Neuromuscular disorders and anaesthesia. Part 2: specific neuromuscular disorders

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Key points
Whilst there are common anaesthetic techniques used for patients with neuromuscular disorders, knowledge of each disease process is vital for optimum management.
Neuromuscular disease can be divided into hereditary and acquired disorders.
Multiple anatomical sites can be affected by neuromuscular disease including pre-junctional, the neuromuscular junction, and post-junctional locations.
Duchenne muscular dystrophy is the most common childhood neuromuscular disorder.
Thorough preoperative assessment and perioperative planning is essential to prevent morbidity and mortality.

Neuromuscular disorders are a heterogeneous group of diseases that share a number of important issues with regard to generic anaesthetic management. However, it is important to remember that each disease state has its own distinct pathophysiology that requires individually tailored perioperative care. This article will discuss both hereditary and acquired neuromuscular disorders, paying particular attention to the specific management of each disease when undergoing anaesthesia (Tables 1 and 2).

Individual disorders: hereditary
Pre-junctional disorders
Peripheral neuropathies
Charcot-Marie-Tooth. This is a hereditary condition with chronic peripheral neuromuscular denervation. This results in atrophy of the muscles leading to spinal and limb deformities. Muscle weakness occurs as well as sensory disturbance. Orthopaedic intervention is often required for foot deformities (pes cavus). Spinal deformities can result in restrictive lung dysfunction.

Anaesthetic considerations. Depolarizing neuromuscular blocking agents should be avoided due to the denervation of muscle. The effect of non-depolarizing neuromuscular blocking agents may be prolonged. Anaesthesia can be maintained with i.v. or volatile agents. Respiratory compromise may lead to ventilation postoperatively. Neurological deficits should be noted before regional anaesthesia.

Fredrich’s ataxia. Fredrich’s ataxia is an autosomal recessive ataxia. Clinically, features include skeletal muscle weakness and progressive limb ataxia. Myocardial degeneration frequently occurs resulting in death from myocardial failure.

Anaesthetic considerations. The diaphragm is often impaired and can result in respiratory failure. Depolarizing neuromuscular blocking agents should be avoided due to denervation. There is a risk of aspiration due to upper motor neurone involvement. Care must be taken with negatively inotropic drugs due to the involvement of the myocardium.

Post-junctional disorders
Dystrophias
Duchenne muscular dystrophy. Duchenne muscular dystrophy is the most common childhood muscular dystrophy with an incidence of 1:3500 live births. It is an X-linked recessive disorder that appears in childhood, with progressive wasting and weakness usually of the proximal muscles. It becomes fatal by late adolescence from respiratory or cardiac failure. Sufferers may present with a waddling gait and pseudohypertrophy of calf muscles between the ages of 3 and 5. Affected males are often wheelchair bound before their teens and suffer from contractures, marked scoliosis, restrictive lung function, and cardiomyopathies with up to 50% of sufferers having a dilated cardiomyopathy by the age of 15. Death occurs from cardiac or respiratory failure in the second or third decade.

Those with the disorder lack dystrophin—a protein that helps to anchor muscle cells to the extra-cellular matrix. In 1985, Kunkel and colleagues discovered the gene coding for dystrophin, which in Duchenne muscular dystrophy is defective. This leads to the absence of dystrophin expressed within the sarcolemma, rendering the sarcolemma weak. Muscle fibres are then inadequately tethered, and these fibres then become replaced with fibrous connective tissue leading to the pseudohypertrophy seen. The sarcolemma also becomes increasingly permeable, with increased intracellular calcium levels.

