Neuromuscular and mitochondrial disorders: what is relevant to the anaesthesiologist?
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Introduction
There are many inherited and acquired neuromuscular disorders that may interfere with vital functions and with the response to surgery and anaesthesia. The diseases with a prejunctional or junctional origin are documented in former reviews [1,2,3], which still apply today. In this review, the accent is on disorders of the muscle and mitochondria.

Upregulation of the nicotinic acetylcholine receptors
Several conditions including upper and lower motor neuron lesions cause denervation of the striated muscle followed by upregulation of nicotinic acetylcholine receptors (AChRs) [4]. Also muscle denervation (by muscle relaxants, drugs, or toxins), immobilization, muscle inflammation and trauma, or both, as seen in burn injury or radiation injury, cause upregulation of AChRs. This involves an increase in number of AChRs spreading throughout the muscle membrane [4]. Patients with Duchenne muscular dystrophy, as a result of muscle regeneration, may also have upregulation of AChRs [1].

There is now evidence that an isoform of AChR, neuronal (nicotinic) α7AChR, is expressed and upregulated in muscle with these conditions [5]. These α7AChRs are more sensitive to succinylcholine and its metabolite, choline, than normal AChRs. This accounts for the persistence of hyperkalemia and the risk of cardiac arrest. The hyperkalemic response to succinylcholine is proportional to the upregulation. The presence of two or more aetiologic factors will magnify the upregulation. Despite the US Food and Drug Administration’s (FDA) warning against the administration of succinylcholine in young children and adolescents in 1992, it continues to be used widely, particularly when a rapid onset and/or offset of muscle relaxation are desirable. However, it is still one of the common causes of paediatric cardiac arrest during anaesthesia [6]. It is advisable to reserve succinylcholine for emergency intubation or when immediate securing of the airway is necessary [6] and to avoid it in patients with aetiologic factors for upregulation.

The α7AChRs in muscle have a lower affinity for nondepolarizing neuromuscular blocking drugs (NMBD), and higher doses are required [5]. Pretreatment with nondepolarizing NMBDs in the usual doses will not prevent succinylcholine-induced hyperkalemia. In conditions of upregulation, even a high dose of a nondepolarizing NMBD (e.g. 1.2 mg/kg rocuronium) will not have an onset time comparable with that of succinylcholine.

Purpose of review
The review provides an up-to-date information to the anaesthesiologist about the more frequent and important neuromuscular disorders for which new basic insights or clinical implications have been reported.

Recent findings
The findings include the mechanisms of the hyperkalemia after succinylcholine in patients with upregulation of acetylcholine receptors. New insights into the mechanism of malignant hyperthermia-like reactions such as rhabdomyolysis during anaesthesia in patients with Duchenne muscular dystrophy have been published. The importance of mitochondrial defects and the effect of agents used in anaesthesia on mitochondrial function are also highlighted.

Summary
The increased understanding of the genetics and pathophysiology of common muscle disorders may lead to a decrease in life-threatening complications related to surgery and anaesthesia. However, there is still a lack of prospective clinical studies to determine which is the safest anaesthetic technique for these patients.

Keywords
children, Duchenne’s muscular dystrophy, mitochondrial disease, myopathy, neuromuscular disorders

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Although the diagnosis of acute hyperkalemia as a cause of cardiac arrest and arrhythmias is confirmed by the measurement of serum potassium levels, treatment should be initiated based on medical history of patients (succinylcholine administration in susceptible pathologic state) and electrocardiographic or cardiovascular changes. For a perioperative hyperkalemic cardiac arrest, the American Heart Association Guidelines recommend the immediate administration of calcium in a dose of 0.5 ml/kg of 10% calcium gluconate (or chloride). Also the cellular uptake of potassium should be promoted by a glucose load (0.5 g/kg) with insulin (0.05 U/kg), sodium bicarbonate and β₂-adrenoceptor agonist (e.g. albuterol via nebulizer).

There is one other mechanism of hyperkalemic cardiac arrest in some muscle diseases, namely, acute rapid rhabdomyolysis [4]. This is due to the breakdown of the muscle-surface membrane with loss of myoglobin, potassium and creatine kinase.

