British Journal of Anaesthesia **107** (S1): i79–i89 (2011)
doi:10.1093/bja/aer335

BJA

PAEDIATRICS

Perioperative management of the paediatric patient with coexisting neuromuscular disease

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Editor's key points

- Malignant hyperthermia is a rare disorder of skeletal muscle calcium handling that can progress to death if not recognized and treated with dantrolene.
- The muscular dystrophies result in weakness, cardiomyopathy, and respiratory dysfunction that can lead to anaesthetic-induced hyperkalaemia and cardiac arrest.
- Mitochondrial myopathies are complex and diverse disorders with muscular, neurological, cardiac, respiratory, and other defects.
- Cerebral palsies are non-progressive neurological disorders with important gastrointestinal, respiratory, and other perioperative considerations.

Summary. Children with neuromuscular diseases present a wide range of clinical manifestations and clinical implications for the anaesthesiologist. Neuromuscular diseases in children affect muscle strength by either directly weakening the muscle fibrils or indirectly by a degenerative nerve supply and weak neuromuscular junction. Of the more than 200 neuromuscular disorders known, the vast majority are genetic in origin. This review focuses on four of the more common neuromuscular disorders with emphasis on their pathophysiology and clinical implications for anaesthesiologists: malignant hyperthermia, the muscular dystrophies (Duchenne's, Becker's, and Emery–Dreifuss), mitochondrial disorders, and cerebral palsy.

Keywords: age, child, preschool; cerebral palsy; dantrolene; malignant hyperthermia; mitochondrial myopathies; muscular dystrophies

Malignant hyperthermia

Malignant hyperthermia (MH), with a prevalence of 1:15 000–1:50 000 in the general population and 1:15 000 in children, is a pharmacogenetic disorder of calcium homeostasis in skeletal muscle.[1] The defect in calcium homeostasis leads to accumulation of calcium in the sarcolemma that causes sustained contractures of skeletal muscles. The anaesthetic drugs that trigger MH are the potent inhalation anaesthetics and succinylcholine.[1–3] *In vitro* contractures are triggered by older anaesthetics in the order: halothane>isoflurane>enflurane>methoxyflurane.[2] Desflurane and sevoflurane are considered weak triggers of MH, but both precipitate MH reactions.[3] The inhaled anaesthetic xenon and nitrous oxide do not trigger MH.[4]

Only two disorders have been directly linked to MH: central core disease (CCD) and King-Denborough syndrome.[1 5 6] The former is a rare muscle disease that is diagnosed in early infancy with generalized weakness and skeletal deformities. CCD arises from a relative deficiency of glycolytic enzymes. It is inherited in an autosomal-dominant pattern, with the defect at 19q13.1. King-Denborough syndrome is another rare muscle disorder that is associated with dysmorphic features, skeletal anomalies (including kyphoscoliosis, pectus carinatum, and short stature), and myopathy.

The inheritance pattern of MH is autosomal dominant with variable penetrance. To date, six loci in the human genome have been linked with MH.[7 8] The first candidate site associated with MH, known as MHS1, was located at 19q3.1 and codes for the ryanodine receptor (RYR). This receptor controls the release of calcium from the sarcoplasmic reticulum. Defects in this receptor cause excessive release of calcium and sustained contractures. The search for the specific defect on MHS1 initially focused on 'hot spots' or areas along chromosome 19 (containing 106 exons) where 40 mutations have been identified. The mutations associated with MHS1 account for 70–86% of all MHS cases, but if the caffeine–halothane contracture test was not performed, only 20% of those tested were positive for RYR mutations.[8] This discrepancy in identifying RYR mutations stems from the poor (50%) positive caffeine–halothane contracture test result in those referred with clinical findings consistent with MH. The caffeine–halothane contracture test remains the gold standard for diagnosing MH. Finally, several other gene loci have been linked with MH (Table 1).

Before the introduction of dantrolene in 1970, the mortality associated with MH reactions was >60%. After the introduction of dantrolene in the 1980s, the mortality decreased, reaching a plateau of 10% in the 1990s. In 2008, the Malignant Hyperthermia Association of the US (MHAUS) reported a 2.4% incidence of cardiac arrest and 1.4% mortality between 1980 and 2000.[9] Fatal MH reactions

Table 1 MH gene defects.[7 8] The six mutations that code for MHS, MHS1-6, their channelopathies, gene locus, and estimated prevalence are depicted. SCNA4 is a voltage-gated sodium channel; CACNA is a voltage-gated calcium channel

MHS mutation	Channel defect and gene	Chromosome	Prevalence of MHS
MHS1	Ryanodine receptor (RYR1)	19q13	70–80%
MHS2	SCNA4 α Na^+ channel	17q11.2–q24	North America and S. Africa
MHS3	Ca^{2+} channel (CACNA2D1)	7q21–22 $\alpha 2\delta$ subunit of dihydropyridine-sensitive L-type calcium channel, voltage sensor for RYR1 on T-tubule	1%
MHS4	Unknown	3q13.1	
MHS5	Ca^{2+} channel CACNA1S	1q32 $\alpha 1_s$ subunit of dihydropyridine receptor skeletal muscle calcium channel	1%
MHS6	Unknown	5p	

continue to occur in part because of a lack of familiarity with the signs of an MH reaction, a lack of dantrolene, or inappropriate or incomplete treatment.

