Malignant Hyperthermia

Autosomal dominant pharmacogenetic myopathy characterized by a rapidly progressive hyper-metabolic state resulting in hypercarbia, increased oxygen consumption, acidosis, hyperkalemia, myoglobinuria / emia, tachycardia and tachypnea and which is only treatable with dantrolene and discontinuation of triggers.

ANESTHETIC CONSIDERATIONS:

- A rapidly progressive, **life threatening condition**, triggered by anesthesia, requiring immediate recognition and management
- Identify those at risk and **avoid triggering anesthetics**
- Recognize a case as early as possible, and provide appropriate management

ANESTHETIC GOALS:

- Trigger free anesthetic
- During MH crisis (See Treatment Below):
  - Rapid treatment with dantrolene
  - Reverse hyper-metabolic state
  - Correct hypoxemia / hypercarbia
  - Normothermia
  - Correct electrolyte and acid / base abnormalities
  - Prevent secondary complications (AKI, DIC, CHF, bowel ischemia)

HISTORY

- History of previous anesthetics and family history of anesthetic problems
  - An MH susceptible patient can undergo numerous anesthetics with triggers and not be affected, only to have the next one elicit the condition
  - A previous uneventful anesthetic does not, therefore, eliminate the possibility of MH
- Previous testing of patient or family members for MH
- Documentation of previous reactions
- The spectrum of disease in MH, along with the fact that many conditions can mimic the symptoms of MH, makes it difficult to specifically identify conditions which label a particular patient as being at risk of MH
- Disorders associated with MH (in bold):
  - **Central core disease (CCD)**
    - The only disease truly linked to MH
    - Most have a defect in RYR1 gene locus
  - **Multiminicore disease**
  - **King-Denborough syndrome**, characterized by short stature, musculoskeletal abnormalities, and mental retardation, is associated with susceptibility to MH
  - ?Evans Myopathy
  - Duchenne dystrophy (controversial) likely does **not** predispose to MH
    - Patients with Duchenne dystrophy can respond to anesthesia with sudden, acute, difficult-to-resuscitate cardiac arrest or sudden, acute rhabdomyolysis, even without the use of succinylcholine (but is not considered MH; rather this is an anesthetic-induced rhabdomyolysis)
  - As mentioned above, myopathic syndromes may have an increased risk of MH, or MH-like reactions: these are termed: "Anesthetic-Induced Myodystrophies" or AIMs
    - Patients with muscular dystrophy / myotonia may develop hyperkalemic arrest with SCh and occasionally with potent volatiles by themselves
    - Signs of dystrophy subtle or not apparent in young children
    - Obtain muscle specimens for dystrophin analysis, genetic testing if cardiac arrest
    - Test CK levels if suspicious

PHYSICAL

- MH susceptible patients can look normal
- **VITALS** and **$ETCO_2$**
- Signs during MH crisis or AIM:
  - **HEENT** - Difficult intubation (muscle rigidity, masseter spasm)
  - **CVS** – hypoTN / HTN
  - **RESP** – tachypnea if spontaneously breathing
  - **MSK** – developmental delay, muscle weakness (in case of myodystrophies)
  - **RENAL** – low u/o, dark urine (AKI / myoglobinuria)
  - **SKIN** – hot skin, sweating, mottled appearance (late)

INVESTIGATIONS

- **Labs**
  - Electrolytes and CK level (70% of MH pts have elevated resting CK)
- **Special**
  - Testing of MH: Skeletal muscle biopsy and caffeine-halothane contracture test is gold standard
    - Sensitivity: 100%
    - Specificity: 80-93%
  - Genetic testing of RYR1 gene (Chromosome 19); because of large number of mutations and other loci, currently sensitivity only about 25%

OPTIMIZATION

- Dantrolene prophylaxis currently not recommended
  - May cause nausea, diarrhea, blurred vision, skeletal muscle weakness
  - MH may still develop in the prophylaxed patient

ANESTHETIC OPTIONS

- Local / regional anesthesia will avoid issues
- General anesthesia w/ TIVA

ANESTHETIC SETUP

- **Drugs**
  - Dantrolene available in sufficient quantities
- **Equipment**
  - CAS monitors, specifically capnography and temperature monitor
  - Consider arterial line for serial blood work
  - Replace disposable breathing circuit and fresh gas outlet hoses, use fresh CO2 absorbent, remove or tape vaporizers and continuous flow of O2 at 10L/min for 10-60 min (depends on anesthesia circuit being used) before using the machine
    - However, no studies have shown that MH was triggered by residual volatiles in machine

