Anaesthesia for children with neuromuscular disease

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Key points

A detailed family history, focused investigations, and genetic testing can help to establish a specific diagnosis, which may facilitate safe anaesthetic management.

In the absence of a precise diagnosis, children presenting with an undiagnosed neuromuscular disease should not have elective surgery or anaesthesia other than as part of the diagnostic process.

All these children should have their functional status assessed before operation and consideration given to transfer to specialist centres with intensive care facilities.

Risks and benefits of the proposed surgery should be considered with the child, their parents, and all members of the multidisciplinary team.

The incidence of anaesthesia-induced rhabdomyolysis is significant; succinylcholine and volatile agents should be avoided in at-risk children.

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Children with neuromuscular disease commonly present for anaesthesia as part of the diagnostic process (e.g. MRI, muscle biopsy), for surgery relating to their underlying disorder (e.g. gastrostomy, corrective orthopaedic surgery, strabismus surgery), or for incidental surgery. In many cases, the diagnosis may be clear from a family history or from clinical or pathological features; in some instances, the underlying aetiology of hypotonia in a child may be unclear. This article focuses on the anaesthetic management of hypotonic patients with disorders of the muscle or the neuromuscular junction (NMJ). The aim of this article is to provide an overview of the various causes and their impact on anaesthetic management, to facilitate a sensible approach towards the perioperative management of these children.

The components required for normal skeletal muscle function involve input from efferent somatic nerves, release of acetylcholine, stimulation of the motor end-plate, and calcium release from the sarcoplasmic reticulum followed by contraction coupling of actin and myosin (myofibrils). All these processes are energy-dependent; therefore, high concentrations of mitochondria are present in the axonal bud and muscle fibre (Fig. 1).

Abnormalities can occur in the release or action of acetylcholine (myasthenic syndromes), in the post-synaptic membrane or the sarcoplasmic reticulum (channelopathies), in the myofibrils (dystrophies and myotonias), or in mitochondria (mitochondrial myopathies).

Myasthenic syndromes

The myasthenic syndromes are caused by a disruption in transmission of the action potential (AP) across the NMJ, involving either the release of acetylcholine (ACh) or its action at the post-synaptic membrane. As in adults, the hallmarks of the myasthenic syndromes are muscle weakness and fatigability.

Myasthenia gravis is caused by an autoimmunological response to components of the NMJ. It rarely presents in childhood, but when it occurs is often associated with a thymoma. Neonatal myasthenia gravis can occur through the passive transfer of anti-nicotinic ACh receptor antibodies from an affected mother via the placenta. Congenital myasthenic syndromes are a rare heterogeneous group of conditions, caused by inherited mutations in genes responsible for the release, manufacture, or recognition of ACh at the NMJ.[1]

Disorders of post-synaptic receptor channels (channelopathies)

This is a group of rare genetic disorders that disturb the normal function of ligand or voltage-gated receptor channels at the NMJ. For example, abnormal chloride channels cause myotonia congenita. Hypokalaemic periodic paralysis and hyperkalaemic periodic paralysis are rare autosomal dominant conditions affecting the voltage-gated calcium and sodium channels, respectively. Patients with hyperkalaemic periodic paralysis suffer from episodes of sudden muscle weakness; these attacks can be severe, and respiratory and cardiac muscles may be affected.[1]

Dystrophies

The muscular dystrophies represent a group of genetically determined disorders where there is dissociation of the muscle cell contraction from surrounding connective tissue. These disorders have absent or abnormal dystrophin, or related glycoproteins that link and stabilize the myofibrils and cytoskeleton. Actin–myosin coupling fails to produce effective muscle contraction due to the absence of stabilizing connective tissue or the membrane components of muscle. In addition to resultant in muscle weakness, the cell membrane is unstable; this results in muscle inflammation, degradation, and atrophy. Eventually, the majority of muscle is replaced with fat and connective tissue. There is a

