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A Child With Mitochondrial Disease and Propofol Allergy Who May be Susceptible to Malignant Hyperthermia

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Stem Case and Key Questions Content

A 10-year-old male presents for laparoscopic cholecystectomy. He has suffered several months of right upper quadrant pain and had an abnormal HIDA scan.

The background includes a long history of mild hypotonia without cognitive delay. He reports cough and intermittent breathlessness, which has been diagnosed as asthma, but says there was no response to bronchodilator therapy. He is blind in his left eye. The parents report that mitochondrial testing at an outside institution exhibited abnormalities in the function of complex IV, and possibly complex II also.

How will you adjust your anesthetic plan in view of the mitochondrial disease?
Mom reports that the child is allergic to propofol. She says he developed a rash and respiratory difficulty in the PACU following anesthesia with this drug at another hospital.

Will you use propofol? Is propofol allergy testing appropriate or helpful?
Ibuprofen is also listed in the child's allergy list, because mom had a 'bad reaction' to it herself. Most of the boy's care has been at a number of other institutions across the US. The only medical condition managed at your hospital is eosinophilic esophagitis. For this condition he has undergone multiple EGDs with biopsies under general anesthesia at your center. The family further reports allergies to almost all foods, including eggs, and the child is on an elemental diet. For each EGD mom has requested he receive just fentanyl, sevoflurane, ondansetron and dexamethasone. These anesthetics have been uneventful.

How do you deal with the patient's multiple allergies? How do you handle family members who seek to dictate every detail of their child's anesthetic care?
On the afternoon before surgery, you receive an urgent email from a colleague in genetics. The provisional results of exome sequencing show that the child carries an abnormal variant of the *RYR1* gene. She feels the patient is at risk of malignant hyperthermia (MH).

What is the implication of the RYR1 *mutation? Do you believe that the patient is truly at risk of MH, given that he has undergone volatile anesthesia so many times without incident?*

Will you avoid MH triggering agents for this patient? What is the latest list of drugs to avoid in MH susceptible patients? How will you prepare the anesthesia machine?

What drugs will you choose for induction and maintenance of anesthesia for this patient? For what adverse effects do you need to be prepared? What are the pros and cons of the different agents available for total intravenous anesthesia?

What will you say to the surgeon? How will you explain the situation to the family? What risks will you counsel?

How will you monitor depth of anesthesia if not using volatile agents or propofol? How do alternative agents affect the EEG and the bispectral index?
You induce anesthesia with alternative agents, and increase to maximum reported doses. The BIS is 65 prior to incision.

Are you concerned about this BIS value? What will you do?

How will you handle emergence from anesthesia and disposition?

Model Discussion Content

Successful management of this case requires appreciation of the clinical features of mitochondrial disease and of the genetics of malignant hyperthermia. The selection of drugs for total intravenous anesthesia is also discussed, as well as their effects on the bispectral index.
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Mitochondrial disorders

Mitochondria are organelles present in all human cells except red blood cells. Their main function is oxidative phosphorylation, which is the aerobic production of energy in the form of ATP. The term ‘mitochondrial disorder’ refers to diseases of this function, which is performed by the respiratory chain made up of five multimeric complexes (I to V) embedded in the mitochondrial inner membrane, plus two small mobile electron carriers, coenzyme Q10 and

cytochrome c. Mitochondria also have roles in the tricarboxylic acid (Krebs) and urea cycles, β-fatty acid oxidation, and lipid and cholesterol synthesis.

Mitochondrial diseases mainly affect organs with high metabolic activity, such as brain, muscle, liver, heart and kidney.[i] Although each mitochondrion contains a small, circular DNA molecule (mtDNA), this encodes only 37 of the ~3000 genes required to make a mitochondrion. Most respiratory chain components are actually encoded by nuclear genes. Accordingly mitochondrial diseases can be autosomal recessive, dominant or X-linked.

mtDNA mutations are maternally inherited, passing to the embryo inside mitochondria within the cytoplasm of the ovum. Resulting diseases therefore exhibit 'heteroplasmy', meaning co-existence of wild type and mutant DNA within the same cell. Sequela therefore reflect the proportion of abnormal mitochondria, and this varies between tissues and even individual cells. Clinical consequences are therefore unpredictable.

