT hyperthermia (MH) susceptibility is an uncommon inherited disorder of skeletal muscle in which commonly used anesthetics trigger sustained skeletal muscle hypermetabolism in patients who may have had no symptoms previously. First characterized in 1962,1 MH presents with multiple nonspecific signs and laboratory findings of variable intensity and time course during and after exposure to anesthetic agents. These signs relate to skeletal muscle hypermetabolism and ischemia and their systemic sequelae and may include tachycardia, tachypnea, hypercarbia, respiratory acidosis, metabolic acidosis, masseter muscle rigidity, generalized muscular rigidity, myoglobinuria, rhabdomyolysis, arrhythmias, cyanosis, skin mottling, hyperkalemia, diaphoresis, rapid temperature elevation, hemodynamic instability, and coagulopathy.2-4

If an individual's MH susceptibility can be predicted before anesthetic administration, acute life-threatening MH events can be prevented through avoidance of MH-triggering medications. For many clinicians and researchers, MH has been a puzzling clinical entity, and there has been little agreement as to what constitutes a "true" MH episode. This lack of precise clinical definition has led to poor prediction of MH susceptibility because the diagnosis of an acute MH reaction by clinical criteria alone is not standardized and is difficult to perform, as a result of the nonspecific nature and variable incidence of many of the clinical signs and laboratory findings.2,3

Efforts to confirm MH susceptibility through laboratory testing began in 1970 with the development of the caffeine halothane contracture test.5,6 That test requires an invasive muscle biopsy, and without the "gold standard" of a clear clinical definition of MH, the test's specificity and sensitivity are poorly estimated. Recent efforts in molecular biology7-11 to identify the genetic markers of MH susceptibility likewise have been frustrated by the lack of agreed-upon methods of discriminating the clear cases from those that are less convincing.12

To improve MH susceptibility prediction, an international group of MH experts used the Delphi process to create a multifactor MH clinical grading scale that comprises standardized clinical diagnostic criteria. This grading scale ranks the likelihood that an adverse anesthetic event represents MH or, that with further investigation of family history, the patient sustaining the adverse anesthetic reaction will be diagnosed as MH susceptible.

Materials and Methods

To develop an international consensus for a standardized MH clinical grading scale, the anesthesiologist director of The North American Malignant Hyperthermia Registry (MGL) and a biostatistician (ARL) implemented the Delphi method, a system of polling opinions anonymously from an 11-member group of MH experts (the other authors), and of facilitating their consensus on the attributes of a MH event and the indicators of MH susceptibility. The Delphi process consists of a series of questionnaires completed by a panel of experts and a controlled feedback at each round in the form of the results of the prior round.13,14 The process ends when the group approaches consensus or when sufficient information has been exchanged to achieve the goals of the process.15 Feedback of information, and anonymous opinions of the experts, ensure that the panel considers a full range of ideas throughout the process. All communications were processed through a central office to ensure that opinions and scores could not be linked to individual experts.

The Delphi method was chosen because it obtains written opinions anonymously, thereby avoiding the potential for domination by the most assertive participants. Also, the Delphi method permits experts to respond and interact by mail or facsimile transmission over extended periods even when they are separated by long distances. MH experts were selected (by MGL) for their stature in the description and diagnosis of MH and were located in Australia, Canada, Denmark, United Kingdom, and the United States of America.

In brief, the consensus process proceeded as follows. Beginning with an initial set of proposed clinical indicators for judging MH events and MH susceptibility (supplied by MGL), experts were asked to identify a group of clinical indicators, to score the relative importance of these indicators, and to assemble the individual scores into a global raw score to rank the likelihood that an observed adverse anesthetic event represented an MH event. Each expert also modified the scoring system to rank the likelihood that a suspect individual was MH susceptible after a thorough investigation of the suspect family's anesthetic history. An individual's MH susceptibility was defined as the probability that an individual will experience an MH event if exposed to MH-trigg ering agents and the probability that an individual's blood relatives may also inherit the MH gene(s) in an autosomal dominant fashion. These
probabilities are not well defined, because MH-susceptible individuals do not consistently develop an MH event even after exposure to MH-triggering anesthetic agents, and penetrance is variable. Evidence of MH susceptibility could come from indicators applicable for MH events as well as from indicators taken from family history. The consensus process required seven separate written information exchanges over 18 months.

During the course of this study, the clinical indicators were refined as the result of comments from the expert group. For example, by the final information exchange, the initially proposed indicator "generalized muscular rigidity" was made more specific by excluding rigidity in the presence of shivering due to hypothermia and the shivering that is commonly seen during and immediately after emergence from inhalational general anesthesia. Similarly, the initially proposed indicator "reversal of MH signs with intravenous dantrolene" was refined to "rapid reversal of MH signs of metabolic and/or respiratory acidosis with intravenous dantrolene." Also, critical values for indicators such as increased creatine kinase (>20,000 IU after an anesthetic that included succinylcholine; >10,000 IU after an anesthetic without succinylcholine) were specified as a result of the group's interaction.

By the sixth information exchange, experts tested the prototype MH clinical grading scale by using it to rank the likelihood of MH events and MH susceptibility for hypothetical clinical case scenarios. Experts independently were able to apply the scoring rules to the six case scenarios with high consistency within scenario (coefficients of variation of 0.0–0.14 and standard deviations of 0–5.6 for the less complex cases and 15.8–17.2 for the two scenarios with many indicators present [vide infra]). The following is an example of a scenario in which all 11 MH experts judged an MH event "unlikely": a previously healthy patient received an anesthetic that included succinylcholine and developed ventricular tachycardia and a serum potassium of 8 mEq/l. In contrast, following is a scenario in which all 11 MH experts judged an individual to be "almost certainly" MH susceptible: a previously healthy patient received an anesthetic that included succinylcholine and controlled ventilation during which he developed generalized muscular rigidity without shivering, mas-seter spasm, inappropriate sinus tachycardia followed by ventricular tachycardia, an inappropriately increasing temperature of 40°C, end-expired carbon dioxide tension of 70 mmHg, arterial carbon dioxide tension of 75 mmHg, base excess –12 mEq/l, pH 6.90, serum potassium 8 mEq/l, serum creatine kinase 26,000 IU, and serum myoglobin 180 ng/ml. This patient's MH signs were reversed with intravenous dantrolene. The patient was subsequently discovered to have had a brother who had died of MH 15 yr earlier.

For the final information exchange, experts were instructed to evaluate 12 new scenarios selected from actual patient reports from the North American Malignant Hyperthermia Registry by assigning a rank of 1 ("almost never") to 6 ("almost certain") for the likelihood that the adverse anesthetic event represented MH or the likelihood that the patient was MH susceptible. Experts were asked to grade these scenarios with a rank of 1–6 by using their clinical judgment and referring, if needed, to the scoring instructions and indicator description, but without strictly applying the scoring system. After the deletion of one scenario, which an expert pointed out as badly flawed in description (rather than just difficult to interpret), the 11 sets of scores from each MH expert were compared and contrasted with the results of strict application (by MGL) of the scoring rules. Only 6 of 121 (6.6%) expert scores varied by more than one rank from that obtained through strict application of the scoring rules. See appendix 1. Statistical tests suggested good agreement among the experts: the intra-class correlation coefficient rating of 11 scenarios was 0.83 (95% confidence interval 0.75–0.92). Pairwise comparison of strict application of the scoring rules with the experts' scoring also revealed high levels of agreement for 10 of the 11 experts. See appendix 2.

The following is an example of a patient report scenario: a 31-year-old white woman was anesthetized for a nonemergent plastic surgical procedure with isoflu-rane and succinylcholine. Immediately after induction, she developed masseter spasm, slight tachycardia after two doses of atropine, and cola-colored urine. No arterial blood gas analysis results were reported. Six hours after induction, her creatine kinase was 22,800 IU. She was treated with volatile anesthetic discontinuation, hyperventilation, and fluid loading. The score of this scenario with strict application of the scoring rules is rank 4, or "somewhat greater than likely" to be MH. Eight experts ranked this scenario as 4; three experts ranked it as 5.
Results

Eleven MH experts created a MH clinical grading system that can be applied to two different situations: first, to estimate the qualitative likelihood that an adverse anesthetic event is clinical MH; and second, to estimate a subject’s qualitative likelihood of MH susceptibility when the subject has a family history of MH susceptibility with or without personal experience of an adverse anesthetic event.

The qualitative likelihood that an adverse anesthetic event represents MH is based on points assigned to specific abnormal signs and laboratory findings (clinical indicators) observed during an acute anesthetic reaction. Points are assigned for each clinical indicator present; these points then are summed to produce a raw score that an adverse anesthetic reaction is a MH event. Additional clinical indicators for family history are added to the raw score to determine an individual’s MH susceptibility. The raw score is designed to translate to a MH rank designating the risk with which MH could occur from 1 (“almost never”) to 6 (“almost certain”). The rank should not be viewed as a percent likelihood; it is a qualitative indicator only.

Table 1 shows the scoring rules created by the MH experts for the MH clinical grading scale. The rules address the following issues. First, several agreed-upon indicators are manifestations of the same physiologic process. For example, increased end-tidal carbon dioxide tension to greater than 60 mmHg during spontaneous ventilation (15 points) and inappropriate tachypnea (10 points) each represent a sign of the same process: respiratory acidosis. Yet the experts believed that the MH score should not be the simple sum of all indicators present because it would overestimate likelihood, depending on how extensively the individual was monitored at the time of the possible MH event. Rather, only the single indicator with the highest point score within a given process would count toward the raw score. Therefore, in the example above, an individual who was inappropriately tachypneic with an end-tidal carbon dioxide tension of 70 mmHg during spontaneous ventilation would receive only 15 points for an end-tidal carbon dioxide tension greater than 60 mmHg and inappropriate tachypnea, and not 25 points, because both of these indicators are signs of the same respiratory acidosis process.

Second, because MH frequently is inherited as an autosomal dominant trait, it is important to ensure that adequate weight is given to a family history of MH (defined as a prior adverse metabolic or musculoskeletal reaction to anesthesia). Therefore, the following additional indicators were developed for use in determining an individual’s MH susceptibility rank: positive MH family history in a relative of the first degree (15 points), positive MH family history in a relative not of the first degree (5 points), positive MH family history together with another indicator from the patient’s own anesthetic experience other than elevated serum creatine kinase (10 points), and resting elevated serum creatine kinase in a patient with a family history of MH (10 points).

The clinical indicators used to determine the MH raw scores are listed in Table 2. The precise wording of

---

**Table 1. Scoring Rules for the Malignant Hyperthermia (MH) Clinical Grading Scale**

<table>
<thead>
<tr>
<th>MH Indicators</th>
<th>Description of Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review the list of clinical indicators. If any indicator is present, add the points applicable for each indicator while observing the double-counting rule below, which applies to multiple indicators representing a single process.</td>
<td></td>
</tr>
<tr>
<td>If no indicator is present, the patient’s MH score is zero.</td>
<td></td>
</tr>
<tr>
<td>Double-counting</td>
<td></td>
</tr>
<tr>
<td>If more than one indicator represents a single process, count only the indicator with the highest score. Application of this rule prevents double-counting when one clinical process has more than one clinical manifestation.</td>
<td></td>
</tr>
<tr>
<td>Exception: the score for any relevant indicators in the final category of table 2 (“other indicators”) should be added to the total score without regard to double-counting.</td>
<td></td>
</tr>
<tr>
<td>MH susceptibility indicators</td>
<td></td>
</tr>
<tr>
<td>The italicized indicators listed below apply only to MH susceptibility. Do not use these indicators to score an MH event. To calculate the score for MH susceptibility, add the score of the italicized indicators below to the score for the highest ranking MH event.</td>
<td></td>
</tr>
<tr>
<td>Positive family history of MH in relative of first degree</td>
<td></td>
</tr>
<tr>
<td>Positive family history of MH in relative not of first degree</td>
<td></td>
</tr>
<tr>
<td>Resting elevated serum creatinine kinase</td>
<td></td>
</tr>
<tr>
<td>Positive family history of MH together with another indicator from the patient’s own anesthetic experience other than elevated serum creatine kinase</td>
<td></td>
</tr>
</tbody>
</table>

**Interpreting the raw score:** MH rank and qualitative likelihood

<table>
<thead>
<tr>
<th>Raw Score Range</th>
<th>MH Rank</th>
<th>Description of Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>Almost never</td>
</tr>
<tr>
<td>3–9</td>
<td>2</td>
<td>Unlikely</td>
</tr>
<tr>
<td>10–19</td>
<td>3</td>
<td>Somewhat less than likely</td>
</tr>
<tr>
<td>20–34</td>
<td>4</td>
<td>Somewhat greater than likely</td>
</tr>
<tr>
<td>35–49</td>
<td>5</td>
<td>Very likely</td>
</tr>
<tr>
<td>50+</td>
<td>6</td>
<td>Almost certain</td>
</tr>
</tbody>
</table>

Anesthesiology, V 80, No 4, Apr 1994
## Table 2. Clinical Indicators for Use in Determining the Malignant Hyperthermia (MH) Raw Score

