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 Ca²⁺ release from the sarcoplasmic reticulum mediated by an overactive Ca²⁺ 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 develop 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 may also stimulate Ca²⁺ release from the SR leads to an increased pump activity and indirectly by the sarcolemmal Na⁺/K⁺ pump (the Na⁺ gradient drives the Na⁺/Ca²⁺ exchanger). In classic malignant hyperthermia, uncontrolled Ca²⁺ release from the SR leads to an increased pump activity and heat production, mainly by the adenosine triphosphate-dependent Mg²⁺ pump and indirectly by the sarcolemmal Na⁺/K⁺ pump, 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

Accepted for publication July 25, 2011. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Copyright © 2011, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2011; 115:915-7
Gene Single RyR1 or CACNTAS mutation 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 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 31P 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

<table>
<thead>
<tr>
<th>Table 1. Summary of the Current Understanding of Malignant Hyperthermia and Similar Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classic Human MH</strong></td>
</tr>
<tr>
<td>Gene</td>
</tr>
<tr>
<td>Inheritance</td>
</tr>
<tr>
<td>Trigger</td>
</tr>
<tr>
<td>Signs</td>
</tr>
<tr>
<td>Pathophysiology</td>
</tr>
<tr>
<td>Acute therapy</td>
</tr>
</tbody>
</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 = stick oxide; RyR1 = ryanodine receptor.
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.  

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.

Frank Lehmann-Horn, M.D., Ph.D., Werner Klingler M.D., Ph.D., Karin Jurkat-Rott, M.D., Ph.D., Department of Neurophysiology, Ulm University, Ulm, Germany. frank.lehmann-horn@uni-ulm.de

Frank Lehmann-Horn is endowed Senior Research Professor for Neurosciences of the nonprofit Hertie-Foundation (Frankfurt, Germany). The Foundation pays, among others, his salary to his university.

References

10. Wu S, Ibara MC, Malicdan MC, Murayama K, Ichihara Y, Kikuchi H, Nonaka 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