Becker’s muscular dystrophy. In Becker’s muscular dystrophy, the dystrophin protein is only partially absent. It affects 1 in 30 000

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Neuromuscular disorders and anaesthesia

**Table 1** Hereditary neuromuscular disease. Key: *, must avoid; ‡, give increased dose; †, give reduced dose; N, normal dose; AIR, anaesthesia-related rhabdomyolysis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Site</th>
<th>DMR</th>
<th>NDMR</th>
<th>Anti-Chol</th>
<th>MH Assoc</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charcot-Marie-Tooth</td>
<td>Pre-junc</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>No</td>
<td>‡ Thiopental dose</td>
</tr>
<tr>
<td>Friedreich’s ataxia</td>
<td>Pre-junc</td>
<td>‡</td>
<td>N</td>
<td></td>
<td>No</td>
<td>Avoid negative inotropes</td>
</tr>
<tr>
<td>DMD</td>
<td>Post-junc—Absent dystrophin</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>?AIR</td>
<td>Resp and Cardiac compromise</td>
</tr>
<tr>
<td>BMD</td>
<td>Post-junc—reduced dystrophin</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>?AIR</td>
<td>Resp and cardiac compromise</td>
</tr>
<tr>
<td>MD</td>
<td>Post-junc—abnormal Na/Cl channel</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>No</td>
<td>Avoid cold, shivering, mechanical, electrical stimulation, PM glucose control</td>
</tr>
<tr>
<td>MC</td>
<td>Post-junc—abnormal Cl channel</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>No</td>
<td>Give Na channel blockers for myotonia contractures</td>
</tr>
<tr>
<td>HyperPP</td>
<td>Post-junc—abnormal Na channel</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>No</td>
<td>Avoid potassium, Avoid long fasting</td>
</tr>
<tr>
<td>HypoPP</td>
<td>Post-junc—abnormal Ca channel</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>Yes</td>
<td>Maintain normokalaemia, normothermia</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Post-junc</td>
<td>‡</td>
<td>N</td>
<td></td>
<td>No</td>
<td>Avoid hypothermia, Substrate infusion</td>
</tr>
<tr>
<td>Mitochondrial</td>
<td>Post-junc</td>
<td>‡</td>
<td>N</td>
<td></td>
<td>No</td>
<td>PM, reduce LA, Propofol exposure</td>
</tr>
</tbody>
</table>

**Table 2** Acquired neuromuscular disease

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Site</th>
<th>DMR</th>
<th>NDMR</th>
<th>Anti-Chol</th>
<th>MH assoc</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MND</td>
<td>Pre-junc—UMN/LMN</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>No</td>
<td>Respiratory compromise</td>
</tr>
<tr>
<td>MS</td>
<td>Pre-junc—demyelination</td>
<td>‡</td>
<td>N</td>
<td></td>
<td>No</td>
<td>Avoid LA, Avoid hyperthermia</td>
</tr>
<tr>
<td>GBS</td>
<td>Pre-junc</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>No</td>
<td>Autonomic instability</td>
</tr>
<tr>
<td>DM</td>
<td>Pre-junc</td>
<td>‡</td>
<td>N</td>
<td></td>
<td>No</td>
<td>Autonomic instability, temp control, gastroparesis</td>
</tr>
<tr>
<td>MG</td>
<td>NMJ—A/b to Ach receptor</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>No</td>
<td>Avoid drugs interfering with NM transmission</td>
</tr>
<tr>
<td>ELS</td>
<td>NMJ—A/b to Ca channel</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>No</td>
<td>Autonomic dysfunction</td>
</tr>
<tr>
<td>CIP/CIM</td>
<td>Post-junc—muscle atrophy</td>
<td>‡</td>
<td>‡</td>
<td></td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Men, with milder symptoms than Duchenne muscular dystrophy that runs a more protracted course. The initial presentation tends to be in the teenage years. Death secondary to cardiac or respiratory failure typically occurs in the fourth or fifth decade. Cardiac disease in Becker’s muscular dystrophy, like Duchenne muscular dystrophy, usually manifests as a dilated cardiomyopathy and cardiac arrhythmia.

**Anaesthetic considerations.** Particular risks during anaesthesia include postoperative respiratory insufficiency and cardiac dysfunction related to cardiomyopathies or arrhythmias. Appropriate preoperative assessment should be completed where possible, especially before any major surgery. Postoperative ventilatory support must be considered and cardiac monitoring should be continued into the postoperative period.

