Pro-Con: Anesthesia and the Patient with Neuromuscular Disease

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There are numerous implications for patients with muscular disorders who undergo (general) anesthesia, which require careful perioperative planning by the anesthetist. The severity of presenting signs and symptoms associated with myopathy will clearly influence management. Patients with weak muscles of respiration may require respiratory support postoperatively, for example. However, even in cases where the myopathy is silent (e.g. malignant hyperthermia), the ramifications for the anesthetist can be quite significant.

It is impossible to discuss the vast number of muscle disorders and detail anesthetic management in this syllabus. (For a substantial review, I refer the reader to Naguib, et. al.). For the purpose of this presentation, I will consider five categories of muscle disorders affecting children. These include:

1. Dystrophies
2. Congenital myopathies
3. Mitochondrial myopathies
4. Myotonias
5. Channelopathies

Dystrophies

Muscular dystrophies are defined by cellular degradation noted on histochemical analysis of skeletal muscle specimens. Two notable dystrophies are associated with defects in the X-linked gene coding for the subsarcolemmal cytoskeletal protein, dystrophin. A marked deficiency or absence of dystrophin causes Duchenne Muscular Dystrophy (DMD). Another myopahy with later onset and less dramatic disability is Becker Muscular Dystrophy, which is associated with a milder dystrophin deficiency.

DMD has become a paradigm for thinking about issues regarding dystrophy. DMD occurs in 1:3,300 live male births; approximately one-third of all cases are spontaneous mutations. Notably, the serum CK is elevated, secondary to chronic muscle fiber necrosis. Although the child may appear normal at birth, the CK is elevated as a neonate. Furthermore, the CK of carrier females is also often abnormal. There is progressive loss of muscle strength, beginning with the lower extremities and extending to the upper. Patients are non-ambulatory by the second decade. Paraspinal weakness results in progressive and severe kyphoscoliosis. Respiratory weakness causes decreased vital capacity and total lung capacity.

Degenerative changes also occur in cardiac muscle fibers, and areas of fibrosis develop in the chambers as well as in the conduction system. Signs of respiratory and cardiac decline are masked by inactivity. Death typically occurs in the early twenties. Approximately half die of respiratory failure; the other fifty percent succumb to cardiac failure.

Notably, in a review of pediatric patients reported to the Malignant Hyperthermia (MH) Registry as suffering cardiac arrest within 24 hours of anesthesia, eight of twenty-five were found to have DMD (Larach, et.al.). Furthermore, succinylcholine has been implicated in several intraoperative cardiac arrests when massive rhabdomyolysis occurred after its administration. Indeed, these reports led to an FDA-mandated warning against routine use of succinylcholine in pediatric patients. There are case reports of cardiac arrest in DMD patients who receive inhalational agents without succinylcholine. Hyperkalemia has been identified in several of these arrests. Unexplained intraoperative cardiac arrest in young children, especially males, should prompt consideration of hyperkalemia. As the diagnosis is pursued, calcium, bicarbonate, and glucose/insulin may be given. If signs of MH exist, dantrolene may also be considered.

In addition to the untoward effects of certain agents in patients with DMD, there are other physiologic characteristics which complicate anesthesia. Airway management is difficult due to obesity, tongue hypertrophy, and limited neck movement. Intravenous access is difficult due to contractures. Restrictive lung disease and weak respiratory muscles may necessitate postoperative ventilation.

Cardiac dysfunction should be assumed as the patient progresses through his second decade of life. Preoperative transthoracic echocardiogram may not reveal the extent of cardiac involvement. Cardiac MRI may be a more useful tool for preoperative assessment of cardiac dysfunction. As fibrosis occurs in the myocardium, cardiomyopathy advances. The stress of cardiac depressant anesthetics, prone positioning, and surgery with large blood loss can all unmask cardiac dysfunction.

Many other muscle diseases are characterized by dystrophic pathology. In all, intrinsic muscle weakness will impact perioperative management. Cardiac disease must be considered in all dystrophies, as cardiac muscle as well as conduction systems can be affected. Succinylcholine should be avoided. Furthermore, I would extrapolate from our experience with DMD to suggest that inhalational agents be avoided as well.

Congenital Myopathies

The hallmarks of congenital myopathies are the early presentation of hereditary generalized hypotonia, small muscle mass, and dysmorphic features. Patients present with weakness and delayed motor milestones. There is no muscle necrosis or degeneration, and the disorders are non-progressive. CK is normal or slightly increased. These myopathies are classified by the histological appearance of muscle tissue.

