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Review

Complications of anaesthesia in neuromuscular disorders

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Abstract

The purpose of this review is to alert non-anaesthesiologists to the various complications from which patients with neuromuscular disorders and those susceptible to malignant hyperthermia can suffer during anaesthesia. The patient's outcome correlates with the quality of consultation between anaesthesiologists, surgeons, neurologists and cardiologists. Special precautions must be taken, since many anaesthetics and muscle relaxants can aggravate the clinical features or trigger life-threatening reactions. Complications frequently occur in these patients, although anaesthetic procedures have become safer by the reduced administration of suxamethonium and the use of total intravenous anaesthesia, new volatile anaesthetics and non-depolarising relaxants. This review provides a synopsis of pre-operative anaesthetic considerations and adverse drug effects on skeletal, cardiac and smooth muscle tissue. It describes the pathogenetic aspects of typical complications and introduces anaesthetic procedures for the various neuromuscular disorders, including regional anaesthesia for patients in whom a restriction of respiratory and/or cardiac function is predicted.

Keywords: Anaesthetics; Muscle relaxants; Rhabdomyolysis; Malignant hyperthermia; Myotonia; Neuromuscular disease; Cardiac complications

1. Introduction

Anaesthesia in patients with neuromuscular diseases is a concern for anaesthesiologists, surgeons, neurologists, pediatricians, cardiologists, pulmonologists and sometimes also for geneticists. It is desirable to discuss with the patient and family members the risks and benefits of the various treatment options. Often the anesthesiologist is not left with a single absolute risk, but in many cases must balance conflicting management strategies, fully bearing in mind the possible deleterious outcomes even with the chosen course of action. In order to reduce patient risk to a minimum, pre-operative considerations in respect of these circumstances and a precise diagnosis (often per biopsy) in advance are essential. It is also important to identify and treat potential anaesthetic complications promptly. Lastly, adverse drug effects or specific risks associated with certain neuromuscular diseases should be taken into account.

This review is an overview of these elements. It deals with the pre-operative anaesthetic considerations, the typical anaesthesia-related exacerbation of skeletal, cardiac and smooth muscle weakness resulting in respiratory distress, cardiac complications and autonomic dysregulation. Adverse drug effects such as rhabdomyolysis, muscle spasms, malignant hyperthermia and similar reactions are discussed with respect to their pathogenesis. Afterwards, typical anaesthetic complications and their prevention and management are described for specific neuromuscular disorders: motoneuron diseases, peripheral neuropathies, neuromuscular transmission disorders, progressive muscular dystrophies, metabolic and mitochondrial myopathies, myotonias and periodic paralyses, and congenital myopathies (Table 1). Lastly, areas are indicated for non-anaesthesiologists to turn to, for more insight into the care of their patients. Further details may be found in [1].

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Table 1
Overview of anaesthetic considerations in neuromuscular diseases

Neuromuscular disease	Respiratory test	Cardiac exam	Volatile anaesth.	NDMR	Comments
Motoneuron diseases					
Amyotrophic lateral sclerosis	x		x	⇩	
Spinal muscular atrophy	x		(x)	⇩	
Neuropathies					
Inflammatory polyneuropathies					
Guillain–Barré syndrome	x	x	x	⇩	Note dysautonomia, consider PM
CIDP	(x)	(x)	x	⇩	
Hereditary polyneuropathies					
Charcot–Marie–Tooth syndrome	x	x	x	⇩	Decrease barbiturate
Friedreich's ataxia	x	x	(x)	x	
Toxic polyneuropathies		(x)	(x)	x	
Disorders of the neuromuscular transmission					
Myasthenia gravis	x		x	⇩	Increase Sx dose
Lambert–Eaton syndrome	x		x	⇩	Decrease Sx dose
Myopathies					
Progressive muscular dystrophies					
Myotonic dystrophy	x	x		⇩	Avoid aChE and respiratory depressants consider PM
Facioscapulohumeral dystrophy	(x)		x	x	
Limb girdle dystrophy		x		x	
Congenital myopathies	x	x		x	
Poly- and dermatomyositis	x	x	x	⇩	
Metabolic myopathies					
Glycogenoses	x	x	(x)	x	Difficult intubation, metabolic acidosis
Disorders of lipid metabolism	x	x		x	Avoid hypoglycaemia
Homozygous MAD deficiency		x		x	
Mitochondrial myopathies		x		x	Consider PM
Ion channel diseases					
Myotonia congenita				⇩	Avoid aChE
Potassium-sensitive myotonias and periodic paralyses	(x)			⇩	Avoid dyskalaemia, hypothermia, ache

x, may be used or should be performed; (x), x with restriction, Sx, suxamethonium; PM, pacemaker; aChE, anticholinesterases; NDMR, non-depolarising muscle relaxants; MAD, myoadenylate deaminase deficiency. Sx is contraindicated in all NMD except myasthenia gravis.

2. Pre-operative considerations

The most obvious pre-operative question is whether the benefit of surgery justifies the anaesthetic risk. Decisions are based on a clear diagnosis with a full workup including histopathological findings, genetic data, or at least family history, and a wider variety of metabolic tests. Since patients with neuromuscular diseases are very challenging and may appear deceptively healthy, it is important to document all choices and their rationale on the medical record for subsequent care-givers, future research in rare disorders, and for medico-legal protection of care-givers and institutions. The optimum result will only be achieved if the various disciplines involved work together closely.

