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

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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

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