MH-related Disorders - Neuromuscular diseases
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Drugs used in general anesthesia, i.e. muscle relaxants and anesthetics, exert strong effects on skeletal muscle and provoke anesthetic complications in patients with neuromuscular disorders. These may then present with some symptoms also found in or closely resembling malignant hyperthermia (MH), such as muscle spasm, metabolic disturbances including heat production, cardiac arrest, rhabdomyolysis, and respiratory failure. The clinical picture may though mimick MH, whereas the pathogenesis is different from true (inherited) MH. Neuromuscular diseases presenting with such anesthetic risks (see table 1) mainly belong to congenital myopathies, progressive muscle dystrophies, non-dystrophic muscle ion channel disorders, neurogenic disorders, and disturbances of neuromuscular transmission. In contrast, true MH is known to be associated only with central core disease and King-Denborough myopathy (see earlier chapters). In the first part of this overview symptoms that are characteristic for MH but may also occur during anesthesia in patients with neuromuscular diseases will be discussed. The second part focuses on anesthesia-related problems with regard to specific neuromuscular disorders.

Rhabdomyolysis. In denervated, atrophic or dystrophic skeletal muscle, cells are very viable to suxamethonium reacting with toxic myolysis and serum potassium elevation possibly initiating cardiac arrest. In combination with halothane, muscle cell damage is increased leading to myoglobinuria and renal tubular obstruction. While muscle tissue in all neuromuscular disorders reacts with some degree of hyperkalemia, rhabdomyolysis is the more severe, the more predamaged the muscle, i.e. the risk is especially high in the early-onset muscle dystrophies and metabolic myopathies. Additonally, for diseases showing reduction of muscle mass, the basal serum potassium level is already elevated adding to the risk of cardiac arrhythmias by myolysis-induced hyperkalemia. In this respect, it is important to mention that for the ion channel disorders, symptoms are sensitive to potassium changes, a hyperkalemia causing a generalized myotonic reaction in potassium-aggravated myotonia during anesthesia, or severe muscle paralysis with possible respiratory failure typically during the re-awakening phase after anesthesia. Various drugs and toxins may also cause rhabdomyolysis and myoglobinuria e.g. alcohol, sympathomimetics, anti-cholinesterases, caffeine, clofibrate, cyclosporine, diuretics, lithium, nifedipine, and ecstasy and others.

Cardiac arrest. Cardiac failure intra- or postoperatively in patients with neuromuscular disease are reported especially under halothane anesthesia. Next to hyperkalemia, cardiac myopathies found in muscle dystrophies or conduction defects as observed in neurogenic disorders are predisposing to heart failure during anesthesia. While the former predisposes to cardiomyolysis, the latter causes arrhythmias that may be dangerously enhanced by myolytic hyperkalemia.

Respiratory failure. Patients having disorders with prominent weakness like spinal muscle atrophies, myasthenia gravis and muscle dystrophies are very subjective to ventilation problems after muscle relaxant administration because the weakness of respiratory muscles is enhanced. Both in myasthenia as well as in periodic paralyses, depolarizing muscle relaxants lead to prolonged respiratory muscle weakness especially visible after finishing anesthesia by postoperative hypventilation or apnea. Contrarily, in dystrophic and non-dystrophic myotonias, myotonic reactions by depolarizing muscle relaxants can inhibit intubation and thoracic movement also leading to ventilation problems during anesthesia. Thirdly, restrictive respiratory dispositions as found in severe dystrophies or Schwartz-Jampel syndrome contribute to respiratory failure.
Muscle spasm. Muscle spasm of masseter and other muscles for patients with neuromuscular disorders represents a myotonic reaction with sarcolemmal depolarization rather than MH-typical rigidity with hyperpolarized muscle fiber membrane. Myotonia is therefore intensified by all drugs that depolarize muscle fiber membrane such as suxamethonium or cholinesterase inhibitors and can cause intubation and ventilation problems. The myotonic reaction is not long-lasting, and usually is not accompanied by hypermetabolism or heat development.

Hyperthermia. Temperature elevation due to myotonic muscle contraction or metabolic disturbances are known, but have not been reported to be fulminant as in true MH. For some dystrophies, hyperthermia up to 40°C has indeed been observed. Much more frequently in neuromuscular disorders is hypothermia due to the decreased metabolism and circulation in atrophic, dystrophic, or paralyzed muscle.

Specific anesthetic considerations in patients with neuromuscular disorders

Congenital myopathies and progressive muscle dystrophies. Myopathies are disorders with functional or structural or degenerative disturbances of skeletal muscle, for example mini cores or nemaline rods etc. Most important and most severe are the muscular dystrophies which are characterized by progressive muscle wasting either with early onset and rapid progression (Duchenne-type) or late-onset and mild progression (Becker-type). Due to muscle wasting, skeletal deformities result such as kyphoskoliosis causing restrictive ventilatory disorder. Additional problems include weakness of cough reflex leading to obstructive ventilatory problems and cardiomyopathy. Also very important is myotonic dystrophy with slowly progressive distal muscle wasting, cardiac and respiratory involvement next to muscle stiffness due to membrane hyperexcitability (myotonia).