In neuromuscular diseases, the thorough pre-operative examination should include the detection of associated cardiac and respiratory dysfunction [2,3]: a neurological examination for scoring neuromuscular disease symptoms, electrocardiogram, an X-ray of the thorax, echocardiography, pulmonary function tests with body plethysmography, arterial blood gas analysis, determination of serum Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}, creatine kinase (CK), and myoglobin levels, and, in the case of respiratory distress, measurement of inspiratory muscle strength.

For pre-medication, substances leading to respiratory depression or decreased muscle tone are often are inadequate in severely affected individuals. In other cases, drugs such as benzodiazepines can be ideal, although only under close monitoring. A possible alternative could be clonidine at low dosage as this leads to sufficient anxiolysis without relevant cardiovascular side-effects. Regional or local anaesthetic techniques can be employed in patients with cardiac and/or respiratory dysfunction [4,5]. However, in patients with autonomic dysfunction, a potential sympathetic block resulting from regional anaesthesia requires careful control of blood pressure. In patients in whom volatile anaesthetics and regional techniques are not indicated, propofol and opioids are recommended; over the last 10 years they have replaced neurolept analgesia.

Neuromuscular block should be checked before the first application of relaxants, and then regularly throughout the procedure [6]. Additionally, invasive measurement of blood pressure enables repetitive blood gas analysis. Temperature monitoring is imperative, even in regional anaesthesia. Instead of volatile anaesthetics, easy-to-control and short-acting intravenous drugs for total intravenous anaesthesia are preferable for most neuromuscular diseases (see Table 1). They facilitate intubation without muscle relaxants. However, intravenous agents are by no means risk-free in patients with neuromuscular disease, e.g. those associated with intracardiac conduction deficits. Suxamethonium is contra-indicated in all diseases that exhibit hypersensitive muscle fibre membrane peripheral to the neuromuscular junction. It is important to pay attention to the advantages and disadvantages of this potent drug in the other cases such as in myasthenia gravis. Even with the pharmacological control of myasthenia, sensitivity to non-depolarising muscle relaxants still remains, demanding a dose reduction [6,7].

After anaesthesia, drugs such as clonidine and nefopam can be used to treat shivering [8]. Respiratory function should be closely monitored. Before being discharged, patients should have adequate respiratory reserve. Post-operative admission to an intensive care unit should be considered in every case, and good reasons presented for not making the choice as a routine.

3. Anaesthetic complications

3.1. Rhabdomyolysis

Depolarizing muscle relaxants such as suxamethonium can lead to rhabdomyolysis in almost all neuromuscular disease, but especially in muscle that is denervated, progressively dystrophic or metabolically altered [9,10]. Suxamethonium activates nicotinic acetylcholine receptors. Therefore, either an ectopic increase of nicotinic acetylcholine receptors extrajunctionally as in denervated or immobilized muscle [11] or an increase of the fetal γ isoforms as in many neuromuscular diseases [12] both lead to suxamethonium hypersensitivity. The activation of the extrajunctional or fetal nicotinic acetylcholine receptors results in membrane depolarization, which ultimately leads to maldistribution of electrolytes including potentially lethal hyperkalaemia, muscle fibre swelling, and rhabdomyolysis. The administration of suxamethonium is not recommended in neuromuscular disease or routinely in young children.

Sustained increase of sarcoplasmic Ca^{2+} can cause hypermetabolism, ATP depletion, and muscle cell damage. Volatile anaesthetics can potentiate the Ca^{2+} increase in neuromuscular disease with disturbed Ca^{2+} homeostasis such as in malignant hyperthermia [13] or in patients taking drugs influencing Ca^{2+} homeostasis such as ecstasy (MDMA, methylene-dioxy-methamphetamine) [14] and cocaine.

Medication used to treat an underlying or concomitant disorder can contribute to a risk of rhabomyolysis by altering ion homeostasis. One example is co-therapy of statins and fibrates used to lower cholesterol and triglyceride levels [15]. These drugs reduce Cl^- conductance [16,17] to a similar extent as seen in chloride channel myotonia and decrease membrane stability [18]. Fibrates additionally activate Ca^{2+} release via the ryanodine receptor [19]. Another example is the K^+ wasting drugs such as most diuretics and licorice [20,21] that can cause acute necrotizing myopathy culminating in rhabdomyolysis [22]. Intra-operative conditions such as additional K^+ wasting medication, ambient temperature, excessive sweating, hypoxia, diarrhoea, infections and endocrine disturbances can induce the anaesthetic crisis [23]. The drop in serum potassium may be masked by K^+ being released from the damaged muscle.

In the event of suspected rhabdomyolysis indicated by CK-levels $>10{,}000$ U/l, myoglobinuria, metabolic acidosis and elevated potassium, life-threatening hyperkalaemia must be corrected and putative causative drugs stopped immediately. Next, aggressive volume resuscitation should be initiated, ventilation should be enhanced with the aim of normocapnia, acidosis corrected by $NaHCO_3$, and myoglobins removed by forced diuresis and urine alkalinisation. Patients require close monitoring for the above, and also for vital signs, liver enzymes, coagulation, blood gases, electrolytes and glucose. Administration of dantrolene may be useful in some cases [24–27], particularly in those with hyperthermia.