MANAGEMENT OF ANESTHESIA

- **Induction**
  - Safe drugs are barbiturates, propofol, opioids, BZD, ketamine, droperidol, NDMR
- **Maintenance**
  - TIVA +/- nitrous
- **Emergence**
  - MH may manifest after surgery, monitoring as below

DISPOSITION & MONITORING

- Check MH postoperative protocol in institution
  - MHAUS suggests 1 hr in PACU q15 vitals, then 1.5 hrs in phase 2 PACU / step down
- If outpatient procedure planned, ensure adequate observation time postoperatively

COMPLICATIONS

- Sudden cardiac arrest in PACU
- Myoglobinuria, renal failure
- Rhabdomyolysis – follow CKs
- Hyperkalemia
- **MH Crisis**

1. **Initial Management**
   - Emergency – Declare an MH Crisis – you need lots of people!
   - Call for help and MH cart
   - Discontinue volatiles
   - Hyperventilate with 100% O_2 at FGF 10L
   - Notify surgeon and have them finish surgery ASAP
2. **Dantrolene 2.5 mg/kg IVP q5-10 minutes**
   - Continue boluses until signs of MH are resolved
   - May require 10 to 30 mg/kg
   - Dissolve each bottle in 60 cc warm sterile H_2O (7.5 cc/kg once mixed)
     - Much more soluble at 40°C than 20°C degrees
     - MHAUS suggests not using water >39C for dissolution
   - Each vial contains 20 mg dantrolene + 3 g mannitol and pH = 9 (2.5 mg x 70 kg = 175 mg or 9 bottles)
3. **Supportive Treatment**
   - Establish appropriate IV access and monitoring:
     - CVP, art line, temperature, u/o, EKG, monitor $ETCO_2$
     - Labs: CBC with platelets, lytes, BUN, Cr, ABG, Lactate, CK, Coags, LFTs, sepsis w/u, TSH, urine for myoglobin
   - **Volume resuscitation**
   - Temperature monitoring and **cooling to target of < 38 degrees**
     - Lavage open body cavities, stomach, bladder
     - Surface cooling – ice packs
     - Cold IV fluids
   - Metabolic:
     - **Bicarbonate** 1-4 mEq/kg for metabolic acidosis and for urine alkalinization
     - Treat hyperkalemia (hyperventilate, calcium, bicarbonate, insulin / glucose)
   - Dysrhythmias
     - Usually respond to treatment of acidosis and hyperK
     - Procainamide 3 mg/kg up to 15 mg/kg
     - Lidocaine 1-1.5 mg/kg
     - **Do not use CCB (may cause hyperK and cardiac arrest with dantrolene use)**
   - Force diuresis with volume, lasix, mannitol
4. **Disposition**
   - Watch for recrudescence in ICU for at least 24 hours – occurs in 25% of cases
   - Continuous core temperature monitoring as well as other monitors
   - Dantrolene 1 mg/kg q4-6 hours or 0.25 mg/kg/h by infusion for 36 h
   - Follow labs as above – care with hypokalemia
     - Measure CK every 4-6 hrs during acute event
   - Patient and family counseling and referral to biopsy center

- **MH Hotline: 1-800- MH-HYPER (1-800-644-9737) or 1-315-464-7079 if outside the U. S.**
- Report patient to the **North American MH Registry of MHAUS: 1-412-692-5464**

PREGNANCY

- Few reports of MH in parturients
  - All followed GAs with known triggering agents
- Special concern regarding MH-negative mother and MH-susceptible father as neonate may have MH-susceptibility (as autosomal dominant inheritance)
  - Small quantities of Sux cross placenta
  - Avoid the use of triggering agents until after neonate is delivered is the safest approach
- Chestnut advocates close monitoring of parturient in labour, especially HR and T
- **Early epidural** advocated for MH-susceptible parturients as can convert for surgical anesthesia should operative delivery, etc. be required
- If neuraxial techniques contraindicated, fully prepare anesthetic machine as you would for any other MH-susceptible patient
- Rapid sequence should be performed with any IV induction agent of your choice followed by a NDMB (e.g. Rocuronium 0.6-0.9mg/kg)
- Nitrous, opioids and propofol are all safe for maintenance
- Reversal for NM blockade is safe
- If uterine relaxation is required, use NTG 50-100mcg IV boluses (obviously, completely avoid volatile halogenated agents!)
- Oxytocin is safe
- Treat an MH crisis as you would any other patient
- Dantrolene does cross the placenta and may theoretically cause neonatal hypotonia (but still use as required)

