

# Malignant Hyperthermia

## Literature Update

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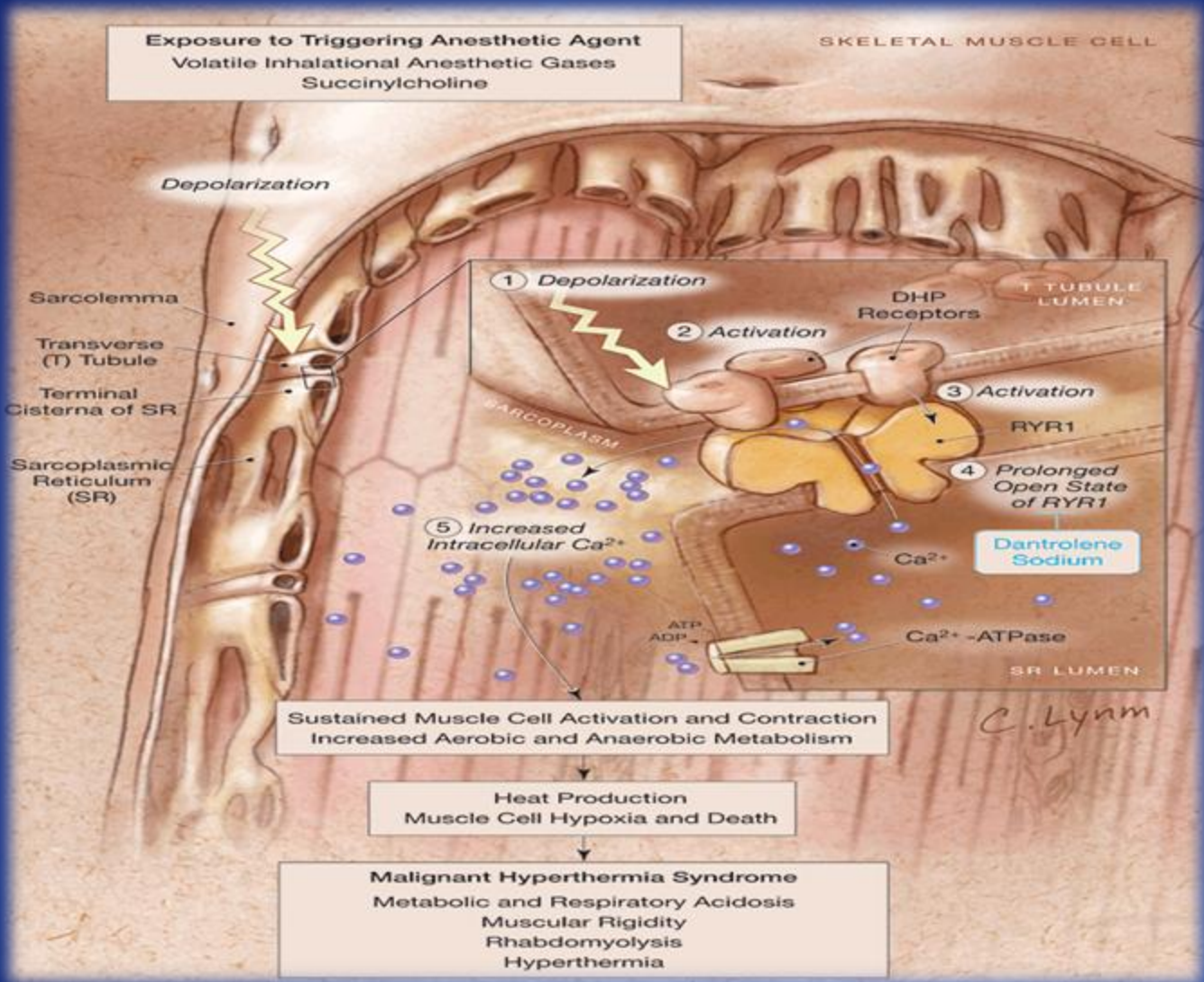
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# Objectives

- Definition
- Presentation
- Preparation
- Treatment
- Genetics of Malignant Hyperthermia
- Literature review