3.2. Cardiac complications

Cardiac muscle and conducting pathways are affected in many neuromuscular diseases, even though many patients may not be aware of this since they are not capable of vigorous exercise, owing to the muscle disorder. Intra- and post-operative stress can cause cardiac failure in these patients [3,28,29]. Hence, understanding the functional cardiac reserve and ability to tolerate surgery in advance is of particular importance. An echocardiogram is often informative, but in large operations a patient's response to blood loss and to supportive inotropes is unpredictable, and pre-admission to an intensive care unit for Swan Ganz monitoring of response to fluid bolus and test doses of inotropes may be the only way to tell whether the patient's heart can survive surgery.

Volatile anaesthetics are cardio-depressive because they reduce the availability of myoplasmic Ca^{2+} and decrease the responsiveness of the contractile filaments to Ca^{2+}. Dysrhythmia caused by volatile anaesthetics results from sensitization of the heart to catecholamines and from inhibitory effects on voltage-gated K^+ channels, which are essential for membrane repolarization [29–31].

Prolongation of the QT interval and isorhythmic dissociation (e.g. with isoflurane), as well as hyperkalaemia produced by suxamethonium-induced rhabdomyolysis may contribute to the arrhythmia. Frequency of death by cardiac arrest is second only to respiratory failure in patients with neuromuscular diseases [32]. The signs of cardiac complications and their treatment should include that for hyperkalaemia and standards as defibrillation, catecholamines and antiarrhythmic drugs [33]. Details and practical guidelines can be found on the websites of the American Heart Association (www.americanheart.org), the American College of Cardiology (www.acc.org) and the European Society of Cardiology (www.escardio.org).

3.3. Respiratory distress

The high incidence of respiratory complications is due to the frequent involvement of respiratory and pharyngeal muscles in patients with neuromuscular diseases and a higher incidence of infantile sleep apnoea in children [34]. Progressive spine deformities as seen in patients with progressive muscular dystrophies and congenital myopathies cause restrictive lung diseases and aggravate chronic respiratory insufficiency. Additional administration of respiration-depressant drugs leads to decompensation of a pre-operatively sufficient muscle function, particularly in patients with disturbed neuromuscular transmission or muscle ion channelopathies [35]. In severely affected individuals there is a dilemma between leaving in an endotracheal tube to assist ventilation and protect the lungs at the expense of further loss of muscle tone and inability to wean from ventilatory support. This is a very real problem, particularly in patients for whom intubation is difficult in the first instance. Clarity on these points with the family and patient, well in advance of surgery, is essential in fully understanding the risk of any surgical procedure.

Post-anaesthetic complications, such as pneumonia due to hypoventilation or recurrent aspiration, may result from impaired respiration and swallowing. For treatment of respiratory distress, postoperative physiotherapy and positive pressure devices (CPAP) are effective tools to improve cough efficacy, gas exchange and to prevent atelectasis in patients with low lung volumes such as in neuromuscular disease [36].

3.4. Myotonic reaction

Myotonia is a symptom that occurs in many disorders: the myotonic dystrophies, the non-dystrophic myotonias, and in Schwartz Jampel syndrome. Subclinical myotonia visible in the EMG (latent myotonia) can be observed in hyperkalemic periodic paralysis, acid maltase deficiency, and in centronuclear myopathy. Myotonic stiffness is caused by involuntary repetitive action potentials of the muscle fibre membrane (Fig. 1), which is made hyperexcitable owing to a permanent sodium influx or a reduced chloride

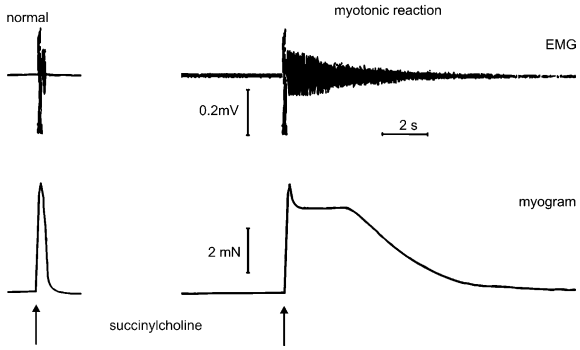

Fig. 1. In vitro muscle contractions. An excised muscle fibre bundle taken from a myotonic patient was exposed to a bolus of suxamethonium added to the bath solution. It reacts by repetitively firing action potentials, which were extracellularly recorded by wire electrodes as EMG (upper right panel). This activity resulted in tetanic muscle contractions of some fibres (lower right panel). In contrast, a normal fibre bundle only showed a single action potential and a twitch.

conductance [37]. A myotonic reaction can be induced or aggravated by depolarising agents, K^+, anticholinesterases, or by opoids [38–40]. Depolarising agents such as suxamethonium often cause myotonia of the jaw (the masseter seems to be the most sensitive muscle) and of respiratory and other skeletal muscles. Also alterations of serum osmolarity, pH, and the ambient temperature as well as hypothermia-induced muscle shivering and mechanical stimuli can exacerbate the myotonic reaction. Following pathophysiological considerations, local anaesthetics and antiarrhythmic drugs of class I, such as mexiletine and lidocaine derivatives, should be the drugs of choice for the treatment of a myotonia-related crisis. The drugs produce a use-dependent block of Na^+ channels and thus reduce the hyperexcitability of the membrane.