PATHOPHYSIOLOGY

- Incidence originally thought to be rare (1/50,000 anesthetics) but current clinically based information shows it to be 1/15,000 to 20,000 in kids and 1/50,000 to 1/100,000 anesthetics in adults, depending on drugs, population
- Molecular genetics based information shows MH trait in 1/2,000-3,000 patients with low penetrance
- A heterogeneous condition, the molecular basis of which is not completely understood
  - Genetic mutation of the ryanodine (Ry1) receptor
    - This receptor is in contact with the sarcoplasmic reticulum, and regulates calcium flux
  - Defect of the dihydropyridamole receptor (DHPR)
    - This receptor sits on the cell surface and contacts the Ry1 receptor
- The inheritance of human MH can not be considered solely autosomal dominant with variable penetrance, because more than one genetic locus has been identified in some families
  - Because of these issues, it is not possible to exclude MH on the basis of genetic testing alone
- The end result is the same:
  - In response to triggering agents, calcium is released, causing continuous contracture and activation of the sarcoplasmic reticulum's ATPase
  - A hyper-metabolic state ensues
- Anesthetic drugs that trigger MH include:
  - Halothane
  - Enflurane
  - Isoflurane
  - Desflurane
  - Sevoflurane
    - Desflurane and sevoflurane are less potent triggers
      - Produce a more gradual onset of MH
  - Succinylcholine
    - The onset may be explosive if succinylcholine is used
    - Non-depolarizing muscle relaxants block the effects of succinylcholine in triggering MH
      - They also attenuate the effects of volatile anesthetics
- Hyper-metabolic State
  - **Hypoxemia** and **Hypercarbia**
  - **Hyperthermia** is a **late sign** but may increase at a rate of 1-2° every 5 minutes
- Contractures
  - **Masseter muscle spasm** may create a situation of **difficult intubation (**BMV should be ok)
    - If it occurs, one should probably reverse anesthetic and postpone surgery as these patients get myoglobinuria and CK rises post-event even without MH
    - Use an MH-friendly anesthetic technique in individuals with a history of MMR
    - Some would suggest that after MMR you can continue the anesthetic using a trigger-free technique and being vigilant for symptoms of MH
  - Contractures **will not break with NDMR**
  - "Jaws of steel" or prolonged spasm warrant cancellation of procedure
  - **Rhabdomyolysis** will occur and potentially lead to **acute renal failure**
- Electrolyte and acid / base disturbances
  - Cellular hypoxia leads to **lactic acidosis**
  - Cell death results in **hyperkalemia**
- Secondary complications
  - **Tachycardia** and **irregular rhythm** may present early from sympathetic activation
  - **Hyperkalemia** produces peaked T waves and **dysrhythmias**
  - **Heart failure** from metabolic derangements and hypoxemia
  - DIC if temp > 41.5 degrees celsius
  - Other complications include bowel ischemia, limb compartment syndrome, acute renal failure
- **Recognition of MH**
  - May occur at any point during anesthesia or emergence
  - **Unexplained increase in $ETCO_2$ is the most common initial sign**

        - **Also the most sensitive and specific sign of MH**
    - Generalized muscle rigidity may or may not be present
        - Can see masseter muscle spasm despite neuromuscular blockade
    - Hyperthermia is a late sign
    - MH Grading Scale developed by Larach, et al (Anesthesiology. 80:771-779; 1994) to determine retrospectively likelihood of an event being MH:
        - **Specific signs of MH:** Muscle rigidity, Increased CO_2 production, Rhabdomyolysis, Marked temperature elevation
        - **Nonspecific signs of MH:** Tachycardia, Tachypnea, Acidosis (respiratory / metabolic), Hyperkalemia
        - **Metabolic Changes during MH**
            - O_2 consumption 3-5x normal
            - $PaCO_2$ 59 +/- 4
            - $PvCO_2$ 107 +/- 10
            - PaO_2 142 +/- 10
            - PvO_2 36 +/- 4

REFERENCES

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- Ali, Syed et al. Malignant Hyperthermia. Best Practice & Research Clinical Anesthesiology. 17(4): 519-533; 2003.