### Congenital myopathies and congenital muscular dystrophies

The group of inherited congenital myopathies is rare and has a heterogeneous genetic and phenotypical expression [7]. Central core disease is a recessive congenital myopathy with hypotonia and weakness from birth, but with slow progression during later life. Like malignant hyperthermia, it is a primary disorder of calcium regulation, and in the majority of cases mutations in the \( RYR1 \) gene on chromosome 19q13.1 are found [8*,9*].

The group of congenital muscular dystrophies is also heterogeneous, mostly autosomal recessive, and characterized by an early onset hypotonia but with dystrophic pattern at muscle biopsy. Creatine kinase levels are frequently increased at baseline. There is a laminin (former merosin) α2 deficient group and a form, which is not laminin linked. Although these dystrophies have not been reported to be malignant hyperthermia susceptible, recently a case of a suspected malignant hyperthermia episode was reported during anaesthesia for posterior spinal fusion in the absence of classical triggering agents for malignant hyperthermia [10].

The anaesthetic problems with these children are mostly related to the common symptoms and signs of children with hypotonia and muscle weakness in general (Table 1).

### Myotonias

Two groups of myotonias are generally distinguished: a dystrophic and a nondystrophic group.

In the dystrophic group of patients, in contrast to the nondystrophic group, progressive muscle wasting and weakness with dystrophic changes in muscle histology is seen. Myotonic dystrophy or Steinert’s disease is a multisystemic autosomal dominant neuromuscular disorder with an incidence of 2.4–5.5 cases per 100 000 births in UK [11]. Onset occurs mostly during early adulthood. In the congenital form hypotonia, respiratory difficulties and swallowing problems are present at birth. With improving care, these patients now present more commonly for anaesthesia and surgery. A thorough preoperative screening is important, with special attention required for respiratory and cardiac (conduction defects and mitral regurgitation) manifestations and possible interactions of long-term medication against myotonic crisis (phenytoin, quinine).

The nondystrophic group is divided into two: one consisting of patients with chloride channel dysfunction (Thomsen and Becker’s myotonia congenita) and the other with sodium channel dysfunction (paramyotonia congenita, hyperkalemic periodic paralysis with myotonia) [12*]. The basic alteration is electrical hyperexcitability of muscle fibres and a prolonged time for relaxation after voluntary muscle contraction and external mechanical stimulation. The main symptom is a persistent muscle contraction following mechanical stimulation, hypothermia, shivering and some medicines. Succinylcholine is contraindicated because a myotonic crisis with subsequent difficulty in ventilation and intubation is possible [13]. When using nondepolarizing NMBDs, one should realize that the duration of paralysis will likely be prolonged. When residual postoperative paralysis occurs, anticholinesterases are better avoided because a myotonic crisis may follow [13].

For these myotonias, an increased risk for malignant hyperthermia susceptibility is sometimes suggested and avoidance of halogenated agents recommended. However, there is little evidence for this [1]. Anecdotally, one report of the death of a 5-year-old child with myotonia congenita who developed a clinical syndrome suggestive of malignant hyperthermia 7 h after surgery occurred after an anaesthetic technique with ‘nontriggering’ agents [14].

### Duchenne and Becker type muscular dystrophy

Duchenne’s muscular dystrophy (DMD) is the most common form of muscular dystrophy, seen in one per
3500 births. It is an X-linked disease caused by mutations in the dystrophin gene, resulting in complete loss of the muscular protein dystrophin, leading to a weakened sarcolemma [15**]. The symptoms of proximal muscle weakness with typical waddling gait and pseudohypertrophy of calf muscles appear at the age of 2–6 years, and patients are usually wheelchair-bound by the age of 10 years. The progressive nature of the disease results in restrictive pulmonary function, multiple contractures, scoliosis and cardiomyopathy. Many DMD patients have markedly increased (50–100 times normal) serum creatine kinases. Becker’s muscular dystrophy (BMD; one in 30 000 men) is an allelic disorder of DMD in which dystrophin is only partially absent.

Patients with DMD often require surgery for muscle biopsy, correction of scoliosis and release of contractures. The risk associated with surgery and anaesthesia is related to progressive respiratory insufficiency and cardiocirculatory involvement with cardiomyopathy, conduction defects and arrhythmias. Cardiac arrests in DMD patients have been reported in the postanaesthetic care unit after uneventful anaesthesia [15**]. Rachymolysis as a result of muscle damage is another important risk factor in patients with DMD. Acute rhabdomyolysis can be triggered by the administration of succinylcholine, which should be avoided in DMD patients [4].