3.5. Masseter and generalised muscle spasms

The masseter is the most frequent muscle presenting with spasms, perhaps because of the high number of muscle spindles. Suxamethonium increases jaw muscle tension in children who had inhalational induction [41]. The incidence of masseter spasms in children was determined to 0.3% of inhalation anaesthetics during which suxamethonium was given [42], but the reported incidence and the recommendation to continue the triggering anaesthetic are a matter for debate among paediatric anaesthesiologists, as some of the patients were later tested as susceptible to malignant hyperthermia. Therefore, any patient with masseter spasm should be treated as soon as possible as though a malignant hyperthermia crisis may ensue.

Muscle spasms can be caused either by electrical activity as in myotonia or without electrical activity in muscle contractures, e.g. due to uncontrolled sarcoplasmic Ca^{2+} release, as in a malignant hyperthermia episode (for review, see Ref. [43]) or by slowed reuptake of Ca^{2+} into the sarcoplasmic reticulum as in Brody's disease (for review,

see Ref. [44]). The Ca^{2+} release from the sarcoplasmic reticulum and thus muscle force generation can be very effectively reduced by dantrolene [45]. This is the basis of the therapy of a malignant hyperthermia crisis. This specific effect of dantrolene on myoplasmic Ca^{2+} leads to reduced heat production and a decrease in body temperature independent of the origin of the hyperthermia. This non-specific effect on temperature is pronounced in all types of hyperthermia caused by increased muscle metabolism and muscle activity, e.g. shivering.

3.6. Hyperthermia and hypothermia

Anaesthesia-induced hyperthermia results from an imbalance in heat production and dissipation. Heat production is primarily increased by muscle activity which can either be myogenic as in myotonia or malignant hyperthermia, or induced by the central nervous system as in the neuroleptic malignant syndrome, in muscle rigor or in epileptic seizures or in iatrogenic heating during anaesthesia. The heat production is greatest in fulminant malignant hyperthermia crises [10,43].

Hypothermia is based on induction vasodilation with increased blood flow to the superficial cool periphery. Upon return of the blood to the core, the temperature drops 2–3 °C within 10–20 min. Patients with neuromuscular diseases are predisposed to hypothermia because of reduced heat production in atrophic or dystrophic muscle. Hypothermia can be prevented in patients by heating the skin 20–30 min prior to induction, using heated blankets or hot air blown across the patient. Hypothermia increases the sensitivity of muscle to depolarising and non-depolarising muscle relaxants, potentially aggravating rhabdomyolysis or myotonic reactions [46]. Apart from the effects on skeletal muscle, hypothermia potentiates dysrhythmias in the predisposed patient, promotes bleeding, alters the haemoglobin dissociation curve, and has many other undesirable consequences in patients with neuromuscular diseases.

3.7. Autonomic dysregulation

In some neuromuscular diseases, the vegetative nervous system may show lesions in pre- and post-ganglionic sympathetic neurons [1], e.g. in synapses, dystrophin-complexes are present, probably stabilizing the membrane and scaffolding signaling proteins [47]. During anaesthesia, reduced blood volume and increased intrathoracic pressure caused by mechanical ventilation may lead to severe hypotension. Additionally, gastrointestinal dysmotility may increase the risk of aspiration during general anaesthesia [1]. In spinal and epidural anaesthesia, the reduced cardiovascular regulatory mechanisms also lead to hypotension [1,7]. If necessary, sympathomimetic drugs can be administered in very small doses because α- and β-receptors may be oversensitive [48,49].

4. Anaesthetic considerations in specific neuromuscular diseases

4.1. Motoneuron diseases

This group of mainly degenerative, hereditary and rarely infectious origin (e.g. post-polio syndrome) encompasses impairment of the motor nervous without affecting the sensory system. Depending on whether the upper, or, as in spinal muscular atrophy, only the lower motor neuron is affected, the main clinical feature is spasticity or atrophy, or a combination of both as in amyotrophic lateral sclerosis. Loss of innervation ultimately leads to muscle atrophy with extra-junctional and hypersensitive nicotinic acetylcholine receptors. Hence, depolarising muscle relaxants can elicit neuromyotonia-like contractions, rhabdomyolsis and severe hyperkalaemia [12]. Non-depolarising muscle relaxants can be administered but the sensitivity to these drugs is altered such *as in upper and lower motoneuron lesions, immobilisation, and burns* [1,7,9]. Respiratory dysfunction and a pathologic reaction to muscle relaxants often lead to anaesthetic complications. A combination of bulbar and respiratory weakness can cause dysphagia, difficulty in clearing secretions and hypoventilation, predisposing to atelectasis, pneumonia and ventilator weaning difficulties. The centrally acting drugs baclofen and diazepam and the muscle ryanodine receptor blocker dantrolene help to control spasticity postoperatively. Abrupt discontinuation of baclofen (e.g. pre-operatively) may resemble malignant hyperthermia in many aspects but requires specific diagnosis and intervention [50].

