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Mitochondrial Disease: Navigating Clinical Uncertainties, Patient Misinformation & Urban Myths

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Objectives:

- Discuss the basic characteristics of mitochondrial disease. What distinguishes this disease from other myopathies?

- Analyze the anesthetic implications of coexisting neuromuscular disease in the pediatric patient. Are all syndromes treated the same? What approaches are considered acceptable if there is no clearly defined diagnosis?

- Discuss the perioperative considerations specific for patients with mitochondrial disease. What do we need to know? Review the recommended preoperative studies and tests needed for perioperative management.

-Identify established correlations between neuromuscular disease and susceptibility to Malignant Hyperthermia. Should we avoid the known "triggering agents" for all pediatric patients affected by mitochondrial disease?

- Discuss strategies for dealing with the concerned parent who may have received conflicting information about viable anesthetic choices and associated risks. Are there consensus statements that we can cite to reassure the anxious parent?

- Is there a safe anesthetic for patients with mitochondrial disease? Based on an individual case, stratify the risks of anesthesia with intravenous vs. inhalational techniques.

Case History:

MR is a 5 year old patient who presents to the pre-surgical area in preparation for a sequence of procedures that have been arranged to be accomplished using a single anesthetic episode. The patient is to have a total spine evaluation MRI in the radiology suite, followed by transport to the main OR for a T&A to address sleep-disordered breathing. Finally, the patient is to remain anesthetized for an echocardiogram.

Questions:

What are the advantages/disadvantages of a single, long anesthetic episode versus multiple anesthetics? Does altering the procedural sequence in a particular way reduce inherent risk? What are the considerations for any patient underdoing multiple procedures in multiple locations under one prolonged anesthetic? What patients might benefit from this complex coordination of care? What specific added risks, if any, should be shared to meet the requirements of informed consent?

Case History (continued):

Accompanied by his mother, he has an evaluation performed in the pre-anesthesia evaluation and testing clinic. His medical history is notable for: prematurity (35 weeks), mitochondrial disease unspecified MELA type (associated w/ hypotonia, lactic acidemia, seizures, optic atrophy with nystagmus, persistent developmental delay), small PFO (left to right shunt), sleep disordered breathing, GERD, and moderate dysphagia. Records indicate three prior anesthetics; one for Left thigh muscle biopsy, placement of myringotomy tubes and the other for spine MRI. Approximately one month after the MRI he was seen in the ER for dysuria and brown colored urine. He was evaluated and discharged to home with some vague follow-up plans for further evaluation with the neurogenetics specialists.

Questions:

What information in the PMH is most likely to influence your approach to the preoperative workup? What are your initial thoughts concerning the feasibility/safety of the planned procedures and coordination of care?

Case History (continued):

On further review, the child takes Cimetidine, Coenzyme Q, Levertiracetam, Levocarnitine and Lamotrigine. Lab studies indicated an elevated lactate and an elevated CPK. His last ECHO (about a year ago) demonstrated normal chamber dimensions and biventricular function.

Questions:

What would be your recommendations concerning the peri-operative dosing of his medications? Should any be withheld? Would you like any other information?

Case History (continued):

His mother reports that when he was initially diagnosed, she was told that he should ALWAYS have MH precautions for any anesthesia. He was diagnosed and treated in another state and is now followed by the neurogenetics team at your hospital, with whom you have not had any contact. They have provided a consult note that recommends the avoidance of multiple medications; Propofol, benzodiazepines, NMB agents and Lactated Ringer's Solution are included in this list.

Questions:

Does the past experience of the mother provide any useful context regarding the patient's disease process? Is this pt at risk for MH due to his mitochondrial disease? What is the relationship of the mitochondrial disease complexes to MH? Where are the biogenetic/chemical alterations? Should we provide a non-triggering technique to all patients affected by mitochondrial disease? What is the difference between mitochondrial disease and muscular dystrophy? Is there a direct link between MD and MH?

Case History (continued):

You have access to the prior anesthetic records: his first anesthetic for muscle biopsy was done using a Propofol-based TIVA technique after nitrous oxide-assisted PIV placement; the second anesthetic for ear tubes was an inhalation induction with Sevoflurane and mask airway maintenance; the imaging anesthetic was an inhalation-assisted IV start then Dexmedetomidine and Remifentanil infusion maintenance. The mother insists that "the machine has *always* been treated" and that "non-triggering agents have *always* been used for his anesthesia."

