PBLD: Perioperative Hyperthermia Riddles - MH and beyond
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Objectives:

1. Describe the differences in physiologic mechanism resulting in fever vs. hyperthermia

2. In the setting of polypharmacy and elevated core body temperatures, discuss the importance of developing a broad differential diagnosis, including:
    a. Infectious etiolgies
    b. Serotonin syndrome
    c. Neuroleptic Malignant Syndrome
    d. Toxic drug ingestion

3. Review our evolving understanding of malignant hyperthermia (MH) as a spectrum disorder ranging from a hypermetabolic syndrome induced by pharmacologic factors and non-pharmacologic stressors.
    a. Discuss new evidence for succinylcholine as a single agent as a culprit for MH.
    b. Recognize the various clinical presentations of MH including the existing evidence for non-anesthetic inducted MH.
    c. Discuss the temporal presentations of MH.

4. Review the *suspected* mechanism of action of dantrolene and its antipyretic properties.
    a. Understand why a response to dantrolene may result in an improvement of hyperthermia, but may not necessarily be pathognomonic for MH.
    b. Discuss various indications of dantrolene in medicine.

Stem Case–Key Questions

A 16 year old (60kg), previously healthy male, presents to a rural community hospital with a fever of 103 F and respiratory distress. Over the next 48 hours, his respiratory status deteriorates, requiring mechanical ventilation with a definitive airway after 8 hours of attempted non-invasive continuous positive pressure ventilation. Intubation is accomplished using etomidate and succinylcholine. After succinylcholine administration, the ER physician notices it is difficult to open the patient's mouth, but with significant force, manages to pry it open 2 cm, and intubate the patient with the use of a videolaryngoscope.

Questions:

1. What additional information would you want to know about the patient's illness on arrival to the ER? What are the differences between masseter muscle spasm and trismus? How do the side effects of succinylcholine vs. etomidate on skeletal muscle differ? Should you suspect any underlying neuromuscular disease in this patient because of his response to the choice of drugs at the time of intubation?

2. His past medical history is significant for being a well-developed male, despite

having been a 33 weeks premature neonate. By his first year of life, he had met his developmental milestones, except for mild speech delays, and occasional cramps when he over-exerted himself playing soccer. He had recently been started on low dose ciltaprolam (Celexa) for treatment of anxiety and depression after discontinuation of methylphenidate (Ritalin) for a misdiagnosis of ADHD.

How is his history of prematurity and mild developmental delay pertinent to his current illness? Is his history of leg cramps relevant to his response to succinylcholine? What role, if any, do his current medication changes play into his illness? What are possible side effects of selective serotonin reuptake inhibitors (SSRI) in combination with medications such as methylphenidate?

3. At the time of this ER presentation, and subsequent need for mechanical ventilation, his pulmonary status continued to deteriorate. His CXR showed correct endotracheal tube placement with bilateral "white out", diffuse air-space opacification, with no evidence of cardiomegaly. To optimize his ventilation, he required neuromuscular blockade with rocuronium, and increased ventilator settings: FiO2 of 1.0 SIMV of TV 450, RR 12, PEEP 7, PIP 25. His ABG results were: 7.24/PO2 178/PCO2 56/HCO3 18.

   Other laboratory results included: WBC 16.2, with an elevated lymphocyte count of 71%, a basic metabolic profile remarkable for potassium of 5.6 and BUN/Cr of 21/1.2. Urinalysis was negative for leukocytes, but blood was observed immediately after Foley catheter placement. Urine subsequently cleared of blood, but remained with a mild dark color. Serum creatinine kinase was noted to be 9,100 U/L.

   a. What disease processes can account for his CXR findings?
   b. What other laboratory studies would you recommend?
   c. Generate a differential diagnosis for his symptoms and lab abnormalities.
   d. What are possible causes for the "dark urine"? Why is his serum creatinine kinase elevated? Can succinylcholine alone induce such muscle damage?

4. Given the patient's worsening clinical course, he is transferred to a larger regional medical center with intensive care facilities. Within hours of arrival, the patient's fever rises to 107°F and his body develops "shaking". Preliminary blood cultures results are negative, and toxic screening is positive for opioids and benzodiazepines.