<table>
<thead>
<tr>
<th>Process I: Rigidity</th>
<th>Generalized muscular rigidity (in absence of shivering due to hypothermia, or during or immediately following emergence from inhalational general anesthesia)</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Masseter spasm shortly following succinylcholine administration</td>
<td>15</td>
</tr>
<tr>
<td>Process II: Muscle Breakdown</td>
<td>Elevated creatine kinase &gt;20,000 IU after anesthetic that included succinylcholine</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Elevated creatine kinase &gt;10,000 IU after anesthetic without succinylcholine</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Cola colored urine in perioperative period</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Myoglobin in urine &gt;60 µg/L</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Myoglobin in serum &gt;170 µg/L</td>
<td>5</td>
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<tr>
<td></td>
<td>Blood/plasma/serum K⁺ &gt;6 mEq/L (in absence of renal failure)</td>
<td>3</td>
</tr>
<tr>
<td>Process III: Respiratory Acidosis</td>
<td>PETCO₂ &gt;55 mmHg with appropriately controlled ventilation</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Arterial PaCO₂ &gt;60 mmHg with appropriately controlled ventilation</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>PETCO₂ &gt;60 mmHg with spontaneous ventilation</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Arterial PaCO₂ &gt;65 mmHg with spontaneous ventilation</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Inappropriate hypercarbia (in anesthesiologist’s judgment)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Inappropriate tachypnea</td>
<td>10</td>
</tr>
<tr>
<td>Process IV: Temperature Increase</td>
<td>Inappropriately rapid increase in temperature (in anesthesiologist’s judgment)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Inappropriately increased temperature &gt;38.8°C (101.8°F) in the perioperative period (in anesthesiologist’s judgment)</td>
<td>10</td>
</tr>
<tr>
<td>Process V: Cardiac Involvement</td>
<td>Inappropriate sinus tachycardia</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Ventricular tachycardia or ventricular fibrillation</td>
<td>3</td>
</tr>
<tr>
<td>Process VI: Family History (used to determine MH susceptibility only)</td>
<td>Positive MH family history in relative of first degree *</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Positive MH family history in relative not of first degree *</td>
<td>5</td>
</tr>
<tr>
<td>Other indicators that are not part of a single process†</td>
<td>Arterial base excess more negative than −8 mEq/L</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Arterial pH &lt;7.25</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Rapid reversal of MH signs of metabolic and/or respiratory acidosis with iv dantrolene</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Positive MH family history together with another indicator from the patient’s own anesthetic experience other than elevated resting serum creatine kinase *</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Resting elevated serum creatine kinase * (in patient with a family history of MH)</td>
<td>10</td>
</tr>
</tbody>
</table>

* These indicators should be used only for determining MH susceptibility.
† These should be added without regard to double-counting.
each indicator, the point value assigned to each indicator, and the grouping of individual indicators into six separate processes are the result of the experts' voting during the Delphi process.

Qualitative ranks are the result of the expert consensual process, which determined how points should be grouped into an interval scale so that one can then qualitatively define the likelihood that an adverse anesthetic event represents MH and the individual's relative chance of being MH susceptible. In the calculation of the individual MH susceptibility rank, points accrued for positive family history should be added to those derived from the highest-ranking adverse anesthetic event.

Ranks for MH events and MH susceptibility were made separate because they may differ when a detailed investigation into an individual's family history reveals a family member with a history of a possible MH reaction that was unknown or unrevealed at the time of the initial anesthetic preoperative interview. Also, a separate rank for MH susceptibility permits the ranking of subjects with a positive family history who have never personally experienced an adverse anesthetic reaction.

Discussion

We used a consensual process among MH experts to construct a MH clinical grading scale because there is a pressing need for a clinical case definition and because no gold standard exists for diagnosing MH events or MH susceptibility. Gold standards do not exist for many medical syndromes, such as sudden infant death syndrome, eosinophilia–myalgia syndrome, and chronic fatigue syndrome. In response to the lack of a gold standard, researchers and clinicians in these fields have used consensus processes to develop clinical case definitions also.16–18

Many early signs of MH episodes present in a variable manner and may be confused with other medical conditions, such as insufficient anesthetic depth, hypoxia, hypercarbia, iatrogenic hyperthermia, heat stroke, sepsis, radiologic contrast material within the central nervous system, thyrotoxicosis, pheochromocytoma, and neurolept malignant syndrome.4,19 Even patients who die from a MH event have no pathognomonic findings on autopsy using current techniques.20 Discussion among MH researchers at annual conferences reveals the disparity of opinions and practices concerning the clinical definition of the MH syndrome. We propose the MH clinical grading scale presented in this report as a means for standardizing and qualitatively defining the decision process whereby experts and researchers use clinical information to diagnose MH. This research provides a new and comprehensive clinical case definition for the MH syndrome.

The MH clinical grading scale requires the anesthesiologist to judge whether specific clinical signs are appropriate for the patient's medical condition, anesthetic technique, and surgical procedure. If the anesthesiologist judges the clinical sign to be inappropriate, then it is counted as a MH clinical indicator. For 30% of the clinical indicators, we rely upon the judgment of the anesthesiologist caring for the patient at the time of the event because we feel that only he or she would have sufficient information to judge the many possible MH clinical signs. For example, the anesthesiologist must consider the appropriateness of hypercarbia, permitting this clinical sign to be evaluated within the context of various important factors, such as preexisting asthma or chronic obstructive pulmonary disease, anesthetic circuit type, fresh gas flow, quality of the airway, prior release of a surgical tourniquet, and use of cardiopulmonary bypass.

The anesthesiologist should accept the critical cutoff values given in the indicators unless unusual circumstances apply. Selection of some of the indicators listed in table 2 assumes that the anesthesiologist has evaluated and ruled out other more prevalent causes of the indicator or sign. For example, inappropriately increased temperature should not be counted in a patient's score if a coexisting active infection is believed to be the source of the fever; similarly, inappropriate sinus tachycardia should not be scored if the elevated heart rate can be attributed to the recent administration of an anticholinergic agent or an increase in the intensity of the surgical stimulus.

The assigned MH rank represents a lower bound on the likelihood of MH. Therefore, several factors including aborting an anesthetic at the beginning of a reaction may lead to an underestimation, but rarely an overestimation, of the likelihood of a MH event or an individual's MH susceptibility. For example, if triggering anesthetic agents are discontinued immediately after the development of masseter muscle rigidity and the patient develops no other clinical indicators of MH, then the patient's MH susceptibility will be ranked as "somewhat less than likely," whereas if triggering an-
esthetic agents were continued and the patient also developed inappropriate hypercarbia, arterial pH less than 7.25, arterial base excess more negative than −8 mEq/l, and an inappropriately rapid increase in temperature, then the patient's MH susceptibility would be ranked as "almost certain."

Also, the assigned MH rank may underestimate the likelihood of an MH event or MH susceptibility if important monitors (e.g., electrocardiogram, capnometer, or temperature monitor) were not in use during the adverse anesthetic event or if relevant blood tests (e.g., creatine kinase, serum and urine myoglobin, arterial blood gases, or potassium) were not obtained at appropriate times. While considered highly desirable, no consensus could be reached on a simple and practical way to differentiate between missing laboratory data (due to incomplete clinical investigation at the time of a possible MH event) and normal laboratory data. The MH susceptibility score might underestimate an individual's likelihood of MH susceptibility if the family anesthetic history cannot be obtained (e.g., if the individual was adopted) or if family members have not been anesthetized with triggering agents. Above all, the scoring rules should be applied as an objective guide to the likelihood of a MH event and MH susceptibility, and there might be situations (e.g., inability to obtain an arterial blood gas during cardiopulmonary resuscitation) in which incomplete data would produce a rank that underestimates the patient's MH susceptibility.

This grading system is intended to assist MH researchers in classifying adverse events that occur within 24 h of the administration of an anesthetic. The MH clinical grading system will be most useful to the researcher when it is used to rank and compare well monitored and well documented adverse anesthetic events.

At this time, the grading scale is not intended for use by the clinician. The physician should always give priority to the appropriate treatment rather than classification of the MH event during a fulminant MH episode.††† Because patients with the rank of "somewhat less than likely" or even "unlikely" may still be susceptible to MH if they were incompletely monitored or evaluated during an adverse reaction to anesthesia, rank achieved on this clinical grading scale should not interfere with clinician referral of patients for further MH diagnostic evaluation.

The results of a caffeine halothane contracture test were intentionally not included in this grading scale because the determination of the sensitivity of any diagnostic test requires a prior clinical definition of the disease being tested. Thus, the sensitivity of the MH diagnostic muscle biopsy depends on a preexisting definition of MH; the test cannot, in itself, be used as a standard for diagnosing MH events or MH susceptibility.

As MacLennan recently emphasized, efforts to determine the specific molecular genetic and biochemical defects underlying MH susceptibility have been hindered by the absence of accurate phenotypic diagnosis.12 Using this grading scale, we now anticipate that researchers can select human study subjects who are "almost certainly" MH susceptible as objectively determined by the MH clinical grading scale, without solely depending upon the caffeine halothane contracture test. This scale should be useful in the evaluation of new diagnostic laboratory tests of MH susceptibility, and in understanding the molecular mechanisms responsible for MH.

A Delphi process is only as strong as the knowledge, skills, and commitment of its participants. The result of our process, a set of rules for the definition of MH must be applied by researchers and updated to gain acceptance. Even without formal or universal acceptance, however, the process of achieving a consensus about the definition of a disease can generate serious dialogue, especially about improved standards for patient monitoring.

The importance of accurate and timely submission of reports of all patients having adverse metabolic or musculoskeletal responses to anesthesia to the North American MH Registry††† or other national registries cannot be overemphasized. Such reports serve as the basis for accurate and standardized information concerning possible MH events for use in patient care and in research. Future studies will be required to refine scientifically this MH clinical grading scale. We view this MH clinical grading scale as an essential step in standardizing the analysis of adverse anesthetic events and improving prediction of MH susceptibility.
Appendix 1. Scoring* of Likelihood of Malignant Hyperthermia by 11 Experts and by Strict Application of Case Definition

<table>
<thead>
<tr>
<th>Case Number</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>Case Definition Score†</th>
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<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>5</td>
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</tbody>
</table>

* Possible scores range from 1 to 6 and indicate the likelihood of malignant hyperthermia: 1 = almost never; 2 = unlikely; 3 = somewhat less than likely; 4 = somewhat greater than likely; 5 = very likely; 6 = almost certain.
† Using strict application of malignant hyperthermia case definition (clinical grading score).

Appendix 2. Agreement among Experts on Likelihood of MH and Experts’ Agreement with Strict Application of Case Definition*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Level of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 experts’ independent judgment of 11 cases (95% CI)†‡</td>
<td>0.83 (0.75, 0.92)</td>
</tr>
<tr>
<td>Individual experts versus case definition score‡</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.96 (0.91, 1.0)</td>
</tr>
<tr>
<td>B</td>
<td>0.96 (0.91, 1.0)</td>
</tr>
<tr>
<td>C</td>
<td>0.88 (0.77, 0.99)</td>
</tr>
<tr>
<td>D</td>
<td>0.90 (0.84, 0.96)</td>
</tr>
<tr>
<td>E</td>
<td>0.92 (0.86, 0.98)</td>
</tr>
<tr>
<td>F</td>
<td>0.94 (0.88, 0.99)</td>
</tr>
<tr>
<td>G</td>
<td>0.87 (0.75, 0.99)</td>
</tr>
<tr>
<td>H</td>
<td>0.89 (0.78, 1.0)</td>
</tr>
<tr>
<td>I</td>
<td>0.74 (0.61, 0.87)</td>
</tr>
<tr>
<td>J</td>
<td>0.70 (0.62, 1.0)</td>
</tr>
<tr>
<td>K</td>
<td>0.90 (0.79, 1.0)</td>
</tr>
</tbody>
</table>

Mean of 11 experts versus case score (95% CI) | 0.89 (0.83, 0.93) |

* Pairwise agreement of each expert individually with MH case definition score. Raw scores appear in appendix 1.
‡ Intraclass correlation coefficients were calculated using the SAS VARCOMP procedure to measure agreement among the experts. This statistical procedure assumes that experts are random effects, and thus it estimates agreement among any group of experts rather than among members of this particular panel. 95% confidence intervals were generated using the jackknife method.
§ Weighted Kappa statistics measured pairwise agreement between the experts and a strict application of the scoring system as applied by one of us (M.O.L.). 95% confidence intervals were computed using variance estimates under the alternative hypothesis of agreement greater than chance.

The authors thank Marcella Diaz Myers, M.D., for help with selecting appropriate clinical scenarios and for applying the clinical grading scale to Registry cases; J. Richard Landis, Ph.D., for help with the study design; Susan Shirk, B.A., for statistical assistance; David R. Larach, M.D., Ph.D., and Julian F. Bichuuy, M.B., D.Phil., for their helpful suggestions; and Pam Myers and Linda Fuhrmann, B.A., for facilitating information exchanges and for preparing the manuscript.