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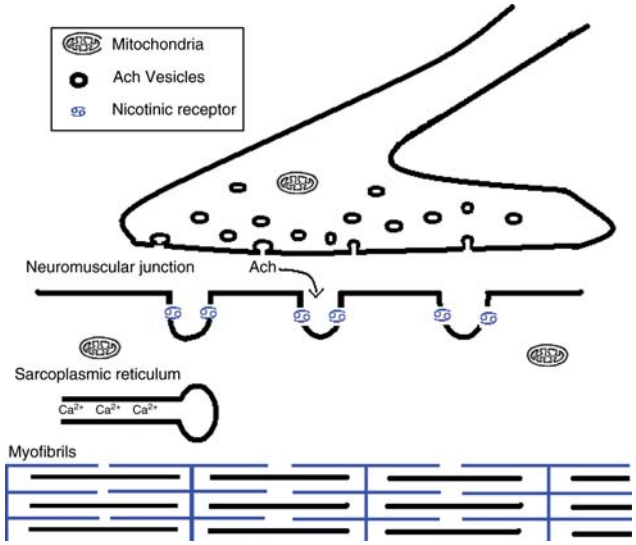

Fig 1 The components of the NMJ. Abnormalities can occur from the myofibrils (myotonias, dystrophies), sarcoplasmic reticulum (malignant hyperthermia), membrane (channelopathies), receptors and acetylcholine (myasthenia), and mitochondria.

variable onset and prognosis, depending on which component of connective tissue is involved.[1]

Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) has an incidence of 1 in 3500 live male births.[2] It is an X-linked recessive inherited disorder, with abnormal or absent dystrophin, and this results in chronic muscle fibre necrosis, degeneration, and regeneration. Degeneration occurs in cardiac and smooth muscle and also in skeletal muscle.

Infants with DMD may appear normal at birth; weakness begins in childhood generally before the age of 8, and is rapidly progressive. The muscles around the pelvis and thighs are affected first, the child presenting with difficulty managing stairs and standing from sitting. By adolescence, patients are usually wheelchair-bound and succumb to cardiac or pulmonary manifestations of the disease in their late 20s to early 30s.[1] Heterozygous females, although not manifesting the disease, have an increased cardiac risk later in life.

Becker muscular dystrophy

Less common than DMD (1 in 30 000), Becker muscular dystrophy has qualitative abnormalities in the same X-linked gene as DMD. It is much milder with a slower onset, presenting on average at 11 yr of age. Life expectancy is virtually normal; however, they can develop severe dilated cardiomyopathy as adults.

Myotonias

Myotonias are characterized by difficulty with initiating muscle contraction and delayed relaxation. The disease is typified by myotonic dystrophy, which is an autosomal-dominant disease, caused by an abnormal nucleotide triplet repeat sequence on chromosome 19. This results in delayed inactivation of sodium channels following an AP at the muscle cell membrane. Thus, there is prolonged stimulation of the actin–myosin complex within the cell, and delayed relaxation of contracted muscle. The severity of the disease is correlated with the length of the repeat DNA sequence.[3] As it is an autosomal dominant condition, there is invariably a family history, so it is usually diagnosed in the neonatal period.

Mitochondrial myopathies

This heterogeneous group of conditions has been increasingly recognized over the last two decades and is now the most common cause of muscle weakness in children, with an incidence of 1 in 4000.[4] The clinical manifestation of this group of disorders is extremely varied. The symptoms are characterized by mitochondrial dysfunction in tissues with a high metabolic demand, for example, the brain, skeletal and cardiac muscle, sensory organs, and to a lesser extent, the endocrine organs and the kidneys. Although some of the conditions have typical constellations of signs and symptoms, the condition is very heterogeneous, and therefore, classification based on clinical or biochemical features is impossible.[5]

The two most commonly recognized syndromes are mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged red fibres (MERRF). In the severest forms, it presents in the neonatal period with profound weakness, systemic acidaemia, liver and renal failure, and substantial neurological impairment. Some varieties have mild weakness with or without other system involvement, presenting later in adulthood.[5]

Mitochondria produce ATP via oxidative phosphorylation. Products of the Krebs cycle interact with electron chain complexes (numbered 1–5) on the inner mitochondrial membrane to generate ATP. If more than one part of the electron transport chain (ETC) is affected the disease tends to be more severe.