The best known of this group of muscle diseases is Central Core Disease. Findings of well-demarcated intracellular cores in Type I fibers give this syndrome its name. Patients are hypotonic at birth, with proximal muscle weakness. The disorder is rarely progressive. CCD was first noted in 1973 to be associated with MH. It is clear now that CCD is genetically linked to the chromosome 19 ryanodine receptor, as are fifty percent of MH cases.

Approximately forty disorders have been identified as congenital myopathies. Nemaline myopathy is characterized by rod-shaped bodies in the muscle fibers. It is associated with early feeding difficulties, hypotonia, facial muscle involvement, and frequent cardiac abnormalities. Amish children are affected with a lethal form exhibiting infantile tremor, hypotonia, and respiratory insufficiency.

Other forms, including multi-minicore disease, myotubular myopathy, etc., are distinguished microscopically. Anesthesia considerations in all cases of hypotonia should be concerned with respiratory sufficiency and airway patency. Cardiac assessment should be performed pre-operatively.

Mitochondrial Myopathies

Mitochondria are the intracellular organelles responsible for aerobic respiration and energy generation via oxidative phosphorylation. Since skeletal muscle is so dependent on aerobic metabolism, the earliest mitochondrial disorders were identified as mitochondrial myopathies. With increasingly sophisticated biochemical and genetic testing, it has become evident that mitochondrial defects are associated with variable dysfunction in virtually every organ system. There are well over one hundred distinct mitochondrial disorders recognized.

Mitochondrial disorders can present with metabolic derangements, including increased serum and CSF lactate and pyruvate. Patients are likely to suffer exaggerated metabolic responses to stresses such as fasting, fever, and illness.

Due to the diversity of clinical presentations and organ involvement, the preoperative assessment and physical exam are important in identifying potential perioperative risks. Weakness will influence recovery following general anesthesia. Prolongation of neuromuscular blockade may complicate use of non-depolarizers.

Cardiac involvement may be in the form of cardiomyopathy or conduction defects. Pre-operative screening is advisable. Encephalopathy and seizures can be prominent features; rarely, strokes occur. Pulmonary disease can result from weakness and aspiration. It is most prominent in Leigh's Disease, and can be exacerbated by general anesthesia. Less commonly, eye, liver, kidney, bone marrow, and endocrine dysfunction are seen.

Because of the distinctive signs unique for each syndrome, anesthetic management must be planned with the identified pathology in mind. It is advisable to avoid prolonged NPO status. Intravenous fluids should not contain lactate. Anesthesia for this diverse group of disorders has been described only in case reports. There are theoretic concerns regarding mitochondrial depression with barbiturates, propofol, and benzodiazepines. These have not been observed clinically, to date. The evidence for association with MH is weak.

Myotonias

Myotonia is the slowed relaxation of a muscle following a normal contracture. It presents in late childhood with facial muscle weakness and ptosis. CK can be normal. There are commonly cardiac conduction defects which can result in life-threatening arrhythmias. These arrhythmias do not correlate with the severity of the muscle disorder. Patients tend to have low blood pressure, perhaps due to arterial smooth muscle involvement. The diaphragm is affected by myotonia and weakness, and can cause hypoventilation. Even mildly affected

patients can have dramatic post-operative problems, including cardiac, pulmonary and apnea issues. MH testing has been positive for some patients with myotonic dystrophy.

A congenital form of myotonic dystrophy may become evident in utero, with decreased fetal movements. At birth, the infant exhibits classic bilateral facial weakness and difficulty sucking. Involvement of the intercostals and diaphragm are a major cause of mortality.

Myotonia is exacerbated by depolarizing muscle relaxants and cholinesterase inhibitors. Muscle spasms can be misinterpreted as MH. Myotonia responds well to agents which block sodium channels. Non-depolarizing agents do not prevent myotonia. Due to the likelihood of postoperative respiratory insufficiency, use of intermediate muscle relaxants, when used, should be carefully monitored. It is best to avoid the need to use anticholinesterases. Anesthesia without muscle relaxant should be considered. Postoperative intensive care may be required.

Channelopathies

This represents a group of muscle disorders typified by disturbance in the transfer of ions across the sarcolemma. Channels are protein complexes which control the transfer by voltage or ligand gating.

Periodic paralysis is marked by episodes of flaccid weakness which occur variably and resolve spontaneously. These are generally brief. Small muscle groups may be affected, or generalized paralysis may occur. Typically, respiratory and cranial muscles are spared.

