

Does Mitochondrial Myopathy (MM) Increase an Individual's Susceptibility to Malignant Hyperthermia (MH)?

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Recommendations

- Review of literature does not indicate an increased susceptibility to MH by patients diagnosed with Mitochondrial Myopathy (MM).
- patients suffering from MM should receive an anesthetic appropriate for the patient's symptoms and the treatment they are receiving as well as the type of surgery they are undergoing
- Volatile agents should not be avoided out of concern for possible MH susceptibility in MM patients.
- Use caution when using succinylcholine in myopathic patients due to evidence suggestive of succinylcholine-induced hyperkalemia in such patients.

Supporting Evidence

Literature Review: Multiple literature searches of the National Library of Medicine, beginning the year 1970, were done using key words: Malignant Hyperthermia; Mitochondrial Myopathy and Cytopathy; Mitochondrial Syndromes; Anesthetic Management; Pediatrics and Perioperative Complications. Individual database searches were performed as well as searches within the major anesthesiology journals (Anesthesiology and Anesthesia & Analgesia) beginning the year 1970. All articles that described anesthetic management of patients with mitochondrial disorders and articles that conducted original research examining the role of mitochondria in relationship to MH were reviewed.

Background:

It is unclear how the attribute of MH first came about in association with MM. The phenotypical presentations of patients with MM involve acidosis that is of a chronic nature and hypotonia of varying severity. Myopathic illnesses that carry known risk for MH such as central core disease (CCD) share similar clinical features and hence an association may have been first considered. The majority of available literature suggests no or weak association between MM and MH.

Evidence Thus Far:

Ohtani et al (1985) in a letter to the editor reported a successfully treated case of MH in a 2 year old diagnosed with MM. The child had clinically evident motor weakness; elevated CK and pyruvate levels, but received halothane and succinylcholine for an unknown procedure. Generalized muscle rigidity, hyperkalemia and rise in temperature to 38.0 C followed the induction of anesthesia. 50 mg dantrolene (patient's weight unknown, but presumably a large dose for a 2 year old myopathic child) an unknown amount of bicarb and cooling were the treatment instituted. The child recovered in 30 minutes and underwent a muscle biopsy performed with local anesthesia the same day, the analysis of which suggested defective oxidative phosphorylation of the mitochondria.

This brief case report describes a clinical situation where MH is diagnosed in a myopathic child after administering succinylcholine and halothane. All the symptoms and signs except for the temperature of 38.0C could be due to cytoskeletal disruption of muscle from succinylcholine (Theroux, 2001; Van der Spek, 1987) especially in a child with evidence of ongoing muscle cell damage (elevated CK preoperatively). This case at best provides weak evidence of an association between MM and

MH. Nevertheless this letter to the editor has been consistently cited and referenced by numerous other authors as evidence for their statement of MH susceptibility of patients with MM.

Thompson et al (1997) reported the anesthetic course of a 20 year old man with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes) syndrome. The patient had difficulty with anesthesia at a different hospital (other than the author's), and the report clearly notes that MH was excluded in that particular event. However, the authors chose a non-triggering anesthesia citing Ohtani et al (1985). **Non-triggering anesthetics limit the choices of anesthetics available to the anesthesia practitioners and might in fact lead to less desirable choice of anesthetics as in 'choice of propofol based anesthetics for MM'. Note that majority of non-triggering anesthesia includes Propofol which is known to further impair mitochondria.**

Wiesel et al (1991) describes the anesthetic for a 13 month old boy for skin and muscle biopsy. MH triggering agents were avoided, citing Ohtani et al (1985). One sees a pattern emerging where a single case report, has a snow balling effect going forward.

Maslow and Lisbon (1993) report a 40 year old man with MM who was given a spinal anesthetic for reduction of an ankle fracture. One of the reasons stated for performing spinal anesthetic was to avoid triggering anesthesia. Authors mention that there is no evidence to believe that MM renders MH susceptibility but they wished to avoid triggering agents citing Ohtani et al (1985).

Casta et al (1997) describe the perioperative course of a 13 month old who had rapid deterioration of CNS function with MRI findings in the immediate post operative period following general anesthesia for gangrenous gall bladder surgery. Anesthetics consisted of thiopental, isoflurane and nitrous. She developed generalized posturing in the postoperative period indicative of significant CNS dysfunction. It was postulated that this child's worsening condition was due to her defect in oxidative phosphorylation further exacerbated by inhibition of complex III of the electron transport chain by circulating cytokines especially TNF. There was no suspicion of MH as a causative factor. Post operative CNS dysfunction is likely in MM and pathophysiology is directly attributable to the patient's primary pathology of dysfunctional mitochondria. This case report describes the effect of stress induced by anesthesia and surgery on a defective mitochondrial energy resource thus resulting in adverse outcome; there is no relation to MH.

Gronert et al (1979), in an animal study using susceptible swine, concluded 'that the reduced respiratory and calcium binding activities in mitochondria from susceptible swine supported the diagnosis of a myopathy, but that these do not account for the functional and biochemical derangement observed in clinical malignant hyperthermia'. Findings in this study do not support a link between biochemical abnormalities described in MH and those found in the swine in their experiment.

Driessen et al (2007) describe 122 patients with MM who received a variety of anesthetic agents. Only 15 patients were anesthetized using 'total intravenous anesthesia' and the rest received potent Inhalational anesthetics. There were no significant adverse effects related to the choice of anesthetics. This is an important study as the discussion about anesthetic agents revolves around 'to use or not to use volatile anesthetics.' This study supports use of volatile anesthetic agents.

