Nonanesthetic Malignant Hyperthermia

Susceptibility to malignant hyperthermia (MH) is viewed as a pharmacogenetic trait dependent on exposure to inhalational anesthetics. Outside of the operating room, individuals susceptible to MH are usually asymptomatic. Events that occurred in the absence of anesthetics have been reported over the years and were originally termed awake episodes. In this issue of Anesthesiology, two cases of nonanesthetic MH-like episodes triggered by either exposure to environmental heat or infection are described. These two cases raise the question of how at risk the MH susceptible individuals actually are.

Classic MH is caused by uncontrolled intracellular Ca\(^{2+}\) release from the sarcoplasmic reticulum mediated by an overactive Ca\(^{2+}\) release channel, the ryanodine receptor 1 (RyR1) (fig. 1). A fulminant anesthetic crisis manifests with tachyarrhythmia and sweating initially, hypercapnia, tachypnea, metabolic acidosis, and rapidly increasing temperature followed by muscle rigidity and rhabdomyolysis. Complications include cardiac arrest, heat stroke, and renal failure. Prompt infusion of dantrolene to block RyR1 is mandatory therapy.

MH susceptibility is inherited in an autosomal dominant fashion in man and horse whereas in swine, it is recessive (table 1). In swine, the disorder is even named for these events, porcine stress syndrome, and the trait has been selectively bred because already heterozygous animals have muscle hypertrophy and therefore more meat. Homozygous pigs developed MH triggered by emotional and physical exertion during long-lasting transport in hot, close confinement. The animals either die spontaneously or their meat shows a very muscular affected quarter horses, nonanesthetic events are frequent in the form of recurrent rhabdomyolysis without evident hyperthermia, spontaneous colic-like episodes, or heat-induced full MH events. In one mare with an especially severe phenotype, a concomitant polysaccharide storage myopathy was identified histologically postmortem.

The two unrelated children reported in this article, a boy and a girl, both showed marked hypertrophy and fever-induced MH-like events or recurrent cramping with rigid gait. The boy also had bilateral ptosis and muscle hypotonia indicative of a congenital myopathy, which may have aggravated the phenotype as in the quarter horse. Although both children harbored the same RyR1 variant, p.R3983C, on one allele, the girl had a second mutation, p.D4505H, on the other allele, possibly suggesting an additive effect comparable with the recessive situation in porcine stress syndrome. The notion of an additive effect of RyR1 mutations with other muscle-damaging traits could be supported by a recent report of a fatal heat-induced MH event with heat stroke in a 2-year-old child harboring two RyR1 mutations, p.R4645Q and p.L4320_R4322dup. Furthermore, a recessive RyR1 myopathy has been described recently that displays symmetrical ptosis and muscle hypotonia. However, in MH-susceptible Japanese patients, 10% have compound heterozygous RyR1 mutations.

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## Table 1. Summary of the Current Understanding of Malignant Hyperthermia and Similar Events

<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Trigger</th>
<th>Signs</th>
<th>Pathophysiology</th>
<th>Acute therapy</th>
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</thead>
<tbody>
<tr>
<td>Single RyR1 or CACNTAS mutation</td>
<td>Dominant susceptibility to MH</td>
<td>Volatile anesthetics; preservative-free succinylcholine under debate</td>
<td>Hypercapnia, combined and severe metabolic and respiratory acidosis, hyperkalemia, generalized muscle rigidity, tachyarrhythmia, hypotension, hyperthermia, skin freckling, acute renal failure, dark urine as a consequence of muscle breakdown, disseminated intravascular coagulation.</td>
<td>Increased sensitivity of RyR1 to activating ligands such as halothane, sevoflurane, desflurane with uncontrolled Ca$^{2+}$ release from sarcoplasmic reticulum, RyR1-mediated release of endogenous pyrogen IL-1β from B-lymphocytes</td>
<td>Stop triggers, intravenous dantrolene, physical cooling, symptomatic therapy aiming at maintenance of adequate ventilation, circulation, and pH regulation</td>
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<tr>
<td>RyR1 mutation(s) and congenital myopathy mutation</td>
<td>Unclear</td>
<td>Extraordinary physical exercise especially in hot surroundings; infectious fever</td>
<td></td>
<td>Increased Ca$^{2+}$ turnover through strong physiologic activation of skeletal muscle promoted by hyperthermia and mutated RyR1</td>
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<tr>
<td>RyR1 mutation</td>
<td>Dominant</td>
<td>Volatile anesthetics; physical or heat stress</td>
<td></td>
<td>Increased resting Ca$^{2+}$ levels, increased NO-levels, which further sensitize RyR1 to pharmacologic or physiologic triggers</td>
<td></td>
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<tr>
<td>Homozygous RyR1 mutations</td>
<td>Recessive</td>
<td>Volatile anesthetics; mental, physical or heat stress; succinylcholine without precurarization</td>
<td></td>
<td>Pathophysiologic principle as above, homozygous RyR1 mutation, therefore muscle extremely prone to both, exogenous and/or endogenous triggers</td>
<td></td>
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<tr>
<td>Caucasian ethnic origin, male sex, other genetic factors such as predominance of muscle fiber type 2 Polygenic</td>
<td>Extraordinary physical exercise, dehydration, hot surroundings; serotoninergic drugs such as MDMA; muscle may be sensitized by drugs such as statins</td>
<td>Central nervous system features such as seizures, compared with a “true” MH event: gradual onset of muscle related symptoms</td>
<td></td>
<td>Ungcoupling of oxidative phosphorylation, loss of cellular integrity, increased muscle metabolism promoted by overactivation of excitation-contraction coupling, heat, and mitochondrial uncoupling</td>
<td></td>
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<tr>
<td>Porcine Stress Syndrome</td>
<td></td>
<td></td>
<td></td>
<td>Rehydration, correction of glucose and electrolyte levels, physical cooling, benefit of dantrolene unclear</td>
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<tr>
<td>Nonanesthetic MH</td>
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<td>Horse MH Mouse MH</td>
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<tr>
<td>Exertional Heat Stroke</td>
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</table>

