Nonanesthetic Malignant Hyperthermia

SUSCEPTIBILITY to malignant hyperthermia (MH) is viewed as a pharmacogenetic trait dependent on exposure to inhalational anesthetics.1,2 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.3 In this issue of ANESTHESIOLOGY, two cases of nonanesthetic MH-like episodes triggered by either exposure to environmental heat or infection are described.4 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 over-active Ca\(^{2+}\) release channel, the ryanodine receptor 1 (RyR1) (fig. 1).5 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 are frequently bred because already heterozygous animals have muscle damage traits. Events that occurred in the absence of anesthetics have been frequent in the form of recurrent rhabdomyolysis without evidence of MH.6 In MH-susceptible individuals actually are.

The boy also had bilateral ptosis and muscle hypotonia in-duced MH-like events or recurrent cramping with rigid gait. The two unrelated children reported in this article,4 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-yr-old child harboring two RyR1 mutations, p.R4645Q and p.L4320_R4322dup.8 Furthermore, a recessive RyR1 myopathy has been described recently that displays symmetrical ptosis and muscle hypotonia.9 However, in MH-susceptible Japanese patients, 10% have compound heterozygous RyR1 mutations.

![Fig. 1. Scheme of the subcellular structures involved in excitation-contraction coupling of skeletal muscle. The dihydropyridine receptor senses the membrane depolarization, alters its conformation, and activates the ryanodine receptor (which releases Ca\(^{2+}\) from the sarcoplasmic reticulum [SR]). A Ca\(^{2+}\)-dependent ATPase (the SR Ca\(^{2+}\) pump) removes Ca\(^{2+}\) from the SR. The Na\(^+\)/K\(^+\) pump (the Na\(^+\)/K\(^+\) exchanger) transports Na\(^+\) out of the cell and K\(^+\) into the cell, creating a Na\(^+\) gradient and an electrochemical gradient that maintains the Na\(^+\)/K\(^+\) pump.](image-url)

**Fig. 1.** Scheme of the subcellular structures involved in excitation-contraction coupling of skeletal muscle. The dihydropyridine receptor senses the membrane depolarization, alters its conformation, and activates the ryanodine receptor (which releases Ca\(^{2+}\) from the sarcoplasmic reticulum [SR]). A Ca\(^{2+}\)-dependent ATPase (the SR Ca\(^{2+}\) pump) removes Ca\(^{2+}\) from the SR. The Na\(^+\)/K\(^+\) pump (the Na\(^+\)/K\(^+\) exchanger) transports Na\(^+\) out of the cell and K\(^+\) into the cell, creating a Na\(^+\) gradient and an electrochemical gradient that maintains the Na\(^+\)/K\(^+\) pump. The dihydropyridine receptor senses the membrane depolarization, alters its conformation, and activates the ryanodine receptor (which releases Ca\(^{2+}\) from the sarcoplasmic reticulum [SR]). A Ca\(^{2+}\)-dependent ATPase (the SR Ca\(^{2+}\) pump) removes Ca\(^{2+}\) from the SR. The Na\(^+\)/K\(^+\) pump (the Na\(^+\)/K\(^+\) exchanger) transports Na\(^+\) out of the cell and K\(^+\) into the cell, creating a Na\(^+\) gradient and an electrochemical gradient that maintains the Na\(^+\)/K\(^+\) pump.

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**This Editorial View accompanies the following article: Groom L, Muldoon SM, Tang ZZ, Brandom BW, Bayarsaikhan M, Bina S, Lee H-S, Qiu X, Sambuughin N, Dirksen RT: Identical de novo mutation in the type 1 ryanodine receptor gene associated with fatal, stress-induced malignant hyperthermia in two unrelated families. ANESTHESIOLOGY 2011; 115:938–45.**

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![Anesthesiology](image-url)
Gene

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

<table>
<thead>
<tr>
<th></th>
<th>Classic Human MH</th>
<th>Nonanesthetic Human MH</th>
<th>Horse MH</th>
<th>Mouse MH</th>
<th>Porcine Stress Syndrome</th>
<th>Exertional Heat Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>Single RyR1 or CACN1AS mutation</td>
<td>RyR1 mutation(s) and congenital myopathy mutation</td>
<td>RyR1 mutation</td>
<td>Homozygous RyR1 mutations</td>
<td>Homozygous RyR1 mutations</td>
<td>Caucasian ethnic origin, male sex, other genetic factors such as predominance of muscle fiber type 2</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Dominant susceptibility to MH</td>
<td>Unclear</td>
<td>Dominant</td>
<td>Recessive</td>
<td>Recessive</td>
<td>Polygenic</td>
</tr>
<tr>
<td>Trigger</td>
<td>Volatile anesthetics; preservative-free succinylcholine under debate</td>
<td>Extraordinary physical exercise especially in hot surroundings; infectious fever</td>
<td>Volatile anesthetics; physical or heat stress</td>
<td>Volatile anesthetics; mental, physical or heat stress; succinylcholine without precurarization</td>
<td>Extraordinary physical exercise, dehydration, hot surroundings; serotonergic drugs such as MDMA; muscle may be sensitized by drugs such as statins</td>
<td></td>
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Signs

- 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.

Pathophysiology

- 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.
- Increased Ca^{2+} turnover through strong physiologic activation of skeletal muscle promoted by hyperthermia and mutated RyR1.
- Increased resting Ca^{2+} levels, increased NO-levels, which further sensitize RyR1 to pharmacologic or physiologic triggers.
- Pathophysiologic principle as above, homozygous RyR1 mutation, therefore muscle extremely prone to both, exogenous and/or endogenous triggers.

Acute therapy

- Stop triggers, intravenous dantrolene, physical cooling, symptomatic therapy aiming at maintenance of adequate ventilation, circulation, and pH regulation.
- Rehydration, correction of glucose and electrolyte levels, physical cooling, benefit of dantrolene unclear.

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,\textsuperscript{10} 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)\textsuperscript{4} and in another child who died of a nonanesthetic MH (p.R3983H)\textsuperscript{11} are in a different RyR1 part that contains an S-nitrosylation site.\textsuperscript{12} Therefore, it is possible that the episodes represent a distinct phenotype. Diagnostic testing may need to be rethought. The \textit{in vitro} contracture test performed on excised muscle exposed to triggering agents, halothane, and caffeine. The standard protocol of the \textit{in vitro} contracture test may not be ideal to determine susceptibility to spontaneous MH-like episodes. The \textit{in vitro} contracture test performed on a muscle biopsy of the boy reported in this article\textsuperscript{4} would be considered by Europeans as MH equivocal. In addition, positive \textit{in vitro} contracture test results were found in only 24% of 45 individuals with exertional heat stroke,\textsuperscript{13} and in 83% of 12 patients with exercise-induced rhabdomyolysis.\textsuperscript{14} Therefore, more appropriate test protocols \textit{in vitro} (heat, oxidative stress, and nitrogen species as triggers) or \textit{in vivo} (using \textsuperscript{31}P MRI)\textsuperscript{15} 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.16 For prevention of nonanesthetic MH, treatment with dantrolene (blocks RyR1) or 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),17 their parents should be particularly careful.

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References