Mitochondrial diseases are notorious for the challenge of their diagnosis. Onset may be at any age. Common clinical presentations include respiratory muscle weakness, swallowing difficulties, cardiomyopathy (typically hypertrophic), atrioventricular conduction defects, proximal myopathy, sensorineural deafness, ptosis, external ophthalmoplegia, optic atrophy, pigmentary retinopathy, and diabetes mellitus. Central nervous system findings are fluctuating encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, and spasticity. It has been said that: "When a common disease has features that set it apart from the pack, or involves 3 or more organ systems, think mitochondria."

In the work up for mitochondrial disease, plasma lactate may found to be above the normal range. An elevated lactate/pyruvate ratio is particularly suggestive. Brain MRI may show characteristic lytic lesions in the basal ganglia and thalamus. Seizures are frequent. In many cases muscle is involved. Muscle biopsy is often performed. The sample is subjected to light and electron microscopy and biochemical studies. Because there are substantial proportions of false positives and negatives, especially when assays are performed on frozen rather than fresh samples, the utility of muscle biopsy is debated.

Open muscle biopsy brings patients with suspected mitochondrial disease to the attention of anesthesiologists. Gastrostomy tube and central line insertions are also frequent.
Although many anesthetic agents have been shown in the lab to inhibit respiratory chain function, the clinical relevance remains unclear, perhaps reflecting the biochemical and clinical variability of these patients. Propofol is an area of particular concern, as inhibition of mitochondrial function has been demonstrated *in vitro*,[ii] and this has been implicated in the pathogenesis of propofol infusion syndrome. Farag *et al* recommend avoidance of propofol in more symptomatic mitochondrial disease patients.[iii] Furthermore, if propofol is felt to be necessary, it is suggested to monitor lactate levels during infusions, ensure adequate carbohydrate intake to suppress fat metabolism, and to avoid prolonged use. Many experts regard valproate and barbiturates to be contraindicated in mitochondrial disorder patients.

Volatile agents inhibit complex I in the laboratory ,[iv,v] but have been used safely in practice, and are the anesthetic agents of choice for mitochondrial disease patients in the author's institution. As for many with central nervous system and/or neuromuscular dysfunction, some individuals with mitochondrial disease may show pronounced sensitivity to opioids or to non-depolarizing muscle relaxants.

In providing anesthesia for mitochondrial disease patients, it is vital to be aware that metabolic decompensation can occur with intercurrent illness, fasting (such as for anesthesia), shivering and hypotension.

Before the molecular basis of malignant hyperthermia (MH) was well understood, there was concern that mitochondria may be implicated in its pathogenesis, with the corollary that mitochondrial disease patients could be at higher risk for MH. With improved scientific knowledge and increased clinical experience, this appears not to be the case.[vi]

Genetic testing for malignant hyperthermia

Malignant hyperthermia is an autosomal dominant disorder triggered most frequently by volatile anesthetics and depolarizing muscle relaxants during general anesthesia. The resulting muscle hypermetabolism leads to rapidly rising temperature, severe acidosis and rhabdomyolysis. Since avoidance of triggering agents prevents development of MH, susceptible individuals must be identified, so that alternative anesthetic techniques may be provided with a 'clean' anesthesia machine.[vii,viii]

In North America the caffeine-halothane contracture test is considered the 'gold standard' for identifying MH susceptible patients. In practice however even this test has limited sensitivity and specificity. Moreover, since muscle biopsy is necessary, it is rather invasive, and relatively few centers offer the test.