4.2. Peripheral neuropathies

Peripheral neuropathies are characterized by flaccid paralysis, vegetative and sensory dysfunction of a focus (e.g. radicular syndrome, complex regional pain syndrome), and scattered or spread symptoms as in polyneuropathy. Several additional conditions such as diabetes mellitus, critical illness, toxic substances, autoimmune disorders (Guillain–Barre), infections and hereditary disease can cause polyneuropathic damage of axons and myelinisation. The key to assessing the risk of surgery and anaesthesia is again to have a clear diagnosis in advance, and to identify as closely as possible the point to which the disease has progressed for each specific patient. For elective procedures, all steps must be taken to ensure that the patient is in the best possible condition to survive the trauma of surgery and anaesthesia.

The risks and benefits of regional anaesthesia must be weighed very carefully on a case-by-case basis and broad recommendations are rarely supportable. In some cases, regional anaesthesia would be never given (e.g. a neuraxial block in a patient with Guillain–Barré). In other cases, the difficulty in sorting out a potential complication of the block from a manifestation of the underlying disease would

preclude regional anaesthesia. In a small proportion of diseases, regional anaesthesia might have advantages over general anaesthesia, as e.g. positive analgetic and microcirculatory effects in complex regional pain syndrome [51]. Risks of general anaesthesia in patients with peripheral neuropathies depend mainly on the nature of the disease itself and on accompanying problems such as gastric palsy, respiratory insufficiency and dysautonomia [7]. Cardiac lability and severe atrio-ventricular blocks may require a temporary pacemaker in the peri-operative period. Certain drugs have to be administered with caution, e.g. thiopental in Charcot–Marie–Tooth patients owing to increased sensitivity [52], or the negative-inotropic agents in Friedreich ataxia because of its frequent cardiomyopathy. Prolonged weaning from a mechanical ventilator can be expected in patients with a vital capacity below 20 ml/kg. In this phase, the increased sensitivity to pressure lesions [7], particularly in patients with hereditary neuropathy with liability to pressure palsy, may produce additional discomfort to the patient [53].

4.3. Disorders of neuromuscular transmission

In myasthenia gravis, neuromuscular transmission is disturbed owing to antibodies against nicotinic acetylcholine receptors. In patients with myasthenia gravis, premedication is to be minimized in order not to depress respiratory function. Concomitant medication impairing neuromuscular transmission such as antibiotics (aminoglycosides, penicillin, sulfonamides, tetracyclines), antiarrhythmics (lidocaine, procaine, phenytoin), beta blockers (propranolol), Ca^{2+} channel blockers, and psychotropic agents (benzodiazepines, chlorpromazine) [54] may need to be discontinued prior to operation. Oral anticholinesterases should be taken until 6 h prior to anaesthesia and then administered intravenously only if necessary, because the drug may aggravate a vagal response and hinder muscle relaxation. In the post-operative period the dose needed to avoid a myasthenic or cholinergic crisis may change unpredictably. Weakness of bulbar and respiratory muscles may cause problems during anaesthesia similar to those described for motoneuron diseases above [55]. A reduced vital capacity may require post-operative mechanical ventilation even if neuromuscular transmission is only slightly reduced [7]. In contrast to all other neuromuscular diseases, volatile anaesthetics and suxamethonium can be administered: however, this should be avoided whenever possible. The required suxamethonium doses may be increased by up to a factor of two [56]. A possible substitute would be an infusion of mivacurium or alternatively application of atracurium, which has the advantage of pseudocholineesterase-independent metabolism. Generally, the sensitivity of the endplate to non-depolarising muscle relaxants is drastically elevated [57]. Pre-anaesthetic train-of-four predicts the intubation dosage, which is usually reduced by a factor of 2–3 [6]. Use of all relaxants requires strict monitoring of neuromuscular function with a train of four device. Avoidance of neuromuscular blocking agents is often possible in myasthenia gravis. The muscle relaxing effect of induction hypnotics (e.g. a potent volatile anaesthetic) is often sufficient for atraumatic intubation. Consultation with the surgeon may be the key to accomplishing the procedure without profound block of the neuromuscular junction.

In Lambert–Eaton syndrome, doses of non-depolarising and depolarising muscle relaxants should be reduced because the release of the endogenous competitor acetylcholine is diminished [1]. Anticholinesterase agents can be administered to reverse the non-depolarising block. Because of the impaired release of acetylcholine, patients suffer from dysautonomic symptoms, requiring close monitoring of blood pressure and respiratory function during and after operation [58]. This syndrome must be anticipated in resections of certain carcinomas, and may first become apparent in such a setting in the immediate post-operative interval when it is not possible to extubate the patients.

No anaesthetic experience is reported for patients with any of the numerous congenital myasthenic syndromes, but anaesthesia would be expected to produce problems. Facial dysmorphies and unpredictable reactions to muscle relaxants may complicate intubation. The underlying weakness may cause respiratory difficulty on its own [1]. Anticholinesterase medication generally ameliorates muscle force in patients with defects in acetylcholine synthesis or with reduced function of nicotinic acetylcholine receptors. Perioperatively, respiratory function may be optimised by 3,4-diaminopyridine. Patients who do not respond to cholinesterase inhibitors, such as those with slow-channel syndrome or end plate acetylcholinesterase deficiency, are at risk of developing severe muscarinic side effects [59].

