

Anaesthesia and the paediatric patient with neuromuscular disease

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Introduction

The anaesthetic management of paediatric patients with neuromuscular disease can be very complicated and requires careful peri-operative planning. These children commonly present for anaesthesia for diagnostic procedures (muscle biopsy, MRI), or surgery relating to their underlying disorder (gastrostomy, corrective orthopaedic procedures, strabismus surgery), or incidental surgery.

For the purpose of this presentation I will concentrate on postjunctional neuromuscular disease:

- Muscular dystrophy
- Myotonias
- Congenital myopathies
- Mitochondrial myopathies
- Channelopathies

Muscular dystrophy

1. Duchenne muscular dystrophy (DMD)

This is the most common childhood dystrophy, with an incidence of 1:3 500 live male births. It is an X-linked recessive inherited disorder, with marked abnormal or absent dystrophin, a large protein necessary to stabilise and link the myofibrils and cytoskeleton in skeletal, cardiac and smooth muscle. This defect results in chronic muscle fibre necrosis, degeneration and regeneration, as manifested in muscle weakness, and pseudohypertrophy of calves. It also accounts for cardiac manifestations and slight mental retardation.

DMD is progressive. Although a neonate may appear normal, serum creatine kinase (CK) will be elevated. A positive family history (90%) and delayed motor milestones are evident: late walkers, difficulty in climbing stairs by age 5, and wheelchair bound from age 6 onwards. Paraspinal weakness leads to progressive kyphoscoliosis. Respiratory weakness causes decreased vital capacity and recurrent chest infections. Degenerative changes in cardiac muscles causes conduction deficits and cardiac failure/dilated cardiomyopathy (also in female carriers). Patients also develop gastric hypomotility and delayed gastric emptying, and a hypertrophied tongue.

Pre-operative assessments

- ECG: will show right ventricular strain, tall R waves, deep Q waves, and inverted T waves.
- Echocardiogram: ventricular systolic dysfunction progresses to dilated cardiomyopathy, limiting physical activity. A resting tachycardia is an early sign of cardiac involvement, and a cardiac MRI can be helpful.
- Chest X-ray, pulmonary function test and blood gases: if the vital capacity (VC) < 30%, there will be a very high pulmonary risk. Hypoxaemia and CO₂ retention suggest postoperative ventilation will be necessary.
- Elevated CK levels: will most likely be 50 - 300 times normal levels.

Anaesthetic considerations

- Suxamethonium is contraindicated. It has been implicated in intra-operative cardiac arrests secondary to rhabdomyolysis and hyperkalemia.
- Can inhalational agents cause hyperkalaemic arrest? There are continued reports of arrest, even during the recovery period. The most at risk group is the patients under eight years of age, with still some muscle generation. This anaesthetic-induced rhabdomyolysis (AIR) is unrelated to malignant hyperthermia. In AIR, it is the instability of the sarcolemma that results in the "leakage" of potassium and CK from necrotic and regenerating muscle cells into the serum.
- Ensure a trigger-free anaesthetic and "clean" anaesthesia machine. Most literature reviews suggest a total intravenous technique.
- Anticipate potentially difficult airway management due to tongue hypertrophy, obesity and limited neck movement. Intravenous access can also be more difficult because of contractures.
- Minimise cardiac and respiratory depression. Prone positioning and large blood losses may unmask cardiac dysfunction dramatically. Peri-operative monitoring should be in accordance with the severity of systemic disease.
- Drugs should be short-acting and rapidly metabolised. There is an increased sensitivity to non-depolarising muscle relaxants. Use opioids sparingly.
- Close post-operative monitoring is needed, and ventilation is often indicated.

2. Becker's muscular dystrophy

This is the second most common form of dystrophy, occurring in 1:30 000 live male births. Dystrophin is abnormal, but still partly functional. The dystrophy is much milder with a slower onset. However, these patients can develop severe cardiac manifestations. Symptoms start at around 11 years of age, often with a history of delayed motor milestones for walking, running and jumping. Later, they struggle with climbing stairs or getting up, fall frequently or walk on their toes.