5. As infectious etiologies have not been found, the admitting intensivist adds MH to the differential diagnosis. What other factors contribute to a differential diagnosis of MH? According to the Larach et al., what is this patient's Clinical Grading Scale score?

6. After two doses of dantrolene, the patient ceases shaking, and his temperature decreases to 103°F. Dantrolene is written as a standing order for 48 hours. The hospital pharmacist consults the MH Hotline for guidance with dantrolene therapy. What is the recommended dosing of dantrolene in suspected acute MH cases? What is the subsequent dosing recommendation to prevent recrudescence? What laboratory studies are recommended after an acute MH episode to guide further dantrolene therapy? How likely is it that this patient is indeed in MH? If not MH, why does dantrolene contribute to temperature reduction?

7. While speaking with the MH Hotline consultant, the patient develops an elevated

blood pressure of 203/172, with a HR of 48 beats per minute, and fixed dilated pupils, with an unrelenting temperature of 103F. Emergent measures are taken to reverse the signs and symptoms of increased intracranial pressure. Subsequent CT/MRI and neurologic consult is performed. CT/MRI imaging is demonstrates cerebral edema. The next 24 hours, the patient's pulmonary condition deteriorates; he develops fulminant SIRS, and is declared brain dead. Post-mortem PCR analysis of blood samples demonstrated the patient was infected with influenza H1N1 virus.

Model Discussion

Physiologic mechanism of fever vs. hyperthermia

Fever is a normal physiologic response, which usually occurs from systemic infections, and results from an increase in the hypothalamic set point. Hyperthermia is a result of thermodysregulation, where the amount of heat generated exceeds the body's ability to dissipate the heat. Excess heat generation can result from increased basal metabolic rate from drugs administered, increased sympathetic tone, increased hormonal presence from endocrine disorders, increased intrinsic muscle tonicity or from seizures or shivering. Environmental factors such as warm conditions can also result in hyperthermia in young children and infants.

Trismus vs. Masseter Muscle Spasm (MMS)

According to a paper published in 1994 by Hannallah and Kaplan, MMR and trismus can be distinguished as follows: 1. MMS: the mouth cannot be fully open despite firm pressure on the incisors, but can be opened far enough to permit intubation of trachea 2. Trismus: the mouth cannot be opened enough to allow intubation. Although MMS is often thought of as an early presenting sign of MH, it can actually occur transiently with administration of succinylcholine. In some instances, the clinical picture can be further clouded by undiagnosed temporomandibular joint abnormalities that may prevent jaw opening in affected patients. (Smith's Anesthesia for Infants and Children by Peter J. Davis, Franklyn P. Cladis, and Etsuro K. Motoyama (8th edition Elsevier)).

Etomidate induced myoclonus vs. succinylcholine induced MMS

Myoclonus movements are sudden, involuntary jerking of *muscles or muscle groups* that cannot be controlled by the person experiences them. These can occur alone or in sequence, with or without pattern, and may occur several times a minute.
Fasciculation are uncontrollable, involuntary twitching of *groups of muscle fibers*.

Administration of etomidate can cause myoclonus, but it is dose-related and its incidence can be decreased by pretreatment of the patient with initial lower doses of etomidate. Succinylcholine induced fasciculations are a known side effect, resulting from succinylcholine's mechanism of action, whereby acetylcholine receptors are initially triggered at the neuromuscular junction and then enter a refractory state until succinylcholine dissipates from the neuromuscular junction. Though these muscular movements differ substantially, to the untrained observer, they may be mislabeled.