4.4. Progressive muscular dystrophies

In Duchenne and Becker muscular dystrophy, the anaesthetic risk is mainly determined by respiratory and cardiac complications, which do not correlate with the severity of the muscle symptoms [1,32,60–62]. Muscles lacking dystrophin are more susceptible to stretch-induced muscle damage and take up Ca^{2+} and Na^{+} [63]. Inhalational anaesthetics are not recommended because they further increase myoplasmic Ca^{2+} by facilitation of release from intracellular stores, as described below. Duchenne muscle also lacks dystrophin-mediated attachment of nitric oxide synthase to the muscle sarcolemma. In non-affected individuals, nitric oxide acts as an inhibitory transmitter to prevent the development of extrajunctional synapses [58]. The resulting expression of extrajunctional acetylcholine receptors leads to the potency of suxamethonium in provoking hyperkalaemia-induced cardiac arrest [29], malignant hyperthermia-like crises [10] and severe rhabdomyolysis [64]. Anticholinesterase drugs are not recommended because, similar to suxamethonium, they

may themselves lead to hyperkalaemia [65]. It has been suggested that dysfunction of smooth muscle and platelets causes increased blood loss [66–68]. To avoid severe intra-operative blood loss the use of hypotensive anaesthesia is recommended [69]. Hypovolaemia often leads to cardiac decompensation in these boys; their heart is stiff and compensates for increased demand not by Starling mechanism, but by increase in heart rate. Often there is resting tachycardia that is worsened by hypotension. In turn, the volume status must be monitored throughout. Moderate to lengthy procedures on Duchenne patients are indications for invasive vascular monitoring, aggressive laboratory testing intra-operatively, and routine intensive care after surgery.

Female carriers of Duchenne and Becker mutations may show elevated serum CK levels, mild myopathic changes and a cardiomyopathy [70,71]. Therefore, anaesthesia without volatile anaesthetics and depolarising relaxants is preferable, although no anaesthesia-related hypermetabolic crises have been reported so far [1].

In patients with myotonic dystrophy, the weakness of ventilatory muscles increases the risk of aspiration and pneumonia [72]. Because of the hypersensitivity to respiratory depressant drugs, agents such as barbiturates should be dosed carefully [73,74]. Additionally, a reduced compensatory reaction to hypoxia and hypercapnia was observed in some patients [75]. As in all forms of myotonia, aggravation of the myotonic reaction by suxamethonium should be avoided. Mivacurium, atracurium and vecuronium have been used successfully to induce muscle relaxation [58]. Cardiac arrhythmia may require a pacemaker [76]. Smooth muscles may also be involved [77], particularly the oesophagus and stomach. The frequently observed disturbance of glucose metabolism can be explained by a lack of insulin receptors in the muscle fibre membrane [78].

In patients with a severe form of facioscapulohumeral dystrophy, weakness of accessory ventilatory muscles reduces the vital capacity. Hypoventilation due to weakening of the diaphragm may occur in limb girdle dystrophy (particularly in Erb's shoulder girdle type).

4.5. Metabolic and mitochondrial myopathies

Patients with metabolic myopathies are not candidates for outpatient surgery. Aggressive metabolic monitoring before and after surgery is essential, with plans in place ahead of time for management. Negatively inotropic agents disturb myocardial function that is impaired in many patients with metabolic myopathies [79]. Potential myoglobinuria requires peri-operative monitoring, adequate hydration, and forced diuresis to avoid acute renal failure [1]. Muscle metabolism is supported by infusing glucose and amino acids [80]. Hypothermia should be prevented, since shivering increases energy consumption and muscle damage. In all forms of acid maltase deficiency, severe respiratory deficiency, recurrent aspiration pneumonia and pulmonary arterial hypertension have been reported [52,81]. In infancy, cardiorespiratory failure raises problems during anaesthesia [79]. In childhood acid maltase deficiency, respiratory failure is common and enlargement of liver, heart or tongue may occur. Cardiac ventricular dilation can compress the airway and generate dystelectasis. The macroglossia can lead to intubation problems. Even in the adult form, respiratory function tests indicate restrictive ventilatory insufficiency, hypoxaemia, hypercapnea, and reduced maximal static inspiratory and expiratory pressures [82]. The diaphragm is disproportionately weak, causing basilar atelectasis. Electrocardiac signs of pulmonary hypertension may appear.

In lipid storage myopathies, several organs such as skeletal muscle, heart or liver [83] may have functional defects with susceptibility to hypoglycaemia, acidosis, generalized muscle weakness, rhabdomyolysis, and progressive cardiac insufficiency. In patients with carnitine-palmitoyl-transferase (CPT) deficiency or carnitine deficiency, hypoglycaemia may be prevented by glucose and fatty acids [83,84]. Monitoring of blood glucose, potential metabolic acidosis [85] and parameters indicative of rhabdomyolysis is recommended [86].

