Review of the MHAUS Symposium at Pediatric Anesthesiology 2008

Symposium on Malignant Hyperthermia-Associated Diseases: Who needs a Non-triggering Technique?

Sponsored by the Malignant Hyperthermia Association of the United States. Program Director Dr Ronald Litman Children's of Philadelphia

Morning session reviewed by Dr Rita Agarwal
Denver Children's Hospital

Dystrophinopathies: Drs. Amanda Brown and Harshad Gurnaney (Children's Hospital of Philadelphia)

Muscular dystrophies such as Duchenne's (DMD) and Becker's Muscular Dystrophy and their association with MH was discussed. The literature was divided into four major subcategories: intra-operative heart failure, rhabdomyolysis with volatile agents, and rhabdomyolysis after succinylcholine and true MH. Intra-operative cardiac arrest is primarily reported in patients with DMD undergoing scoliosis repair who may have pre-existing cardiomyopathy. The stress of the surgery, positioning, mechanical ventilation and volume changes are probably significant contributing causes of cardiac arrest. Patients with dystrophic muscle have alterations in the architecture of their sarcolemma, making them more susceptible to volatile anesthetic or succyinlcholine-induced rhabdomyolysis, hyperkalemia and cardiac depolarization abnormalities. The incidence of true MH in these patients is unknown, but it seems unlikely that the 2 are related. The authors note that DMD is an X-linked mutation, while MH occurs as a result of mutations on chromosome 19. Some patients with DMD do have positive caffeine halothane contraction (CHCT) test, but the authors question whether this may be a false positive. Their final recommendations are: succinylcholine is absolutely contraindicated in patients with known DMD or Becker's dystrophy unless required for a life-threatening airway emergency. Patients with known or suspected muscular dystrophy should have their exposure to volatile agents minimized. DMD patients without a known positive muscle contracture test should not be considered to be MH susceptible.

Congenital Myopathies: Dr. Thierry Girard (University Hospital of Basel)

It is important to understand not only the diagnosis and symptoms of particular myopathies but also the underlying molecular mechanisms. Different channels and genetic mutations may be involved and will contribute in varying ways to susceptibility to MH and depolarizing agents. The table is modified from Dr Girard's handout:

CLCN1 = skeletal muscle chloride channel, SCN4A = sodium channel alpha-subunit gene, CACNA1S = Alpha1 subunit of voltage-dependent L-type calcium channel, RYR1 = Ryanodine receptor Type 1, SEPN1 = selenoprotein N, ACTA1 = alpha-actine, NEB = Nebuline, TPM3 = Tropomyosin 3, TNNT1 = troponin T1, TPM2 = beta-tropomyosin.

Myotonias: Dr. Jerome Parness (Children's Hospital of Philadelphia)

Myotonias are a class of myopathy that are characterized by abnormal relaxation after a sudden, voluntary, muscle contraction. They have a wide variety of causes and modes of inheritance but result from membrane hyper-excitability. The myotonias can be divided into dystrophic and non-dystrophic. The non-dystrophic myopathies include myotonia congenita (Becker's and Thomsen's Disease), paramyotonia, potassium aggravated myotonias, hyper-

Table of Myopathy	***estimated risk of MH***	
Disease	***Pathophysiology***	***MH risk***
Myotonia congenita Becker or Thomson	chloride channelopathy	low
Hyperkalemic periodic paralysis	sodium channelopathy (SCN4A)	low
	calcium channelopathy	moderate
Central Core Disease (CCD)	Mutation in ryanodine receptors and presence of central core in muscle fiber	high
Multiminicore disease	Selenoprotein gene	unclear
	Alpha-actine gene	unclear
	Ryanodine receptor	high
Nemaline rod myopathy	NEB, TPM3, TNNT1, TPM2, ACTA1	low
	RYR1	high

kalemic periodic paralysis. Succinylcholine can cause total body rigidity and difficulty with ventilation or intubation in patients with myotonia congenita. There seems to be no other association with MH in this group of patients.

The dystrophic myopathies are autosomal dominant, multisystem disorders with significant neuromuscular findings. Although no case reports link the dystrophic myopathies with MH there have been positive CHCT tests which may or may not be false positives.