Impaired ETC function results in decreased production of ATP and an increased production of free radicals. The reduction in ATP levels results in inefficient muscle function with a reliance on anaerobic metabolism and lactate production. The acidosis and excess free radical production further damage the mitochondria by inappropriate oxidation of mitochondrial proteins, lipids, or DNA.[6]

The inheritance of this group of genetic diseases is somewhat complicated. The protein complexes involved in the ETC are under dual genetic control with an influence of mitochondrial DNA, which is maternally inherited. Mitochondria in different tissues vary in their level of activity; different populations of

Table 1 The molecular basis of common types of neuromuscular disorder

Disorder	Biochemical abnormality
Myasthenic syndromes	Decreased absolute or relative levels of acetyl choline
Myotonia	Delayed inactivation of sodium channels after an AP
Mitochondrial myopathies	Diverse collection of abnormalities of mitochondrial function, particularly effecting ETC
Duchenne muscular dystrophy	Absent or reduced levels of dystrophin
Becker muscular dystrophy	

mitochondrial DNA may be inherited by different offspring and mitochondrial DNA is 10–20 times more likely than nuclear DNA to undergo mutation (Table 1).

Anaesthetic management

Preoperative assessment

A thorough preoperative assessment is mandatory to identify the relative risk of some of the conditions and their impact on the anaesthetic technique.

History

Important questions include: How long has the child been weak? Is the weakness stable or progressive? Is the muscle weakness associated with fatigability? What limits activity? Specific indicators of neuromuscular disease include the older child that crawls upstairs, bottom shuffles, or uses assistance to get up from sitting to standing. Good discriminators for more severe disease are how quickly the child recovers from a respiratory tract infection and can they comfortably sleep supine.

Myasthenia and the channelopathies usually do not have a positive family history. Myotonias may have a family history, but in the muscular dystrophies, this may be positive in as many as 90% of those with DMD.

A previous general anaesthetic history may reveal problems with perioperative temperature control, renal function, and recovery, including the need for postoperative respiratory support. Previous uneventful use of succinylcholine or volatile agents does not guarantee that they can be used safely for subsequent anaesthetics.

Examination

Indicative findings of specific conditions include hypertrophied calf muscles in DMD; patients with neonatal myotonic dystrophy have typical facies: ptosis, diplegia, and a tent-shaped mouth. The majority of children, particularly in the early stages, look completely normal. The inability to sit or stand can give them a 'relaxed' appearance (Fig. 2).

The functional capacity is of great importance. Can the child sit, stand, or walk unaided? Or are they supine and immobile with obvious respiratory and airway compromise? Is there paraspinal weakness with kyphoscoliosis and restrictive lung disease? Does the child have an adequate cough?