# Malignant Hyperthermia

- Pharmacogenetic condition
  - Autosomal dominant, incomplete penetrance, variable expression
- MH susceptibility (MHS) + Triggering agents
  - Hypermetabolic state
- Ryanodine receptor isoform 1 (RyR<sub>1</sub>)
  - Ca<sup>2+</sup> channel on sarcoplasmic reticulum (SR)
  - Chromosome 19q12-13.2
  - 6 loci identified for MHS



DHP: dihydropyridine

# Presentation

## Clinical Findings

- HR, RR, BP
- Hypercarbia (earliest sign)
- MV
- Generalized muscle rigidity
- Skin mottling
- Arrhythmias
- Temperature
- Tea-color urine (late sign)
- DIC (late sign)

## Laboratory Findings

- PaCO<sub>2</sub>
- Acidosis (mixed)
- Hypoxia
- Increased A-a gradient
- Hyperkalemia
- Increased lactate
- Coagulation study (late)
- Myoglobinuria, -emia
- Increased CPK (late)

# MH Registry

- From 1987 to 2006
- 286 cases met entry criteria
- 16/248 patients + FMH, 9/248 patients + heat stroke
  - 77/152 patients > 2 uneventful GA
- Initial signs: hypercarbia (38%), sinus tachycardia (31%), masseter spasm (21%)
- Respiratory acidosis + muscular rigidity (58.2%)
- MH sign(s) occurs sooner in patients < 19 years
  - Male (75%) >> female

# Preparation

## Patient

- Presenting complaint
- Co-existing pathology
  - Myopathy
- FMH from both parents
  - Any anesthetic event
  - Death
  - Neuromuscular disease

## Anesthesiologist

- Non-triggering anesthetic
  - TIVA and/or regional
- No succinylcholine
- New CO<sub>2</sub> absorbent, soda lime
- New anesthesia circuit
- FGF O<sub>2</sub> 10L/min x min. 20 minutes
  - Breathing bag onto Y piece
  - Ventilator to inflate bag
- Lowest trace of vapor for MH
  - ~ 10 ppm

# Anesthesia Machine

- Drager Fabius (sevoflurane)
  - < 10 ppm, 75 minutes, < 5 ppm, 104 minutes
  - Charcoal scrub/Quick Emergence Device/QED
    - Remove ~ 90% of residual volatile agent
  - QED “off” mode, 5 minute flush
    - 10 L/min,  $V_T$  600ml, RR 10/min, I:E 1:2
  - QED “On” mode, 5 minute flush
  - FGF 10 L/min for 1<sup>st</sup> 5 minutes, then 2 L/min
  - Good for 6 hours

- Drager Fabius (isoflurane)
  - Control: 151 minutes
  - Autoclave ventilator diaphragm & hose: 42 minutes
  - Flush ventilator diaphragm & hose: 137 minutes
  - Autoclave compact breathing system: 122 minutes
  - Dedicated vapor-free workstation maybe a preferable option

# Dantrolene

- Bolus 2.5mg/kg, up to 10 mg/kg
- 1 mg/kg iv q6 hours x 24 to 48 hrs post MH reaction
  - Prevent recrudescence
- Larach et al
  - Median total dantrolene dose was 5.9 mg/kg
  - Time to first sign and dantrolene use
    - 1.61x in complication rate

# Genetics of MH

- MHS on chromosome 19q12-13.2
  - RyR<sub>1</sub> gene
- 6 chromosome locations known to be MHS to date
- 29/300 variants for RyR<sub>1</sub> receptor are MHS
- MHS is not an “all or none” condition
- Certain RyR<sub>1</sub> variants are associated with specific MH phenotypes that are at risks for MHS

# Pediatric patients

- Undiagnosed rare or unusual conditions without overt clinical signs/symptoms during infancy present for elective surgery
- Induction of anesthesia
  - Potential difficult IV access
  - Airway and cardiovascular management during induction
- Case report of pediatric patients with neuromuscular disease with GA
  - Hyperkalemia, rhabdomyolysis, myoglobinuria
  - ? MH or MHS....how is the valid assessment determined