Non-dystrophic muscle ion channel disorders. Finally ion channel disorders such as myotonia congenita, periodic paralysis and paramyotonia congenita present episodically with either over-(myotonia) or underexcitability (paralysis) of muscle membrane which shows a strong tendency to depolarize. Patients have varying degrees of myopathy and occasionally progressive weakness. Muscle mass is decreased for the paralyses and increased for the myotonias. Usually, there is no cardiac involvement, but respiratory muscle may be affected in very severe paralysis attacks.

Metabolic myopathies. Most of these rare diseases are associated with exercise-induced, electrically silent muscle spasms, muscle pain and myoglobinuria. Particularly, McArdle’s disease, a myophosphorylase deficiency syndrome belonging to the group of glycogen storage disorders, may present as intermittent myoglobinuria. A characteristic feature of this recessive disease is the “second wind” phenomenon which is experienced as progressive fatigue and weakness of exercised muscles followed by rapid and complete recovery at continued exercise. Carnitine palmitoyl transferase deficiency type II is a lipid storage disease which can lead to painful muscle spasms and transient muscle weakness potentially followed by myoglobinuria and renal failure. Brody’s disease is characterized by painless muscle cramping and exercise-induced impairment of muscle relaxation.

Disorders of neuromuscular transmission. Most import disorder of neuromuscular transmission is myasthenia gravis which is characterized by abnormal fatigability and fluctuating weakness caused by antibodies directed against nicotinergic acetylcholine receptors. Ocular involvement is typical while respiratory and bulbar muscles may supplementarily be affected. Untreated worsening of symptoms may lead to a myasthenic crisis with respiratory insufficiency, dysphagia and diminished cough reflex.
Neurogenic disorders. Neurogenic disorders of interest include spinal muscle atrophies with muscle weakness, atrophy, and muscle hypotony with various ages of onset, distribution, and progression (Werdnig-Hoffmann, Kugelberg-Welander, Duchenne-Aran). Next to general muscle atrophy, also important for this context are the spinal and bulbar involvement leading to weakness of cough reflex and swallowing and thus, recurrent aspiration and pneumonia. In contrast, the peripheral neuropathy-associated muscle atrophies, for example Charcot-Marie-Tooth or Friedreich ataxia, do not present with respiratory difficulties but rather with cardiac conduction blocks in addition to the muscle atrophy.

Consequence for the anesthesiologist is a detailed preoperative assessment with clinical history including medication (anticholinesterases, steroids etc.), blood chemistry (highly elevated creatine kinase, potassium, transaminases, lactate dehydrogenase), cardiological examination (to exclude cardiomyopathy and arrhythmias), pulmonary function tests, chest X-ray (cardiac enlargement), extensive neurological examination, including provocation tests, and, where appropriate, muscle biopsy (e.g. histology, biochemistry and electron microscopy). With this knowledge, the use of volatile anesthetics must be considered very carefully and regional or general anesthesia without using triggering agents should be preferred for these patients. Depolarizing muscle relaxants should be avoided in all neuromuscular disorders, non-depolarizing muscle relaxants may be applied, but often at a lower dosage than usual (especially for myasthenia gravis in which the acetylcholine receptor targets are reduced in number). Careful monitoring of electrocardiogram, body temperature, and ventilation is recommended during the whole procedure. Postoperative spontaneous breathing should be observed for several hours and if necessary, ventilatory assistance given. Any MH-testing center can give additional individual recommendations.

References
Table 1: List of neuromuscular disorders for which narcotic complications have been described and reference of first report.

<table>
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<tr>
<th>Muscle Diseases</th>
<th>Reference</th>
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<tr>
<td><strong>Congenital myopathies and myopathies with structural anomalies</strong></td>
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<td>Nemaline / Rod myopathy</td>
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<td>Minimal change myopathy</td>
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<td><strong>Muscular dystrophies</strong></td>
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<td>Facioscapulohumeral dystrophy</td>
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<td><strong>Myopathies associated with endocrine diseases</strong></td>
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<td><strong>Metabolic myopathies</strong></td>
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<tr>
<td>Glycogenoses (e.g. McArdle’s Disease)</td>
<td>Edelstein G et al. Anesthesiology 52:90, 1980</td>
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<tr>
<td>Lipid myopathies (e.g. Carnitine palmitoyl transferase deficiency, Carnitine deficiency)</td>
<td>Mortier W. Acta Anaesth Belgica 41:119, 1990</td>
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<tr>
<td>ATPase deficiency of the sarcoplasmic reticulum (BRODY’s disease)</td>
<td>Brownell AKW. Br J Anaesth 60:303, 1988</td>
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<td><strong>Mitochondrial Myopathies</strong></td>
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<td><strong>Rhabdomyolysis</strong></td>
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<td><strong>Myotonic dystrophy</strong></td>
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<td><strong>Myotonias</strong></td>
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<tr>
<td>Myotonia fluctuans</td>
<td>Ricker K et al. Arch Neurol 51:1095, 1994</td>
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<td><strong>Dyskalemic periodic paralyses</strong></td>
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<td>Hypokalemic periodic paralysis</td>
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<td><strong>Disorders of the neuromuscular transmission</strong></td>
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<td><strong>Neurogenic disorders</strong></td>
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<tr>
<td>Peripheral nerve diseases, immobilisation atrophy</td>
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<tr>
<td>Spinal muscle atrophy</td>
<td>Heiman-Patterson TD et al. Muscle Nerve 11:453, 1988</td>
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