Patients with mitochondrial myopathies are very difficult to anaesthetize. They differ greatly both within and between disease categories. Some case reports describe that intravenous and volatile anaesthetics as well as muscle relaxants have been used safely in patients with mitochondrial myopathies. Nevertheless, most anaesthetic drugs have depressant effects on mitochondrial function. Atracurium and vecuronium at low doses with close train-of-four monitoring are favourable, whereas affected muscle was hypersensitive to mivacurium [58]. Suxamethonium and pancuronium are to be avoided mainly due to cardiac side effects. Anaesthetic risk in mitochondrial myopathies results mostly from the danger of a total atrio-ventricular block that requires implantation of a pacemaker [3,87]. Therefore, an external pacemaker should be in the operating theatre and recovery room. Respiratory failure [88] and increased sensitivity to sedatives, hypnotics, and opioids have been described [89]. Severe cardiac arrhythmia can be provoked by halothane [90]. MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) and MERFF (myoclonus epilepsy with ragged red fibres) affect the protein translation coded by mitochondrial DNA. These syndromes require anticonvulsive and symptomatic therapy [7]. All mitochondrial myopathies require stringent peri-operative glucose adjustment to prevent hypo- and hyperglycaemia, the latter leading to increased oxidation and lactic acidosis. Excessive pre-operative fasting, metabolic stress and infusion of Ringer's lactate should be avoided. Chronic lactic acidaemia can be reduced by intravenous administration of dichloroacetate which stimulates the pyruvate dehydrogenase to cause transition of lactate to pyruvate.

4.6. Non-dystrophic myotonias and periodic paralyses

Depolarising reagents including K^+ can induce masseter spasms and stiffness of respiratory and other muscles and can therefore impair intubation and mechanical ventilation [91]. Depolarising muscle relaxants are therefore strictly contraindicated. The incidence of such events seems to be highest in families with myotonia fluctuans, the mildest form of sodium channel myotonia, a potassium-aggravated myotonia. Most likely, it relates to the frequent absence of clinical signs in this type of myotonia, leaving the anesthesiologist unaware of the condition. In the other forms, the anesthesiologist is warned by the patient or the obvious clinical features [35]. An induction sequence incorporating inhalation of oxygen, cricoid pressure, thiamyal or thiopental, and two times the ED95 dose of an intermediate or short-action non-depolarizing muscle relaxant, followed by intubation, would be a reasonable approach to securing the airway in myotonic patients [92]. Alternatively, inhalational induction may also be a possibility for hyperkalaemic paralysis and is well tolerated in the elective patient.

For these diseases, respiratory distress in the recovery room has often been reported. The weakness is aggravated by drugs that depress respiration and by the hypothermia induced by anaesthesia. Paramyotonia congenita and hyperkalaemic periodic paralysis patients may be paralysed for several hours upon awakening from general anaesthesia. Preventive therapy before surgery, maintaining a normal body temperature and keeping serum potassium at low level and avoiding hypoglycaemia, will help to prevent such attacks [93]. Operation-induced stress leads to K^+ uptake into muscle via release of catecholamines, insulin, and other hormones. The resulting hypokalaemia, potentially worsened by sodium chloride infusions, as well as mild hypothermia can induce a paralytic attack in patients with hypokalaemic periodic paralysis. Keeping the patients warm and serum K^+ at high level and avoiding hyperglycaemia are essential measures in preventing such attacks [94]. Careful monitoring of pre-existing QT prolongation during and after anaesthesia is a must [95]. A malignant hyperthermia crisis has once been convincingly described for a patient supposed to have hypokalaemic periodic paralysis [96], but the diagnosis has not yet been verified by molecular genetics. Regional anaesthesia whenever feasible seems to be preferred despite its well-documented consequence of hypokalaemia [97].

The generalized muscle spasms induced by suxamethonium in myotonic patients may resemble a malignant hyperthermia crisis, particularly when they are associated with an increase in body temperature [98–100]. Therefore, myotonic patients are often considered to be susceptible to malignant hyperthermia. However, these life-threatening crises may have been rather induced by severe myotonic reactions or mistaken for other diseases, e.g. polymyositis [101–103].

4.7. Malignant hyperthermia

Malignant hyperthermia susceptibility is a genetic predisposition to life-threatening crises usually triggered by volatile anaesthetics and suxamethonium. Outside general anaesthesia most individuals do not present with symptoms, but some suffer muscle cramping and a few heat stroke under heavy exertion in hot environments (so-called awake episode). During a malignant hyperthermia reaction, Ca^{2+} is uncontrolled, released from the sarcoplasmic reticulum via the mutant ryanodine receptor type 1 (Fig. 2). Myoplasmic Ca^{2+} elevation leads to an increase in muscle metabolism with excessive heat and lactate production and, if exceeding the mechanical threshold, causes contractures of the (often first noticed) masseter and other muscles (for review, see Refs. [43,104]). The released Ca^{2+} upregulates glycogenolysis and activates the oxidative cycle, leading to high oxygen consumption and carbon dioxide production followed by muscular ATP depletion and systemic changes such as acidosis, hypercapnia and hypoxaemia. Tachycardia is observed as an early clinical sign, followed by rapid hyperthermia (1 °C/5 min)

