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Malignant Hyperthermia: Pathophysiology, Triggers, & Clinical Manifestations

Announcer:
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Here's your host, Dr. Matt Birnholz.

Dr. Birnholz:
Malignant hyperthermia is a severe and potentially fatal reaction that occurs when a patient is exposed to certain medications during general anesthesia. But how does malignant hyperthermia present? What triggers it? And what do we need to know and do when it presents in ORs and ERs alike?

This is *The Pulse of Emergency Medicine* on ReachMD. I'm Dr. Matt Birnholz. And joining me to focus on malignant hyperthermia is Dr. Christopher Edwards, Assistant Professor of Pediatric Anesthesiology at the University of Florida. Dr. Edwards, great to have you with us.

Dr. Edwards:
Thanks for having me.

Dr. Birnholz:
So let's dive right in. And to start us off, maybe you can shed some more light on what's currently understood about this reaction, and how it comes about.

Dr. Edwards:
Sure. So malignant hyperthermia, which for brevity from here on out, I'll refer to as MH, is a pharmacogenetic disorder of skeletal muscle. So when we say it's a pharmacogenetic disorder, that means that the susceptible individual has genetically abnormal skeletal muscle. So most often, this is a defect and the ryanodine receptor, which is a calcium release channel in the sarcoplasmic reticulum. And when susceptible individuals are exposed to certain pharmacologic agents, an uncontrolled release and interim bioplasmic calcium occurs. So these pharmacologic agents tend to be the volatile inhaled anesthetics that we use in our vaporizers in the operating room like sevoflurane or the depolarizing muscle relaxant, succinylcholine. And when you have this uncontrolled release of intra mycoplasmic calcium, sustained skeletal muscle activity results, and you have hypermetabolism, hyperthermia, and a cascade of other dangerous events.

Dr. Birnholz:
And that's a great pathophysiological review. But what do we know about the burden of MH in procedure settings and emergency departments? Is this a vanishingly small incidence rate, or more frequent than most people know?

Dr. Edwards:
So we see this in about 1 in somewhere between 35,00 and 65,000 surgical cases. About 600 MH cases are reported to the U.S. Malignant Hyperthermia Association each year. So it's rare, but not incredibly so. We get calls to the malignant hyperthermia hotline essentially every day. The prevalence of the genetic mutations associated with MH susceptibility are actually more common. So more like 1 in 3,000.

So you might be asking, why do we only see a clinical MH event and only, you know, maybe 1 in 50,000 surgical cases? And that's

really a couple of reasons. So first, MH susceptibility generally follows autosomal dominant inheritance, so many patients know have a family history of MH susceptibility. They tell us this preoperatively, and then we use non triggering anesthetics, so we might use a total intravenous anesthetic rather than inhaled anesthetics, and we would avoid succinylcholine.

Additionally, the genetics of MH aren't quite as simple as just autosomal dominance. There's also incomplete penetrance and expressivity so even patients that have MH susceptibility may not manifest a clinical episode on each and every anesthetic.

Dr. Birnholz:
So in that sense, there are many patients out there who could have subacute or even completely under the radar MH with risk factors we're not aware of when they're undergoing a procedure or coming into the emergency rooms. Is that right?

Dr. Edwards:
Yeah, absolutely. Most cases of MH won't occur in a patient who was preoperatively identifiable as somebody who is MH susceptible. The number of patients who are MH susceptible that happen over neuromuscular condition or weakness are few, and much more common is that this is seen in seemingly healthy individuals. And there's even some evidence to suggest that males and those with muscular bodybuilder are associated with that major susceptibility.

There are a few named muscular disorders that are fairly rare that are linked with MH susceptibility. So things like central core disease and King Denborough syndrome. And then perhaps the last association to be aware of is there's still a lot of active research into the relationship between MH susceptibility and those who were predisposed to exertional heat illness, exertional rhabdomyolysis.

Dr. Birnholz:
Well, for those just tuning in your listening to *The Pulse of Emergency Medicine* on ReachMD. I'm Dr. Matt Birnholz. And today I'm speaking with Dr. Christopher Edwards about malignant hyperthermia, or MH.

So Dr. Edwards, now that we have a better understanding of what's going on at the physiologic level, let's talk about the time and order of symptom onsets, because as I understand it, that can be pretty variable. Is that right?

Dr. Edwards:
Yeah, absolutely. If we start talking about time course, we usually expect MH symptoms to present within 30 to 60 minutes of a triggering anesthetic agent. However, that's not always the case. There are certainly case reports of patients whose signs and symptoms of MH were first identified a couple hours after an anesthetic in the postoperative care unit.