Blood loss may be increased due to smooth muscle and platelet dysfunction. Hypotensive anaesthesia has been recommended to avoid large blood loss volumes. However, hypovolaemia should be avoided due to the relatively fixed cardiac output state secondary to non-compliant ventricles. In cases where there is felt to be potential for hypovolaemia to occur, volume status should be monitored invasively.

Female carriers may show elevated CK levels, mild myopathic changes, and cardiomyopathy. For this reason, it has been suggested that volatile anaesthesia and depolarizing neuromuscular blocking agents are avoided if possible.

Depolarizing neuromuscular blocking agents must be avoided due to the extra-junctional synapse development that occurs in Duchenne muscular dystrophy and Becker’s muscular dystrophy. Catastrophic hyperkalaemia can result from depolarization of the synapses, as well as from rhabdomyolysis that occurs due to damage caused to the muscle cell membrane.

Non-depolarizing neuromuscular blocking agents should be used sparingly as a delay in onset and offset is seen, potentially leading to a prolonged block. Their use can often be avoided with an appropriate i.v. anaesthesia technique. If used however, their use should be coupled with neuromuscular monitoring.

Inhalation anaesthetics have been implicated in the rhabdomyolysis seen in Duchenne muscular dystrophy patients secondary to their effects of further increasing mycoplasmic calcium. It has been difficult to elucidate whether the metabolic reaction seen is related to an anaesthesia-related rhabdomyolysis or a true malignant hyperthermia, and may not even occur on every exposure to halogenated compounds. Nevertheless, their use in Duchenne muscular dystrophy is advised with extreme caution, with total i.v. anaesthesia and a clean anaesthetic machine being advisable. For those children where induction using volatile anaesthesia is indicated such as in a difficult airway, then the inhalation agent should be discontinued as soon as possible with conversion to TIVA and a clean anaesthetic machine.

**Myotonias**

The myotonias can be divided into two groups: the dystrophic and non-dystrophic group.

In patients with dystrophic myotonias including myotonic dystrophy, muscle wasting and weakness are seen. This is in contrast to the non-dystrophic myotonias (myotonia congenita and familial periodic paralysis) where the main symptom can be prolonged muscle contraction following stimulation.
Myotonic dystrophy. This is an autosomal dominant disorder with an incidence of 2.4–5.5 cases per 100 000 in the UK, with the locus for myotonic dystrophy on chromosome 19. Multisystem signs and symptoms usually manifest in early adulthood. Findings include myotonia (incomplete muscle relaxation, especially the inability to ‘let go’ after a hand grip), muscle wasting, cardiac abnormalities (conduction defects, cardiomyopathy, structural deformities), respiratory abnormalities (restrictive lung disease and obstructive sleep apnoea), endocrine dysfunction, and intellectual impairment.

The underlying pathophysiology is related to abnormal sodium or chloride channels, which results in the muscle being in an abnormal hyperexcitable state. This results in repetitive action potentials and sustained muscle contraction, manifesting in the inability to relax muscle groups. Anaesthetic considerations. Factors that may precipitate myotonia must be avoided where possible. These include hypothermia, shivering, and mechanical and electrical stimulation.

There may be increased sensitivity to sedatives and analgesics, due to the respiratory involvement and therefore these agents should be used judiciously.

Depolarizing neuromuscular blocking agents may induce generalized muscular contractures and are therefore not recommended. Non-depolarizing neuromuscular blocking agents are not associated with myotonias; however, the use of anti-cholinesterase drugs may precipitate contractures due to the increased sensitivity to acetylcholine.

Glucose metabolism may be affected as part of the disease, and therefore levels should be monitored perioperatively. Bulbar muscle weakness may result in aspiration. Conduction defects may require access to pacemaker equipment.