Hyperkalemic periodic paralysis is an autosomal dominant disorder. It is associated with hyperkalemia-induced weakness, usually brief and sparing muscles of respiration. It may be brought on by ingestion of foods high in potassium. Genetic mutation in the Na+ channel causes sustained Na+ currents, and does not allow formation of action potentials during an attack. Anesthesia concerns involve monitoring of serum potassium, avoiding exogenous potassium administration, and maintaining normothermia. Succinylcholine is contraindicated due to its increasing serum potassium. Furthermore, there has been described genetic linkage of MH to the same Na+ channel gene, putting the use of inhalational agents in question. Non-depolarizing relaxants do not appear to affect the disease.

Hypokalemic periodic paralysis is autosomally dominant. It results from a mutation in a calcium channel. These attacks can be severe, resulting in respiratory compromise as well as cardiac disturbances. The severest form presents in early childhood. Triggers are strenuous exercise, high carbohydrate intake, and low serum potassium. Perioperative management involves maintaining normal serum potassium, glucose, and acid-base status. Prophylactic intravenous administration should be considered in light of the risks of hyperkalemia. As is the case with many muscle disorders, a few case reports of MH risk exist. (The calcium channel does interact with the ryanodine receptor. Can there be a “common final pathway”?)

Malignant hyperthermia is an occult myopathy, inherited as an autosomal dominant trait. It is unmasked by exposure to depolarizing muscle relaxants and inhalational anesthetic agents. Multiple mutations in the ryanodine receptor have been identified. This gene encodes the channel mediating release of calcium form the sarcoplasmic reticulum. Abnormal calcium release upon exposure to “triggering” anesthetic agents causes sustained muscle contraction and rhabdomyolysis. Incidence is generally quoted as 1:50,000 adult anesthetics.

Assessing MH susceptibility relies on caffeine-halothane contracture testing of fresh muscle tissue. This test is 97-99% sensitive, but only 80-90% specific (Rosenberg, et.al.). Management of patients suspected of having MH requires avoiding use of depolarizing muscle relaxants and inhalational agents. MH should be suspected with the clinical appearance of rigidity, tachycardia, hypercarbia, acidosis, fever and myoglobinuria. Signs may be variably present. Following an episode, CK is greatly elevated over baseline values.

Treatment requires prompt diagnosis and administration of dantrolene. Early administration of dantrolene has reduced the mortality from sixty to approximately ten percent.

Discussion

Despite the vast number of myopathies, and numerous types of pathology associated with muscle disease, certain general anesthetic management principles should be applied to all. The preoperative management must assess muscle strength, with particular attention to respiratory function. Many patients will also develop restrictive lung disease on the basis of scoliosis. Preoperative pulmonary function testing may be helpful.

Cardiac dysfunction and/or conduction abnormalities should be considered. Preoperative EKG and CXR should be performed in all myopathic patients, including those for whom a specific diagnosis has not been made. Evaluation by a cardiologist, including cardiac echo or MRI may be required, based on age, exam, symptoms, and risk associated with the underlying diagnosis.

Metabolic considerations may be prominent features in many patients, and appropriate intraveneous management will be dictated.

As noted, many myopathies have been associated with case reports of MH. Are all these patients truly at risk? Evidence for MH susceptibility associated with some myopathies consists of a few case reports, interpreted by the anesthesiologist. Not all reports provide enough information to assign a more objective diagnosis of MH. Rarely is MH testing data available. Hopefully, genetic testing will clarify/validate associations, as ryanodine linkage has demonstrated Central Core Disease as a risk factor. In the case of other disorders with known genetic causative defects (ie., some mitochondrial disorders with identified mitochondrial DNA mutations), one must invoke a coincident genetic susceptibility to MH.

Could it be that, in certain muscle diseases such as the dystrophies, there is a propensity to hypermetabolism and rhabdomyolysis on the basis of a “hyperexcitable,” or vulnerable, sarcolemma? We know that exposure to succinylcholine is associated with muscle breakdown in DMD. Perhaps inhalational agents also disrupt the integrity of the muscle membrane, resulting not in “true” MH, but nonetheless in a critical anesthetic complication.

Clearly we with must provide careful preoperative evaluation of patients with muscle disease, to anticipate specific issues which may complicate anesthesia care. For patients with known diagnoses, associated risks should be understood and managed appropriately. For patients undergoing muscle biopsy for diagnosis, it seems prudent to standardize care by avoiding MH "triggering" agents, lactate, and long-acting muscle relaxants. Regional anesthesia should be considered. On the basis of cardiac evaluation, there may be an indication for invasive monitoring to assist in assessing need for volume, blood pressure support, and use of inotropes in patients with identified cardiac involvement. Use of anti-arrhythmics or pacemaker may be necessary. Proper anesthesia care of the myopathic patient assumes an appreciation for identified, as well as potential physiologic factors which may complicate management.

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