For prevention of nonanesthetic MH, treatment with dantrolene or N-acetylcysteine might be useful (see text). We combined the entities heat stroke and exertional rhabdomyolysis with exertional heat stroke because this term takes into account the same pathogenesis. MDMA = 3,4 methylenedioxymethamphetamine; MH = malignant hyperthermia; NO = nitric oxide; RyR1 = ryanodine receptor.

mutations without any clinical signs of myopathy, so that no generally valid conclusion can be drawn.

The causative RyR1 mutations in the MH-susceptible animals (p.R614C homozygous in swine and p.R2454G dominant in horses) are both in hot spots of RyR1 where very frequent human MH susceptibility mutations reside. The mutations in the two children reported in this article (p.R3983C) and in another child who died of a nonanesthetic MH (p.R3983H) are in a different RyR1 part that contains an S-nitrosylation site. Therefore, it is possible that the episodes represent a distinct phenotype. Diagnostic testing may need to be rethought. The in vitro contracture test is performed on excised muscle exposed to triggering agents, halothane, and caffeine. The standard protocol of the in vitro contracture test may not be ideal to determine susceptibility to spontaneous MH-like episodes. The in vitro contracture test performed on a muscle biopsy of the boy reported in this article would be considered by Europeans as MH equivocal. In addition, positive in vitro contracture test results were found in only 24% of 45 individuals with exertional heat stroke, and in 83% of 12 patients with exercise-induced rhabdomyolysis. Therefore, more appropriate test protocols in vitro (heat, oxidative stress, and nitrogen species as triggers) or in vivo (using $^{31}$P MRI) need to be developed.

Which individuals should be considered at high risk for nonanesthetic MH? As long as no more specific tests for nonanesthetic MH susceptibility are available, we have to consider which individuals require counseling. Although a single RyR1 mutation predisposes to anesthesia-related MH, two mutations on different alleles seem to be required for
nonanesthetic MH susceptibility. Alternatively, only one RyR1 mutation (i.e., in only 16% of the tetrameric RyR1 complexes, all four RyR1 subunits are impaired) might be sufficient if combined with a second mutation that is associated with a congenital myopathy. Therefore, MH-susceptible individuals presenting with ophthalmoplegia and muscle hypotonia, hypertrophy, or spasms will be at risk for nonanesthetic MH. At least such individuals should avoid excessive heat exposure, exhausting physical exertion, high fever, and all drugs that increase heat production and reduce heat dissipation or have been reported to cause rhabdomyolysis.\textsuperscript{16}

For prevention of nonanesthetic MH, treatment with dantrolene (blocks RyR1) or \textit{N}-acetylcysteine (protects against oxidative damage) might be useful. In case of an episode, rapid cooling at home and during transport to the hospital could significantly contribute to RyR1 stabilization. At the hospital, dantrolene should be infused as in a typical MH crisis. Because children have less developed compensation mechanisms for increased body heat and a higher incidence of MH events than adults (1:15,000 vs. 1:100,000),\textsuperscript{17} their parents should be particularly careful.

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References

10. Wu S, Ibarra MC, Malicdan MC, Murayama K, Ichihara Y, Kikuchi H, Nonachi I, Noguchi S, Hayashi YK, Nishino I: Central core disease is due to RYR1 mutations in more than 90% of patients. Brain 2006; 129:1470–80