Myotonia congenita. Myotonia congenita is an autosomal dominant disease linked to chromosome 17, with an incidence of 2 per 50 000 population. Symptoms are related to widespread muscle hypertrophy. This results in a more severe state of muscle contraction than the other muscular disorders, with significant stiffness on initiating movement. There is characteristically no muscle weakness but palatopharyngeal dysfunction can occur, resulting in difficulty in swallowing and an aspiration risk. A cardiomyopathy may also be present.

The defect in myotonia congenita is based around a dysfunctional chloride channel, which reduces chloride conductance. The muscle fibres become hyperexcitable resulting in myotonic contractures. Anaesthetic considerations. Depolarizing neuromuscular blocking agents should be avoided due to the intractable myotonia that may be induced. Attempts should be made to avoid cold environments, postoperative shivering, and excessive physical manipulation. If myotonia is elicited, non-depolarizing neuromuscular blocking agents will not relax the contractions nor does regional or peripheral nerve block. Sodium channel blockers may be useful in breaking the contracture, as may be the topical administration of local anaesthetic to cut nerve bundles.

Familial periodic paralysis

Hyperkalaemic periodic paralysis (HyperPP). This is characterized by episodes of flaccid paralysis. Its locus has been identified on chromosome 17 with autosomal dominant penetrance, and affects ~1 in 100 000 people. The paralysis is associated with increased serum potassium concentrations and precipitated by cold, hunger, and stress. Respiratory muscles are usually spared. Dysrhythmias may occur.

The underlying abnormality is a dysfunctional sodium channel, which following a hyperexcitable period becomes inactive resulting in weakness.

Anaesthetic considerations. Preoperative potassium depletion has been recommended with the use of loop diuretics. Any drugs that cause potassium release from cells should be avoided, including depolarizing neuromuscular blocking agents, as should potassium-containing fluids. ECG monitoring should be continuous, and calcium should be available for the emergency treatment of hyperkalaemic-induced weakness. Fasting should be minimized and glucose containing fluids infused during fasting periods. Hypothermia should be avoided. HyperPP patients may remain paralysed for hours after surgery, but good perioperative care should help to negate this risk.

The use of volatile agents and non-depolarizing neuromuscular blocking agents is thought to be safe.

Hypokalaemic periodic paralysis (HypoPP). This is a different entity to HyperPP. The genetic defect is a rare autosomal dominant condition that results in defective calcium channels and in most cases it is related to mutations within the dihydropyridine receptor gene. Patients usually present in the second decade of life with severe muscle weakness and asymmetrical muscle paralysis associated with a low serum potassium.

Mutations from another region of the dihydropyridine receptor gene have been associated with malignant hyperthermia and there have been HypoPP patients who have exhibited hypermetabolic states after the administration of malignant hyperthermia triggering drugs. There is, therefore, a theoretical risk that malignant hyperthermia and HypoPP may be linked in some patients due to the proximity of their loci within the same gene. However, the location of the loci is separate and there has been no definite link between the two proven as yet.

Anaesthetic considerations. Because of the potential link between malignant hyperthermia and HypoPP, the use of volatile agents should be left to the discretion of the anaesthetist, with knowledge of the risk of a potential hypermetabolic reaction.

Depolarizing neuromuscular blocking agents should not be given. Non-depolarizing neuromuscular blocking agents used should have a short duration.

Perioperative management should be directed towards avoiding drugs that cause serum potassium shifts including salt and glucose loads, maintaining normothermia and ensuring serum potassium is kept within the normal range. Anxiety can precipitate weakness and should be avoided if possible.
A perioperative attack may result in the need for postoperative ventilation. Cardiac arrhythmias may also occur.

Metabolic and mitochondrial disorders

Metabolic
Metabolic myopathies such as acid maltase deficiency are a heterogeneous group of conditions that result from an inborn error of metabolism resulting in skeletal muscle dysfunction. Abnormalities of metabolism can be related to glycogen, lipid, purine, or mitochondrial metabolism. Muscle contraction depends on the supply of ATP from three major sources: glycogen, lipid, and purine metabolism. If these pathways are interrupted, muscle cramps, myalgia, and myoglobinuria occurs. Muscle weakness and atrophy develop which can involve both the cardiac and respiratory systems.