Muravchick et al (2006), in an extensive review of MM state, "Only the very rare mitochondrial myopathies with multicore or minicore histology seem to warrant concerns of an increased risk of MH. Therefore, at least at the present time, there is inadequate data to support the recommendation of some authors that the anesthetic plan for patients with mitochondrial disease should routinely include MH precautions."

Cheam et al (1998) reported the use of a non triggering anesthetic to anesthetize a known case of MM in a child from the Chinese University of Hong Kong. The authors refer to several articles only remotely related or associated with MH.

Fricke et al (1997) describe a 41 year old man with severe exercise intolerance and myalgia with CK 3,700 admitted for MH work up prior to hernia repair. He carried a combined diagnosis of MM and Myoadenylate Deaminase deficiency. [These authors also cite 'Ohtani et al (1985)]. An IVCT test with caffeine and halothane (contracture at 1.5 mm caffeine: 4.5 mN and at 0.11 mm halothane: 2.5 mN, respectively) established the diagnosis MHS (contracture thresholds: more than 2 mN at ? 2 mm

caffeine and 20.44 mm halothane). This study describes a situation where an IVCT performed is positive for MH in an individual with two myopathic conditions. While it proves that this particular patient may be MH susceptible it cannot be extrapolated to mean an increased susceptibility of patients with MM to MH. It must be remembered that results of contracture testing is difficult to interpret when the patient has a co-existing muscle disease especially in the absence of a clinical presentation.

With regard to the use of succinylcholine in MM patients, although the literature does not support an outright statement regarding use of succinylcholine leading to hyperkalemia in MM, there are reports (Al-Takroui et al., 2004, Larach et al., 1997) which indicate fatalities from succinylcholine-induced hyperkalemia and rhabdomyolysis in patients with undiagnosed myopathies. Therefore, caution must be utilized when using succinylcholine in myopathic patients due to evidence suggestive of succinylcholine-induced hyperkalemia. Though not directly related to MH, due to the profound and often irreversible adverse effects from succinylcholine in some myopathic patients, a cautionary statement is warranted in the recommendations.

Author Commentary

Mitochondrial diseases are a group of myopathic conditions encompassing a broad spectrum of defects in mitochondria, the clinical features of which can be worsened by illness or stress. Any surgical intervention would mean a finite amount of stress on an individual and in a mitochondrial myopathic patient this stress itself could worsen their clinical status. No controlled clinical trials have been conducted in patients with mitochondrial myopathy to study the effects of anesthetic agents. As such available clinical evidence of Malignant Hyperthermia Susceptibility (MHS) in mitochondrial myopathy predominantly consists of level 4 evidence (case reports, retrospective reviews of patient's anesthetics and expert opinion). One could speculate on a scenario which if MH occurs in a mitochondrial myopathic patient the burden on the already defective mitochondria might result in a clinical presentation which may be completely unrecognizable.

References

1. Al-Takroui, H., T. W. Martin, et al. (2004). Hyperkalemic cardiac arrest following succinylcholine administration: The use of extracorporeal membrane oxygenation in an emergency situation. *J Clin Anesth.* 2004; 16(6):449-451.
2. Casta A, Quackenbush EJ, Houck CS, Korson MS. Perioperative White Matter Degeneration and Death in a Patient with a Defect in Mitochondrial Oxidative Phosphorylation. *Anesthesiology* 1997; 87:420-5.
3. Cheam EW, Critchley LA: Anesthesia for a child with complex I respiratory chain enzyme deficiency. *J Clin Anesth* 1998; 10:524-7.
4. Driessen J, Willems S, DERCKSEN S, Giele J, van der Staak F, Smeitink J. Anesthesia-related morbidity and mortality after surgery for muscle biopsy in children with mitochondrial defects: *Pediatric Anesthesia* 2007; 17: 16-21.
5. Fricker RM, Raffelsberger T, Rauch-Shorny S, Finsterer J, Müller-Reible C, Gilly Hermann, Bittner RE. Positive Malignant Hyperthermia Susceptibility In Vitro Test in a Patient with Mitochondrial Myopathy and Myoadenylate Deaminase Deficiency: *Anesthesiology*: December 1997; 97:1635-37.
6. Gronert GA, Heffron JJA. Skeletal Muscle Mitochondria in Porcine Malignant Hyperthermia. *Anesthesia & Analgesia.* 1979;58(2):76-81.
7. Larach, M. G., H. Rosenberg, et al. Hyperkalemic cardiac arrest during anesthesia in infants and children with occult myopathies. *Clin Pediatr (Phila).*1997; 36(1):9-16.
8. Maslow A, Lisbon A. Anesthetic Considerations in Patients with Mitochondrial Dysfunction. *Anesthesia & Analgesia.* 1993;76(4):884-6.
9. Muravchick S, Levy RJ. Clinical Implications of Mitochondrial Dysfunction. *Anesthesiology* 2006;105(4):819-37.
10. Ohtani Y, Miike T, Ishitsu T, et al. A case of malignant hyperthermia with mitochondrial dysfunction [letter]. *Brain Dev.* 1985;7:249.

11. Theroux MC, Rose JB, Iyengar S, Katz MS. Succinylcholine pretreatment using gallamine or mivacurium during rapid sequence induction in children: a randomized, controlled study. *J Clin Anesth.* 2001;13(4):287-92.
12. Thompson VA, Wahr JA. Anesthetic considerations in patients presenting with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. *Anesth Analg.* 1997;85(6):1404-6.
13. Van der Spek AF, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. The effects of succinylcholine on mouth opening. *Anesthesiology.* 1987;67(4):459-65.
14. Wiesel S, Bevan JC, Samuel J, Donati F. Vecuronium neuromuscular blockade in a child with mitochondrial myopathy. *Anesth Analg.* 1991;72(5):696-9.