Dr. Birnholz:
So that's a great reminder, that context is often key to this. We could have a patient reacting within minutes of receiving a triggering agent, *or* someone well into postop recovery, or a patient who presents in the emergency department.. Which brings up the next question, which is trying to understand if there are any sequences of clinical signs that really strongly point toward the development of MH. What can you tell us about that?

Dr. Edwards:
So the initial signs of MH usually include tachycardia and progressive hypercarbia since we have a hypermetabolic state. In some cases, you'll see masseter muscle or even generalized muscle rigidity, and progressive hyperthermia. I think a lot of times we use skin temperature monitoring in the OR, and that can sometimes be responsible for this not being identified as quickly as it could be if we are using core temperature monitoring, it can really be a rather early sign as well, in addition to tachycardia and hypercarbia.

It's probably useful to acknowledge that those kind of three main signs and symptoms that I've described tachycardia, hypercarbia, and fever are not that specific. So that's part of the challenge of promptly responding to an MH crisis is kind of putting the picture together when you see those three things in combination or you see things that aren't really fitting the normal picture.

Dr. Birnholz:
And I think that provides a really nice segue for us to turn to the subject of rapid treatment. Can you just speak to this based on the experiences that you or your colleagues have been through?

Dr. Edwards:
Yeah, so I think that's a lot of the difficulty of MH is that some of the signs and symptoms are not that specific, but it's also a very unforgiving disease process if you don't get on top of it quickly. So you do sort of need to move from the point of considering the possibility of MH to going ahead and calling for the MH card and getting dantrolene available as soon as possible because complications increase about two-fold for every 30 minutes between the first sign of MH and the beginning of dantrolene administration and about three-fold increase in complications for every 2 degrees Celsius increase in maximum core temperature that the patient reaches. So it's really important to go ahead and call for dantrolene and begin mixing up the initial dose of 2.5 milligrams per kilo.

Dr. Birnholz:
Let me ask you then what the consequence of a false positive would be if the indicators and signs of MH actually start to diminish, as rare as that might be when you're seeing this progression happen.

Dr. Edwards:
Yeah, so the main side effects associated with dantrolene are muscular weakness and phlebitis, which is why we generally advise giving it through a large bore peripheral I.V. or even central access if central access has already been acquired, but we would not want to delay while achieving central access. So if you have a patient with borderline respiratory status, there's a possibility they may need to stay intubated for a period of time until that weakness resolves. Most patients can probably tolerate that degree of muscular weakness, still be extubated, and be monitored carefully afterwards. But if you're in a gray zone, I think the consequences of delaying dantrolene treatment are much worse than the false positive scenario.

Dr. Birnholz:
And I do want to ask about protocols or precautionary steps that you think our audience should incorporate into their practices if they're not already, just to make sure that the worst doesn't come to pass. Is there anything that you've seen that isn't quite up to par from one health system to another in that regard?

Dr. Edwards:
So I mean, I think it's important for folks to know where their MH cart is and where they can go to get dantrolene and sterile water to mix that if needed. And then having folks that have some familiarity with mixing dantrolene can be important, whether that's folks that have actually done it in a true clinical setting before or folks that have done it in a simulation setting which can sometimes be done with expired dantrolene that's been given to you by the manufacturers. So having folks that know the protocol and know where dantrolene is and have potentially some experience with mixing it in the past are all important.

Dr. Birnholz:
And Dr. Edwards, just to take us home, can you reiterate for our listeners some of the best resources for being able to confirm the next steps if MH is suspected in surgical or emergency medical settings?

Dr. Edwards:
Sure. So I'm a big believer in cognitive aids and critical event checklists. I suspect most of our colleagues in emergency medicine feel similarly about those things as we do in anesthesia. I personally think one of the best ones is the Stanford critical events checklist that can be downloaded for free at emergencymanual.stanford.edu that has a number of critical events, including malignant hyperthermia, and nice concise visuals of the most important 14 or 15 steps in managing an MH crisis.

Malignant Hyperthermia Association of the United States, or MHAUS, also staffs a 24-hour hotline where we always have three to four clinical consultants like myself on call for two-week periods. So you should always, at any hour of the day, be able to be patched into one of the three or four of us that's on for that two-week period to run by clinical questions. And then MHAUS also produces a poster with the most important 8 or 10 steps in MH management and a lot of the ORs have this on a wall, a lot of places put this poster on top of their MH cart so that when somebody wheels it into the room for treatment, that it's apparent what the most important steps are. So a lot of those cognitive aids can be very helpful.

Dr. Birnholz:
Well, those are great insights to take back into practice. And with that, I want to thank my guest, Dr. Christopher Edwards from the University of Florida, who helped talk us through current understandings of malignant hyperthermia. Dr. Edwards, it was great having you on the program.

Dr. Edwards:
Thank you. I enjoyed being here.

Announcer:
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