- How do we define anesthetic management for these patients?
- No RCT, only case report or series w/o genetic linkage
- No validation of CHCT in patients with neuromuscular disease or enzymopathy
- State of uncertainty

**Table 1.** Descriptive Risk of Malignant Upper Trauma<sup>a</sup>

Disease	Risk of MH
Duchenne muscular dystrophy	No increased risk over general population. Weak evidence for MH
Becker dystrophy	No increased risk over general population. Weak evidence for MH
Noonan syndrome	Weak evidence for MH. But closer to zero than dystrophinopathies
Osteogenesis imperfecta	Weak evidence for MH. But closer to zero than dystrophinopathies
Arthrogryposis	Weak evidence for MH. But closer to zero than dystrophinopathies
King Denborough	MHS
Carnitine palmitoyltransferase II deficiency	MHS plausible but unproven. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies. Weak evidence
Myophosphorylase B deficiency (McArdle syndrome)	Weak evidence for MH. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies
Myoadenylate deaminase deficiency	Weak evidence for MH. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies
Brody disease	Weak not zero but Rx patients for MH because intracellular Ca <sup>+2</sup> abnormal. Less risk of MH than in dystrophinopathies
Asymptomatic hyperCKemia	Weak evidence for MH. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies
Myotonia congenita	No increased risk over general population
Paramyotonia congenita	No increased risk over general population
Potassium aggravated myotonia	No increased risk over general population
Myotonia fluctuans	No increased risk over general population
Myotonia permanens	No increased risk over general population
Acetazolamide-responsive myotonia	No increased risk over general population
Hyperkalemic periodic paralysis ± myotonia	No increased risk over general population
Myotonic dystrophy Type I (Steinert disease)	No increased risk over general population
Myotonic dystrophy Type II	No increased risk over general population
Hypokalemic periodic paralysis	Unclear, may be greater risk than in general population but less risk of MH than in dystrophinopathies
Central core myopathy	MHS
Multi-minicore disease with RYR1 mutation	MHS
Multi-minicore disease without RYR1 mutation	MHS less risk of MH than in dystrophinopathies
Nemaline rod myopathy without RYR1 mutation	No increased risk over general population
Nemaline rod myopathy with RYR1 mutation	MHS risk of MH not yet determined

MH = malignant hyperthermia; MHS = malignant hyperthermia susceptibility.

<sup>a</sup> Described in Refs. 1, 3, 4, 5, and 7.

# MH and Muscular Dystrophies

- Association between Duchenne muscular dystrophy (DMD) and Becker dystrophy (BD) and MHS
  - Intra-operative heart failure
  - Rhabdomyolysis
  - Hyperkalemic cardiac arrest (no sux)
  - Hyperkalemia w/ succinylcholine (sux)
  - MH

# Intraoperative Heart Failure

- Safe use of inhaled volatile agents w/o sux
- Reports of heart failure in DMD patients during spinal fusion
  - Prone position
  - PPV
  - Anesthetic exposure
  - On-going blood loss
  - Volume resuscitation
- Pre-op echo and invasive monitoring

# Rhabdomyolysis w/o sux

- 7 cases of DMD intra-operative cardiac arrest
  - Halothane
  - Variable onset time, potassium > 8 mEq/dL
  - Dantrolene: mixed acidosis +/- hypermetabolic state
- 8 cases of DMD post-operative cardiac arrest
  - Halothane, isoflurane, and seveoflurane
  - K > 8 mEq/dL
  - 3 patients were undiagnosed at time of incident
- 3 cases of BD cardiac arrest
  - Dantrolene: hyperkalemia minus hypermetabolic process
  - Ages 2.5 to 18 y.o.