MH reactions occur far less frequently today, in part because caffeine–halothane contracture testing has been used to identify most families with the MH defect. Blood creatine kinase (CK) concentrations and other blood markers do not reliably predict MH susceptibility. Nonetheless, sporadic MH reactions continue to occur. Given its rarity, clinicians are often unprepared to manage these reactions. The majority of MH reactions occur during anaesthesia, with the risk of a reaction commencing >1 h after operation being exceedingly small.[10]

The natural course of an MH reaction is variable, ranging from the immediate onset of skeletal muscle rigidity after induction of anaesthesia with triggers to an insidious and delayed onset of a low-grade fever and limited metabolic response in the recovery room. In the past, when anaesthesia was induced with halothane and paralysis with succinylcholine, temporo-mandibular joint rigidity (also known as masseter muscle spasm) occurred in 1% of children.[11] These reactions were often self-limiting, although skeletal muscle rigidity and a hypermetabolic state developed in some, particularly if triggers were continued or dantrolene was not administered. Masseter spasm has all but disappeared as sevoflurane replaced halothane and succinylcholine is infrequently administered to children.

During the preoperative preparation of MHS children, a history of an MH reaction in the proband or a blood relative should be established. The MH gene defect is transmitted through blood relations, irrespective of their genetic distance from the proband, without skipping generations. An accurate history of an MH reaction should be sought, preferably with documentation of the event, and also biopsy or genetic results. There is no reason to administer preoperative dantrolene.

All elective MH cases should be scheduled as first case of the day in an operating theatre that was unused during the preceding evening to minimize the concentration of inhalation anaesthetic in ambient air. An MH-designated clean anaesthetic workstation should be installed in the operating theatre or the usual anaesthetic workstation should be flushed to reduce the concentration of inhalation anaesthetic to <10 ppm. Most institutions have abandoned the former because the expense of maintaining an extra anaesthetic machine, the risk that parts will be parasitized for other machines, and that someone inadvertently contaminates the machine. A 10 min flush of the Ohmeda Excel 210 anaesthetic machine with a high fresh gas flow ($\geq$10 litre min^{-1}) reduced the concentration of halothane and isoflurane to <10 ppm.[12] Preparation should also include using the ventilator during the washout and changing the carbon dioxide absorbent and breathing circuit. The minimum anaesthetic concentration that triggers an MH reaction *in vivo* is unknown, but no MH reactions have been reported to date using this approach. Time to washout anaesthetics from the newer anaesthetic workstations (Siemens Kion, Drager, and GE Ohmeda) is far greater and more complex than in the original studies.[12–15] The washout for these newer workstations can require up to 100 min of flushing,[13] although changing components of the anaesthesia workstation might speed the washout.[16] Recrudescence in the anaesthetic concentration in the circuit can occur,[12] if the fresh gas flow is reduced to <10 litre min^{-1}. Thus, I recommend maintaining a high fresh gas flow rate during anaesthesia. Recently, the addition of a charcoal filter into the inspiratory limb of the breathing circuit reduced the concentration of inhaled anaesthetics to <5 ppm for up to 90 min irrespective of the fresh gas flow.[14 15]

An MH reaction should be suspected with the presence of a metabolic and respiratory acidosis (a rapidly increasing end-tidal P_{CO_2} is the earliest sign in an evolving MH reaction), tachycardia, tachypnoea, hyperthermia, electrolyte imbalance, and rhabdomyolysis (with myoglobinuria).[7 17] Unfortunately, most reactions are not classic presentations, making the diagnosis more difficult. To assist in the diagnosis of MH, a clinical grading scale was developed.[18] Preliminary evidence suggests that it correlates well with the caffeine–halothane contracture test.[19] A differential diagnosis for MH reactions is shown (Table 2). MH should always be suspected and treated until it can be ruled out because an untreated reaction can continue, if untreated, relentlessly

Table 2 Differential diagnosis of an MH reaction

Inadequate ventilation/anaesthesia
Iatrogenic external heating
Sepsis
Malignant hyperthermia-like disorders: osteogenesis imperfecta
Endocrinopathy: thyroid storm, pheochromocytoma
Drug overdose: cocaine, amphetamine, amphetamine derivatives, and monoamine oxidase inhibitors and meperidine
Ischaemia: tourniquet
Neuroleptic malignant syndrome

Table 3 Management of an unexpected MH reaction

Stop malignant hyperthermia triggers; stop exogenous warming sources—set to cooling mode
Notify surgeon
Call for assistance
Institute trigger-free anaesthetic (total i.v. anaesthesia)
Hyperventilate
Hyperoxygenate
Call for and insert charcoal filters into inspiratory/expiratory limbs of breathing circuit
Call for dantrolene; prepare and deliver 2.5 mg kg^{-1} dantrolene as quickly as possible
Call for help to prepare dantrolene
Establish large-bore i.v. access and hyper-hydrate
Obtain venous (or arterial) blood gas, and blood for creatine phosphokinase (CK) and electrolytes
Insert bladder catheter
Refer to local malignant hyperthermia society guidelines for guidelines and/or advice (e.g. MHAUS in North America: 1-800-644-9737 or outside the USA: 001-303-389-1647) or www.MHAUS.org

to disseminated intravascular coagulopathy, severe hyperthermia, renal failure, cardiac failure, brain damage, and death.