The modern understanding of the pathogenesis of MH is that triggering agents lead to an acute rise in muscle intracellular ionized calcium concentration, due to a failure of the normal regulation of excitation-contraction coupling. This calcium is both released by the sarcoplasmic reticulum (SR) and also enters the cell through sarcolemma invaginations known as T-tubules. The ryanodine receptor (RyR1) calcium release channel of the SR interacts with the dihydropyridine receptor (DHPR), an L-type voltage-dependent calcium channel in the T-tubule membrane. The genes encoding the ryanodine receptor *(RYR1)* and the α_{1S}-subunit of the DHPR *(CACNA1S)* are the only ones in which mutations causing MH in humans have been found. Together these genes account for only 50-70% of cases, so other loci are suspected to be important too.[ix] On this note, individuals with central core disease (CCD) and King-Denborough syndrome must be considered MH susceptible, since they are due to *RYR1* mutations.[x,xi]

With the discovery of MH-causing mutations came the hope that muscle biopsy testing would be rendered obsolete by genetic testing. Most variants associated with MH are single nucleotide

changes. In contradistinction to genetic diseases such as cystic fibrosis, where a small number of mutations account for a large proportion of cases, MH is very heterogeneous with a substantial number of associated variants identified. Indeed the distribution and frequency of mutations varies across the world. Experience has furthermore shown that there are many more polymorphisms of *RYR1* and *CACNA1S* that do not cause MH (as judged by their presence in unaffected relatives of probands). A further challenge in determining MH susceptibility from genetic testing is that more than one gene is believed to be associated within some families. Attempts to test variants for abnormal function *in vitro* are time-consuming, expensive and unreliable.

The rapid uptake of 'next generation sequencing' (NGS) techniques threatens to increase substantially the number of patients who may believe themselves to be at risk for MH. Various NGS technologies are available, but they have in common a massively parallel process of DNA fragment sequencing, followed by a highly sophisticated computer-based assembly to give vast quantities of patient-specific genetic data for comparison with canonical sequences derived from the human genome project.[xii] Sequencing of an individual genome (or at least the protein-coding parts of it) is now commercially available for less than $1000. The approach has hence become an attractive option for physicians and families eager to investigate chronic, unexplained signs and symptoms, of any type, where a genetic etiology is suspected. (This includes, but is not limited to, suspected mitochondrial disease.) The incidence in unselected patients with NGS data of *RYR1* variants of unknown or potential association with MH is as high as 5-10%.[xiii] This may soon lead to a substantial increase in patients requesting avoidance of MH triggering agents, as exemplified by the case presented. Many of these patients will require total intravenous anesthesia (TIVA).

Total intravenous anesthesia

Volatile anesthetic agents have long been the mainstay of anesthesia, but they are absolutely contraindicated in patients susceptible to MH. Features of an ideal agent for TIVA include: rapid, painless onset; easy titratability; smooth and fast offset; consistent pharmacokinetics; ability to monitor depth of anesthesia; good surgical conditions; cheap; free from side effects.

Propofol

Many practitioners find that *propofol* comes closest to the ideal agent for TIVA. Onset of anesthesia occurs in little over an arm-brain circulation time (90-100 seconds). There is some pain on injection, but this can be reduced by the prior or co-administration of lidocaine. Propofol's pharmacokinetics are complicated in requiring multi-compartment modeling, but detailed and reliable models are so well developed that target-controlled infusion pumps have been developed and are widely used (outside the US[xiv]) even for children.[xv] Propofol is metabolized in the liver, but also outside this organ, such that it can be used with minimal modification of technique even in patients with hepatic impairment. The context-sensitive half-time for propofol after infusions of up to 8 hours is less than 40 minutes, but offset is much slower after infusions of many hours. Patients report a good quality of wake-up.

Providers find that the hypnotic effect of propofol can be monitored fairly reliably with BIS. In practice, if used alone, there may be unwanted patient movement, even at anesthesia depth where the patient has no recall. For this reason, and because it permits lower doses of propofol and facilitates even more rapid wake-up, a remifentanil infusion is often co-administered.[xvi] (Remifentanil is unsuitable for sole use in TIVA due to its lack of amnestic properties.) Propofol's profound suppression of airway reflexes is often harnessed as an advantage, in that laryngospasm is suppressed and endotracheal intubation is facilitated. A degree of hypotension is often noted during propofol TIVA, associated with a drop in systemic vascular resistance. Propofol TIVA is linked with low rates of post-operative nausea and vomiting (PONV), and may indeed be selected primarily for this reason in susceptible patients. Propofol's poor solubility in water means that commercial formulations are lipid-based.