Inhalational anaesthetic agents have also been implicated as a cause of rhabdomyolysis and preoperative and postoperative metabolic reactions that resemble malignant hyperthermia in DMD patients. The retrospective interpretation of these rare case reports [15**] is difficult and the diagnosis of malignant hyperthermia is often rather a matter of exclusion. Furthermore, in most of the case reports on malignant hyperthermia in DMD patients, no in-vitro contracture test (IVCT) on muscle biopsy has been done to confirm the malignant hyperthermia diagnosis.

Richards [16] in 1972 reported a case of series of 43 patients with DMD who received a total of 61 general anaesthetics without problems, including 37 patients who received halothane. Other retrospective case series [17,18] could not show a clear relationship between malignant hyperthermia reactions and halogenated agents. In Gronert’s review [4], rhabdomyolysis-induced cardiac arrest plays an important role in DMD patients. He concluded that succinylcholine is contraindicated in DMD patients but that halogenated anaesthetic agents can be briefly tolerated. Breucking et al. [19] reported an evaluation of 200 questionnaires in 147 families with DMD and 53 with BMD for anaesthesia complications. They found six cardiac arrests, all successfully resuscitated. In five of these patients, an inhalational agent and succinylcholine were used; in the sixth patient no information was available regarding anaesthetic and NMBA use. There were no more cardiac arrests reported in the series of patients after the FDA warning in 1992. In the previous years, two prospective studies [20,21] on DMD patients receiving anaesthesia with halogenated agents for corrective spine surgery found no complications, which could be interpreted as malignant hyperthermia or life-threatening rhabdomyolysis.

Halogenated anaesthetics should, however, be used with caution in patients with DMD as hyperkalemia in boys and myocardial depression in adolescents with DMD may occur [22]. These complications are more frequent in DMD children and may also be caused by other drugs and conditions (e.g. cardiomyopathy, upregulation of AChR). Two case reports of acute heart failure during spinal surgery in DMD patients during propofol–opioid anaesthesia [23,24] demonstrate that using total intravenous anaesthesia (TIVA) in DMD still may cause major problems. A recent report of an infant who developed postoperative rhabdomyolysis and death due to sepsis after the last of nine uneventful anaesthetics with halogenated agents illustrates the complexity of the topic [25**]. The controversy about the choice of the preferred anaesthetic agent in DMD is illustrated in recent reviews or editorials [15**,22,26,27**]. The use of dantrolene in anaesthesia-induced rhabdomyolysis is doubtful [15**,22].

In patients with DMD, the onset of blockade by nondepolarizing NMBA’s may be significantly delayed, which should be kept in mind in situations when a rapid airway protection is necessary. Furthermore, the prolonged recovery from rocuronium-induced block emphasizes the need for neuromuscular monitoring in DMD patients [28].

DMD patients require a comprehensive preoperative assessment and extensive and directed peroperative monitoring. Monitoring of creatine kinases and cardiorespiratory function should be continued postoperatively.

**Mitochondrial diseases**

Mitochondria are the main sites of the electron transfer chain and oxidative phosphorylation (OXPHOS) resulting in ATP production. Organs such as brain, heart and skeletal muscle are highly energy-dependent and vulnerable to mitochondrial defects.

Mitochondrial disorders are genetically and phenotypically a heterogeneous group with an estimated incidence of one in 4000. Besides mitochondrial DNA mutations [e.g. mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS), myoclonic epilepsy and ragged-red fibres (MERFF) syndromes] and deletions (Kearns–Sayre syndrome), there are primary deficiencies of the respiratory chain complexes I–V [29]. Classification of mitochondrial disorders into specific clinical syndromes
has been attempted (Kearns–Sayre, Leigh, MELAS, MERRF, etc.), but there is a large overlap and no clear correlation between clinical findings and the site of biochemical defect. Another approach is to classify the patients according to the measured enzyme activities of the different complexes of the OXPHOS system [30,31].

Mitochondrial myopathies often present with proximal weakness with raised lactic acid levels.