- Unlikely genetic association between DMD and MH
- ? validity of CHCT in patients with MD
- “Clinical MH” in the absence of hypermetabolism
- Inhalation agent: rhabdomyolysis & hyperkalemia
- Succinylcholine for life-threatening airway emergency
- Unlikely to be at risk for MHS
- Motor delay → neurology w/u prior to elective surgery

# MH & Co-existing disorders

- Certain syndromes and enzymopathies are suggested MHS
- No available metric system to quantify risks
- No uniformed recommendation and risk stratification

Table 1. Evidence for MHS

Condition	Weak evidence for MHS	Strong evidence for MHS
Noonan syndrome	X	
Osteogenesis imperfecta	X	
Arthrogryposis	X	
King-Denborough syndrome		X
CPT II deficiency	X	
Myophosphorylase B deficiency	X	
Myoadenylate deaminase deficiency	X	
Brody disease	X	
Idiopathic hyperCKemia	X	

MHS = malignant hyperthermia susceptibility; CPT II = carnitine palmitoyltransferase II.

# Noonan Syndrome

- Autosomal dominant or sporadic inheritance
- 1:1000 to 1:2500
- Protein-tyrosine phosphatase nonreceptor-type II mutation
- Turner-like syndrome
  - Short stature, webbed neck, low set ears, pectus excavatum
  - Micrognathia, high-arched palate
  - Kyphosis, scoliosis
  - CHD (PS)
  - Coagulopathy

- Case series of 60 patients scheduled for PSF
  - Muscle rigidity, T<sub>max</sub> to 40°C, metabolic acidosis
  - No dantrolene administered
  - No CHCT post-op



# Osteogenesis Imperfecta (OI)

- Autosomal dominant, autosomal recessive (II & III)
- 1:30,000
- Mutation in Type I collagen
- OI patient scheduled for mandible fracture repair
  - Halothane
  - Hyperthermia to 42°C, metabolic acidosis
  - Cooling measure, dantrolene
- No report of MH in OI patient with positive CHCT
- Hyperthermia resolves with cooling measures

# Arthrogryposis

- Sporadic incidence
- 0.3 to 3: 1000
- 2 case reports of MH like events
  - Acidosis responsive to dantrolene
  - Negative CHCT in 1 subject
- Hyperthermia and hypermetabolism
- Avoid succinylcholine



# King-Denborough Syndrome

- Autosomal dominant, report of recessive mode
- Males >> female (5:1)
- ~ Noonan syndrome w/o CHD, MR, or webbed neck
- 1 case report
  - MH event
  - Mutation in RyR<sub>1</sub> receptor
  - Elevated CK level at baseline



# Anesthetic Management

- These neuromuscular diseases and enzymopathies are not common to our daily practice
- Search about the condition & its associated co-morbidities
  - Genetics, neurologic and metabolic consultations
  - Assess risks and benefits of each plan
  - Discuss care plan with parents
  - Post-operative care
- No case report of MH/MH like event in patients with above conditions to brief exposure of inhalation induction
- ↓ sensitivity, specificity, and predictive value in patients with neuromuscular diseases and enzymopathites for CHCT

# Exertional Heat Illness, Rhabdomyolysis and MH

- Exertional heat illness (EHI)
  - Heat production >> heat dissipation
- Exertional rhabdomyolysis (ER)
  - Complication of EHI
  - Can occur in absence of high environmental or core body temperature
  - Muscle pain, fatigue, CK 5x normal
- Hypermetabolic state, stress to muscle, intracellular  $\text{Ca}^{2+}$

- The relationship
  - Higher central temperature
  - Survivors of EHS with positive CHCT
  - ER patients: positive CHCT and common RyR1 variant
- No case report linked the relationship between clinical MH episodes between EHI or ER to MHS
- Cost of the genetic and CHCT testing
- Advisable to provide non-MH triggering anesthesia

# Prevalence of MH

- Variation in the indicated prevalence of MH between 1:200 to 1:250000
- RF: young age, male, orthopedic, ENT, central core myopathy, EHI, ER
- 1: 100000 surgical patients
- Male >> female (2.5 to 4.5x)

# Postoperative MH

- Analysis of N. America MHAUS registry
- 528 possible or suspected MH cases
- 64 cases with possible postoperative MH
- 10 cases were determined to have post-op MH
  - Volatile agent + succinylcholine
  - 0 to 40 minutes post-op
  - ~ 1.9%