The high lipid load is thought to be an important factor in propofol infusion syndrome, an uncommon complication seen mainly with longer and higher dose infusions of propofol.[xvii] Since only a proportion of individuals exposed to such doses develop the syndrome, it is suspected that this reflects an unmasking of an inborn sub-clinical metabolic defect, probably of fatty acid metabolism. Because mitochondrial dysfunction has been implicated in the pathogenesis, there has been concern that mitochondrial disease sufferers may be at higher than average risk, as alluded to previously. Propofol infusion syndrome has been reported most commonly in PICU use, but the risk must also be considered in anesthetic practice. The resulting severe metabolic acidosis and multi-organ dysfunction is associated with high mortality.

Allergy to propofol has also been reported. Such reactions can occur on first use, and often take place in those with histories of atopy.[xviii] Most exhibit a positive skin test (to propofol or its lipid solvent) or leukocyte histamine release assay, or the presence of drug-specific IgE. In providing anesthesia for esophagoduodenoscopy in pediatric patients, it is not uncommon to find patients with histories of allergies to egg or soybean, both of which give rise to components present in some propofol formulations. In a study of 43 children with egg allergy documented by recent skin prick test, only one had a reaction and this was judged to be a non-anaphylactic immediate allergic reaction.[xix]

Ketamine

The phencyclidine *ketamine* is also a possible choice for TIVA. The S(+) isomer of this NMDA antagonist is more potent and associated with less side effects,[xx] but the racemic form is not available in the US. Onset of action occurs within 30 to 60 seconds of administration with maximal effect in about 1-2 minutes. The offset of ketamine is rather slower than for propofol. After a single dose this occurs by re-distribution with a half-life of 11 to 16 minutes. Ketamine offers the advantage of analgesia in addition to hypnosis.[xxi] Post-operatively there is a decrease in opiate use or improved analgesia and a decrease in opiate-induced side effects, especially PONV. The quality of anesthesia is rather different to other agents, in that patients often keep their eyes open and maintain (at least to some extent) protective airway and other reflexes. It may be disadvantageous to the surgeon that muscle tone is increased. Purposeless movements are often seen. As a single IV dose of 2-4 mg/kg provides consistent anesthesia for 10-15

minutes, ketamine is a useful drug for short procedures. Because cerebral metabolism, blood flow and intracranial pressure are increased by ketamine, it is contraindicated in those for whom those effects could prove deleterious, particularly after traumatic brain injury. In newborn animals ketamine increases neuronal apoptosis. Except for increased salivation and laryngospasm, ketamine's respiratory effects are benign. Indeed its bronchodilatory effects make it a suitable agent for patients with brittle asthma. Unique amongst IV induction agents, ketamine increases blood pressure, heart rate, and cardiac output, which is useful in many patients with heart disease of non-ischemic origin. Common but undesirable emergence reactions are the major disadvantage of ketamine. They include vivid dreaming, 'out of body' experiences and misperceptions/illusions, often associated with negative emotions such as confusion and fear. These are less common in children than adults, and their incidence can be reduced by co-administration with benzodiazepines.

Etomidate

Hemodynamic stability, minimal respiratory depression, and pharmacokinetics enabling rapid recovery after either single dose or continuous infusion of *etomidate* contribute to the popularity of this drug. On the negative side are pain on injection and PONV, but most crucially temporary inhibition of steroid synthesis after either single dose or infusion. Of most concern, several studies have associated etomidate with increased mortality even when steroid replacement doses are administered, although studies have also been published which do not find this association.[xxii,xxiii,xxiv]