I.V. dantrolene is the definitive treatment for an MH reaction. It inhibits the RyR, preventing the abnormal release of calcium from the sarcoplasmic reticulum.[20] However, additional interventions should be prepared (Table 3). Total i.v. anaesthesia should be established immediately with oxygen and ventilation delivered manually via a resuscitation bag while charcoal filters are inserted into both limbs of the breathing circuit to restore the use of the workstation and the ventilator. Cooling strategies (such as tepid water, fans) should be applied, recognizing that extreme cold temperatures can cause cutaneous vasoconstriction, reducing the ability to discharge excess heat and reducing blood flow to skeletal muscles. Arrhythmias should be treated as deemed appropriate (see treatment of hyperkalaemia below). Venous (or arterial) blood gas and biochemical profile (electrolytes and CK) should be collected for baseline metabolic and respiratory indices as soon as an MH reaction is suspected and before dantrolene is administered, as signs of the reaction abate, and every 6 h for the next 24 h. A bladder catheter should also be inserted since the standard loading dose of dantrolene (2.5 mg kg^{-1}) includes 0.375 g kg^{-1} mannitol.

Dantrolene is formulated as a lyophilized powder in a dose of 20 mg per vial along with 3 g of mannitol and sodium hydroxide to adjust the pH to 9.4. Each vial is reconstituted with 60 ml of sterile water by shaking vigorously or by adding warmed water.[21] Dantrolene dissolves in ~1 min. As soon as the solution turns orange, I aspirate much of the solution and inject it, while continuing to shake the remainder. Two new formulations of dantrolene that dissolve 20–30 times faster than the standard formulation, Ryanodex® (Lyoptropic Therapeutics, USA) and Azumolene, have been studied in swine.[20 22] Their pharmacology and clinical effects are identical to those of the original formulation.

The initial treatment of an acute MH reaction includes 2.5 mg kg^{-1} i.v. dantrolene,[23] administered as a rapid i.v. bolus. Slow infusions cause chronic phlebitis and thrombosis of the venous drainage of the extremity.[24] Additional complications after dantrolene include muscle weakness, gastrointestinal upset, and respiratory failure.[24] Pharmacokinetic data show that therapeutic blood concentrations (≥3 μg ml^{-1}) persist for ~7 h after 2.5 mg kg^{-1} i.v. dantrolene in MHS children, after which concentrations decrease steadily with a 10 h half-life (Fig. 1).[25]

Recrudescence of an MH reaction can occur any time during and after anaesthesia. The risk of recrudescence increases in patients with greater muscle bulk and when the interval from induction of anaesthesia until the reaction begins.[26] These should be treated with repeat i.v. dosing of dantrolene after blood for venous blood gases, electrolytes,

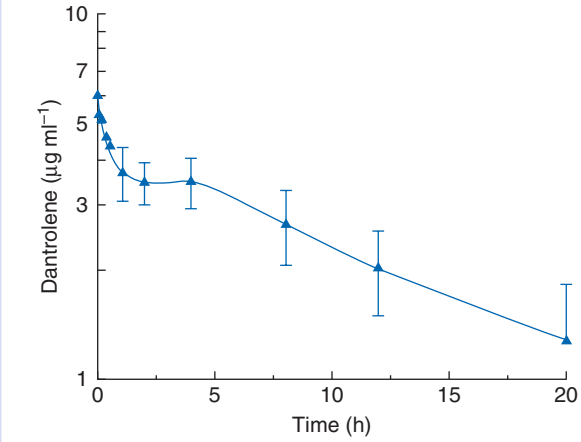

Fig 1 Whole-blood dantrolene concentration–time profile. Dantrolene (2.4 mg kg^{-1}) was administered to 12 MH-susceptible children. The dantrolene concentration is shown on a logarithmic scale. Therapeutic blood concentrations (≥3 μg ml^{-1}) were maintained for the first 6 h after which the concentration decreased with a half-life of 10 h. Data are means (standard deviations). Reproduced with permission.[25]

and CK are obtained. There is no upper limit to the dose of dantrolene.

Patients suspected of having MH require counselling regarding its implications on their lives (in terms of military duty) and that of blood relatives and its implications on future anaesthetics. They should be referred to an MH centre for possible muscle biopsy and genetic testing, and advised to wear a MedicAlert® bracelet (www.MedicAlert.org).

Duchenne's muscular dystrophy

Duchenne's muscular dystrophy (DMD) has a prevalence of 1:3500 male births.[1 27 28] It is inherited as an X-linked recessive gene at Xp21, which explains its male predominance. Ninety per cent of cases have a family history of DMD,[29] and only 10% of cases are sporadic. Children with DMD lack dystrophin (<3% of the normal content) in muscle, an essential protein in the cytoskeleton of muscle both reinforcing the inner strength of the myocyte during lateral stretching as well as involved in signal transduction (Fig. 2).[27] In addition to membrane tears from the lack of dystrophin, muscle damage and membrane permeability are attributed to an increased intracellular calcium, which activates proteases and reactive oxygen species.[28 30 31] The origin of the increased calcium is unclear, but it might be due to more permeable calcium channels in the sarcolemma or to calcium release from the sarcoplasmic reticulum. As a result of the muscle damage and regeneration, there is up-regulation of fetal and adult acetylcholine receptors as in a chronic denervation state.[1] Succinylcholine and inhaled anaesthetics contract muscles, increase intracellular calcium, or both, which further damage the already fragile muscle membrane (in the order, halothane>sevoflurane>isoflurane) with the release of intracellular potassium, myoglobin, and CK reaching >10 000 IU litre^{-1}. Hyperkalaemic cardiac arrests during halothane/succinylcholine anaesthesia in young males were the sentinel scenario that led to the black box warning cautioning against the use of succinylcholine in males two decades ago.