References


Editorial

Muscular dystrophy versus mitochondrial myopathy: the dilemma of the undiagnosed hypotonic child

ALLISON KINDER ROSS MD
Division of Pediatric Anesthesia, Duke University Medical Center, Durham, NC, USA

As pediatric anesthesiologists, it is unusual in these days of complex technology and advances in genetic research to find ourselves presented with conflicting information and continued controversy regarding anesthesia plans for a particular group of children. This still occurs, however, when presented with the task of determining the best management for the child with an undiagnosed myopathy (1–6). Drs Flick et al. (1) in this issue of Pediatric Anesthesia have taken their 13 years of experience to help guide the thought processes for this population of children. The authors reviewed the charts of all children who had undergone muscle biopsies to rule out suspected neuromuscular disorders (NMD). All of the children received volatile anesthetic agents with or without succinylcholine and no child in the review of 274 charts developed malignant hyperthermia (MH) or rhabdomyolysis from the delivered anesthetic. Seven of the patients had biopsies consistent with muscular dystrophy and three consistent with mitochondrial disorder. Although the results of this review should be comforting, no child in their population was subsequently diagnosed with Evans myopathy, King syndrome or central core disease, the only known disorders that are truly associated with malignant hyperthermia (7). Any of these diagnoses would have certainly changed the results, but not the conclusion. Appropriately, Flick et al., rather than assigning a risk of zero based on their findings, have estimated the risk of a patient with NMD to have MH or rhabdomyolysis from exposure to a volatile anesthetic at less than or equal to 1.09%. This is in comparison with the 0.46% risk in an MH-susceptible child of developing an episode of malignant hyperthermia after nontriggering anesthesia (6).

Over the years there has been great controversy as to how to manage the child with hypotonia of unknown etiology for a surgical procedure. There are essentially two families of diseases that deserve consideration, the muscular dystrophies and the mitochondrial myopathies. The incidence of neuromuscular disorders in children is as frequent as 1 in 3200 male births vs an incidence of up to 1 in 4000 children having a mitochondrial disorder of some variety (8). Being faced with a child having one of these disorders is therefore not necessarily a rare event in common pediatric practice. Knowing the differences between the management of these two disorders is imperative so that the appropriate anesthetic plan is formulated. As alluded to previously, a main concern for these children are the risks of malignant hyperthermia or rhabdomyolysis that may result in perioperative morbidity or mortality. The risk or association of malignant hyperthermia with certain muscular dystrophies has been a well-known entity and a subject of controversy in the literature and book chapters. As Flick et al. discussed, although muscular dystrophy is often considered to be associated with MH, several studies and reviews have demonstrated that NMDs other than the three disorders previously mentioned are not truly associated with MH and experienced practitioners deliver inhaled agents to children with muscular dystrophy without sequelae (1,9).

It is not always easy to determine which child with neuromuscular disease may be at risk for perioperative events and muscle contracture testing may be inaccurate (10,11). Only about 50% of
patients who have muscle contracture testing indicating MH susceptibility actually have mutations in the ryanodine receptor (12). It is unclear why the other half has abnormal contracture testing. With the inability to truly determine risk of MH, it is often recommended that children with hypotonia and suspicion of NMD be anesthetized with nontriggering agents to avoid the issue all together (1,10,11,13). Additionally, knowing that MH may not be a risk does not imply that rhabdomyolysis does not present as a separate and significant risk.

To address the concerns that surround the anesthetic management in children with muscular dystrophy, a recent Editorial in Pediatric Anesthesia by Yemen and McClain revisited the issues and made recommendations in the interest of patient safety (14). These authors presented a series of patients with DMD who had undergone uneventful surgery and anesthesia but who suffered unexpected events including hyperkalemic cardiac arrest in the recovery room. To avoid the risks of malignant hyperthermia and rhabdomyolysis, these authors suggest that inhaled agents be avoided in this population of patients. Others agree with these recommendations as the availability of other agents precludes the need for volatile anesthetic use (15). In a separate editorial during the days when succinylcholine was considered to be primarily responsible for the hyperkalemic cardiac arrest that were reported, Morris suggested that succinylcholine be contraindicated in patients with DMD but went on to state that inhaled agents are not contraindicated as there was a lack of strong evidence against the volatiles (16). Several years later, Gronert reviewed the cardiac arrests associated with succinylcholine and disagreed stating that practice need not change based on these isolated case reports (17). Flick et al. suggest that their series should provide the clinician with reassurance when using volatile anesthetics in children undergoing diagnostic muscle biopsy. They also suggest that this interpretation should be made with care, particularly as the sample size is not large enough to truly capture the rare episodes of MH or rhabdomyolysis.

It seems clear from the literature that there remains some disagreement as to whether using inhaled agents is worth the risk in patients with neuromuscular diseases. It is also clear that the risk of malignant hyperthermia is extremely low in this population due to the small numbers of patients who are truly susceptible, but when the risk of rhabdomyolysis is added, there is an increased possibility of perioperative adverse events. Assuming that the recommendations to avoid triggering agents are followed for procedures on children with unknown etiology for their hypotonia, a total intravenous technique using propofol as the primary agent is a logical choice. Can it be assumed that a total intravenous anesthetic (TIVA) technique is appropriate for all children with myopathies? One must consider the anesthetic implications in patients with mitochondrial myopathies in particular.

Mitochondrial disorders are a rare set of diseases that manifest themselves through defects in electron chain transport or oxidative phosphorylation (2,5,18). There are three basic categories that constitute the mitochondrial myopathies. There are respiratory chain deficiencies, mitochondrial DNA mutations that include mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), mitochondrial neurogastrointestinal encephalopathy (MNGIE) and myoclonic epilepsy with ragged red fibers (MERRF) syndrome and mitochondrial deletions such as Kearns-Sayre syndrome. Although there is considerable overlap in these categories, it allows for some ability to organize these complex disorders. Alternatively, classification by specific enzyme activity of the different complexes in the oxidative phosphorylation system has been used to associate the clinical findings with the biochemical defect (5). A comprehensive review by Shipton and Prosser described the underlying abnormalities in the disorder and outlined the significant issues associated with mitochondrial myopathies and anesthesia (2). Central to this review and to a prior review that was published in Pediatric Anesthesia in 1998 is the notion that there is a wide range of mitochondrial diseases and there are no true recommendations for anesthesia techniques that rely on evidence-based medicine (2,5,18–22). Early in the understanding of the mitochondrial defects, these diseases were considered to be associated with malignant hyperthermia and therefore children with mitochondrial myopathies were often managed perioperatively with nontriggering anesthetics (4,5,20,23–26). A TIVA using propofol as the primary agent was once considered the preferred technique in these patients who were considered susceptible to
malignant hyperthermia. The association between mitochondrial myopathies and malignant hyperthermia has now mostly been dismissed. Although propofol has been used in children with mitochondrial myopathies without event, the choice of a TIVA anesthetic using propofol may no longer be considered the anesthetic of choice for this group of children. Within the past year it has been suggested that propofol with its lipid carrier composed of long-chain fatty acids may have an adverse effect on fatty acid oxidation and mitochondrial respiratory chain function, and therefore put patients with mitochondrial disorders and closely-related carnitine deficiency syndromes at risk for a clinical scenario similar to propofol infusion syndrome (PRIS) (27).

Propofol infusion syndrome is known as a potentially fatal reaction that may occur in children who receive high-dose propofol infusions, typically for sedation in intensive care units (28,29). This condition is characterized by bradycardia, metabolic acidosis, rhabdomyolysis, and lipidemia and may lead to cardiac failure. Early reports of propofol infusion syndrome came from the British literature and described the condition in children receiving doses of propofol at >4 mg·kg⁻¹·h⁻¹ for greater than 48 h (28,29).

The suggested dose of >4 mg·kg⁻¹·h⁻¹ and length of infusion >48 h that were associated with propofol infusion syndrome were described in patients who did not have underlying mitochondrial perturbation (28–30). If a child has a mitochondrial disorder, and is therefore more susceptible to the effects of an increased lipid load, the true dose that may result in PRIS is unknown and may have unpredictable results. Although the chance of propofol infusion syndrome occurring during a surgical procedure of a finite duration would be extremely rare, there remains concern that even a short-term high-dose propofol infusion may result in propofol infusion syndrome, particularly if a child has impaired fatty acid utilization (31–33).

This use of propofol in children with mitochondrial myopathies is further complicated by the fact that children who suffer from propofol infusion syndrome often have a clinical picture that is similar to malignant hyperthermia. Metabolic acidosis, rhabdomyolysis with myoglobinuria, hypotension, and cardiovascular collapse may occur with either condition (34,35). In order to differentiate these two processes, one should consider the time to onset. A malignant hyperthermia episode typically occurs within 4–5 h of the delivery of a triggering anesthetic and the arrhythmias present early from the hyperkalemia that ensues. Propofol is considered a non-triggering anesthetic and its sole use without contamination from other triggering agents should allow immediate dismissal of a diagnosis of MH. However, if there remains some question as to etiology of the presenting signs, propofol infusion syndrome typically would occur after a prolonged infusion over a day to days. Perioperative evaluation for lactate levels are deceiving as they are elevated with mitochondrial disease with or without an associated anesthetic or PRIS. In light of these considerations, it has been suggested that patients with known mitochondrial disease should not receive propofol (36).

The risks of using alternative IV anesthetics in children with mitochondrial myopathies remain under investigation. As one might expect, all anesthetics have been used for children with mitochondrial disorders without complications (5). It has been reported that these children are sensitive to thiopentone and etomidate, however reports are inconsistent (23,37–39). With the dilemma of using volatile agents versus propofol and the side effects or risks associated with each technique depending on the underlying diagnosis, other agents such as ketamine, etomidate, or dexmedetomidine should be considered.

The use of muscle relaxants in children with mitochondrial disease has presented conflicting reports. Some reports have touted no increased sensitivity or complications with atracurium, vecuronium, and pancuronium although there may be patient variability depending on severity and type of mitochondrial myopathy (18,25,40–42). Others have demonstrated increased sensitivity to atracurium, rocuronium, mivacurium, and cisatracurium (18,40,41,43–45). This is not dissimilar to the use of muscle relaxants in children with muscular dystrophy where reports of sensitivity have been inconsistent (46–49). Any child with hypotonia should be considered at risk of variable response to muscle relaxation and doses adjusted accordingly. Succinylcholine is best avoided as it has been associated with at least one case of malignant hyperthermia in a child with mitochondrial disease.
There have been no follow-up case reports of MH in this population from succinylcholine and it has been used in other children with mitochondrial disease without complication, however if succinylcholine can be avoided, nondepolarizers should be used in its place (42).

Pain management is essential in children with mitochondrial disorders as the response to pain may worsen their risk of lactic acidosis from depletion of energy stores and increased oxygen demand. Although narcotics have been used without adverse events, they should be used with caution and titrated to effect (3). Nonsteroidal adjuncts and nonopioid analgesics should be used as appropriate to decrease opioid requirements. If a regional anesthesia technique is possible, this may be a technique of choice as the increased risk of respiratory depression that may occur with opioids can lead to worsening acidosis. A straight regional technique also negates the question of MH risks as well as issues associated with potential sensitivity to muscle relaxants.

The use of sevoflurane is certainly considered acceptable based on the work of Morgan et al and is considered the agent of choice by some clinicians (3,50). Children with Complex I respiratory chain disorders are at greatest risk of sensitivity to inhaled agents and reach anesthetic depths according to bispectral index values at lower concentrations of sevoflurane than controls (50). Despite this, there is no contraindication to using inhaled agents in children with mitochondrial disorders of any known type, although arrhythmias with halothane have been reported in patients with Kearns-Sayre syndrome due to the underlying conduction defects in children with this disorder (3,51).

Whether or not one chooses inhaled or intravenous techniques in the child with a mitochondrial myopathy, other considerations must be weighed during the perioperative period (5). The preoperative fasting period should be kept to a minimum to avoid hypovolemia and depletion of glucose stores. Likewise, intravenous fluids must contain glucose and should avoid lactate that might worsen an underlying lactic acidosis. Any stress that may provoke increased energy requirements such as perioperative pain or hypothermia must be avoided. Children with Kearns-Sayre syndrome are at risk for arrhythmias and must have adequate preoperative workup and perioperative monitoring (3,19).

Children with hypotonia may present for a variety of surgical procedures. In addition to muscle biopsies for diagnosis, many will require endoscopies for gastrointestinal symptoms, gastrostomy tubes for feeding disorders, radiologic procedures or EEGs for seizures, strabismus surgery, and hearing tests. If presented with a child who has an undiagnosed myopathy, there are several clues to help provide the anesthesiologist with the best information to make an educated guess as to the etiology of the muscular disease. For example, a child who has muscular dystrophy of any variety will typically have a history of muscular dystrophy in the family. Physical exam clues include the presence of hypertrophic calves despite global hypotonia in a young child or an elevated creatine kinase (52). Without a family history of neuromuscular disease, and with a suspicion of mitochondrial disorder, the anesthetic plan may lean towards the assumption that the child may have an undiagnosed mitochondrial myopathy. A preoperative elevated serum lactate is a useful marker for the disease.

The dilemma remains. If the etiology of the myopathy is known, this information may be applied to formulate an appropriate anesthesia plan. With the knowledge of the two groups of diseases at this time, the choice of a TIVA for the patient with muscular dystrophy and the decision to use an inhaled agent for the child with mitochondrial myopathy would be most appropriate. The issue remains with the truly undiagnosed myopathic child. Administering an inhaled agent to a child with muscular dystrophy is an accepted technique and will be without incident the vast majority of the time. Based on the population statistics presented by Flick et al. (1), there should be no significant risk of rhabdomyolysis or malignant hyperthermia in nearly 99% of the anesthetics. The remaining 1.09% is the population that causes others to question the use of inhaled agents at all in children with muscular dystrophies and results in the overall recommendation that a total intravenous technique is preferred.