Anaesthetic considerations. Aggressive metabolic monitoring is required in the perioperative phase. Adequate hydration with forced diuresis to avoid myoglobinuria is required. Glucose and amino acid infusions should be run to aid muscle metabolism. Hypothermia should be prevented to avoid shivering and increased muscle activity.2 6

Mitochondrial
These myopathies are related to primary mitochondrial dysfunction. Mitochondria are the main sites of ATP production from oxidative phosphorylation. Organs including skeletal muscle that have high energy demands are particularly vulnerable if mitochondrial dysfunction is present. Symptoms can range from muscle weakness and exercise intolerance to heart failure, movement disorders, and death.

Anaesthetic considerations. These patients are difficult to anaesthetize, as most anaesthetic drugs have a depressant effect on mitochondria. Total atrio-ventricular block can occur, so access to a temporary pacemaker is required in theatre. Stringent glucose control is essential, and avoidance of stress, prolonged fasting, and infusing compound sodium lactate infusions is important. Respiratory failure can occur postoperatively. There may be impaired swallowing leading to aspiration.

Low dose volatile inhalation anaesthetic and ketamine have been recommended for anaesthesia in sufferers. Drugs to be avoided or given in reduced concentrations include local anaesthetics and propofol due to their depressant effects on mitochondria.2 6

Disorders: acquired

Pre-junctional disorders

Motor neurone disease
This is a pre-junctional disorder that can affect both the upper (primary lateral sclerosis) and the lower (progressive spinal atrophy) neurones and even both (amyotrophic lateral sclerosis). Loss of innervation to muscle ultimately leads to muscle atrophy and the development of extra-junctional acetylcholine receptors. There is no sensory loss, which distinguishes motor neurone disease from multiple sclerosis and other polynuropathies. It never affects cranial nerves. Signs include both upper and lower motor neurone of limbs and bulbar muscles. Fasiculations, weakness, and atrophy are often present.4

Anaesthetic considerations. Depolarizing neuromuscular blocking agents should be avoided. Non-depolarizing neuromuscular blocking agents may be used in reduced doses due to increased sensitivity. Respiratory complications are common, with the risk of postoperative ventilation and subsequent weaning difficulties, infection, and atelectasis.

Multiple sclerosis
This is the most frequently occurring demyelinating neuromuscular disorder. It is a chronic relapsing condition characterized by the formation of plaques within the brain and spinal cord. These plaques cause demyelination around the axons, resulting in weakness and spasticity as well as sensory dysfunction.

Anaesthetic considerations. Local anaesthetics may exacerbate symptoms due to the increased sensitivity of demyelinated axons to local anaesthetic toxicity.

Non-depolarizing neuromuscular blocking agents may be used in normal doses. Caution should be exercised when using depolarizing neuromuscular blocking agents if the patient is debilitated. Temperature maintenance is important as symptoms can deteriorate with an increase in temperature, as demyelinated axons are also more sensitive to heat.

Guillain–Barré syndrome
Guillain–Barré syndrome is an immune-mediated polynuropathy that often follows a viral or bacterial illness within the preceding 4 weeks. The weakness typically ascends from the legs and is symmetrical. Sensory and autoimmunne dysfunction can also occur. Ascending weakness can lead to respiratory compromise requiring prolonged ventilatory support and bulbar dysfunction.

Anaesthetic considerations. Rapidly progressing respiratory muscle weakness may result in intubation and ventilation. Invasive monitoring should be used due to the risk of autonomic instability. The use of depolarizing neuromuscular blocking agents should be avoided even following a long period after recovering from the neurological deficit as the risk of hyperkalaemic cardiac arrest after depolarizing neuromuscular blocking agents may persist. There may be increased sensitivity to non-depolarizing neuromuscular blocking agents. Epidural anaesthesia may be useful to avoid postoperative opioid use.