Differential Diagnoses for elevated core body temperature

a. Infectious: bacterial or viral pneumonia, aspiration pneumonitis from loss of consciousness, sepsis, and systemic inflammatory reaction syndrome.
    i. H1N1 first presented in Mexico in the spring of 2009, and went on to effect patients all over the world. Clinical course can be uncomplicated and present as influenza-like symptoms with fevers, cough, rhinorrhea, malaise and muscle aches. Complicated or severe influenza cases develop lower respiratory tract infections, often times requiring ventilator support due to hypoxia and tachypnea. It also involves altered mental status, severe dehydration, often progressing to persistent high fevers, renal failure, multisystem organ failure, septic shock, rhabdomyolysis, myocarditis, or systemic inflammatory response syndrome (SIRS). Patients suspected of having H1N1 infection

were confirmed with PCR reactions or viral cultures.

ii. SIRS is a hyperinflammatory state that develops during sepsis or hemorrhagic shock. Enhanced expression of adhesion molecules on activated monocytes, neutrophils, and endothelial cells lead to organ infiltration by these cells. In addition, complement system activation contribute to organ damage through release of proinflammatory cytokines. These biochemical changes result in inflammation by creating an oxidant state and low levels of available anti-oxidants, generating reactive oxygen species, hence worsen tissue damage.

b. Polypharmacy from neuropsychiatric medications can result in elevated metabolism. Culprits include SSRIs and psychostimulants such as methylphenidate (Ritalin), which act by modulating levels of dopamine and norepinephrine. Other drugs such as over-counter medications (i.e. diphenhydramine, metoclopramide), may interact and alter neurotransmitter levels, resulting in conditions such as:

i. Serotonin Syndrome (SS): occurs from excess serotonergic agonist of the central nervous system receptors and peripheral serotonergic receptors. It is an adverse drug reaction resulting from therapeutic drug use of medications such as SSRIs, or from intentional overdose, or from inadvertent drug-drug interactions with other neurotransmitter altering medications. Clinical symptoms vary from agitation, tremors, and confusion to severe delirium, neuromuscular rigidity and hyperthermia from autonomic dysregulation that can be life-threatening if not recognized and treated. Clinical presentation occurs within hours of drug ingestion. Treatment includes discontinuation of serotonergic drugs, supportive care, and control of agitation with benzodiazepines, control of autonomic instability and hyperthermia. Symptoms usually resolve within 24 hours.

ii. Neuroleptic Malignant Syndrome (NMS) is most often caused by adverse reactions to neuroleptic or antipsychotic drugs that specifically affect the dopaminergic system. NMS presents over several days to weeks and can be life-threatening if not recognized early. Clinical presentation includes high fevers, labile hemodynamics, stupor, muscular rigidity, and autonomic dysfunction. Pathophysiology is thought to be due to decreased levels of dopamine, via dopamine receptor blockade as in the case of haloperidol (D1 and D2 receptor antagonist) or abrupt withdrawal of dopamine agonists as seen in parkinsonian patients prescribed L-DOPA. Treatment includes stabilizing the autonomic dysregulation and cooling the hyperthermic patient, while restoring dopaminergic levels with bromocriptine. Dantrolene has been used to treat hypermetabolism/muscle rigidity, along with benzodiazepines to control agitation.

c. Toxic drug ingestion/overdose/drug diversion such as

i. Sympathomimetics (i.e. ecstasy, cocaine, PCP, amphetamines, bath salts)—these alter the levels of neurotransmitter agonists of alpha and/or beta-receptors in the central nervous system and mimic sympathetic system activation (i.e. norepinephrine, epinephrine, dopamine). The result is behavioral and psychotropic effects, impairing heat dissipation via normal mechanisms such as cutaneous vasodilatation or sweat production, and also resulting in excess psychomotor agitation leading to increased heat production. Treatment involves controlling the agitation and supporting hemodynamics. Intervention may require benzodiazepines, airway control, possible need for neuromuscular blockade to control muscular hyperactivity, and active cooling measures. NSAIDs are not effective because the hyperthermia in these cases is toxin induced, not prostaglandin mediated.

ii. Anticholinergic exposure to toxins such as pesticides, herbals or medications such as antihistamines (i.e. Diphenhydramine) impair heat dissipation. Centrally, acetylcholine receptor blockade can lead to agitation and excess heat production, while peripheral acetylcholine blockage affects sweat glands resulting in anhidrosis. Prostaglandin mediated antipyretics are not effective because they do not reverse the acetylcholine mediated blockade of anticholinergics. Some antidepressants, such as TCAs, which affect multiple neurotransmitters also block acetylcholine receptors and can have anticholinergic effects when taken in excess. Treatment also involves restoring hemodynamic stability and management of agitation to prevent secondary organ damage from hyperthermia or rhabdomyolysis.