Questions:

How do you plan to proceed? What discussion will you have with the mother, especially in light of the successful use of both triggering and non-triggering techniques? Does the list of drugs to be avoided agree with your initial plans for drug selection? Are there specific anesthetic risks that should be addressed regarding the mitochondrial disease? Does the anticipated length of the procedure(s) affect your decision? How do you reconcile the mother's past experiences and presumptions about what constitutes a "safe anesthetic"?

Case History (continued):

During your discussion of the care plan with the mother, she becomes very upset and fixated on the fact that the anesthesiologist who was consulted at the time of her son's pre-anesthesia appointment (one of your senior colleagues), strongly emphasized the need for MH precautions and cited some medical literature. The mother is clearly frustrated and confused by this conflicting information from multiple care providers (anesthesia and neuro/genetic/developmental medicine). She is uncertain that she even wants to proceed with the planned procedure at your hospital.

Questions:

How do you best collaborate with the mother to resolve her doubts about your ability to provide safe and effective care to her child? What information/recommendations can be obtained from the MHAUS website? Is this an appropriate patient for a complex coordination of care under one anesthetic? What is the safest anesthetic (if any) for a patient with mitochondrial disease? Is their reliable research data or published consensus statements to guide our decision?

Case Conclusion:

The anesthesiologist consults with the department's Medical Director, to better coordinate a comprehensive and thoughtful plan due to the number of anesthesia providers scheduled to participate in the care of this patient. A decision is made and the plan is discussed with the mother, who agrees to proceed after her concerns have been addressed. The procedures are performed and the patient tolerates the anesthetic without complications. They are discharged to home later that day. Should the same method be utilized for every future anesthetic?

DISCUSSION:

The mitochondrial disorders represent a heterogeneous group of mtDNA mutations and deletions that affect the respiratory chain complexes I-V at multiple sites and with variable severity. They manifest themselves as significant dysfunctions of energy-intensive organ systems (most commonly affecting the brain, cardiac conduction, respiratory system and the gastrointestinal tract). The presentation and clinical severity of specific syndromes (specifically the ragged-red fiber disorders such as Kearns-Sayre syndrome) are also variable, and remain a challenge for the pediatric anesthesia provider to deliver an effective but safe anesthetic regimen that minimizes the risk of exacerbating existing respiratory chain abnormalities.

As our understanding of the mitochondrial disorders has evolved, so has our collective focus upon the concepts of appropriate drug selection. In years past, there was significant concern that a child with Kearns-Sayre syndrome or some other suspected mitochondrial myopathy was MH-susceptible, and would be best served with a non-triggering technique. A retrospective review by Flick et al examined the records of 274 pediatric patients who received a volatile agent or succinylcholine for diagnostic biopsy of suspected neuromuscular disease (NMD), none of whom developed MH or rhabdomyolysis. The estimated risk of a patient with suspected NMD developing MH after exposure to volatile agents was just over 1% [Flick]. This finding may be interpreted as reassuring, especially when compared to the 0.46% risk in an MH-susceptible child who experiences MH following a non-triggering technique [Carr].

The preponderance of recent literature has mostly dismissed the prior association of MH with mitochondrial disease (notable exceptions being King syndrome, Evans myopathy and central core disease) [Ross]. However, this has failed to resolve some remaining concerns involving the use of volatile agents for anesthetic maintenance. Morgan and colleagues presented a small case series in which children with complex I defects demonstrated abnormal sensitivities to low Sevoflurane concentrations (in one case requiring an end-tidal concentration of only 0.8% to achieve a BIS of 60) [Morgan]. There is also persistent controversy about the relative risk of rhabdomyolysis and subsequent hyperkalemic cardiac arrest.

TIVA-based techniques utilizing Propofol seemed for a time to be a logical choice to avoid potential complications in patients with mitochondrial disorders, though this position has also evolved. Propofol has been demonstrated to inhibit complex I and interfere with long-chain fatty acid metabolism. It has been reported that even short-term utilization of Propofol in children with mitochondrial disease may be associated with prolonged recovery and the need for post-procedure ICU management [Farag]. Variations on the TIVA formula have been forwarded, including a recent discussion about the use of dexmedetomidine and remifentanil infusions [Burnett].

Unfortunately, our current level of understanding provides no clear, consistent answers. All types of anesthetics have been successfully deployed without complications to treat children with mitochondrial disease [Driessen]. The choice of anesthetic maintenance with volatile agents or Propofol and their potential side-effects remains a troubling clinical dilemma. Human studies are minimal and to date have not helped resolve all of our unanswered questions. Additional large scale studies will be needed to further describe and validate the optimal anesthetic technique for the child with mitochondrial disease.

References:

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Further Reading:

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