DMD appears in the first decade of life, between 2 and 6 yr of age, although the clinical signs can be subtle. This disease classically presents with weakness of the proximal muscle girdle (hips and shoulders) as evidenced by Gower's sign.[28] By 6 yr of age, these children lose more than 40% of their muscle power and by 10–13 yr of age, they are wheelchair-bound. Pulmonary disease is restrictive in nature as forced vital capacity increases in the first decade of life, plateaus in the second decade, and then decreases linearly in the third decade. Dystrophin is also present in the heart and brain, and its absence yields interesting clinical findings.[27] Cardiac disease first becomes prevalent during the second decade of life with cardiac findings in 30% of boys by 14 yr of age and 50% by 18 yr.[28 32 33] Electrocardiographic

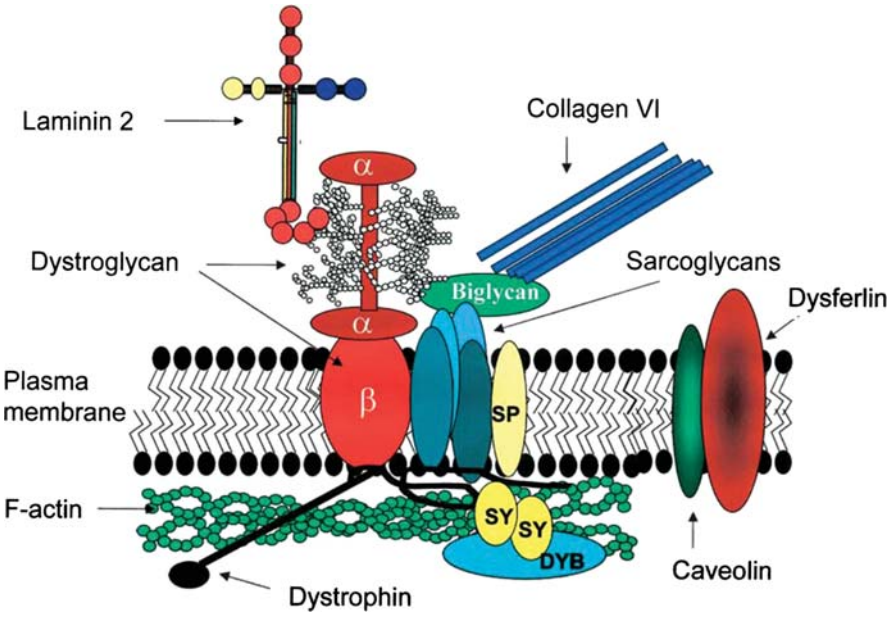

Fig 2 Schematic of proteins associated with dystrophin in skeletal muscle cells. The three key elements of the membrane skeleton and signal transduction path are: laminin 2, the extracellular component; dystrophin-associated protein complex (DAPC) (dystroglycan, sarcoglycan, and cytoplasmic subunits), the transmembrane component; and dystrophin, the intracellular component. The cytoplasmic subunit of the DAPC comprises syntrophin (SY) and dystrobrevin (DYB). Dystrophin is not only the pivotal element that reinforces the muscle cell cytoskeleton, but it also mediates signal transduction across cell membranes through its interactions with syntrophin, dystrobrevin, and neuronal nitric oxide synthase. Note non-contractile F-actin binds to the N-terminus of dystrophin. Reproduced with permission.[32] DyB, dystrobrevin; SP, sarcospan; SY, syntrophin.

abnormalities include Q-waves in the lateral leads, increased ST-segments, poor R-wave progression, resting tachycardia, and conduction defects.[33] Cardiomyopathy is present in 100% of children with DMD by 18 yr of age.[33] Although the cardiomyopathy can be undiagnosed and unapparent due to their sedentary life, exposure to general anaesthesia could be fatal if it is not detected before operation and managed. The natural course of this disease is to succumb due to cardiorespiratory failure before reaching 30 yr of age.

The clinical features of children with DMD depend on the age of presentation. Young children usually present with skeletal muscle weakness, the result of muscle damage and breakdown. Muscle mass is lost rapidly in the first decade and replaced with fatty infiltration leading to one of the hallmark signs of this disease, pseudohypertrophied calf muscles. By the beginning of the second decade, muscle breakdown wanes from a lack of viable muscle and cardiac involvement begins to develop. The loss of muscle and strength results in reduced mobility, which in turn leads to obesity. Limb disuse results in joint contractures, which is a common reason to undergo surgery. With progressive truncal motor weakness, 60–90% of children with DMD develop scoliosis. These children can require surgical stabilization or correction of the spinal deformity. Often preoperative cardiac assessment with electrocardiography and echocardiography is the first evidence of cardiac involvement in these children.