In a retrospective review of 155 children who underwent a diagnostic surgical muscle biopsy in a tertiary centre, 122 patients had a mitochondrial disorder diagnosis [31*]. At the preoperative assessment, signs of encephalopathy (epilepsy, psychomotor retardation) were most frequent, followed by muscle weakness, lactic acidosis, cardiomyopathy and/or conduction defects and chronic respiratory problems. Anaesthesia was mostly induced with a rapid sevoflurane technique and maintained with halogenated agents. With standard preoperative assessment, monitoring and anaesthesia management, there were no major anaesthesia-related complications in children with a mitochondrial disorder diagnosis.

Patients with mitochondrial disorders often have many preoperative problems, predisposing them to anaesthetic complications such as refractory epilepsy [31*], decreased respiratory and cardiac reserve, impaired swallowing and metabolic dysfunction. Unusual sensitivity to intravenous anaesthetics can occur [29]. Morgan et al. [32] reported a case of four children with main defects in complex I, who required very low sevoflurane concentrations to reach a bispectral index (BIS) value of 60, although the apparent increased sensitivity did not correlate with adverse effects.

The association between mitochondrial myopathies and malignant hyperthermia has now mostly been dismissed [27**]. Control of excessive stress and maintenance of stable cardiovascular and respiratory functions are the primary goals of anaesthesia in children with mitochondrial disorders [27**,29]. It is also very important to regularly assess glucose levels to give adequate intravenous glucose and fluid solutions and to avoid lactated solutions to prevent lactic acidosis.

Mitochondria also act as a target for anaesthetic agents. These effects can be toxic (e.g. local-anaesthetic induced cardiotoxicity) or beneficial (e.g. myocardial protection by inhalational agents) [33**].

Particularly, propofol has several effects on mitochondria [33**,34]:

1. inhibition of the OXPHOS complex I;
2. inhibition of carnitine palmitoyl transferase I, responsible for inhibition of the transport of long-chain fatty acids;
3. inhibition of β-oxidation.

It is proposed that these mitochondrial depressant effects account for the propofol infusion syndrome (PRIS). Bray [35] reported 18 critically ill children who under propofol sedation developed a typical clinical entity of metabolic acidosis, refractory cardiac failure, fever and muscle cell damage. Farag et al. [36] reported that even short-term use of propofol in children with mitochondrial disorders may be associated with delayed recovery and the need for ICU admission. They proposed that children who develop metabolic acidosis and myocardial failure after propofol infusion may have subclinical forms of mitochondrial disorders. Reviews on this rare complication have recently been published [37,38,39**]. Kam and Cardone [39**] recorded 61 patients with PRIS in the literature. Seven of these patients (four paediatric) developed PRIS during anaesthesia. Impaired tissue perfusion (e.g. in sepsis) may be a common underlying mechanism [38,40*]. The use of TIVA with propofol may no longer be considered the anaesthetic of choice for children with mitochondrial disorders or predisposing aetiological factors for PRIS.

Severe organ toxicity and mortality with similar characteristics to PRIS in humans have recently been demonstrated in a prospective study [41**] on propofol-sedated rabbits under prolonged mechanical ventilation. Sevoflurane proved to be a safe alternative.

Clinically relevant concentrations of bupivacaine, levobupivacaine and ropivacaine in vivo in the rat produced a significant decrease in mitochondrial ATP synthesis and a global reduction in enzyme activities of the respiratory chain [42*]. This suggests that caution is required with the dose of local anaesthetics given to patients with mitochondrial disorders.

Several agents used during anaesthesia (local anaesthetics, propofol, high concentrations of inhalational anaesthetics) may influence the result of a diagnostic muscle biopsy for determining the presence and severity of mitochondrial disorders. This is an unsolved problem, but with the present knowledge, ketamine and low-dose halogenated anaesthetics are the best choice for diagnostic muscle biopsy for suspected mitochondrial disorders.

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**The child with suspected/undiagnosed myopathy: which is the best anaesthetic management?**

The child with an undiagnosed myopathy represents a difficult problem regarding optimal anaesthetic management. Historically, several case reports and reviews confront the anaesthesiologist with a dramatic scenario,
that is, these children have a serious risk of developing malignant hyperthermia and rhabdomyolysis.

A special problem exists when a neonate or infant with hypotonia is presented for anaesthesia and the diagnosis is not yet established. A recent retrospective study [43] on 144 infants diagnosed with neonatal hypotonia showed that actually 82% of the patients had a cerebral cause and only 10% had peripheral neuromuscular origin (e.g. spinal muscular atrophy 6% and myotonic dystrophy 4%).