For many pediatric anesthesiologists who consider a 1% risk to be unacceptable, a total intravenous technique may be used in all children with undiagnosed myopathy. If propofol is used as
the primary agent in moderate doses (<4 mg·kg\(^{-1}\)·h\(^{-1}\)) and for short periods of time (<48 h), risks should remain at a minimum for malignant hyperthermia, rhabdomyolysis, or propofol infusion syndrome.

As anesthesiologists, we typically serve as consultants for patients with known disorders and provide the safest anesthesia possible based on the information that is obtained. When information is lacking, as in the case of a hypotonic child who presents for a muscle biopsy, our skills at obtaining a focused history to provide clues for our management are essential. As more knowledge is gathered regarding the true risks based on the pathophysiology of the various neuromuscular diseases, and with the additional investigation of other agents in this population of children, an educated guess will hopefully be a thing of the past. More large scale studies and reviews are needed to answer this important question that has been readressed by Flick et al.

References

40 Kelly A, O’Connor M. Mitochondrial myopathy and anaesthesia. *Anaesthesia* 1990; 45: 596.

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The risk of malignant hyperthermia in children undergoing muscle biopsy for suspected neuromuscular disorder

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Summary

Background: It is assumed that those children with known or suspected neuromuscular disorders (NMD) are at increased risk for malignant hyperthermia (MH). Despite the lack of conclusive data, most of these children are managed with a nontriggering anesthetic. This study examined the risk of MH in children exposed to a triggering anesthetic while undergoing muscle biopsy for suspected NMD.

Methods: Between 1992 and 2005, the medical records of 351 children under 21 years of age were identified as having undergone muscle biopsy for suspected NMD. Of these, only 274 received a volatile anesthetic agent or succinylcholine and were included for study. Records were examined for evidence of MH or rhabdomyolysis.

Results: No patient exhibited signs or symptoms suggestive of MH. One patient was found, by muscle biopsy, to have evidence of rhabdomyolysis prior to exposure to a volatile anesthetic. Of 274 patients, only three received succinylcholine. None developed MH or rhabdomyolysis. The estimated risk of a patient with suspected NMD developing MH as a result of exposure to volatile anesthetic agents during muscle biopsy is 1.09% or less.

Conclusion: The estimated risk of MH or rhabdomyolysis is 1.09% or less in a diverse population of children with suspected NMD.

Keywords: malignant hyperthermia; muscle biopsy; myopathy; rhabdomyolysis; children; succinylcholine; anesthesia; inhalation

Introduction

Despite continuing controversy, it is widely assumed that children with known or suspected neuromuscular disorder (NMD) are at increased risk for malignant hyperthermia (MH) (1). Previous reports have suggested a relationship between MH risk and a variety of NMD including Duchenne type muscular dystrophy (DMD), osteogenesis imperfecta, myotonia congenita, the Schwartz–Jampel syndrome, and others (2). Additionally, Kearns–Sayre syndrome and other mitochondrial myopathies have also been associated with an increased risk for MH (3,4). Others have failed to demonstrate an association between mitochondrial disorders and MH.
There are currently only two disorders for which a clear link to MH has been established; they are central core disease and King syndrome. Both are quite rare, well-defined clinically, autosomal dominant and frequently diagnosed without muscle biopsy.

Neuromuscular disorders such as myopathies, dystrophies and channelopathies are relatively rare disorders only infrequently encountered in anesthesia practice except in tertiary care settings especially those caring for children. Many of these disorders are diagnosed clinically or with relatively noninvasive testing such as chromosomal analysis, skin biopsy or serum, urine, or cerebrospinal fluid chemistries. However, in some the diagnosis remains uncertain after routine testing and muscle biopsy is required to determine what, if any, identifiable disorder exists. It is these patients that represent the challenge faced by anesthesiologists concerned about the potential association between MH and NMD’s especially myopathies.

The aim of this study was to describe, retrospectively, the anesthetic outcomes of a diverse population of children with a suspected NMD exposed to volatile anesthetics and/or succinylcholine and to estimate the upper limit of risk for the development of signs and symptoms consistent with the diagnosis of acute MH.

**Methods**

With approval from the Institutional Review Board, the medical records of 351 children under age 21 undergoing muscle biopsy between 1 January 1992 and 30 June 2005, were obtained for review. Of these, 274 children with known or suspected NMD undergoing muscle biopsy for indications other than the diagnosis of MH and having received either volatile anesthetic agents or succinylcholine were included for review.

Records were examined for evidence of MH developing either in the operative or postoperative period prior to discharge. Additionally, records were searched to identify any patient for whom death was reported within 30 days of the date of operation. Evidence of MH was defined as any reference within the record to muscle rigidity, acidosis (respiratory or metabolic), rhabdomyolysis, fever, and elevated creatine kinase (CK). Those patients whose biopsy was submitted for contracture testing were eliminated from further review.

**Results**

The anesthetic records of 274 individual patients undergoing muscle biopsies were reviewed. No patient demonstrated signs or symptoms consistent with MH or rhabdomyolysis. One child was found to have biopsy evidence of rhabdomyolysis felt to be due to prolonged seizures (Table 1).

Of the 274 patient records reviewed 11 were missing biopsy results. Among the remaining 263, 117 biopsies were described as either minimal nonspecific abnormalities, indeterminate, or were negative. Of those biopsies in which an abnormality was found there were 39 separate diagnoses among which 27 patients were found to have biopsies consistent with myasthenia gravis (including myasthenic syndrome), and 16 were an inflammatory myopathy. Muscular dystrophy was found in the biopsies of seven patients two of which were of the Duchenne type. Of the 39 patients with a suspected mitochondrial disorder, three were confirmed with biopsy. No biopsy was suggestive of either King syndrome or central core disease.

It could clearly be determined that two thirds of the 261 inductions were by inhalation (67.2%). Of volatile agents, isoflurane was most frequently used for maintenance (54.7%) whereas sevoflurane was the most common volatile agent employed for induction (46.7%). Propofol was the most frequently used intravenous agent for both induction (19.7%) and maintenance (21.5%).

Table 2 shows agents used for induction and maintenance. Percentages do not add up to 100 as many patients received more than one agent simultaneously and may have received a volatile agent for

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<td>Details of 274 patients undergoing muscle biopsy for undiagnosed NMD between the years 1992 and 2005</td>
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<tr>
<td>Age (n = 274)</td>
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<tr>
<td>Weight (n = 273)</td>
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<tr>
<td>Gender [n = 274 (%)]</td>
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<tr>
<td>I, 6 (2.2)</td>
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<td>II, 126</td>
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<td>IV, (49.6)</td>
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induction but not maintenance. All patients received a volatile agent either during induction or maintenance of anesthesia (Table 2). The mean duration of anesthesia was 124.7 min (SD: 63.1) and the mean procedure duration was 65.3 min (SD: 49.1). Anesthesia time ranged from a minimum of 39 min to a maximum of 480 min. Anesthesia and procedure times are inclusive of additional procedures performed during the same anesthetic.

Nondepolarizing muscle relaxants were employed in 38% of cases. Three patients received succinylcholine, a 19-year-old subsequently diagnosed with a neurodegenerative disorder that included a myopathic component, a 13-year-old with gait abnormalities suggestive of neuromuscular disease, and a 2-year-old with weakness and an electromyogram suggestive of a NMD. Of those receiving succinylcholine, no additional signs or symptoms consistent with MH were found with the exception of a temperature elevation to 38.5°C in the 13-year-old, which was attributed to a postoperative urinary tract infection. None of those receiving succinylcholine had abnormal CK measurements preoperatively and none had CK’s measured in the 48 h following the procedure. The 2-year old was found to have a biopsy suggestive of a dystrophinopathy. Biopsy results for the others were unavailable (19-year-old) or indeterminate (13-year-old).

Each of the 274 patient records were examined for evidence of MH including a positive family history, fever, muscle rigidity, acidosis, elevated CK, use of dantrolene, cardiac arrest, or death within 30 days of the procedure. No patients had a documented family history of MH or death related to anesthesia.

Of the seven patients with temperature elevation >38.5°C intraoperatively or in the 48 h following the procedure, all had alternative explanations such as urinary tract infection, pneumonia, and atelectasis. None had other signs or symptoms consistent with MH.

Four patients had CK determinations within 48 h following the procedures. The mean CK was 515 U·L⁻¹ with a range of 139–1448. Again, no patient had other evidence to suggest MH. The highest CK was seen in a 16-year-old female with intractable seizures who underwent muscle biopsy. The biopsy showed evidence of rhabdomyolysis, attributed to uncontrolled status epilepticus, but was otherwise normal. Subsequently, she was again given volatile anesthesia (isoflurane) in an attempt to control her seizures. Support was eventually withdrawn and she died without a clear diagnosis. Her clinical course was not consistent with MH.

One additional patient died within 30 days of the procedure; an infant found at biopsy to have spinal muscular atrophy. Three patients were readmitted within 48 h of an outpatient procedure; one admission was for further testing, and two for respiratory distress. Biopsies for those admitted with respiratory distress were indeterminate. None of the readmissions or deaths could be attributed to MH.

Discussion

Malignant hyperthermia is a rare disorder of calcium metabolism in skeletal muscle. The reported incidence of acute MH episodes is between 1 in 4200 and 1 in 250 000 anesthetics depending primarily on the age of the patient, setting, and presentation (7). It is characterized by evidence of a hypermetabolic state and is manifested by muscular rigidity, fever, hypercarbia, tachycardia, acidosis and, if untreated, death. In most cases, the triggering event for the development of MH symptoms is exposure to volatile anesthetic agents and/or succinylcholine.

As it was first described in 1960 by Denborough et al. (8), MH has been associated with a variety of risk factors including exposure to many commonly used anesthetic agents and the presence of coexisting disorders, particularly NMD.

It remains unclear, however, whether an association exists between MH and dystrophies such as

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<td>Anesthetic agents used for induction and maintenance among 274 children undergoing muscle biopsy for undiagnosed NMD</td>
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<td>Agent</td>
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<td>Propofol</td>
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<td>Other</td>
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DMD, channelopathies other than central core disease, and any or all of the mitochondrial disorders (9). There is a substantial body of literature consisting primarily of case reports and small series suggesting an increased risk of MH in patients with NMD (10–13). However, no large study has, as yet, examined the question.

In a small study, Wappler et al. (14) sought to determine whether an increased risk of MH existed for 24 patients with a variety of known NMD. Although they found a high incidence of positive contracture tests among those with NMD, the authors expressed uncertainty as to the accuracy of the contracture testing in patients with neuromuscular disorders. The specificity of contracture testing in patients with dystrophies and myopathies has been questioned by others as well (15). Wappler et al. (14) concluded, however, that patients with known NMD should be treated as MH susceptible and therefore should not be exposed to triggering anesthetic agents.

In a 1992 study of contracture testing in a group of patients with NMDs, Heytens et al. (16) found that of the 60 patients biopsied only two were found to be MH susceptible, 10 equivocal and 48 were negative. Although Heytens’s series was similar to ours, dystrophies such as DMD were more common representing 14 of 60 patients whereas only two of 274 biopsies in our series were consistent with DMD. Like Wappler et al. (14), Heytens et al. (16) speculated that the large number of equivocal biopsies was the result of a lack of specificity of the test in patients with NMD.

Of particular concern are patients with DMD. Several authors and most major texts of pediatric anesthesia suggest that patients with DMD are at increased risk for MH (17,18). In the animal model of DMD, muscle samples from mdx mice, deficient in dystrophin, have been found to have both normal and abnormal results when exposed to halothane and caffeine (19,20).

In the Wappler et al. (14) study, two of three patients with DMD were found to be MH susceptible according to the European protocol. However, in a study of 47 procedures in 23 patients later diagnosed with DMD, Herr et al. (21) found that no child developed evidence of MH despite 93% having received volatile anesthetic agents and 4% having received succinylcholine.

Much of the difficulty associated with defining the relationship between MH and DMD is related to the separate and distinct phenomenon of isolated acute rhabdomyolysis. Acute rhabdomyolysis leading to hyperkalemic cardiac arrest has been reported in association with DMD and has been understandably confused with MH. Like MH, most reported cases of rhabdomyolysis have been associated with the use of succinylcholine although several have occurred in its absence (22). A decade ago, the clear association between succinylcholine and rhabdomyolysis led to the United States Food and Drug Administration to advise against the use of succinylcholine in children. Despite this, reports of hyperkalemic cardiac arrest in DMD patients continue to occur (23). In those cases where succinylcholine was not used, volatile anesthetic agents have been implicated although the mechanism by which this occurs remains, to a large extent, unexplained.

As suspicion for most children eventually diagnosed with DMD is strong prior to biopsy the use of volatile agents was usually avoided. Among our 274 patients only two were found to have DMD. Five others had dystrophies of other types. Not surprisingly, of those 77 records excluded because of lack of exposure to triggering agent, 10 had clinical histories or biopsies diagnostic or strongly suggestive of a dystrophy.

None included for study developed signs or symptoms consistent with either MH or rhabdomyolysis despite all having received volatile anesthetic agents. Although the relationship between succinylcholine and rhabdomyolysis appears evident, it is less clear whether volatile agents can be implicated in these events.