There is no treatment for DMD. Glucocorticoids, gene therapy, and cardiorespiratory support have met with mixed success.[34] Respiratory sequelae vary from upper airway dysfunction and sleep apnoea to impaired nocturnal respiration. Some respond to steroids, others to non-invasive ventilation.[35 36] Sitting, walking, breathing, and feeding become progressively more difficult, which culminates in progressive respiratory failure and cardiac collapse.

Becker's muscular dystrophy

The prevalence of Becker's muscular dystrophy (BMD) in the general population is 1:40 000–1:100 000.[28] It represents a milder form of DMD that occurs predominantly in males in the second decade of life. BMD is characterized by a reduced amount of dystrophin; hence, the progression of the weakness is slower and less severe than in DMD, with life expectancy of the fifth decade. Cardiac involvement is rare $<$16 yr of age, although almost 75% with BMD present with electrocardiographic abnormalities.[32]

Emery–Dreifuss muscular dystrophy

Emery–Dreifuss muscular dystrophy (EDMD) is a distinct type of MD that is either X-linked recessive or autosomal dominant, primarily affecting males at Xq28. The mutations cause defects in the production of essential proteins, emerin, or lamin A or C, all of which are integral to the muscle cytoskeleton. The onset of EDMD is usually by 10 yr of age or adolescence, with progressive proximal muscle weakness. Cardiac involvement distinguishes this disease with syncope being common, the result of cardiac conduction defects. Cardiomyopathy is not as common as with DMD.[32] A cardiac pacemaker can be required.

Anaesthetic considerations for children with all forms of muscular dystrophy

The anaesthetic implications of MD are in part dictated by the stage and severity of the disease. In general, the severity of MD in DMD is greater than in BMD and EDMD. Temporally, the clinical manifestations of DMD are bimodal: during early childhood when skeletal muscle is being destroyed, rhabdomyolysis and hyperkalaemia can occur in response to triggers, whereas during adolescence and adulthood, progressive cardiac and respiratory failure are the overwhelming concerns.

Although children with MD are not considered MHS, administering inhalation anaesthetics, succinylcholine, or both during their first decade can cause massive release of potassium, myoglobin, CK, and lysosomal enzymes. Succinylcholine is infrequently used today, leaving the potent inhalation anaesthetics as the most likely cause of rhabdomyolysis. In children with MD, there is insufficient evidence to absolutely contraindicate inhalation anaesthetics. Indeed, many children have been anaesthetized with inhalation anaesthetics without consequences, particularly older children. Nonetheless, a conservative approach is to avoid their use, and use a total i.v. anaesthetic technique. The minimum inhalation agent concentration that triggers muscle breakdown in MD is unknown, so the use of a clean anaesthetic workstation is advisable (see above).

Children with MD are at risk for sleep-disordered breathing and nocturnal desaturation, and up-regulation of endorphin receptors can increase their sensitivity to opioids.[37] The dose of opioids should be titrated to avoid perioperative respiratory complications.

Many seemingly 'normal' children with MD receive general anaesthesia for routine surgery without evidence of, or a diagnosis of, MD. A simple anaesthetic can suddenly deteriorate and become very unstable as rhabdomyolysis and hyperkalaemia threaten cardiovascular stability. Numerous cardiac arrests have been reported in these children, mostly males, with unrecognized DMD and BMD during inhalation anaesthesia with and without succinylcholine.[28] The mortality associated with a succinylcholine-induced hyperkalaemic arrest is 30%.[28] In adolescents, ventricular arrhythmias and congestive heart failure as manifested by hypotension have resulted in several reports of cardiac arrest during spine surgery.[28] Unexplained tachycardia should raise suspicion of cardiomyopathy.[32] Before operation, an electrocardiogram and echocardiographic assessment should be reviewed in all adolescent and adult MD patients before surgery to both optimize cardiac function and control arrhythmias.[38]

Acute hyperkalaemia is a life-threatening electrolyte disturbance that continues until the extracellular concentration of potassium returns to normal. It is not a presenting sign of

an MH reaction. Arrhythmias occur during hyperkalaemia because the increased concentration of extracellular potassium raises the resting membrane potential of ventricular myocytes to the threshold potential for ion channel activation, at which point the cells depolarize. This leads to the ventricular premature contractions. The definitive treatment is to increase the threshold potential by administering exogenous i.v. calcium chloride (10–20 mg kg^{-1}) or calcium gluconate (20–40 mg kg^{-1}). Calcium also prolongs the refractory period of the cardiac action potential, which stops the arrhythmias immediately. However, the effect of the calcium is evanescent, necessitating repeat boluses if the arrhythmias persist or resume. I.V. calcium should always be on hand if succinylcholine is administered. Ancillary treatments for hyperkalaemia include salbutamol, hyperventilation, and insulin and glucose. Hyperhydration and diuresis should be instituted to prevent the precipitation of myoglobin in the renal tubules.

