Relationship Between MH Susceptibility and Heat or Exercise Related Rhabdomyolysis

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Topic

What is the relationship between malignant hyperthermia susceptibility and heat or exercise related rhabdomyolysis?

Supporting Evidence

Background:

There is a poorly-defined relationship between MH susceptibility and the development of a non-anesthetic MH-like illness during conditions of heat, exercise, stress, or viral illness.[1,2] This non-anesthetic-induced MH-like condition may demonstrate many of the same clinical signs as anesthetic-induced MH including hyperthermia, muscle rigidity, rhabdomyolysis, and life-threatening hyperkalemia. Animal and anecdotal human data suggest that dantrolene is effective in ameliorating consequences of heat stroke.

Many questions remain. In the absence of previous diagnostic testing, when should patients with a history of a non-anesthetic MH-like syndrome related to external conditions be considered to be at special risk for MH when they present for general anesthesia? When should these patients be referred for diagnostic testing for MH susceptibility? Are patients with a suspected or proven susceptibility to MH at greater than normal risk of developing a non-anesthetic MH-like syndrome during non-extreme levels of exercise or heat exposure? If so, should their lifestyles be altered to avoid those conditions? Should competitive athletics be avoided?

Discussion:

The relationship between MH and non-anesthetic MH-like illnesses has been confirmed by experimental human[4] and animal[5] studies as well as human case reports and series.[6] Multiple case reports exist of patients with a history of heat- or exercise-induced rhabdomyolysis who either subsequently developed MH during exposure to anesthetic triggering agents or tested positive when an MH diagnostic muscle biopsy was performed (CHCT or IVCT) or exhibited a pathogenic mutation in the main gene, the RYR1 gene, that is causal for Malignant Hyperthermia.[6-12] These non-anesthetic episodes of rhabdomyolysis have ranged from mild symptoms such as persistent cramping during exposure to heat or exercise,[13] to severe muscle breakdown that resulted in clinically significant rhabdomyolysis,[14] or death due to hyperkalemia.[15]

Conversely, several case reports exist of patients known to be MH susceptible who subsequently developed a serious or fatal MH-like syndrome during exposure to heat or as a result of intense exercise, or both.[16-20] It has been estimated that MH-related *RYR1* pathogenic variants are found in 20 and 30% of cases of heat-or exercise-induced rhabdomyolysis.[21]

Conclusions:

After review of the literature and extensive debate, the hotline consultants were unable to definitively answer the question of whether the patients who have experienced heat or exercise related illnesses should be anesthetized with MH susceptibility precautions. Therefore, the consultants agree that surgical patients with a previous history of a non-anesthesia-related MH-like illness should be considered on a case-by-case basis.

Due to the complex nature of non-anesthesia related MH-like illness, there may be occasions when an anesthesiologist might wish to have the patient evaluated by an expert in neuromuscular disorders to rule out non-MH related etiologies. Evaluation might include endocrine-, inflammatory-, and medication-related myopathies, illicit drug use, muscular dystrophies, and muscle channelopathies (e.g. myotonias). Screening might also include metabolic disorders causing exercise intolerance.

The MH hotline consultants agreed that certain factors related to the clinical characteristics of the MH-like illness may place the patient at a higher-than-normal risk for MH susceptibility. These include (a) delayed return to baseline muscle function (more than a week) after physical exercise; (b) persistent creatine kinase (CK) elevation above five times the upper limit of the

laboratory normal range despite rest for at least 2 weeks; (c) rhabdomyolysis complicated by acute kidney injury that does not return to baseline within two weeks; (d) personal or family history of rhabdomyolysis; (e) personal or family history of recurrent muscle cramps or severe muscle pain that interferes with activities of daily living; (f) personal or family history of rhabdomyolysis in response to statin administration; (g) and CK peak > 100,000 U/L.[22]

However, if many other people suffered exercise-related heat stroke or rhabdomyolysis at the same time as the individual or family member, the hotline consultants felt that the event would be less suspicious for an underlying MH susceptibility. Examples would include marathons or football team drills that were conducted despite hot and/or humid conditions.

The hotline consultants also agreed that there is insufficient evidence to determine the estimated risk of non-anesthetic MH-like illness in patients with suspected or confirmed MH susceptibility and thus requires a confident risk-benefit analysis which is currently not possible. It was agreed that as providers, we must communicate with families, coaches, athletic trainers, and the patient's physicians to ensure that signs and symptoms of an MH-like event are quickly recognized and treatment is rapidly instituted. The consultants agreed that MH-susceptible patients who have not experienced adverse effects of heat and exercise should not restrict their activity, and may participate in competitive athletics. However, consultants advise patients to carry identification of their susceptibility and inform those responsible for their care of their MH status. MH susceptible patients who have experienced adverse effects of heat or exercise should restrict their activity based on their own experience and consult with an MH expert, expert neurologist or sports medicine physician familiar with both MH and the adverse effects of heat and exercise. Relatives of MHS patients should be informed and remain aware of their family history of MH. At the present state of the art, deciding which relatives are at risk is a matter of clinical judgement and will remain so until reliable, non-invasive tests are widely available.

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