iii. Uncouplers of oxidative phosphorylation at the mitochondrion: the electron transport chain is vital for energy production during aerobic metabolism. By transferring electrons through a series of cytochromes in the mitochondria, energy is produced in the form of ATP. When the electron transport energy is uncoupled from ATP production, by toxins such as salicylic acid, heat is generated and causes unregulated elevation in body temperature.
Signs and symptoms include hyperthermia, respiratory alkalosis along with a metabolic acidosis, altered mental status and gastritis.

iv. Antidepressants: SSRIs, TCA, MAOI—result in altered neurotransmitter levels (i.e. serotonin, norepinephrine, epinephrine, dopamine, and acetylcholine); when taken in excess, it can lead to serotonin syndrome, neuroleptic malignant syndrome or anticholinergic syndromes

v. Drug withdrawal must also be included: i.e. baclofen, heroin, opioids, benzodiazepine, ETOH withdrawal, which can result in diaphoresis, hyper-reflexia, and delirium.

d. Environmental factors such as: travel history, exposure to vector-borne illness, and climatic temperature changes. Specifically, exertion under austere conditions may predispose some individuals to experience mild symptoms ranging from myalgias to extremes of hypermetabolism. (Capacchione, J. et. al. The relationship between exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia. Anesth Analg. 2009 Oct;109(4)1065-9.

    i. Exertional heat stroke (EHS) is not related to MH. EHS is usually due to extreme temperatures of vulnerable patients such as elderly, the young or deconditioned patients with no access to cooling measures. They may progress to experience tachycardia, hypotension, poor hydration, and eventually rhabdomyolysis and multiorgan system failure.
    ii. Exertional heat illness (EHI) has been an association with MH via case reports and series. EHI is described as a disorder of excessive heat production, in the setting of insufficient heat dissipation. It can progress to heat stroke, leading to multisystem organ injury. Some case reports have linked patients who exercised in hot climates and who experienced EHI to positive CHCT or IVCT. Positive CHCT or IVCT, however, does not mean that these patients will indeed develop MH; they may be labeled MH susceptible by CHCT results, but not by clinical presentation, hence the loose association with MH.
    iii. Exertional rhabdomyolysis (ER) is a complication of EH. It can occur in the absence of high environmental or core body temperatures. ER can develop from either strenuous exercise, damage to skeletal muscle via mechanical or metabolic injury, resulting in myoglobinuria, elevated serum CK, hyperkalemia and renal failure. According to Capacchione et.al., some patients who have experienced ER have had persistently elevated CPK levels, and upon further workup, tested positive for CHCT or IVCT.
    iv. EHI, ER, and MH all result in hypermetabolic states where high demand for ATP, overwhelm the cellular regulatory mechanisms and result in severe muscle damage. According to Capacchione et.al., some patients with EHI and ER will have positive CHCT or IVCT results, and some will have RYR1 variants. However, at this point, it is not clear whether these RYR1 variants are MH-causative or not.

e. Undiagnosed metabolic disorders or endocrinopathies can have signs and symptoms similar to hypermetabolism. These conditions include pheochromocytoma, thyrotoxicosis, and initial presentation of diabetes mellitus/diabetic ketoacidosis.

Malignant Hyperthermia--discuss the temporal presentations of MH

Historically, MH has been known to trigger as a result of exposure to volatile anesthetics and/or succinylcholine. However, in the recent past, case reviews by Brandom, B. (Paediatr Anaesth. 2013 Sep;23(9):851-4) have reported fatal cases of exercise-induced MH in patients later testing positive for known RYR1 receptor gene mutations.