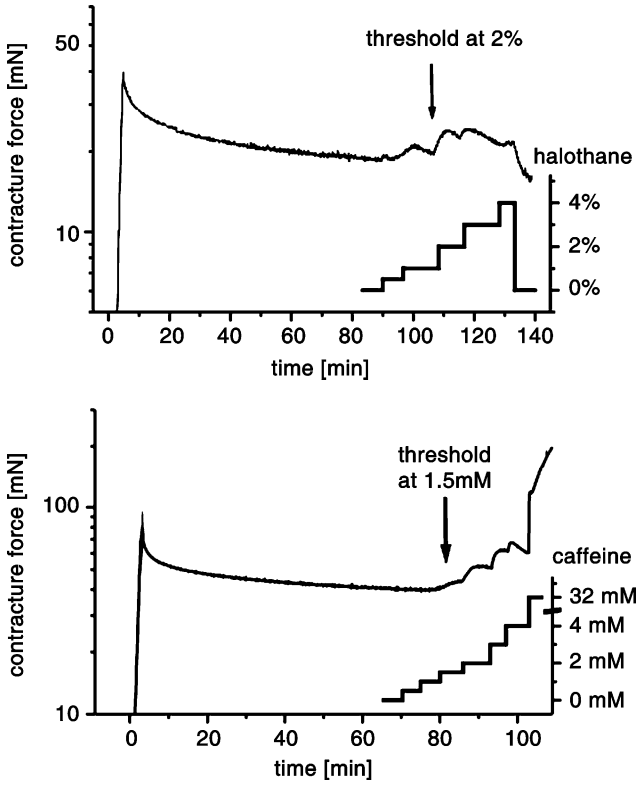

Fig. 2. In vitro muscle contractures following exposure to halothane and caffeine. Excised muscle bundles of a patient who had suffered from an anaesthesia-related crisis indicative of malignant hyperthermia were, after initial pre-stretching (peak in the curve), exposed to halothane (upper panel) and caffeine (lower panel). Note the development of contractures ($\geq$200 mN) at 2 vol% halothane and 1.5 mM caffeine. According to the protocol of the European Malignant Hyperthermia Group, the contractures were pathologic, and therefore the diagnosis 'susceptibility to malignant hyperthermia' made.

and stiff muscles. Serum CK and K^+ levels increase subsequent to rhabdomyolysis. The hyperkalaemia potentially leads to ventricular fibrillation or cardiac arrest even before body heat is generated, and myoglobinuria leads to the possibility of renal failure. If an episode is survived, normalization of edematous muscle and creatine kinase levels occur within 10–15 days. During this period, the rhabdomyolysis can be best observed histologically.

It has been shown that the potency for Ca^{2+} release from the sarcoplasmic reticulum varies in the group of inhalative drugs (halothane > sevoflurane > desflurane) [105,106]. Suxamethonium exacerbates a crisis triggered by volatile anaesthetics. Suxamethonium alone has not been reported to trigger a crisis in humans. However, this does happen in the higher susceptible swine model, known also as porcine stress syndrome [107,108]. The most effective treatment is rapid infusion of dantrolene, a specific blocker of the ryanodine receptor. Further treatment aims at correction of hyperkalaemia and prevention of secondary complications as described above. More information and links about management of a malignant hyperthermia crisis are found on the websites of the Malignant Hyperthermia Association of the United States (www.mhaus.org) and the European Malignant Hyperthermia Group (www.emhg.org). Total intravenous anaesthesia is the method of choice when regional techniques are inappropriate. Safe drugs are propofol, opioids, nitrous oxide, barbiturates, benzodiazepines and all local anaesthetics [109]. Notably, volatile anaesthetics and suxamethonium have been safely used in patients with mutations of the cardiac ryanodine receptor type 2 [110].

4.8. Congenital myopathies

Respiratory distress is frequent in congenital myopathies owing to the pre-existing muscle weakness. Non-depolarising muscle relaxants should therefore be dosed sparsely to avoid post-operative respiratory failure. Undue weakness and respiratory failure can also occur where dantrolene had been given in the pre-operative period. This may extend to the post-operative period [111]. Patients with central core disease, King–Denborough syndrome, Noonan syndrome, fingerprint body myopathies and rare forms of minicore disease are usually susceptible to malignant hyperthermia [109,112,113]. Therefore, anaesthesia using volatile anaesthetics and suxamethonium are not recommended. A few reports describe difficult intubation in nemaline myopathy, probably due to cranial dysmorphisms [1].

5. Anaesthesia in surgical emergency

Even in a surgical emergency it is often possible for the anaesthesiologist to search the OMIM database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) to get a regularly updated, concise and reliable summary on the disease in the shortest possible time. With this information the anaesthesiologist is at least alerted to adverse reactions during anaesthesia. Another key point is registration with MedicAlert or a similar service, and use of the bracelets, necklaces etc. as a life-saving intervention. All physicians involved in the care of patients with neuromuscular disease must encourage their patients and often their families to do this.

6. Conclusions

Anaesthetic procedures in neuromuscular disorders have become safer. The reduced administration of suxamethonium as a muscle relaxant has led to a decreased incidence of hyperkalaemic induced cardiac arrest in patients with pre-symptomatic muscular dystrophies. Total intravenous anaesthesia using newer short-acting anaesthetic agents, opioids and non-depolarising muscle relaxants, as well as the more recently introduced volatile anaesthetics sevoflurane and desflurane, accelerate recovery and thus reduce post-operative complications.

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