Anaesthetic considerations

- ECG/echocardiogram: dilated cardiomyopathy often presents before skeletal muscle symptoms, and arrhythmias can also occur.
- Respiratory: optimise chest infections, and assess function (deterioration may occur as a result of scoliosis, muscle weakness, and aspiration pneumonia)
- Post-operative ventilatory assistance may be necessary.
- CK level elevation will be less marked than DMD : 50 - 100 times.

Myotonias

1. Myotonic dystrophy (Steinert's disease)

This autosomal dominant dystrophy is characterised by consistent contracture of muscle following stimulation. An abnormal nucleotide sequence on chromosome-19 causes prolonged stimulation of the actin-myosin complex due to a larger sodium current, causing delayed relaxation of contracted muscle. It may manifest in early childhood and is a multisystem disease.

The ECG reveals cardiac conduction defects in 50 - 90% of cases, with first-degree AV block and left anterior hemiblock occurring most commonly. Echo reveals cardiac enlargement, interstitial fibrosis and mitral valve prolapse (30%). Significant left ventricular function impairment occurs later.

Bulbar weakness leads to recurrent aspiration pneumonia. Involvement of the intercostal muscles and diaphragm lead to poor cough and chronic alveolar hypoventilation, necessitating postoperative ventilation.

Swallowing and feeding difficulties due to severe dysphagia, as well as muscle wasting, makes nutritional status assessment and support necessary pre-operatively.

Glaucoma, cataracts, retinal detachment and strabismus can occur, as well as seizures, severe mental retardation, and myoclonic jerks. CK levels do not correspond with the level of severity, but are often highest in infants.

Anaesthetic considerations

- Sedatives pre-operatively can alleviate fear and anxiety in an

aggressive child prone to myotonic episodes, but has the risk of serious respiratory depression.

- Temporomandibular joint contractures might limit mouth opening and make direct laryngoscopy difficult.
- Neither muscle relaxants nor regional anaesthesia prevent or reverse myotonic contractions. Procainamide, diphenylhydantoin, volatiles and steroids might attenuate contractions. Infiltration of muscles with local anaesthetic can help. Depolarising muscle relaxants and cholinesterase inhibitors exacerbate myotonia.
- Patients are at increased risk for peri-operative aspiration.
- Succinylcholine has resulted in fatal rhabdomyolysis with hyperkalaemia.
- Postoperative cardiac, respiratory and apnoeic complications can be dramatic.
- Prevent peri-operative hypothermia and pain to limit myotonia.

2. Congenital myotonic dystrophy

This presents in infants born to mothers with myotonic dystrophy. Neonates present with feeding and respiratory difficulties, hypotonia, facial diplegia with ptosis, and tent-shaped mouth. These patient commonly require admission to the neonatal unit.

Congenital myopathies

The hallmarks are early presentation of hereditary generalised hypotonia, small muscle mass and dysmorphic features. Patients present with weakness and delayed milestones. There is no muscle necrosis or degeneration, and the disorders are non-progressive. The CK levels are normal or slightly increased, and classification takes place by histology of muscle tissue.

The best known of this group is central core disease (CCD). A rare cause of hypotonia in infancy, it must be considered in the hypotonic child presenting for muscle biopsy. Patients are hypotonic at birth, have proximal muscle weakness and tire when feeding. The disorder is rarely progressive. CCD is genetically linked to the chromosome-19 ryanodine receptor, making affected patients susceptible to malignant hyperthermia.

Mitochondrial and metabolic myopathies

This heterogeneous group of disorders is now the commonest cause of muscle weakness in children, with an incidence of 1 in 4 000. Mitochondria are responsible for aerobic respiration and energy generation, in the form of ATP, via oxidative phosphorylation. Products of the Krebs cycle interact with electron chain complexes on the inner mitochondrial membrane to generate ATP. Impaired electron transport chain (ETC) function results in decreased ATP production, and an increased production of free radicals. The acidosis and excess free radicals further damage the mitochondria by inappropriate oxidation of mitochondrial proteins, lipid and DNA. Tissues that are dependent on high metabolic demand,

like that of the skeletal muscle and central nervous system are most affected. With increasingly sophisticated biochemical and genetic testing, it is now evident that mitochondrial defects are associated with variable dysfunction in virtually every organ system.