Given the rarity of both MH and rhabdomyolysis, a study of this size cannot, by any means, demonstrate clearly the safety of volatile anesthetics in the setting of a suspected NMD. However, using statistical methods to assess risk in the setting of no observed events, one can estimate the likelihood (with 95% confidence) of encountering either MH or rhabdomyolysis is ≤1.09% (24). This risk can be viewed against the background risk of triggering among patients with known MH managed with a nontriggering anesthetic.

Carr et al. (25), in Toronto, reported that in patients known to be MH susceptible, the incidence of triggering after exposure to a nontriggering
anesthetic is not zero. In their study of 2214 patients undergoing muscle biopsy to rule out MH, 1082 had a positive contracture tests. Of those patients found to be positive, five developed MH in the perioperative period yielding an incidence rate of 0.46% (CI: 0.058–0.866), an estimated risk comparable with that found in our series (CI: 0.0–1.09%).

The most commonly mentioned alternative to the use of volatile anesthetics in this population is propofol. However, the use of propofol in undiagnosed myopathic patients is likewise controversial given reports of rhabdomyolysis, unrelenting acidosis, and death, mostly in sedated pediatric patients (26,27). Among myopathic patients, it has been recommended that those caring for children that have or may have mitochondrial disorders consider avoiding the use of propofol because of concerns that this group may be at particular risk for the propofol infusion syndrome (28,29).

Of our 274 patients, at least three were found to have a mitochondrial disorder, although it was suspected in at least 39 others. Clearly, the clinician caring for undiagnosed myopathic patients inevitably finds him or herself in a position of uncertainty given the real or potential risks associated with the use of either volatile anesthetics or propofol.

One can conclude from this series that in a diverse population of children undergoing muscle biopsy for known or suspected NMD, the estimated risk of MH or rhabdomyolysis is ≤1.09%. Each clinician must decide, based on these results, whether a risk of 1.09% or less is sufficient to justify the use of an alternative anesthetic agent such as propofol or some other approach such as the use of etomidate, ketamine, or a regional technique.

Obviously, our patient population was diverse and included a variety of NMD or suspected NMD and, as a consequence, one must be careful in interpreting these results especially given the knowledge that of patients with known MH many had triggering anesthetics without the development of MH prior to diagnosis. Additionally, despite the diversity of our population, it is limited to the subset of those with suspected NMD that both required muscle biopsy and received a triggering anesthetic. Many or most patients with NMD (known or suspected) do not require muscle biopsy and therefore would not be included in this series. Other patients such as those with DMD are underrepresented in our population as most either do not require muscle biopsy or were managed with a nontriggering anesthetic. Although care must be exercised in the interpretation of this data, the information does provide the clinician with reassurance with regard to the use of volatile anesthetics in those undergoing diagnostic muscle biopsy.

References


Accepted 3 May 2006
EMERGENCY THERAPY FOR
MALIGNANT HYPERThERMIA

SIGNS OF MH:
- Increasing ETCO
- Trunk or total body rigidity
- Masseter spasm or trismus
- Tachycardia/tachypnea
- Mixed Respiratory and Metabolic Acidosis
- Increased temperature (may be late sign)
- Myoglobinuria

SITUATION:
Sudden/Unexpected Cardiac Arrest in Young Patients:
- Presume hyperkalemia and initiate treatment (see #6)
- Measure CK, myoglobin, ABGs, until normalized
- Consider dantrolene
- Usually secondary to occult myopathy (e.g., muscular dystrophy)
- Resuscitation may be difficult and prolonged

MALIGNANT HYPERThERMIA:

ACUTE PHASE TREATMENT

1 GET HELP. GET DANTROLENE – Notify Surgeon
- Discontinue volatile agents and succinylcholine.
- Hyperventilate with 100% oxygen at flows of 10 L/min. or more.
- Halt the procedure as soon as possible; if emergent, continue with non-triggering anesthetic technique.
- Don’t waste time changing the circle system and CO2 absorbant.

2 Dantrolene 2.5 mg/kg rapidly IV through large-bore IV, if possible
- Each 20 mg bottle has 3 gm mannitol for isotonicity. The pH of the solution is 9.

To convert kg to lbs for amount of dantrolene, give patients 1 mg/lb (2.5 mg/kg approximates 1 mg/lb).

- Dissolve the 20 mg in each vial with at least 60 ml sterile, preservative-free water for injection.
- Prewarming (not to exceed 39º C.) the sterile water may expedite solublization of dantrolene. However, to date, there is no evidence that such warming improves clinical outcome.
- Repeat until signs of MH are reversed.
- Sometimes more than 10 mg/kg (up to 30 mg/kg) is necessary.

3 Bicarbonate for metabolic acidosis
- 1-2 mEq/kg if blood gas values are not yet available.

4 Cool the patient with core temperature >39ºC.
- Lavage open body cavities, stomach, bladder, or rectum. Apply ice to surface.
- Infuse cold saline intravenouslly. Stop cooling if temp. <38º C and falling to prevent drift <36º C.

5 Dysrhythmias usually respond to treatment of acidosis and hyperkalemia.
- Use standard drug therapy except calcium channel blockers, which may cause hyperkalemia or cardiac arrest in the presence of dantrolene.

6 Hyperkalemia
- Treat with hyperventilation, bicarbonate, glucose/insulin, calcium.
- Bicarbonate 1-2 mEq/kg IV.
- For pediatric, 0.1 units insulin/kg and 1 ml/kg 50% glucose or for adult, 10 units regular insulin IV and 50 ml 50%-glucose.
- Calcium chloride 10 mg/kg or calcium gluconate 10-50 mg/kg for life-threatening hyperkalemia.
- Check glucose levels hourly.

7 Follow ETCO2, electrolytes, blood gases, CK, core temperature, urine output and color, coagulation studies. If CK and/or K+ rise more than transiently or urine output falls to less than 0.5 ml/kg/hr, induce diuresis to >1 ml/kg/hr and give bicarbonate to alkalize urine to prevent myoglobinuria-induced renal failure. (See D below)
- Venous blood gas (e.g., femoral vein) values may document hypermetabolism better than arterial values.
- Central venous or PA monitoring as needed and record minute ventilation.
- Place Foley catheter and monitor urine output.

POST ACUTE PHASE

1 Follow urine myoglobin and institute therapy to prevent myoglobin precipitation in renal tubules and the subsequent development of Acute Renal Failure. CK levels above 10,000 IU/L is a presumptive sign of rhabdomyolysis and myoglobinuria. Follow standard intensive care therapy for acute rhabdomyolysis and myoglobinuria (urine output >2 ml/kg/hr by hydration and diuretics along with alkalization of urine with Na-bicarbonate infusion with careful attention to both urine and serum pH values).
- Counsel the patient and family regarding MH and further precautions; refer them to MHAUS. Fill out and send in the Adverse Metabolic Reaction to Anesthesia (AMRA) form (www.mhreg.org) and send a letter to the patient and her/his physician. Refer patient to the nearest Biopsy Center for follow-up.
- Trismus or Masseter Spasm with Succinylcholine
- Early sign of MH in many patients
- If limb muscle rigidity, begin treatment with dantrolene
- For emergent procedures, continue with non-triggering agents, evaluate and monitor the patient, and consider dantrolene treatment
- Follow CK and urine myoglobin for 36 hours.
- Check CK immediately and at 6 hour intervals until returning to normal. Observe for dark or cola colored urine. If present, liberalize fluid intake and test for myoglobin
- Observe in PACU or ICU for at least 12 hours
- If limb muscle rigidity, begin treatment with dantrolene
- For emergent procedures, continue with non-triggering agents, evaluate and monitor the patient, and consider dantrolene treatment
- Follow CK and urine myoglobin for 36 hours.
- Check CK immediately and at 6 hour intervals until returning to normal. Observe for dark or cola colored urine. If present, liberalize fluid intake and test for myoglobin
- Observe in PACU or ICU for at least 12 hours

CAUTION:

This protocol may not apply to all patients; alter for specific needs.

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**Some Articles**

**Review: Mitochondrial myopathies and anaesthesia**


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Summary

The mitochondrial myopathies consist of a heterogeneous group of disorders caused by structural and functional abnormalities in mitochondria leading to involvement of the nervous system and muscles as well as other organ systems. The peculiar genetic characteristics of mitochondrial DNA impart distinctive properties to these disorders. The pathophysiology is presented. The methods employed in making the correct diagnosis, the preoperative patient assessment and correction of metabolic dysfunctions and anaesthetic techniques used, are highlighted. The conditions are briefly reviewed and suggestions are made for the safe anaesthetic management of affected patients.

(Accepted October 2003)

Key Words: ANAESTHESIA, general, regional; MITOCHONDRIAL MYOPATHIES, MELAS syndrome, Kearns-Sayre syndrome, MERRF syndrome, Leigh disease.

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**Core Myopathies and Risk of Malignant Hyperthermia**

A & A October 2009 vol. 109 no. 4 1167-1173

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Abstract

In this article, we analyze myopathies with cores, for which an association to malignant hyperthermia (MH) has been suggested. We discuss the clinical features, the underlying genetic defects, subsequent effects on cellular calcium metabolism, and in vitro muscle responses to MH triggers. We describe in detail central core disease, multiminicore disease, and nemaline rod myopathy. We categorize the diseases according to the affected proteins and discuss the risk for MH, which is high or theoretically possible when the calcium-conducting proteins are affected.

Footnotes

Accepted for publication June 16, 2009.

W. Klingler and H. Rueffert are co-first authors.
Tetanus

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MANAGEMENT OF TETANUS

MCQ

1. Clostridium tetani
   a. is a Gram-positive coccus
   b. is commonly found in soil
   c. may be found in human faeces
   d. secretes harmful endotoxins
   e. spores are destroyed by boiling for 1 hour

2. Regarding the clinical features of tetanus,
   a. incubation period describes time from injury to first spasm
   b. incubation period may be as long as 30 days
   c. onset time describes time from first symptom to first spasm
   d. autonomic dysfunction is common
   e. laryngospasm may occur

3. In tetanus,
   a. involvement of the cranial nerves has a better prognosis
   b. neonatal disease commonly arises from the umbilicus
   c. neonatal tetanus is preventable by maternal vaccination
   d. neonatal tetanus carries a lower mortality
   e. catecholamine levels are often elevated
4. Differential diagnoses may include
   a. drug reaction
   b. hypocalcaemia
   c. strychnine poisoning
   d. sepsis
   e. encephalitis

5. Regarding the management of tetanus,
   a. muscle relaxants form the main treatment
   b. tetanus immunoglobulin is recommended
   c. oral metronidazole is the antibiotic of choice
   d. infection leads to immunity
   e. surgical debridement can be delayed for 12 hours to allow resuscitation

The answers can be found at end of article.

CASE REPORT

A 52-year-old woman was admitted to the surgical ward, having been assaulted three days previously. She had suffered a head injury and her conscious level had gradually reduced over the 24 hours prior to admission. Her Glasgow coma score on admission was 12/15 and she had an open wound on her scalp, which smelt offensive. She was admitted to the surgical ward but the consultant was called when she began to have seizures 6 hours after admission. On closer observation of the patient the consultant recognized these ‘seizures’ to be severe spasms of her back muscles. Her jaw was clenched closed, her neck was stiff, her GCS had fallen to 10/15 and she had a temperature of 38.7°C. Tetanus complicating severe head injury and scalp wound infection was diagnosed. The differential diagnosis of meningitis was excluded by microbiological CSF examination.

She was transferred to theatre for urgent debridement of the wound and managed on the Intensive Care Unit postoperatively. Tetanus immunoglobulin was not available from pharmacy and she was treatment with intravenous penicillin, flucloxacillin and metronidazole. She returned from theatre ventilated and was sedated with intermittent intravenous doses of 10mg diazepam and 50mg pethidine. The spasms were partially controlled on this regimen, but addition of nasogastric phenobarbitone achieved complete suppression of the spasms by the second postoperative day. She required ventilation for 11 days, having a tracheostomy inserted on the seventh day of her admission and required two further trips to theatre for debridement of the scalp wound. She was discharged to the ward on day 23, with the tracheostomy removed. She had a residual mild hemiparesis, but otherwise made a good recovery.
INTRODUCTION

Tetanus causes approximately 1 million deaths worldwide and remains endemic in the developing world. Approximately half of these deaths are in neonates and most occur in Africa and Asia. Immunization has dramatically reduced the number of cases in developed countries, with 12-15 cases per year reported in the UK (0.2 per million population).

Tetanus is caused by a gram-positive bacillus, Clostridium tetani, which is commonly found in soil, but may also be isolated from animal or human faeces. It is a motile, spore-forming, obligate anaerobe. Spores are not destroyed by boiling but are eliminated by autoclaving at 120°C for 15 minutes (at one atmosphere pressure). Tetanus is usually diagnosed clinically as the bacterium is rarely cultured.

PATHOPHYSIOLOGY

Under the anaerobic conditions found in infected or necrotic tissue, the bacillus secretes two toxins: tetanospasmin and tetanolysin.

Tetanolysin damages the surrounding viable tissue and optimizes conditions for bacterial multiplication.