Nondepolarizing neuromuscular blocking drugs should be titrated to effect since children with MD may be more sensitive because of the loss of muscle mass and/or from up-regulation of extrajunctional acetylcholine receptors (see above).[1] In one study of the responses to rocuronium in adolescent DMD patients, the time interval to 95% twitch suppression was twice and the time to recover one twitch to 90% triple that in normal patients.[39]

Scoliosis surgery is the most common major surgery that MD patients undergo as young adults. The requirements for motor-evoked potentials have shifted the anaesthetic management away from inhalation anaesthetics and towards total i.v. anaesthesia. For adolescents and adults with MD, intraoperative echocardiography or central venous pressure monitoring combined with arterial pressure monitoring is appropriate. Patients with MD also present a greater risk of intraoperative bleeding during this surgery. Although this has been attributed to platelet dysfunction, recent evidence supports a defect in vascular reactivity due to the absence of dystrophin in vascular smooth muscle cells.[40] To offset this effect, some recommend antifibrinolytics such as ε-aminocaproic acid in a loading dose of 75 mg kg^{-1} i.v. over 15–20 min before skin incision followed by a maintenance infusion of 15 mg kg^{-1} h^{-1} until surgery is completed.

Mitochondrial myopathies

Mitochondrial myopathies (MMs) are a heterogeneous group of inborn metabolic errors of energy (adenosine triphosphate) production in mitochondria with an estimated prevalence of 1:5000 live births.[41–44] Energy in mitochondria is produced by the respiratory chain (RC), which comprises five protein/enzyme complexes (I–V) located on the inner mitochondrial membrane. RC defects arise from two sources due to their bigenomic control: (i) nuclear genome (nucDNA), which codes for 85% of the protein subunits and also the DNA replication and translation machinery and follows a Mendelian inheritance pattern, and (ii) mitochondrial genome (mitoDNA), which codes for the remaining 15% of the protein subunits and the mitochondrial RNA and is inherited along maternal lines by a 9:1 ratio.[45] The majority of paediatric MMs are determined by nucDNA, whereas those in adults are determined by mitoDNA.

RC defects can present at age, although presentation in childhood tends to be more severe and frequently involves multiple organs. The variability covers a spectrum from encephalopathic, acidotic death in infancy to mild myopathy in adults.[45] Weakness begins in childhood or adolescence and progresses at a varying rate. It can be accompanied by one or more extra-muscular findings, including gastrointestinal difficulties, visual, neurological, and cardiac defects. These findings depend on the tissue distribution of the defective nucDNA and mitoDNA, which is determined in the embryo stage.[46] The severity of the clinical manifestations depends on the relative concentration of the defective and normal DNA in the involved tissues: central nervous system (CNS), skeletal muscle, heart, kidney, liver, and pancreas. Thousands of copies of mitoDNA are present in each cell; when both the wild (normal) and mutated types coexist, known as heteroplasmy, a threshold concentration of mutated mitoDNA must be present for the phenotype.[47] Hence the varied clinical presentation of MM.

Several diagnostic strategies have been used to classify these disorders. Ragged red fibre is the histological finding that is pathognomonic of MM.[45 47 48] This is the subsarcolemal accumulation of defective mitochondria and complex IV deficient fibres that stain red with the Gomori trichrome stain. Electron microscopy might also reveal intramitochondrial paracrystalline inclusions. Genetic markers and amino acid substitutions primarily for nucDNA have been identified for several MM. Plasma CK concentrations are usually normal, but lactic acid can be increased. In adults, RC defects commonly occur in complexes I and III, whereas in children, complexes I, IV, and multiple combinations are most frequent (~20% each).[44 49]

Classification of MM has been difficult, in part, because the genetics are complex and the clinical phenotypes overlap. To date, 10 common syndromes have been described: Kearns–Sayre syndrome, Leigh's syndrome, mitochondrial DNA depletion syndrome, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), myoclonus epilepsy with ragged red fibres, mitochondrial neurgastrointestinal encephalomyopathy, neuropathy, ataxia and retinitis pigmentosa (NARP), and external ophthalmopledgia.[41 50]

In general, children present with signs of CNS involvement (including encephalopathy, seizures, strokes, ataxia), myopathy (non-specific), hearing and visual loss, gastrointestinal disorders (from swallowing difficulties to bowel dysmotility), cardiomyopathy (conduction defects and cardiomyopathy), respiratory insufficiency (aspiration, pneumonia), hepatic and renal insufficiency/failure, hypoglycaemia, increased plasma lactate levels, and anaemia.[51] The myopathy can be as minimal as exercise intolerance or as widespread as generalized hypotonia. The prevalence of cardiomyopathy in children with MM is reported to be 20%, with a substantive

mortality rate of 70% (triple the rate of those without cardiomyopathy) before 30 yr of age.[52] Interestingly, most patients with cardiomyopathy responded to therapy. Some children with MM (e.g. Leigh's syndrome) can develop nocturnal hypoventilation and desaturation, which can increase opioid sensitivity.[37] Owing to the heterogeneous nature of the RC defects, the clinical manifestations are varied and complex.

There is no definitive treatment for MM, although some have improved with specific therapies such as coenzyme Q10 (an essential electron transport carrier in complex I).[47 53] Some children with seizures respond to a ketogenic diet.