Review of afternoon MH session submitted by Dr. Dheeraj Ahuja
Denver Children's Hospital

The first speaker in the Thursday afternoon session of the MH symposium, Dr. John Capacchione (Uniformed Services University of the Health Sciences), presented an interesting talk on "Heat and Exercise related Rhabdomyolysis"

Heat and/or exercise-induced rhabdomyolysis (HER), is a problem that occurs not infrequently in well trained and conditioned athletes. At their institution, this problem was observed in military recruits who are physically fit well-conditioned military service members. There have been a few publications in the literature suggesting association between unexplained exercise-induced rhabdomyolysis, asymptomatic hyperCKemia and MH. A new protocol was developed at their center to investigate the link between MH and exercise-induced rhabdomyolysis. They perform Caffeine Halothane Contracture Test (CHCT) for patients with repeated unexplained exercise-induced rhabdomyolysis. Patients with positive CHCT are then screened for RYR1 gene mutation responsible for causing MH. CHCT was developed and validated as a diagnostic test for MH following a clinical event suspicious for MH. CHCT was 97% sensitive, but the specificity was only 78%,**5** indicating a 22% false positive rate. Since clinical correlation of MH was used to validate the CHCT, it is difficult to know if patients with rhabdomyolysis and positive CHCT are truly MH-susceptible or false positives. There is not enough evidence available yet to make any recommendations but at their institution a patient with repeated episodes of unexplained exercise-induced rhabdomyolysis and/or asymtomatic elevated CK levels is anesthetized with a non-triggering technique.

Drs. Joan Benca and Kirk Hogan (University of Wisconsin) opened the session "Miscellaneous Disorders" by discussing various rare genetic disorders like Noonan Syndrome, Osteogenesis Imperfecta and arthrogryposis and their association with MH. There was also discussion on patients with CPT II deficiency, myophosphorylase deficiency, myoadenylate deaminase deficiency, Brody's disease, asymptomatic hyperCKemia and metabolic disorders of skeletal muscle. Speakers agreed that there is not a lot of evidence available to make a definite conclusion about correlation between these rare genetic disorders and MH. There have been case reports of hyperthermic reactions and MH in some of these patients. There is very little science, mostly anecdotes and theories. At their institution, they get a consultation with geneticist, neurologist or metabolic specialist and then discuss the management with perioperative team and parents. If the patient has rhabdomyolysis, they avoid succinylcholine. For brief exposures they use sevoflurane or desflurane.

Dr. Thomas Crawford (Johns Hopkins School of Medicine) presented his views on "Differential Diagnosis of the Hypotonic Infant presenting for Muscle Biopsy".

The indications for, value of, and potential problems associated with muscle biopsy in hypotonic infants is changing with advances in medical practice. Widespread use of pre-diagnostic genetic testing has eliminated the need for many biopsies, but in some cases the potential for false positive and ambiguous genetic tests make the accurate diagnosis by conventional means all the more important. Extensive focused history taking and clinical evaluation is essential prior to subjecting an infant to muscle biopsy. Delaying the muscle biopsy could be a very powerful diagnostic tool, as it will allow more time for the emergence of other signs and symptoms. Prior to muscle biopsy, a very extensive neurological exam should be performed. Assess muscle power, tone and bulk. Look for fatigability, joint range of motion, tendon responses. Evaluate the CNS: cortical functions, seizures, corticospinal involvement, extrapyramidal involvement. The causes for hypotonia in an infant may be classified into four major categories: central, neuronal, neuromuscular junctional or muscular disorders. Vast majority of the causes for hypotonia are central. Patients with myopathies have the highest yield for diagnosis on muscle biopsy.

Online sources include www.genetests.com and www.neuro.wustl.edu/neuromuscular .

Dr. Barbara Brandom (Children's Hospital of Pittsburgh) concluded the MH symposium with her presentation on "Anesthetic management of hypotonic infant presenting for muscle biopsy". There are challenges faced when taking care of a hypotonic infant scheduled for muscle biopsy. This subgroup of patients may have an occult disease, which has not yet completely manifested to be diagnosed. Comprehensive pre-operative evaluation is the key to planning an anesthetic. Pre-operative evaluation should be focused on neurologic and cardiovascular status. If there are findings suggestive of cardiomyopathy, an echocardiogram should be done.

Airway management is important as is IV access for delivery of fluids, intravenous anesthetics and vasoactive drugs in case of an emergency. Cardiovascular stability and rapid awakening and return to preoperative baseline status is also desirable. In her practice, Dr. Brandom administers general anesthesia with nitrous oxide, oxygen and sevoflurane to infants for muscle biopsy. After securing airway and intravenous access, she performs regional anesthesia such as femoral nerve block. Audience expressed their views about regional anesthesia like spinal, caudal or fascia iliaca block for muscle biopsy. She stressed that there is no substitute for being cautious and vigilant and then it doesn't matter which anesthesia technique is used. During the post-operative period, checking urine for myoglobin, measuring core body temperature and monitoring EKG for hyperkalemia can be useful in early recognition and treatment of rhabdomyolysis.