Tetanospasmin causes the clinical syndrome of tetanus, by entering peripheral nerves and traveling via axonal retrograde transport to the central nervous system. Tetanospasmin disables release of neurotransmitter from presynaptic vesicles (particularly the inhibitory neurotransmitters GABA and glycine). The result is disinhibition of motor and autonomic neurons, causing rigidity, muscle spasms and autonomic dysfunction. A relative deficiency of synaptic acetylcholine (similar to that caused botulinum toxin) causes flaccid paralysis that is clinically mild in humans.

High toxin load results in diffusion of toxin via the blood to nerves throughout the body.

CLINICAL FEATURES

Tetanus usually follows a recognized injury, which may be trivial or occur indoors. Other routes of entry include burns, ulcers, gangrene, snakebites, septic abortion, childbirth, intramuscular/intravenous injections and surgery.

The incubation period (time from first injury to first symptom) averages 7-10 days (range 1-60 days), whilst the clinical onset time (time from first symptom to first spasm) varies between 1-7 days. Shorter incubation and onset times are associated with more severe disease. Muscle spasms and rigidity are predominant in the first week and reduce after 2-3 weeks. Autonomic disturbance usually starts several days after spasms, and persists for 1-2 weeks. Recovery from the illness occurs due to re-growth of axon terminals.

The clinical triad consists of muscle rigidity, spasms and autonomic dysfunction. Early symptoms are neck stiffness, sore throat and poor mouth opening. Increased muscle tone may affect agonist and antagonist muscle groups together, resembling a convulsion. Spasms may be spontaneous or triggered by visual, auditory or emotional stimuli and can be severe enough to cause fractures or avulse tendons. Pharyngeal and laryngeal spasms may lead to aspiration or airway obstruction. Continual spasms may lead to respiratory failure.
The most common form of tetanus (80%) is generalized tetanus, with muscles throughout the body affected. Muscles of the head and neck are usually affected first, giving rise to masseter spasm (trismus or ‘lockjaw’) and a typical facial expression (risus sardonicus). Neck stiffness and dysphagia are also common. Truncal rigidity with predominant extensor spasm may lead severe arching of the back during spasm, called opisthotonus.

Poor cough, inability to swallow, gastric stasis all increase the risk of aspiration. Respiratory failure continues to be a major cause of mortality in developing countries, whereas severe autonomic dysfunction causes most deaths in the developed world.

Autonomic dysfunction results from paroxysmal increases in sympathetic activity, with basal catecholamine levels rising ten-fold. This results in tachycardia, hypertension and pyrexia, with a hyperkinetic circulation, low/normal systemic vascular resistance and normal right and left sided cardiac filling pressures.

Other features include excessive salivation and sweating (may lead to dehydration), cardiomyopathy and myocardial infarction. Gastric stasis, ileus, diarrhea and high output renal failure may also be related to the autonomic disturbance. The effects on the parasympathetic system are less clear.

Localized tetanus is seen with lower toxin loads or peripheral injuries. Mortality is much lower in this group unless the cranial nerves are involved (cephalic tetanus).

Neonatal tetanus, with a particularly high mortality, is rare in developed countries but common in the developing world. Neonates present within a week of birth with fever, vomiting and ‘convulsions’. Differential diagnoses include sepsis and meningitis. The cause is usually poor umbilical hygiene and the disease is preventable by maternal vaccination, even when administered during pregnancy.

ABLETT CLASSIFICATION OF SEVERITY

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (mild)</td>
<td>Mild trismus, general spasticity, no respiratory embarrassment, no spasms, no dysphagia</td>
</tr>
<tr>
<td>II (moderate)</td>
<td>Moderate trismus, rigidity, short spasms, mild dysphagia, moderate respiratory involvement, respiratory rate &gt; 30, mild dysphagia</td>
</tr>
<tr>
<td>III (severe)</td>
<td>Severe trismus, generalized spasticity, prolonged spasms, respiratory rate &gt; 40, severe dysphagia, apnoeic spells, pulse &gt; 120</td>
</tr>
<tr>
<td>IV (very severe)</td>
<td>Grade 3 plus severe autonomic disturbances involving the cardiovascular system</td>
</tr>
</tbody>
</table>

MANAGEMENT OF TETANUS

Three principles apply:

1. Prevent further toxin release.

   ■ Organise early surgical debridement of wounds, repeated as necessary.

   ■ Give antibiotics: Metronidazole 500mg IV 8 hourly is the antibiotic of choice and benzylpenicillin 1MU IV 6 hourly is an alternative (but is a GABA antagonist). Erythromycin, tetracycline, chloramphenicol and clindamycin are acceptable choices. Remember that heavily contaminated wounds need additional antibiotic cover for other bacteria.
2. Neutralise toxin present in the body outside the CNS.
   ■ Give human tetanus immunoglobulin (Ig) 150 units/kg IM into different sites within 24 hours of diagnosis. An intravenous preparation may be available in some centres (5000-10000iu). An alternative, where human Ig is unavailable, is to use 1500-10000 units anti-tetanus horse serum IM – anaphylaxis is a risk with this preparation and sensitivity tests are recommended.

3. Minimise the effects of the toxin already in the CNS.
   ■ Control rigidity and spasms with sedation, give respiratory support where necessary and control autonomic dysfunction.

SPECIFIC TREATMENT

Intensive care management is desirable, especially if respiratory and/or autonomic features are present.

Sedation

Sedation and avoidance of unnecessary stimulation is the primary treatment for controlling spasms and autonomic dysfunction. This is usually achieved using benzodiazepines (GABA agonists), such as diazepam or midazolam (both 0.1mg/kg IV or IM 1 - 4 hourly). Midazolam can be given as an intravenous infusion (2 -10 mg/hr). Opioids, such as morphine (0.1 mg/kg IV/IM 2-6 hourly) or pethidine (1 mg/kg IV/IM 2-6 hourly) sedate well in combination with benzodiazepines and morphine can be infused intravenously (1 – 10 mg/hr). Where available, propofol is replacing these drugs as it has less accumulation. Anticonvulsants, particularly phenobarbitone (up to 200 mg IV or PO/NG 12-hourly), and phenothiazines (usually chlorpromazine) may be added as an adjunctive sedative. Heavy sedation may be required, necessitating close monitoring of the need for formal airway control and mechanical ventilation.

Muscle relaxation is indicated where sedation alone is inadequate. Vecuronium (0.1 mg/kg IV as needed) or atracurium (0.5 mg/kg IV) are appropriate. Pancuronium may worsen autonomic instability by inhibiting catecholamine reuptake. Prolonged usage of aminosteroid muscle relaxants has been associated with critical illness neuromyopathy and myopathy.

The use of other drugs, such as dantrolene and intrathecal baclofen (a GABA–B agonist) is unproven.

Treatment of autonomic dysfunction

Fluid loading is a useful in minimizing autonomic instability.

Magnesium sulphate is an effective adjunct in relaxation, sedation and controlling the autonomic disturbance in tetanus. It is a pre-synaptic neuromuscular blocker, reduces catecholamine release from nerves and the adrenal medulla, and reduces receptor responsiveness to released catecholamines. A loading dose of 5g should be given over 20 minutes, followed by an intravenous infusion of 2g/hr. The dose may be increased by up to 0.5 g/hr until spasms are relieved, or the patellar reflex disappears. If infusion devices are unavailable, give 2.5g IV every 2 hours, titrating the frequency of administration to symptoms. By antagonizing calcium metabolism, magnesium causes weakness and paralysis in overdose. Monitoring of serum magnesium levels is important to prevent
the normal serum magnesium level is 0.7 – 1.0 mmol/l, whilst an acceptable therapeutic level is 2 - 3.5 mmol/l.

Beta-blockers (particularly long-acting agents) have been implicated in sudden cardiac death and are not recommended. The short-acting beta-blocker esmolol may be used to manage tachycardia and hypertension, where invasive monitoring is available.

The alpha-2 agonist, clonidine inhibits the release of norepinephrine from prejunctional nerve endings and may have a useful role.

GENERAL MANAGEMENT

Enteral feeding should be started early in order to prevent malnutrition caused by inability to swallow, increased metabolic rate, autonomic gastrointestinal dysfunction and muscular activity.

For patients needing artificial ventilation, steps should be taken to prevent ventilator-associated pneumonia, such as nursing in the semi-recumbent position. Prevention of respiratory complications by chest physiotherapy, mouth care and regular tracheal suctioning may be necessary due to increased secretions. Where ventilation is likely to be required for more than 8-10 days consider early tracheostomy. Adequate sedation for all procedures should minimize autonomic disturbance.

As with all patients with long-term critical illness, measures to minimize the risks of thromboembolism, gastrointestinal haemorrhage and pressure sores should be implemented. Psychological support for both the patient and relatives should be provided.

OUTCOME AND PREVENTION

Mortality varies greatly amongst units and is about 5-10 % in mild-moderate cases but rises significantly where ventilation is required, particularly in developing countries. Autonomic dysfunction and hospital-acquired infections are common causes of death.

All patients with tetanus require active immunization with tetanus toxoid, as infection does not confer immunity. In the UK, a course of five injections is recommended: a primary course at the age of 2, 3, 4 months and boosters at 5 and 15 years. In the USA, 10 yearly boosters are still recommended. Current UK guidelines for the management of wounds may be found at http://www.dh.gov.uk/assetRoot/04/11/78/31/04117831.pdf

FURTHER READING


ANSWERS TO MCQ

1. a, d and e are false. Tetanus is a bacillus. Exotoxins are secreted. Spores are destroyed by autoclaving, not boiling.

2. a is false. See section on Clinical Features.

3. a and d are false. Cephalic tetanus has a poor prognosis. Neonatal tetanus has a high mortality.

4. All are true. The differential diagnoses are important to know since the diagnosis of tetanus is based on clinical features.

5. a, c, d and e are false. Sedatives are the mainstay of treatment nowadays. IV not oral metronidazole is the drug of choice and infection does not confer immunity (vaccination is still required). Surgical debridement should proceed as soon as possible.

ZF Notes: A useful overview. Perhaps emphasise Magnesium more in South African setting. PEG is useful when doing tracheostomy as helps minimise oropharyngeal stimulation
The use of neuromuscular blocking agents in patients with neuromuscular disorders

Shields M, McCaffrey J, Mirakhur RK.

Many of the differences in pharmacokinetics and pharmacodynamics observed when using neuromuscular blocking drugs in patients with disorders of the nervous or muscular systems can be explained in terms of an alteration in the distribution of nicotinic acetylcholine receptors (nAChR). In health these receptors are mainly confined to the neuromuscular junction (NMJ) but in disease states they can spread out from the NMJ along the length of the muscle fibres.

In health the main type of nAChR expressed at the neuromuscular junction is the adult type with 2 α (alpha), 1 β (beta), 1 δ (delta) and 1 ε (epsilon) subunits. The expression of this receptor can be up or down regulated in various disease states. Other sub-types of nAChRs may also be expressed. This mainly includes the foetal nAChR that has a γ (gamma) subunit in place of the ε subunit. This foetal sub-type is the most predominant nAChR receptor at the NMJ in-utero but is replaced by the mature adult receptor within the first few days of life. The ability to synthesize foetal nAChR receptor is retained by the cells and a large increase in the messenger RNA required to make such receptors can be found in cells at the NMJ within days of the onset of conditions such as a neural insult, burns or immobilisation.

**Functional differences between the ‘Adult’ and ‘Foetal’ acetylcholine receptors**

* Adult receptors open for a shorter time compared with the foetal receptor.
* Adult receptors have a higher conductance of Na+, K+ and Ca2+.

These two receptors behave differently in the presence of neuromuscular blocking agents.

**Time to complete block**

Foetal nAChR receptors are resistant to non-depolarising NMBAs and more sensitive to succinylcholine.

**Potassium release**

Once depolarised, foetal type receptors open for longer. As a result more potassium escapes from the cells into the extra-cellular fluids and ultimately may lead a rise in plasma potassium levels. This may precipitate a cardiac arrest.

**The differences in pharmacokinetics and pharmacodynamics noted with Ageing**

- Decrease in muscle mass with age
- Decreased total body water, GFR, liver mass.
- Delayed onset of NMBAs
- Prolonged duration of action (may be less so with agents that have non-organ dependent degradation)
Reversal

Duration of action of anticholinesterases is prolonged.

Higher doses of anticholinesterases may be required

**Alteration in pharmacodynamics in patients with neuromuscular disorders**

The neuromuscular disorders can be divided into two groups, those conditions that are associated with an up-regulation of acetylcholine receptors and those with a down-regulation of the receptors although there are other methods for their classification such as pre-junctional, junctional and post-junctional conditions.

Table 1: Conditions Associated with Up- and Down-regulation of Acetylcholine Receptors

<table>
<thead>
<tr>
<th>NACHR Up-regulation</th>
<th>NACHR Down-regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord injury</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Stroke</td>
<td>Anticholinesterase poisoning</td>
</tr>
<tr>
<td>Burns</td>
<td>Organophosphate poisoning</td>
</tr>
<tr>
<td>Prolonged immobility</td>
<td></td>
</tr>
<tr>
<td>Prolonged exposure to neuromuscular blockers</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Guillian-Barré syndrome</td>
<td></td>
</tr>
</tbody>
</table>

**Up-regulation**

In the conditions listed in table 1 there is a spread of the newly formed foetal type nACHR receptors along the full length of the muscle (extrajunctional sites). This change may be noted as early as 24-48 hours after injury. In these conditions there is also a decrease in the total number of post-synaptic Adult type receptors. The overall effect of these changes is a resistance to non-depolarising NMBAs with a slower than expected onset time. There may also be large rises in serum potassium levels.