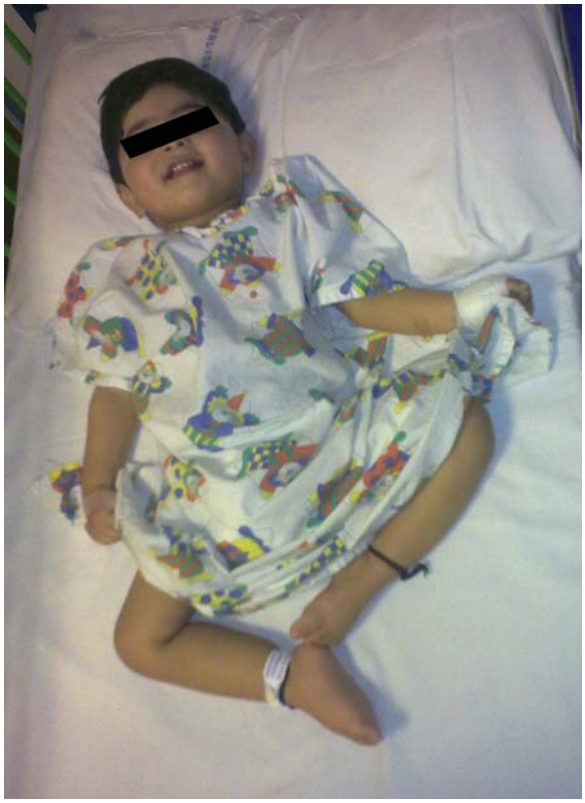

Fig 2 This bright toddler who has a sibling with mitochondrial myopathy presented for a muscle biopsy. Unable to sit or stand, he also had obvious loss of muscle bulk in his legs. (Image reproduced following parental permission.)

Functional capacity in other systems can be difficult to assess in the presence of extreme weakness. Inactivity may mask the severity of both cardiac and respiratory diseases.[5] In DMD, there is progressive degeneration of cardiac muscle fibres, resulting in conduction defects and cardiomyopathy.

Developmental delay occurs particularly with mitochondrial disorders. Dysphagia and reduced gastric motility are common.

Investigations

If not previously performed, all of these children should have an ECG, EMG, and creatine kinase (CK) level measured. Recent electrolytes including potassium, bicarbonate, pH, and lactate should be available. Conditions associated with cardiac dysfunction warrant echocardiography, being aware that a resting study can fail to detect significant diastolic dysfunction.

Genetic tests exist for nearly all of the inherited diseases; the best investigations have a positive predictive value of >95%; however, false negatives occur in as many as 60%. Genetic testing

gives no indication of the severity of the condition; therefore, muscle biopsy may still be required. A raised serum lactate test may indicate mitochondrial disease.

In the older child, spirometry and the degree of reduction of vital capacity is a good indicator of postoperative respiratory complications.

Anaesthetic considerations

Teams that fully understand these conditions should manage these children, particularly for long or complex surgery. If there is a definite diagnosis, it is worth consulting specific review articles or case reports to identify the recommended safe anaesthetic technique and if there are any contraindicated drugs. In general terms, an anaesthetic technique that minimizes cardiac and respiratory depression should be used utilizing drugs that are short-acting and rapidly metabolized.

Most children with neuromuscular disease will have an increased sensitivity to non-depolarizing neuromuscular blocking agents. The use of a nerve stimulator and short-acting neuromuscular blocking agents only if required is recommended. Succinylcholine should always be avoided. Myotonia may be induced by succinylcholine or cholinesterase inhibitors. In the channelopathies, there can be dramatic, life-threatening increases in serum potassium in response to succinylcholine. Malignant hyperpyrexia and anaesthesia-induced rhabdomyolysis (AIR) (see below) can also be precipitated.

Electrolyte disturbances with rapid changes in potassium and blood glucose can occur; these fluctuations are made worse by physiological stresses like dehydration and hypothermia.

Patients with cardiac abnormalities should be monitored and treated accordingly.

Postoperative respiratory insufficiency is the greatest concern after anaesthesia in these patients. Opioids should be used sparingly; effective local anaesthetic blocks help to reduce the requirements for other analgesics or agents. Close postoperative monitoring in a high-dependency environment is warranted. After major or prolonged surgery, consideration should be given to a period of postoperative ventilation, particularly if associated with other physiological stresses such as significant blood loss, hypothermia, or both.

For major surgery, a multidisciplinary approach is recommended involving all the involved health-care providers, but even for minor surgery, appropriate discussion of risk must take place with the parents and surgeon. Occasionally, very impaired children are scheduled for cosmetic procedures or surgery associated with borderline benefits; in these cases, it is generally wise to have an open, sensitive, and frank discussion about the advisability of proceeding well in advance of the day of surgery.

The specific diagnosis is so important in both the risk assessment and anaesthetic management that wherever possible it should be ascertained before surgery. Any proposed elective surgery, other than as part of the diagnostic process, should be deferred until after a diagnosis is made. This applies particularly to minor surgery where a possible fatal outcome is even more disastrous.