- Mitochondrial DNA mutations include:
 - MELAS: mitochondrial encephalopathy, lactate acidosis.
 - MERRF: myoclonic epilepsy with red fibres syndrome.
- The severest forms can present in the neonatal period with profound weakness, liver and renal failure, and substantial neurological impairment.
- The patient is typically a floppy infant, a poor feeder with small stature, displays developmental delay, is hypotonic or hypoglycaemic, with or without positive family history.
- Mild weakness can present later in adulthood in some varieties.
- Metabolic derangements can include increased serum and CSF lactate and pyruvate.
- In acid maltase deficiency, severe respiratory deficiency, recurrent aspiration pneumonia and pulmonary arterial hypertension might occur.
- In lipid storage deficiencies, patients are susceptible to hypoglycaemia, acidosis, general muscle weakness, rhabdomyolysis, and progressive cardiac insufficiency.
- Patients have exaggerated metabolic responses to prolonged fasting, fever and illness.
- ECG and Echo might reveal cardiomyopathy or conduction deficits, and ventricular dilatation can compress the airway.

Anaesthetic considerations

- Evaluate pre-operative cardiac and respiratory status. Total AV block requires pacing.
- Evaluate metabolic status: glucose, lactate, liver enzymes and serum creatinine.
- Overnight fasting can cause hypoglycaemia, dehydration and mild metabolic acidosis. Maintain intravenous infusion containing glucose and electrolyte pre-operatively, avoid lactate-containing fluids.
- Increased sensitivity to sedatives, barbiturates, and propofol.
- Variable sensitivity to nondepolarising muscle relaxants.
- Avoid succinylcholine; at least one case has been described of malignant hyperthermia in a child with mitochondrial disease.

Inhalation or total intravenous anaesthesia?

The pendulum has now swung towards inhalation anaesthesia for known mitochondrial diseases, or has it?

Recent data suggests that propofol, which is a lipid carrier consisting of long-chain fatty acids, may have an adverse effect on fatty acid oxidation and impair mitochondrial respiratory chain function, and therefore put patients with mitochondrial disorders and carnitine deficiency syndromes at risk for a clinical scenario similar to propofol infusion syndrome (PRIS).

PRIS is a rare and often fatal syndrome described in critically ill children undergoing long-term propofol infusion at high doses. The main features are cardiac failure, rhabdomyolysis, severe metabolic acidosis and renal failure. The affected patients had acute neurological or inflammatory disease complicated by severe infection or sepsis, and were administered catecholamines and/or steroids in addition to propofol. The propofol was infused for longer than 48 hours, and at doses greater than 5 mg/kg/h.

There are concerns that the dose of propofol that elicits PRIS might be lower in mitochondrial disease. PRIS also present clinically similarly to malignant hyperthermia in children, although the time to onset differentiates the two clinical pictures. Many experts now suggest avoiding propofol in children with mitochondrial disease. If used, combine with remifentanyl and regional techniques and infuse at doses lower than the recommended 4 mg/kg/h, and for short periods of time (< 48 hours).

Many clinicians now consider sevoflurane as the agent of choice in these patients. Some respiratory chain disorders are more sensitive to inhaled agents and require lower MAC.

Alternative intravenous anaesthetics that are under investigation include ketamine, etomidate, and dexmedetomidine. Reports about increased sensitivity to these drugs are inconsistent.

Anaesthetic considerations

Pain management is essential, as the response to pain may heighten the risk of lactic acidosis from depletion of energy stores and increased oxygen demand. Use opioids sparingly and consider NSAIDs, nonopioid analgesics and regional techniques. Prevent hypothermia.