Anaesthesia for children with MM has been confusing and contradictory. In those with lactic acidosis (>90% of children with MELAS), excessive fasting and i.v. solutions with lactate should be avoided. A basal rate of glucose should be infused in the perioperative period, recognizing that they might have difficulty controlling excess glucose. There are no contraindications to anaesthesia in children with MM, although all anaesthetics moderately suppress the RC.[50 54 55] Conversely, several anaesthetics have neuroprotective effects and can provide anaesthetic preconditioning. Most inhalation anaesthetics and propofol in particular suppress complexes I and II of the RC. Large doses (>5 mg kg^{-1} h^{-1}) of propofol administered for extended periods (>48 h) have led to a life-threatening scenario in a number of fasted and stressed children that has been attributed to the inhibition of both cytochrome oxidases II and IV in the mitochondria and carnitine palmitoyltransferase on the membrane surface of the mitochondria.[56 57] The resulting disorder is known as propofol infusion syndrome. Sporadic reports of unexplained metabolic acidosis in children who were anaesthetized with infusions of propofol that lasted only a few hours but resolved with discontinuation of, or a reduction in the dose of, propofol suggest that these reactions may be a *forme fruste* of propofol infusion syndrome. Although propofol infusion syndrome impairs mitochondrial oxidation and transport of free fatty acids in a manner not unlike that in MMs, patients who develop propofol infusion syndrome have not been diagnosed with a (subclinical) form of MM. Even though propofol interferes with fatty acid metabolism and the RC, many other anaesthetics and medications do so as well. In the absence of evidence that propofol poses a greater risk for anaesthesia in children with MMs than inhalation anaesthetics, the use of propofol for brief procedures appears reasonable in children with MM.

Both sensitivity and resistance to non-depolarizing neuromuscular blocking agents have been reported in MM.[58 59] The latter could be due to up-regulation of acetylcholine receptors due to anticonvulsant drugs, a CNS event, and/or muscle regeneration. Neuromuscular blocking agents should be titrated and the blockade monitored when a relaxant is used.

A history and examination for the presence of serious respiratory effects (pneumonia, aspiration), cardiac defects (conduction defects, congestive heart failure), neurological complications (hemiplegia, stroke, bulbar palsy), and myopathy should be assessed before operation and the anaesthetic modified accordingly.[42 43 47 52] A preoperative electrocardiogram and echocardiogram are strongly recommended. Preoperative glucose, lactate levels, kidney, and liver function tests should be reviewed.[43] Knowing the precise gene defect will help identify the anticipated clinical manifestations.[51] Two retrospective reviews totalling 180 children with MM yielded few serious complications and none related to anaesthesia, despite the use of a panoply of anaesthetics, including inhalation agents.[42 60]

Cerebral palsy

Cerebral palsy (CP) is a heterogeneous group of chronic non-progressive disorders of motor development and posture in children that are associated with cognitive and neurosensory disabilities.[61 62] The prevalence in the general population is 1:500 live births.[62 63] Although traditional belief has held that CP is an asphyxial birth injury, the evidence is overwhelming that most cases of CP arise from intrauterine, antepartum events that could not be prevented (Table 4). The vast majority have antecedent intrauterine causes, the nature of which is incompletely understood.

Although the aetiology of CP might be traced to a single severe event *in utero*, more often than not multiple causes are involved. The risk of CP in premature births is almost 100-fold greater than in term births.[64] Premature births account for only 5% of births, but they account for 50% of all cases of CP. The risk of CP is also greater with multiple births: triplets>twins>singleton births (Table 4). The frequency of CP is even greater with the demise of one fetus *in utero*. One intriguing theory for the occurrence of CP in singleton births is the 'vanishing' twin phenomenon, which refers to an intrauterine demise in a twin in the first trimester that was resorbed before the first ultrasound.[64] With ultrasounds now performed in the second month of pregnancy, non-viable, dead, or remnant fetuses have been identified to lend credence to this theory. Whether the fetal demise causes an inflammatory response, vasculopathy, or placental complication (e.g. thrombosis), there is now mounting evidence that points to *in utero* events to account for the vast majority of cases of CP rather than birth asphyxia.

Preoperative considerations for the child with CP vary with the severity of the disease and the associated medical conditions. CP can be classified according to the anatomical

Table 4 Estimates of aetiology of CP in term infants. Data reproduced with permission[80–84]

Neuro-based imaging	
Perinatal ischaemic stroke	22%
Congenital malformation	15
White matter disorder	12
Hypoxia-ischaemia	5
Clinical studies	
Intrauterine exposure to inflammation	11–12%
Birth asphyxia	6
Complications of multiple birth	5

Table 5 Classification of CP[65]

Spastic (70%)
Quadriplegia (27%)
Diplegia (21%)
Hemiplegia (21%)
Dyskinetic (10%)
Dystonia (twisting torso)
Athetosis (slow purposeless, distal movement)
Chorea (quick, jerky proximal movement)
Ataxia (10%)
Intention tremor
Mixed (10%)
Spastic athetoid

defect: hemiplegia, spastic diplegia, quadriplegia and the associated medical conditions, or by the type of neurological impairment (Table 5).[62 65]

In the preoperative history, all current medications should be recorded, including anticonvulsants, anti-spasticity, and anti-reflux medications.[65] Importantly, baclofen should not be withheld abruptly as this can precipitate acute withdrawal. Clonidine can be used for attention-deficit and hyperactive disorder or spasticity. This medication is also an effective sedative that has resulted in a cardiac arrest during induction of anaesthesia after an overdose was administered before operation by a parent.[66] Oral dantrolene can also be used for spasticity. Note that baclofen and dantrolene cause weakness and complicate resumption of adequate respiratory effort during emergence from anaesthesia.