Peripheral neuropathies: diabetes mellitus
Diabetic polyneuropathy may include sensory, motor, and autonomic dysfunction following damage to axons and myelin and can be widespread or localized to a focal neuropathy. The pathophysiology is unclear to date, but vascular, metabolic, and autoimmune factors have previously been implicated.2 4
**Anaesthetic considerations.** Autonomic instability may occur and therefore invasive monitoring should be considered. Gastroparesis is a feature and care should be taken at induction and in the postoperative period. There is an increased likelihood of becoming hypothermic and so temperature control is imperative.5

**Neuromuscular junction disorders**

**Myasthenia gravis**

Myasthenia gravis is an autoimmune disease where there are IgG auto-antibodies produced against the nicotinic Ach receptors within the neuromuscular junction. The autoantibodies lead to destruction of the receptors. Symptoms include a fatigable weakness, which can be localized to specific muscle groups (ocular, bulbar, and respiratory) or become widespread. Treatment may involve cholinesterase inhibitors, plasma exchange, immunosuppressants, and i.v. immunoglobulins. Patients may present to anaesthetists for definitive thymectomy surgery the thymus gland is abnormal in up to 75% of cases, and thought to be the site of the abnormal antibody production.4

**Anaesthetic considerations.** In contrast to other neuromuscular disorders, myasthenia gravis patients exhibit a relative resistance to depolarizing neuromuscular blocking agents and the dose used may need to be increased. Conversely, patients show a sensitivity to non-depolarizing neuromuscular blocking agents, requiring only 10% of normal dose. Cholinesterase inhibitors should be avoided as they cannot only prolong the duration of a depolarizing neuromuscular blocking agents block, but also precipitate a cholinergic crisis. Drugs that interfere with neuromuscular transmission should be avoided. Postoperative ventilation may be necessary.

**Eaton–Lambert syndrome**

Eaton–Lambert syndrome is an immune-related condition usually associated with malignancy, with ectopic production of antibodies against calcium channels in the pre-synaptic membrane. Without an influx of calcium into the presynaptic membrane, Ach cannot be released into the cleft.

In contrast to myasthenia gravis, the weakness in Eaton–Lambert syndrome usually improves with exercise. There is also less cranial nerve involvement.4

**Anaesthetic considerations.** Eaton–Lambert syndrome patients have both a sensitivity to depolarizing neuromuscular blocking agents and non-depolarizing neuromuscular blocking agents. Anti-cholinesterases can be given. There is potential for autonomic dysfunction to the relative lack of Ach. There may be a need to ventilate postoperatively.

**Post-junctional disorders**

**Critical illness polynuropathy**

Critical illness polynuropathy is a condition acquired during critical illness that manifests with muscle weakness and atrophy. Failure to wean from a ventilator and limb weakness are common signs. The pathophysiology of critical illness polynuropathy is due to axonal degeneration of both motor and sensory nerve fibres with cranial nerves being spared. Myopathic changes occur with atrophic and occasionally necrotic fibres. It is a frequently occurring condition related to patients with multi-organ failure or sepsis and is thought to occur in up to 80% of all intensive care patients.10

**Critical illness myopathy**

Critical illness myopathy can occur simultaneously with critical illness polynuropathy. It presents with a diffuse weakness or flaccid paralysis, which again can compromise weaning. Critical illness myopathy is associated with an acute respiratory disorder and the concomitant use of intra-venous steroids, non-depolarizing neuromuscular blocking agents and aminoglycosides.

Diagnosis requires clinical examination, electro-physiological studies, and ultimately a muscle biopsy to determine the underlying disorder.

**Anaesthetic considerations.** Prevention in intensive care patients is paramount as there is no specific treatment. Prolonged infusions of non-depolarizing neuromuscular blocking agents should be avoided especially when high dose steroids are used. Due to the denervation involved, depolarizing neuromuscular blocking agents should be avoided to prevent hyperkalaemic cardiac arrest.

**Conflict of interest**

None declared.

**References**


Please see multiple choice questions 5–8.