**Stroke and spinal cord injury**

In patients that have suffered a stroke it may be advisable to avoid succinylcholine after the first 24 hours to avoid hyperkalaemia and its associated cardiac arrhythmias. Succinylcholine may cause hyperkalaemia for many months after such an insult.

**Immobility**

There is a slower development of extrajunctional adult and foetal receptors in patients that are confined to bed such as those in the intensive care unit. In such patients it may be best to avoid succinylcholine after 24-48 hours of total body immobilisation.
Demyelination disorders and Motor Neurone Disease

There are different considerations required when using NMBAs depending on the clinical picture of the disease. In patients with chronic muscle weakness there is likely to be up-regulation of the nAChR receptors. In this scenario succinylcholine should be avoided and there may be resistance to non-depolarising NMBAs. On the other hand patients may have a greatly reduced muscle mass and in turn they may exhibit an increased sensitivity to non-depolarising NMBAs followed by a prolonged duration of action.

Guillain-Barré Syndrome

Again, due to a proliferation of nAChR receptors succinylcholine is contraindicated. There may also be an increased sensitivity to non-depolarising NMBAs.

Charcot-Marie-Tooth Syndrome

There is some sensitivity to non-depolarising NMBAs as a result of the loss of muscle units. Succinylcholine has been used safely in this condition.

Muscular Dystrophies

Post-synaptic receptors are mixed foetal and adult types; therefore there is a high risk of hyperkalaemia if succinylcholine is given to these patients. Succinylcholine should also be avoided due to the increased risk of malignant hyperpyrexia in muscular dystrophies. There is increased sensitivity to, and prolonged duration of action of non-depolarising NMBAs despite the up-regulation of post-synaptic foetal nAChR receptors.

Dystrophica Myotonica

Patients with Dystrophica Myotonica show an increased sensitivity to non-depolarising NMBAs. Succinylcholine may cause extreme muscle rigidity which may require the administration of non-depolarising NMBAs in order to overcome it.

The administration of anti-cholinesterases to patients with Dystrophica Myotonica may result in precipitation of myotonia due to an increased sensitivity to the stimulatory effect of acetylcholine.

Several patients with Dystrophica Myotonica have been given succinylcholine with no increase in plasma potassium levels but there are also reported deaths in such patients given succinylcholine with no verification of hyperkalaemia as the cause and the deaths may have been due to underlying cardiac abnormalities. Overall succinylcholine is not recommended in this group of patients.

Burns

There is a proliferation in the number of foetal nAChR receptors in the area immediately beneath the burn and in areas distant to the burn as early as 72 hours after a major thermal injury. Succinylcholine should therefore be avoided after the first 48 hours in such patients in order to prevent fatal hyperkalaemia. Hyperkalaemic arrests have been reported in patients with as little as 8-9% burns after they received succinylcholine.
Down-regulation

**Myasthenia Gravis**

Myasthenia Gravis (MG) is an autoimmune disease with auto-antibodies binding to the extracellular portion of the nAChR receptor resulting in their destruction either by focal lysis of the post-synaptic membrane or by internalisation and degradation of the receptors. This results in a decrease in the numbers of nAChR receptors by 70% or more, leading to impaired neuromuscular transmission and muscle weakness. The antibodies do not react with the nicotinic receptor subtypes present in autonomic nerves or within the central nervous system.

The decreased in number of nAChR receptors may cause a decreased sensitivity to succinylcholine although any action may be potentiated due to a decreased plasma cholinesterase activity caused by pre-operative anti-cholinesterases or plasmapheresis.

Patients with MG may show a marked sensitivity to non-depolarising NMBAs due to the lower numbers of nAChR receptors although with careful titration and neuromuscular monitoring they have been used safely in cases.

**Further reading**


Maclennan N, HeimbnAChR DM, Cullen BF. Anesthesia for major thermal injury. Anesthesiology 1998; 89: 49-70


**ZF Notes:**

A revision overview definitely add detailed article on:

- Myaesthenia gravis
- Guillain Barre
- Organophosphate poisoning

Motor neuron disease is topical at the moment

An upregulation disease with hyperkalemia as an issue and difficult airway think Steven Hawking
Anaesthesia Tutorial of the Week (TOTW)

Neuromuscular disorders and anaesthesia (126)

Ed. Richard Hughes All tutorials, General Anaesthesia, Intensive Care Medicine

23RD MARCH 2009

Dr. Nicola Ross, Leeds General Infirmary, UK

Dr. Sarah Marsh, Leeds General Infirmary, UK

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INTRODUCTION

The neuromuscular disorders are a heterogeneous group of diseases effecting skeletal muscle via abnormalities of the motor nerves, neuromuscular junction, cellular matrix, ion channels and metabolic derangements. They are often grouped together in relation to anaesthesia due to common considerations in the perioperative period. An understanding of these disorders is especially helpful in paediatrics where the first presentation of a subclinical myopathy may be under general anaesthesia. Infants presenting for repair of clubfoot, for example, have a high incidence of myopathic changes on muscle biopsy, but may be asymptomatic.

This review will discuss the broad implications of anaesthesia for patients with neuromuscular disease (NMD) and then visit the six main categories of NMD to highlight any specific issues. PLEASE NOTE: Myaesthenia gravis is not discussed in depth in this tutorial as it is covered in detail in aToTW 122

MULTIPLE CHOICE QUESTIONS (True/false; Answers are at the end.)

Question 1  Common associations with neuromuscular disorders include:

A  obstructed sleep apnoea
B  autonomic dysfunction
C  reduced creatinine kinase levels
D  hypothermia

Question 2  Myotonic spasms may be precipitated by:

A  suxamethonium
B  change in osmolality
C  anticholinesterases
D  opioids
Question 3  At preassessment:

A  premedication with benzodiazepines should be avoided due to respiratory depression
B  all patients should have a bed in either HDU or ITU
C  an ECG is necessary
D  a baseline creatinine kinase may be useful

Question 4  When anaesthetising patients with neuromuscular disorders:

A  suxamethonium should always be avoided
B  peripheral nerve stimulators precipitate muscle spasm and should be avoided
C  inhalational induction is the technique of choice
D  masseter spasm is an indication for dantrolene

PRE-ASSESSMENT

Table 1 categorises the NMD into 6 groups and clearly with such varied pathophysiologies one anaesthetic technique does not fit all these conditions.

Table 1. Classification of Neuromuscular disease

<table>
<thead>
<tr>
<th>Motor Neurone Disease</th>
<th>Amyotrophic Lateral Sclerosis, Spinal Muscular Atrophy, Spinal Bulbar Muscular Atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Neuropathies</td>
<td>Charcot-Marie Tooth Disease, Friedreich’s Ataxia, Dejerine-Sottas Disease</td>
</tr>
<tr>
<td>Disorders of Neuromuscular Transmission</td>
<td>Myasthenia Gravis, Eton-Lambert Syndrome, Congenital Myasthenic Syndrome</td>
</tr>
<tr>
<td>Muscular Dystrophies</td>
<td>Duchenne, Becker, Limb-Girdle, Fascioscapulohumeral, Emery-Dreifuss, Oculopharyngeal, Distal, Congenital and Myotonic Dystrophy</td>
</tr>
<tr>
<td>Metabolic and Mitochondrial Myopathies</td>
<td>Lactate Dehydrogenase Deficiency, Carnitine Deficiency, Mitochondrial Myopathy, Phosphofructokinase Deficiency, Acid Maltnase Deficiency, Phosphorylase Deficiency, Debrancher Enzyme Deficiency</td>
</tr>
<tr>
<td>Non-Dystrophic Myotonias</td>
<td>Myotonia Congenita, Paramyotonia Congenita, Periodic paralysis, Central Core Disease, Myotonia fluctuans</td>
</tr>
</tbody>
</table>

However, some basic principles can be applied to any anaesthetist faced with the challenge of anaesthetising these patients:

• Precise diagnosis. Not always possible as occasionally anaesthesia is required for diagnosis.
• Full discussion with the patient and family members regarding potential risks and benefits of all treatment options
• Thorough preassessment of function and associated conditions
• Anaesthetic strategies and preparation

• Planning post-operative care

It is important to get full functional assessment. Many patients presenting for surgery may appear deceptively healthy having learnt to function within their capabilities. Cardiorespiratory reserve may not be tested with a limited exercise tolerance. Many NMD are associated with cardiac, respiratory, renal and metabolic disorders and these must be actively sought.

**Systems affected in Neuromuscular Disease**

**Respiratory**

• Dysmorphic features suggesting a difficult airway

• Obstructive sleep apnoea

• Restrictive lung disease from scoliosis

• Respiratory insufficiency secondary to respiratory and pharyngeal muscle involvement

**Cardiovascular**

• Autonomic dysfunction

• Cardiomyopathy

• Conduction abnormalities due to abnormal conducting tissue or metabolic derangements.

**Metabolic**

• Na, K, Mg, Cl, Ca may be deranged

• Sustained muscle contraction may cause rhabdomyolysis and a pre-operative baseline urine myoglobin is useful to ascertain postoperatively if there has been any increase.

**Investigations**

Arterial blood gases, pulmonary function tests, chest X-ray ECG, and an echocardiogram are all extremely helpful in this population.

**Premedication**

Many of the commonly used premedicating drugs should be used with caution in patients with NMD. Anxiolytic agents can be advantageous in those patients in whom crying and fear can precipitate muscle spasm due to release of catecholamines. If administered, agents causing central respiratory depression or reduce respiratory muscle tone should be given at a reduced dose with close, continuous monitoring.
PERIOPERATIVE MANAGEMENT

The aim when anaesthetising patients with NMD, is a stress free anaesthetic. Increased neuromuscular and catecholamine activity can trigger myotonic reactions and decompensate a dysfunctional cardiorespiratory system.

Monitoring

Oxygen saturation, NIBP, ECG, capnography, minute ventilation, peripheral nerve stimulator and temperature monitoring are all mandatory. Invasive blood pressure monitoring is invaluable in those with an element of autonomic dysfunction and enables regular blood gas analysis for patients with electrolyte disturbances.

Temperature

Patients with NMD are susceptible to both hyperthermia and hypothermia. A predisposition to hypothermia is due to the decrease in heat production by dystrophic or atrophic muscle. However, hyperthermia can also occur due to increased muscle activity as seen in myotonias. There are many well-documented, undesirable consequences of hypothermia but those specific to NMD include triggering of muscle spasms, increased sensitivity to muscle relaxants and aggravation of rhabdomyolysis.

Careful monitoring of temperature, both peripheral and core, and the use of forced air blankets, fluid warmers and overhead heating can minimise these complications.

Regional techniques

After a thorough neurological assessment has been documented, regional anaesthesia may be invaluable in this patient population in whom respiratory depression with opiates is disadvantageous. In rapidly progressive disorders however, many will avoid the use of regional techniques as complications of the procedure may be difficult to distinguish from progression of the disease process. In those with cardiovascular complications and autonomic dysfunction, severe hypotension may result from neuroaxial blockade.

Intravenous or Volatile Agents

Intravenous anaesthetic agents can facilitate intubation without the use of neuromuscular blocking drugs and the use of TIVA with short acting agents and opioids can accelerate recovery and reduce postoperative respiratory failure. Some patients with NMD are very sensitive to these drugs and prolonged apnoea and respiratory depression may occur.

Volatile anaesthetics have a cardiodepressant effect by decreasing release of calcium from the sarcoplasmic reticulum, reducing availability of calcium in the myoplasm and decreasing the responsiveness of the contractile filaments to calcium. The sensitisation of the myocardium to catecholamines caused by halothane can precipitate arrhythmias as can the prolonged QT interval caused by isoflurane. These agents have been used widely but should be used with caution.
Neuromuscular blocking drugs

The effect of neuromuscular blocking agents depends on the disease process but, on the whole, suxamethonium should be avoided in all NMD except myasthenia gravis, in whom the dose may need to be doubled. The use of non-depolarising muscle relaxants can often be avoided by judicious use of intravenous induction agents. However, if required, it should be given in reduced doses (10–20%) due to increased sensitivity. Atracurium is a popular choice due to its spontaneous Hoffman degradation but the key to muscular blockade is careful titration and close monitoring with a peripheral nerve stimulator (PNS). Neuromuscular block should be checked with a PNS before administration of any muscular relaxants.

COMPLICATIONS

Rhabdomyolysis

Depolarising muscle relaxants can lead to rhabdomyolysis and hyperkalaemia in almost all neuromuscular diseases, especially in denervated, dystrophic and metabolically altered muscle. Extrajunctional or foetal isoforms of the acetylcholine receptor lead to widespread membrane depolarisation, hyperkalaemia, rhabdomyolysis and potentially cardiac arrest. Sustained release of calcium from the sarcoplasmic reticulum can also cause hypermetabolism and muscle cell damage and this may be potentiated by volatile anaesthetic agents. Myotonias may spontaneously induce rhabdomyolysis due to sustained muscle contraction and it is wise to measure serum creatinine kinase (CK) and myoglobinuria preoperatively if this is suspected. Features consistent with rhabdomyolysis are: frothy urine, metabolic acidosis, hyperkalaemia, myoglobinuria, CK > 10,000 U/l.