Gastro-oesophageal reflux is a common, chronic problem for which a Nissen fundoplication is often required. These children require G-tube feeding with or without the fundoplication because of bulbar palsies and difficulties chewing and swallowing. For those with active reflux, tracheal intubation is strongly recommended. Two respiratory concerns are common in these children: (i) chronic pneumonia from aspiration or failure to clear secretions and (ii) reactive airways disease. An adequate course of antibiotics after an acute pneumonia is required before considering a general anaesthetic. Preoperative wheezing should be assessed with either a deep cough manoeuvre or a bronchodilator. If wheezing does not resolve, further evaluation and treatment might be indicated. During the preoperative interview, one often finds a spastic, non-communicative child with joint contractures. Most relevant information is obtained from the parents or caregivers. The chest should be auscultated for evidence of chronic aspiration, asthma, or both. The airway is usually normal and should not present any greater challenge to laryngoscopy than any other child. The presence of kyphoscoliosis can require careful positioning of the head and neck, particularly for laryngoscopy.

Thirty per cent of children with CP have seizures.[67] Anticonvulsants should be taken on the day of surgery with a sip of water, rectally, or if necessary i.v.

Preoperative anxiety is an issue for these children, particularly since many cannot communicate effectively and have undergone multiple surgeries. Oral (or i.v.) midazolam premedication should be administered if appropriate. Anaesthesia can be induced either i.v. or by inhalation. Since i.v. propofol regularly causes pain when administered through a small i.v. in the hand, a mini-Bier block with 1 mg kg^{-1} i.v. lidocaine can be helpful before administering propofol.[68 69] Alternatively, the child might request a mask for induction if it is not contraindicated.

Depending on the surgical requirements and child's medical condition, the airway can be supported with either a laryngeal mask airway or a tracheal tube. To facilitate tracheal intubation during sevoflurane anaesthesia, i.v. propofol or a neuromuscular blocking agent can be given.[70] The induction dose of propofol increases with decreasing age, although the effect of cognitive dysfunction on the dose has not been determined. Succinylcholine has been used in children with CP for more than 50 yr without a single report of a hyperkalaemic response.[71] Although there is laboratory evidence that children with CP have minimal up-regulation of nicotinic acetylcholine receptors, these extrajunctional receptors are not widespread but close to the neuromuscular junction and appear to have a weak-to-no effect to augment the response to succinylcholine.[72] One theory to explain why CP patients do not mount a substantive hyperkalaemic response to succinylcholine holds that their muscles were never fully developed and functionally innervated. Children with CP can demonstrate resistance to vecuronium as determined by a rapid recovery from neuromuscular block.[73] It is prudent to monitor neuromuscular block in these children.

The MAC of halothane is reduced in children with CP and cognitive impairment.[74] In the presence of anticonvulsants, MAC is reduced 30%, whereas in their absence, it is reduced 20%.[74] Bispectral index values were 10–20 units less after premedication and 1% sevoflurane in children with CP than in unaffected children, although no differences were present at induction and 3% sevoflurane.[75]

Pain is a difficult symptom to assess in the perioperative period in cognitively impaired children. Children with CP receive less opioids than those without.[76] It has been suggested that children with CP are more sensitive to the respiratory depressant effects of opioids than those without.[67] The reason for this effect remains elusive, although these children can have an obstructive sleep apnoea pattern with intermittent nocturnal desaturation that up-regulates endorphin receptors and hence, increases opioid sensitivity.[77]

Maintaining thermal homeostasis can be difficult in children with CP. They have very little subcutaneous fat to insulate them against heat loss and are generally inactive thus generating little heat. Furthermore, their shivering set point can be reset as a result of their neurocognitive dysfunction. Heat loss from redistribution of heat from the body core at the onset of anaesthesia is difficult to prevent, although pre-heating the operating theatre and using a forced-air warmer reduces radiation and convective

heat losses, which comprise the majority of the heat loss in the operating theatre.

Haematological profiles can be abnormal. Chronic nutritional difficulties combined with chronic disease (such as aspiration and pneumonia) increase the frequency of anaemia in these children, which results in more frequent transfusions during surgeries with modest blood loss. Platelet function and numbers can be reduced for the same reasons and may also be a side-effect of chronic administration of anticonvulsants. These platelet effects combined with reduced clotting factors for similar reasons increase the risk of bleeding during major surgery such as scoliosis, which occurs in 20% of children with CP.[67] Scoliosis surgery is often extensive, involving segments from the thoracic region to the sacrum, with pelvic stabilization to assist in sitting. Taken together, these factors increase the risk of bleeding during scoliosis surgery. As a result, ε-aminocaproic acid should be considered for major surgery in these children (see dosing above).

In the postoperative period, parents can be better at managing their child's pain than healthcare personnel. Few complications have occurred with parent- or nurse-controlled analgesia in children $<$6 yr of age.[78] Under closely monitored conditions, parent-controlled analgesia can be effective with small risks in children with cognitive impairment. Regional anaesthesia including epidural analgesia and continuous nerve blocks can be very effective.[65] Continuous infusion of local anaesthetic has been effective in lower extremity surgery in CP children.[79] However, caution must be exercised in the presence of a baclofen pump.

Conflict of interest

None declared.

Funding

This report was funded from no external sources.

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