Typically, MH presents intraoperatively after exposure to volatile anesthetics with

or without succinylcholine. Larach et al. reported that the most frequent and earliest clinical signs of MH are hypercarbia (despite increased minute ventilation), sinus tachycardia, or masseter muscle spasm, with temperature abnormalities also a relatively early sign. (Anesth Analg. 2010 Feb 1;110(2):498-507). If left untreated, MH progresses to profound metabolic acidosis, hypercarbia, severe hypoxia, rhabdomyolysis from sustained muscle contractures and myocyte destruction, electrolyte derangements, including hyperkalemia, resulting in acute renal failure. Cardiac arrhythmias and unstable hemodynamics develop, leading to coagulopathies, pulmonary edema, cerebral hypoxia and cerebral edema. According to Riazi et.al.,each ten-minute delay in the administration of dantrolene causes substantial increase in complications (Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands. Anesth Analg 2014;118:381-387). Also, Litman et.al. demonstrated that while 6.2% of acute MH cases present in the post anesthesia care unit, no cases of MH have been found to occur after patients are discharged from that unit (Anesthesiology. 2008 Nov;109(5):825-9). Reversal of symptoms usually occurs within 3-5 minutes with dantrolene administration, and should be repeatedly administered until the patient's MH episode is aborted or if the patient recrudesces. Recrudescence occurs in approximately 20% of the cases and it is associated with muscular body habitus and greater time interval between the induction of anesthesia and the development of initial reaction (Parness, J. (2013) Malignant Hyperthermia: In A Practice of Anesthesia for Infants and Children: Fifth Edition by Drs. Charles J. Cote, Jerrold Lerman, and Brian J. Anderson. P817-834. Philadelphia, PA: Elsevier).

Recognize the various clinical presentations of MH including the existing evidence for non-anesthetic inducted MH:

Stress-induced MH has also been documented, but the time course is difficult to describe, as the cases are rare and varied in clinical presentation. Reports by Gronert et.al (Malignant hyperthermia: human stress triggering. Biochim Biophys Acta. 2011 Dec;1813(12):2191-2; author reply 2193-4) describe four patients with non-anesthetic triggered MH episodes who eventually succumbed as a result of environmental triggers (i.e. elevated outside temperature or viral illness causing stress). Some of those patients had previously experienced intraoperative MH episodes from volatile anesthetic exposure, but their fatal MH episodes resulted from non-anesthetic induced stressors. Though their non-anesthetic MH events occurred under varying conditions, once triggered their demise was rapid and fulminant. Post mortem analyses in some cases showed positive genetic mutations of the RYR1 gene consistent with MH susceptibility. Based on case reports as these, Brandom et. al. (Paediatr Anaesth. 2013 Sep;23(9):851-4) keenly advises that avoidance of volatile anesthetics does not absolve one from the need to continuously reevaluate patients for potential signs and symptoms of MH.

Brief review of the Clinical Grading Scale

Prior to 1994, interpretations and definitions of malignant hyperthermia cases varied. The clinical grading scale (CGS) was developed to create a standardized tool for estimating the likelihood that suspected cases of MH were more accurately diagnosed. A panel of experts reviewed MH suspected cases, and agreed on a set of scoring rules (examining factors such as rigidity, serum creatinine kinase levels, degree of respiratory and metabolic acidosis, temperature increases, etc.). Each factor was assigned a grade from 0-15; the raw score was computed from the summation of these factors. The raw score was then given an "MH rank" to describe the likelihood that the case represented MH. Scores ranging from 0-19 correlated to "somewhat less than likely" that the case

was MH. Scores greater than 20, ranged from "somewhat greater than likely" to almost certain (for scores of 50+). The CGS provided means to objectively define MH, given its varied clinical presentation. Although the CGS was not initially intended for use by the clinician, it has become a guiding tool both intra-operatively and post-operatively to assist in defining and, at times, guide clinical decisions in suspected MH cases.

What further testing/follow-up should the patient undergo based on a dantrolene response?