An interesting finding is that of a retrospective review [44] of a large population of patients (n = 2214) who underwent muscle biopsy for malignant hyperthermia diagnosis. With ‘trigger-free’ anaesthesia, the incidence of malignant hyperthermia reactions was still 0.46%. These reactions occurred mostly in the immediate postoperative period.

The importance of hyperkalemic cardiac arrest by succinylcholine in children with occult myopathies has already been underlined [4,45]. The use of halogenated agents has long been controversial, and some have suggested that halogenated agents should only be used briefly for induction until an intravenous catheter is placed, or when higher risks such as a difficult airway exist [4,15**,26]. Recently, Flick et al. [46**] reviewed 274 charts of children with suspected neuromuscular disorders, who had undergone muscle biopsy for the occurrence of malignant hyperthermia or rhabdomyolysis. All of the children received halogenated anaesthetic agents with or without succinylcholine, and no child developed malignant hyperthermia or rhabdomyolysis. Rather than assuming a risk of zero, they estimated the risk of a patient with neuromuscular disorder for developing malignant hyperthermia or rhabdomyolysis from exposure to a volatile anaesthetic agent at less than or equal to 1.09%.

Is a total intravenous technique with propofol a safe alternative to halogenated agents and appropriate for all children with myopathies? One must consider the child with mitochondrial myopathies and with difficult airway management. The use of propofol in undiagnosed myopathic patients is also controversial given recent reports of rhabdomyolysis, unremitting acidosis and death, mostly in sedated paediatric patients [34,39**,46**]. More large-scale studies are needed to elucidate the existing dilemma of what is the best anaesthesia for the child with undiagnosed myopathy. For minor surgery such as muscle biopsy, ketamine may be a safe alternative to propofol and halogenated agents. Also locoregional anaesthesia may be considered, at least if no mitochondrial disorder is suspected.

**Conclusion**

Children with neuromuscular and mitochondrial disorders often have several signs and symptoms (respiratory and cardiac compromise, difficult swallowing and regurgitation, rhabdomyolysis), which may increase the risk associated with anaesthesia and surgery. Careful pre-operative assessment should help to make the best choice of the type of anaesthesia for the individual child. Also perioperative monitoring requires the highest possible standards.

More large-scale prospective clinical studies are needed to determine the safest anaesthetic technique in this heterogeneous group of patients.

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**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 418).


The differentiating features of the nondystrophic myotonias are summarized.
Discusses the lack of evidence about the optimal anaesthetic agent in children. Evidence against an association of DMD and malignant hyperthermia is now available. This article reviews alternative mechanisms for these perioperative ‘malignant hyperthermia-like’ reactions reported in DMD patients. Evidence against an association of DMD and malignant hyperthermia is now available. This article reviews alternative mechanisms for these perioperative ‘malignant hyperthermia-like’ reactions reported in DMD patients.


Mitochondria act as a target for the anaesthetic agents. The effects can be toxic as in the case of local anaesthetic-induced myocardial protection/preconditioning. Mitochondrial metabolism could be disturbed in many critical situations.


Wysowski DK, Pollock ML. Reports of death with use of propofol (Diprivan) for nonprocedural (long-term) sedation and literature review. Anesthesiology 2006; 105:1047–1051.


On the basis of analysis of 61 patients reported in the literature, it is proposed that the propofol infusion syndrome is caused either by a direct mitochondrial respiratory chain inhibition or impaired mitochondrial fatty acid metabolism mediated by propofol.


Mitochondrial dysfunction seems to be intrinsically involved in the pathogenesis of multiple organ failure.


Continuous infusion of 2% propofol at large doses for the sedation of rabbits undergoing prolonged mechanical ventilation induced a fatal multorgan dysfunc- tion syndrome similar to the propofol infusion syndrome seen in humans. Sevo- flurane proved to be a safe alternative medication for prolonged sedation.


Bupivacaine, levobupivacaine and ropivacaine caused a global decrease (around 50%) in all of the enzyme activities of the respiratory chain.


In 274 children who underwent muscle biopsy, inhalational anaesthetic agents with or without succinylcholine were given. None of the patients actually developed malignant hyperthermia or rhabdomyolysis.