Is there a risk of malignant hyperthermia?

The only conditions shown to have a definite linkage with malignant hyperthermia (MH) are King–Denborough syndrome, central core disease, and Evans myopathy.[7] Patients with other neuromuscular disorders have shown MH-type symptoms under general anaesthesia, but the link between these symptoms and true MH remains unclear. There is no association between DMD and MH; previously described 'normothermic MH' reports were almost certainly rhabdomyolysis.

What is the risk of rhabdomyolysis?

The muscular dystrophies with an absence of dystrophin in the muscle cell have an unstable and more permeable sarcolemma. Inhalation agents and succinylcholine may increase the underlying instability and permeability of the sarcolemma, resulting in increased intracellular calcium levels and leakage of potassium and CK into the serum.

Succinylcholine is contraindicated in DMD. It has been implicated in producing intraoperative cardiac arrests secondary to rhabdomyolysis and hyperkalaemia.

There continue to be reports of children suffering hyperkalaemic cardiac arrests after the use of inhalation anaesthetic agents. These sometimes occur in patients during the recovery period, and may be related to emergence shivering.[8] Although this can occur at any age, the most 'at risk' group are children aged <8 yr of age, where there is less muscle fibrosis and still some muscle regeneration.

Although only a small proportion of patients with DMD develop hyperkalaemia and rhabdomyolysis after exposure to volatile anaesthetics, the outcome is often fatal. The trend in recent literature is to recommend avoidance of volatile agents in patients with DMD, and rely instead on total i.v. anaesthesia (TIVA).[2]

The rhabdomyolysis and hyperkalaemia that develop in DMD is unrelated to that which develops in MH, with a distinct difference in pathophysiology. This has given rise to the term AIR.[2] In AIR, it is the instability of the sarcolemma that results in 'leak' of potassium and CK from necrotic and regenerating muscle cells into the serum.

Are volatile agents safe to use in the undiagnosed 'floppy child'?

The risk of AIR or MH in a floppy child with an uncertain diagnosis depends really on the stage of investigation. Children presenting for muscle biopsy have a 10–20% chance of a positive finding, and around half of these have a diagnosis of muscular dystrophy. There is an estimated risk in these children of $\leq 1.09\%$ of rhabdomyolysis or MH.[3] In these circumstances, volatile agents should be avoided. The safest anaesthetic technique for these children is an i.v. induction followed by maintenance with TIVA.

If features such as family history, CK levels, and genetic testing make an 'at risk' diagnosis unlikely, then the use of inhalation induction is not unreasonable. It is prudent to restrict the use of volatile agents for induction only, changing to a TIVA technique for maintenance. It is important to note that a previous uneventful volatile anaesthetic in an individual is not a guarantee of safety. Many of the reported fatal AIRs have had a previous apparently uneventful volatile-based anaesthetic.[2]

For longer operations, particularly in children with mitochondrial conditions, there is a theoretical risk of propofol infusion syndrome (PrIS), if TIVA is used because many of the features of the mitochondrial myopathies are very similar to PrIS (lipaemia, metabolic acidosis, renal and liver failure). The combined use of regional anaesthetic techniques and remifentanil mean that the infusion of propofol can generally be kept less than the recommended maximum of 4 mg kg^{-1} h^{-1}.[9]

Conclusion

Children with neuromuscular disease commonly present requiring anaesthesia for diagnostic and surgical procedures. The specific diagnosis is very important to inform a logical plan for the anaesthetic technique, ensuring awareness of possible triggers for serious adverse events. Succinylcholine and volatile anaesthesia should be avoided.

Clinical assessment of functional capacity with a high suspicion of co-existing cardiac or respiratory disease combined with focused investigations allows assessment of risk.

In all cases, there should be close perioperative monitoring and access to postoperative intensive care with ventilatory support if required.

Conflict of interest

None declared.

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Please see multiple choice questions 9–12.