In prepubescent children weighing less than 40lbs: CHCT is not performed in this age group, rather it may be feasible to alert medical personnel by having child wear Medic Alert bracelet. Post-pubertal children: may have CHCT if they meet the weight requirements of > 40lbs. If the child was treated for an MH episode, both the child and a first-degree relative may be referred to an MH diagnostic center for consideration of a CHCT on the adult relative. The CHCT is 97% sensitive and 78% specific. Patients who experienced an MH episode but have negative CHCT results, should be referred to neurologists whose emphasis is neuromuscular diseases to determine if the patient has an occult myopathy that may have clouded the diagnosis. Patients with positive CHCT results should be referred to genetic screening of the RYR1 and/or CACNA1s genes via DNA obtained from a blood sample or cheek swab. The inability to identify a genetic mutation in these patients does not indicate a negative MH diagnosis, since more than one gene is associated with MH susceptibility and many are not yet known. Genetic counseling should follow. (Parness, J. (2013) Malignant Hyperthermia: In A Practice of Anesthesia for Infants and Children. Fifth Edition by Drs. Charles J. Cote, Jerrold Lerman, and Brian J. Anderson. P817-834. Philadelphia, PA: Elsevier).

The case for succinylcholine as a trigger—revisited:

Can Succinylcholine alone in absence of volatile anesthetics cause MH? Yes, but less commonly. According to Visoiu et al., the incidence of MH induced by succinylcholine alone is 2.9% in the NAMHR population and Riazi et al. report an incidence of 15.5% in the Canadian population referred to the Toronto testing center [(Visoiu et al. Anesth Analg 2014; 118:388-96) and (Riazi et al Aneth Analg 2014 118:381-387). The differences between the two reports are likely due to differences in reporting to these centers.

Dantrolene's suspected mechanism of action and its antipyretic properties:

Dantrolene suppresses the Ca^{2+}-dependent portions of excitation-contraction coupling so intrinsic to the mechanism of skeletal muscle contraction, but its effects on the temperature sensing mechanisms of the central nervous system in modulating temperature regulation are unknown. Dantrolene's mechanism of action as an intracellular skeletal muscle relaxant can ease the hypermetabolism occurring intramuscularly by direct inhibition of calcium release from the SR and calcium entry into the cell from extracellular stores, and thereby abort the elevated temperature from excess metabolic energy released from a normally-contracting or hyper-contracted muscle. Hypermetabolic conditions caused via central nervous system etiologies (i.e., Infectious, CVA, toxins, etc.) will not be aborted by dantrolene, even if the temperature elevation is suppressed by the drug, because those cases of temperature elevation occur through central, likely hypothalamic mechanisms, on which dantrolene has no known effect. (Herlich A. Perioperative temperature elevation: not all hyperthermia is malignant hyperthermia. Paediatr Anaesth. 2013;23(9):842-50).

Dantrolene can be a useful antipyretic in treating conditions resulting in elevated core temperature. Dantrolene has been shown to both inhibit release of calcium from the sarcoplasmic reticulum and inhibit calcium entry from outside the cell, presumably via action of RYR1, but this has not been proven. (Brandom, B. (2010). Malignant Hyperthermia;Smith's Anesthesia for Infants and Children. 8th Ed. Edited by Drs. Peter J. Davis, Franklyn P. Cladis, and Etsuro K. Motoyama. pp1184-1199. Philadelphia, PA: Mosby, Inc.)

Discuss alternative clinical indications of dantrolene:
Because of dantrolene's intrinsic properties of alleviating intracellular calcium dysregulation, dantrolene can be helpful in treating muscle spasm, cramping and general muscle "tightness" caused by central nervous system disorders. These conditions include muscle spasms secondary to strokes, cerebral palsy, spinal cord injury, or multiple sclerosis.

Learning Summary:

1. Distinguish the physiologic differences between fever and hyperthermia.

2. Recognize the consequences of polypharmacy, and the effects it may have on patient's metabolism, especially in the perioperative setting. Develop robust differential diagnoses to account for elevated core body temperatures.

3. Discuss our evolving understanding of malignant hyperthermia (MH) as a spectrum disorder ranging from a hypermetabolic syndrome induced by pharmacologic factors and non-pharmacologic stressors.

4. Review the suspected mechanism of action of dantrolene and its antipyretic properties.

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