Dexmedetomidine

The imidazole drug *dexmedetomidine* is a highly-specific α_2-agonist.[xxv] Its pharmacokinetics are non-linear (mostly because significant cardiovascular effects alter its own metabolism) but can be described by a three-compartment model.[xxvi] A loading dose is generally required, typically up to 1 microgram/kg over 10 min. The context-sensitive half-time ranges from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion. Dexmedetomidine is licensed by the FDA only as a short-term sedative for ventilated adult ICU patients. In pediatric practice, off-label use has gained ground for sedation in the PICU and for non-painful radiologic use such as for MRI scans, especially sleep studies.[xxvii] Dexmedetomidine is believed to stimulate endogenous sleep pathways and, like natural sleep, patients can be roused and follow commands at dosage levels within its product license, though not at ten-times higher plasma concentrations.[xxviii] Brain and spinal cord α_{2A}- and α_{2B}-receptors mediate sympatholysis, sedation, and antinociception. Dexmedetomidine has opioid-sparing effects[xxix] and reduces postoperative analgesia requirements.[xxx] Outside the CNS presynaptic α_{2A}-adrenoreceptors inhibit the release of norepinephrine promoting vasodilatation, but α_{2A}-adrenoreceptors on peripheral blood vessels mediate vasoconstriction. In practice, sympatholysis is predominant at lower concentrations with bradycardia and hypotension, but hypertension can occur at higher levels, and reflex bradycardia may be a risk. Hypotension and bradycardia appear related to the administration of a loading dose, such that either slowing or reducing this reduces their incidence. Dexmedetomidine has relatively minimal effect on the respiratory system, but improves arterial oxygenation and reduces intrapulmonary shunt during one-lung ventilation.[xxxi]

Few reports have been published of dexmedetomidine as the primary or sole hypnotic agent for TIVA. Ramsay and Luterman describe three adult patients for whom dexmedetomidine at 5-10 microgram/kg/h was chosen in view of its minimal respiratory effects. Naguib *et al* used dexmedetomidine at up to 2 microgram/kg/h, along with high dose narcotic and benzodiazepine, for cardiac surgery on a 5-month old at risk of MH.[xxxii] Shukry and Kennedy used the drug as a sole agent for a series of 4 infants undergoing direct laryngoscopy and bronchoscopy.[xxxiii] Dewhirst and colleagues used dexmedetomidine at up to 1 mcg/kg/h supplemented with nitrous oxide for three MH susceptible patients undergoing adenotonsillectomy, femoral nailing and craniotomy, respectively (with the addition of remifentanil for the craniotomy).[xxxiv] They reported also decreasing BIS values in response to dexmedetomidine administration at anesthetic doses, which confirmed studies conducted previously in healthy volunteers at sedative doses.[xxxv]
In high doses, benzodiazepines and barbiturates are also possible TIVA agents, but the long half-lives of currently available drugs render them less desirable, in view of the lengthy wake-up that would follow.

Depth of anesthesia monitoring
The use of processed EEG to guide anesthetic management remains an area of debate. Of commercially available devices, a recent systematic review concluded that the BIS monitor (Covidien) remains most supported by the published evidence base.[xxxvi] BIS incorporates time-domain, frequency-domain, and bispectral analysis of the EEG. It is displayed as a dimensionless number between 0 (deep anaesthesia) and 100 (awake), with 40 to 60 usually considered suitable for surgical anesthesia. Compared to standard monitoring alone, use of bispectral index monitoring showed a reduction in the incidence of awareness by 82% in a large, international randomized controlled trial in a high-risk adult patient population.[xxxvii]
In pediatric practice, in particular, there has been concern that the bispectral index is not reliable in the youngest patients, whose electrical brain activity exhibits substantial developmental differences when compared to the adult population for whom the technology was originally validated. Jeleazcov and colleagues however have shown that BIS provides reasonable accuracy above the age of 12 months.[xxxviii]

A meta-analysis supports the superiority of BIS to prevent awareness in comparison to clinical signs alone but not over monitoring of end tidal anesthetic gases.[xxxix] Depth of anesthesia monitoring techniques are therefore more useful when utilizing TIVA with muscle relaxation, when neither end-tidal volatile agent concentrations nor patient motor responses are available to confirm adequate anesthesia. BIS is useful for titrating propofol infusion in children,[xl] but effects of other intravenous agents are less well known. Dexmedetomidine reduces the bispectral index in a dose-dependent manner when used in addition to volatile anesthetic agents[xli] or propofol[xlii] or propofol and remifentanil.[xliii] This is also true of etomidate.[xliv] Ketamine however as a sole agent does not reduce the bispectral index even when patients are unconscious, and actually increases BIS when used with propofol and fentanyl[xlv] or with dexmedetomidine and morphine.[xlvi]

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