Channelopathies

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

Familial periodic paralysis

Hyperkalaemic

- Early onset, sometimes in infancy (autosomal dominant).
- Periodic paralysis is marked by brief episodes of flaccid weakness, which occur variably and resolve spontaneously. Respiratory and cranial muscles are typically spared.
- Attacks are precipitated by food high in potassium, cold, exercise and fasting, but not stress.
- Genetic mutation that affects sodium channels causes sustained sodium currents which don't allow the formation of action potentials during these brief attacks.
- ECG signs of hyperkalemia, also ectopic beats or paroxysmal tachycardia.

- Pre-operative management consists of potassium-free dextrose-containing solutions.
- Avoid cold, hyperkalaemia and carbohydrate depletion.
- Succinylcholine is contra-indicated.

Hypokalemic

- Most common type, onset during adolescence (autosomal dominant).
- Results from a mutation in a calcium channel.
- Attacks can be severe, resulting in respiratory compromise and cardiac disturbances.
- Triggers are strenuous exercise, high carbohydrate intake, low serum potassium, mental stress, cold, trauma and infection.
- Maintain normal serum potassium, glucose and acid-base status peri-operatively.
- Adequate premedication needed to avoid stress.
- Maintain normothermia.
- Avoid overeating the day before surgery.
- Avoid intravenous fluids with dextrose and sodium.

Ligand-gated calcium channelopathy

Malignant hyperthermia

Inherited as an autosomal dominant trait, malignant hyperthermia (MH) is an occult myopathy unmasked by triggers such as depolarising muscle relaxants and inhalation anaesthetics. Abnormalities in intracellular calcium homeostasis result in muscle rigidity, increased metabolism, rhabdomyolysis, hyperkalaemia, acidosis and cardiac arrest or death, if untreated. The inheritance ranges from 1:15 000 in children to 1:50 000 in adults. Multiple mutations in the ryanodine receptor (RYR1) have been identified. This gene encodes the channel-mediating release of calcium from the sarcoplasmic reticulum. When exposed to "triggering" anaesthetic agents, this abnormal calcium release causes sustained muscle contraction and rhabdomyolysis.

It is very important to identify "at risk" patients pre-operatively:

- Positive family history;
- Definite association with MH in CCD, King-Denborough syndrome and Evans myopathy;
- Unclear link, but rhabdomyolysis has been reported in other neuromuscular disorders.

In vitro caffeine-halothane contracture tests are recommended to assess MH susceptibility, particular in cases with a strong family history. This test is 97 - 99% sensitive, but only 80 - 90% specific.

Anaesthetic considerations

- Avoid triggers in high risk patients.
- Early administration of dantrolene reduces mortality from 60% to 10%.

Conclusion

Children with hypotonia may present for a variety of surgical procedures. A thorough pre-operative history and assessment is necessary to evaluate functional capacity with a high suspicion of co-existing cardiac and respiratory disease, as well as metabolic disease. Pre-operative optimisation, fluid and electrolyte correction, and careful post-operative planning is vital.

The dilemma remains with the anaesthetic management of the undiagnosed floppy child. There are, however, several clues to help the anaesthetist make an educated guess as to the aetiology of the neuromuscular disease. A child with any variety of muscular dystrophy will typically have a history of muscular dystrophy in the family. Physical exam will reveal hypertrophic calf muscles, despite global hypotonia, and elevated creatine kinase levels. In the absence of a positive family history, and with pre-operative elevated serum lactate, it is more likely to be a mitochondrial disease.

When the specific diagnosis is known, it would be appropriate to choose a TIVA technique for the child with muscular dystrophy, and an inhaled agent for the child with mitochondrial myopathy.

The risk of rhabdomyolysis or malignant hyperthermia when using inhalational anaesthesia is 1.09% (Flick et al). For many paediatric anaesthesiologists this is unacceptably high, and a total intravenous technique may be used in all children with undiagnosed myopathy. If using propofol as the primary agent, risks for propofol infusion syndrome and rhabdomyolysis are minimised by using moderate doses (< 4 mg/kg) and for short duration (< 48 hours).

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