Treatment includes:

- cessation of potentially causative drugs
- correction of life threatening hyperkalaemia
- aggressive volume resuscitation to maintain a urine output > 1ml/kg/hr
- urine alkalisation with sodium bicarbonate
- monitoring of liver enzymes, coagulation, blood gases, electrolytes and glucose.
- occasionally Dantrolene may be helpful in hypermetabolism, especially if hyperthermia is present

Respiratory Complications

Respiratory failure is the most common cause of death in patients with NMD. Complications are related to:

- involvement of bulbar muscles causing repeated aspiration and chronic insufficiency
- respiratory and pharyngeal muscle involvement
• higher incidence of OSA in affected children
• progressive spinal deformities causing restrictive defects

Pulmonary function tests and arterial blood gases may be very useful preoperatively to assess the level of dysfunction. Administration of respiratory depressants in the perioperative period can lead to acute decompensation and respiratory insufficiency in recovery is not uncommon. Premature extubation must be avoided, especially in those with a difficult airway secondary to anatomical abnormalities. Intensive care may be required postoperatively to allow time for respiratory depressants to be eliminated.

A careful balance between prolonged postoperative intubation to protect the airway and the inherent loss of respiratory muscle tone during this period is difficult. Effective postoperative physiotherapy and CPAP are invaluable tools in this group with low lung volumes and in whom avoidance of atelectasis, poor cough and respiratory infection are paramount.

Cardiac Complications

Cardiomyopathy and cardiac conduction abnormalities are common in many neuromuscular disorders, with death secondary to cardiac arrest being the second most common cause of death in this patient group. Dysfunction is often silent as the patient often has a very limited exercise tolerance. Identification of conduction abnormalities or limited reserve may warrant preoperative treatment or alteration of the anaesthetic plan.

Perioperative stresses or anaesthetic agents may precipitate cardiac dysrhythmias or cardiac failure. Echocardiograms are helpful but awareness of unpredictable responses to fluid boluses, vasopressors and ionotropes are still possible and careful titration of these drugs is required.

Autonomic Dysfunction

Autonomic dysfunction is not uncommon in NMD and can be responsible for severe hypotension on induction or after regional anaesthesia. Gastric stasis may also present as aspiration if not anticipated. Diagnosis may be difficult but the possibility of autonomic impairment must be suspected and sympathomimetic drugs available. Response to these agents may be exaggerated due to sensitisation of alpha and beta adrenoreceptors.

Myotonic Reactions

Myotonic contraction is caused by repetitive action potentials leading to a permanent sodium influx or reduced chloride efflux across the muscle membrane. This then renders the membrane hyperexcitable. Myotonic reactions can be caused by:

• suxamethonium
• anticholinesterases
• opioids
• alterations in temperature
• acidosis
• shivering
• change in osmolality

Preventative measures for myotonias may include maintaining a serum potassium of 4.0 – 4.5 mmol/l and a diet generous in complex carbohydrates to lessen stiffness. In hyperkalaemic periodic paralysis thiazides, acetazolamide and sodium restriction may be therapeutic.

In the event of a myotonic reaction the precipitant should be sought and corrected. Drugs that cause a use-dependent block of sodium channels (class one antiarrhythmics) are the treatment of choice: mexiletine, tocainide.

Masseter spasm is an example of a common myotonic reaction that can occur in patients with NMD. Spasm of muscles may be caused by increased electrical stimulation as in myotonia, by uncontrolled release of calcium from the sarcoplasmic reticulum as in Malignant Hyperthermia (MH) or impaired reuptake of calcium as in Brody’s Disease. Although masseter spasm does not always herald the onset of MH, all children that present with this sign should be treated as if a MH crises may follow.

**Malignant hyperthermia**

There has long been a hot debate as to whether patients with NMD have an increased susceptibility to MH. Some suggest that just three myopathies; Evans myopathy, King Denborough syndrome and Central Core Disease are predisposed to MH, while others believe all myopathies are at increased risk. It is possible that the tests used in the diagnosis of MH may be affected by the electrical after-activity in myotonia, and increased resting myoplasmic calcium in myotonic dystrophy interfering with the diagnosis. However, there have been cases of increased muscle injury and metabolism after prolonged inhalational anaesthesia in patients with myopathy and it is therefore advisable to have a low threshold for suspicion of MH. Irrespective of the pathophysiology of the muscle injury, close monitoring as described earlier is recommended in all patients with NMD and prompt treatment of electrolyte disturbances, acidosis, hyperthermia and myoglobinuria is essential. Dantrolene has been used for hypermetabolism not associated with MH to good effect.

**Postoperative Care**

Extubation should not occur until the patient is able to maintain adequate tidal volumes and airway reflexes have returned, as respiratory failure and aspiration are common. Post-operatively careful monitoring must be continued and there is a low threshold to manage these patients in a high dependency or intensive care environment.

Hypoxia, hyperkalaemia, rhabdomyolysis, electrolyte disturbance, hypothermia can all have catastrophic consequences in the post-operative period and should be monitored closely. A urine dip for myoglobin or serum CK may be sent to assess level of muscle injury.

**SPECIAL CONSIDERATIONS**
**Motor Neurone Disease**

Motor Neurone Disease (MND) is a degenerative impairment of the motor neurones. It is most commonly sporadic, but can also be hereditary or infectious in origin. MND can affect the lower motor neurones, upper motor neurones or both. The result is denervation of the skeletal muscle leading to spasticity or atrophy depending on the location of the abnormality.

The main problems for the anaesthetist involve respiratory insufficiency, poor cough and bulbar dysfunction leading to aspiration. Over-expression of the extra-junctional or foetal acetylcholine receptor can then occur over the surface of skeletal muscle resulting in life threatening hyperkalaemia if suxamethonium is used. There may also be increased sensitivity to non-depolarising muscle relaxants.

Baclofen, diazepam and dantrolene have all been used perioperatively to control spasticity. Baclofen should not be withdrawn abruptly as it may precipitate a MH-like crisis.

**Peripheral Neuropathies**

These are an extremely diverse group of NMD and may be associated with a number of conditions such as diabetes mellitus, autoimmune disorders such as Guillain Barre, critical illness, toxic substances, infections and hereditary disease. Characterised by flaccid paralysis, sensory dysfunction and spread of symptoms as in polyneuropathy, a precise diagnosis is the key to planning an anaesthetic in this group.

Cardiac and autonomic dysfunction is common in peripheral neuropathy and cardiovascular lability may be augmented by the use of cardiodepressant anaesthetic agents. A higher degree of atrio-ventricular blocks may require temporary pacemaker insertion perioperatively. Specific associations in this group include the high sensitivity to thiopentone in Charcot-Marie-Tooth-Syndrome and the high incidence of cardiomyopathy in Friedreich’s Ataxia.

Due to the progressive nature of these disorders it may be difficult to distinguish the natural manifestation of the disorder from a complication of regional anaesthesia and for this reason some anaesthetists will avoid regional blocks in some of these patients. Meticulous documentation of preoperative disability and discussion with the patient is mandatory if a regional technique is used.

**Disorders of Neuromuscular Transmission**

Myasthenia Gravis is the subject of another TOTW and will not be discussed at length here. Suffice to say that uniquely among the NMD, Myasthenia patients can receive suxamethonium, and may in fact need up to double the normal dosage. However, the sensitivity of the motor end plate to non-depolarising agents is elevated. Volatile anaesthetic agents also appear to be safe.

Eaton Lambert Syndrome, however, exhibits the more familiar reaction to muscle relaxants and the dosage of depolarising and non-depolarising agents should be reduced. Drugs reducing neuromuscular transmission such as antibiotics and beta-blockers may enhance muscle weakness and should be avoided.
Muscular Dystrophies

Myotonic disorders

There are three syndromes: Myotonic Dystrophy, Myotonic Congenita and paramyotonica. The most common is Myotonic Dystrophy which is a disorder of chloride conductance characterised by incomplete muscle relaxation; myotonia. Extramuscular features include cardiomyopathy, conduction abnormalities, restrictive lung disease, OSA, delayed gastric emptying, dysphagia, hypothyroidism, and diabetes mellitus.

Muscular Dystrophies

Muscular dystrophies are a group of progressive genetically determined degenerative myopathies. There are several different types, the most commonly known being Duchennes muscular dystrophy.

The basis of the dystrophies is an abnormality (as in Becker Muscular Dystrophy (BMD)) or absence (as in Duchenne Muscular Dystrophy (DMD)) of the dystrophin gene, leading to a progressive deterioration of the muscle. Dystrophin is a protein that conducts the force of muscle contraction by the anchoring the cytoskeleton to the extracellular matrix. It is also involved in cellular signalling.

Scrupulous attention must be paid to functional assessment in all these patients as respiratory and cardiovascular symptoms correlate poorly with muscle symptoms. There are commonly intra-atrial conduction abnormalities in patients with disorders of dystrophin with 90% have an abnormal ECG. By the age of 14, around one third of patients with Duchenne Muscular Dystrophy have cardiomyopathy. Cardiac arrhythmias may require a temporary pacemaker perioperatively.

Respiratory insufficiency due to weakness of the respiratory muscles is aggravated by the hypersensitivity to respiratory depressant drugs. Fascioscapulohumeral dystrophy affects the accessory muscles of ventilation significantly decreasing vital capacity. Hypoventilation can also be a feature of Limb Girdle Dystrophy where the diaphragm may be affected. Some patients have also shown a reduced compensation to hypoxia and hypercapnia.

Smooth muscle involvement results in dysmotility of the stomach and oesophagus increasing the risk of aspiration. Disturbed glucose metabolism is also common.

In DMD there is over-expression of extrajunctional acetylcholine receptors that can lead to hyperkalaemia and rhabdomyolysis if suxamethonium is used. Similarly anticholinesterases are not recommended due to the potential to causes severe hyperkalaemia. Inhalational anaesthetic agents have also been implicated as a cause of rhabdomyolysis and malignant hyperthermia-like reactions.

Smooth muscle and platelet dysfunction are suggested by some, to cause increased blood loss. Hypovolaemia is poorly tolerated due to stiff myocardium that compensates with an increased heart rate and not increased force of contraction. Attention to perioperative volume status is important and may necessitate the use of invasive monitoring in prolonged procedures and intensive care postoperatively.

Female carriers of mutations to the dystrophin gene show signs of mild myopathic changes and cardiomyopathy and should be treated with caution.
**Metabolic and Mitochondrial Myopathies**

The pathophysiologies behind the multiple metabolic and mitochondrial myopathies are manifold. In those patients with metabolic disorders, muscle metabolism should be supported by the administration of substrates depending on the disorder such as glucose or amino acids. Aggressive metabolic monitoring in the perioperative period is essential and the generic considerations for all NMD should be applied.

- Acid maltase deficiencies can cause respiratory insufficiency, aspiration pneumonia, pulmonary hypertension, macroglossia, cardiomegally and hepatomegally.
- Lipid storage myopathies are susceptible to hypoglycaemia, acidosis, rhabdomyolysis and cardiac failure.

Mitochondrial myopathies are a similarly diverse group. Most anaesthetic drugs have a depressant effect on the mitochondria and all should be used with care. All patients with a mitochondrial myopathy should have tight glycaemic control in the perioperative period to avoid lactic acidosis. Suxamethonium should be avoided and atracurium appears to be safe at low doses.

Risk of third degree heart block is such that preoperative pacemaker implantation may be advisable and external pacemakers should be available in the theatre. Some mitochondrial myopathies are associated with seizures and require anti-convulsant therapy.

**Non-Dystrophic Myotonias and Periodic Paralyses**

As with other myotonic conditions depolarizing muscle relaxants are contraindicated. Inhalational or intravenous induction with thiopentone are both acceptable followed by non-depolarising neuromuscular agent. Reversal with acetylcholinesterases should be avoided due to the danger of triggering muscle spasms in patients with myotonic disease. Preoperative stressors and postoperative shivering should also be avoided.

Paramyotonia Congenital and Hyperkalaemic Periodic Paralysis require meticulous attention to avoid hypoglycaemia, which can cause hyperkalaemia and precipitate paralysis. On the contrary, hyperglycaemia, release of catecholamines, fluid infusions and mild hypothermia can all cause hypokalaemia and paralysis in Hypokalaemic Periodic Paralysis.

**ZF Comments:**

A useful review classic mistake of calling for “adequate tidal volume” before extubation. Adequate tidal volume is never enough and one needs to look at VC and MIPs and MEPs. After assessment and successful extubation always talk about good observation and a readiness to reintubate and support.
MCQ Answers

Question 1
A  T
B  T
C  F  (raised)
D  T  (decreased metabolic rate due to muscle atrophy)

Question 2
A  T
B  T
C  T
D  T

Question 3
A  F  (BDZ can be useful with adequate monitoring)
B  F  (HDU or ITU is not mandatory)
C  T  (cardiac disease is common)
D  T  (allows a more informed assessment of a raised postoperative level)

Question 4
A  F  (can be used in myasthenia)
B  F  (PNS are invaluable for guiding muscle relaxant dosage)
C  F  (induction technique should be weighed up for each individual patient)
D  F  (suspicion of MH with masseter spasm but dantrolene not automatically indicated)

REFERENCES

