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Editorial

Exertional Rhabdomyolysis, RYR1 Gene Sequence Variations and Association with Malignant Hyperthermia Susceptibility

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Rhabdomyolysis is an acute syndrome determined by skeletal muscle breakdown and massive release of the intracellular content into blood circulation, which can lead to potentially fatal events, such as acute renal failure, hyperkalemia, and other metabolic complications. These events have a broad etiology including inherited diseases, drugs, toxins, muscle compression, overexertion, and infections [1,2] in every case, the direct injury to the membrane or the failure of energy supply within the muscle cell lead to an increase of free intracellular Ca^{2+}, persistent contraction, energy depletion and cell death. Rhabdomyolysis may also result from a strenuous or not strenuous physical exercise (exertional rhabdomyolysis or ER) often in hot and humid climates, although ER cases have also been reported in physically fit and acclimated subjects. Events similar to those occurring in ER are triggered after exposure to anesthetic agents in malignant hyperthermia susceptible (MHS) patients. Moreover, cases of malignant hyperthermia (MH)-like events in the absence of anesthetic agents caused by high environmental or core body temperature, or even by emotional stress, have been described. An association between these non-anesthetic MH events and malignant hyperthermia susceptibility has been reported (for a review [3]).

Malignant hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscle Ca^{2+} regulation. The MHS trait is inherited in an autosomal dominant fashion. On exposure to halogenated anesthetics and depolarizing muscle relaxants MHS patients may experience an MH crisis as a consequence of an abnormally high release of intracellular Ca^{2+} in skeletal muscle. The symptoms include skeletal muscle rigidity, metabolic acidosis, tachycardia and fever. The condition is potentially life threatening and is one of the main causes of morbidity and mortality during general anesthesia. The estimated prevalence of MH is 1:10,000 to 1:220,000 [4]. The only reliable test to assess the individual's risk from developing an MH crisis is the *in vitro* contracture test (IVCT). Patient's skeletal muscle biopsy is exposed to incremental doses of triggering agents (halothane, caffeine) and the contracture response measured. The IVCT has been standardized by the European Malignant Hyperthermia Group [5] and has high diagnostic sensitivity (99.0%) and specificity (93.6%). MHS exhibits genetic heterogeneity, with 6 *loci* (MHS1, OMIM #145600; MHS2, OMIM %154275; MHS3, OMIM %154276; MHS4, OMIM % 600467; MHS5, OMIM# 601887; MHS6, OMIM %601888) so far implicated. Four (MHS2-MHS4, MHS6) of them have been identified only in isolated families across Europe. However, the MHS1 *locus* (*RYR1* gene) accounts for the majority of MHS cases (about 70%). The *RYR1* gene encodes the skeletal muscle calcium release channel of the sarcoplasmic reticulum, also known as ryanodine receptor type 1 (RyR1). Dantrolene, a RyR1 antagonist that blocks Ca^{2+} release from the sarcoplasmic reticulum stores, is the only specific agent available for the treatment of an MH attack. Mutations in the *RYR1* gene are one of the most common causes not only of the MHS trait but also of various congenital myopathies associated with both dominant and recessive inheritance [6]. Moreover, sequence variations (SVs) of the *RYR1* gene, associated or possibly associated to MHS, have been identified in patients who experienced ER or stress induced-MH events. I recently reviewed this issue [3]; few months later Dalmini et al. [7] reported the screening of *RYR1* SVs in 39 unrelated families from the United Kindom and from The Netherlands, where one or more members had presented with rhabdomyolysis and/or exertional myalgia and where disorders of lipid metabolism, glycogenoses, mitochondrial or other metabolic myopathies have been excluded. *RYR1* SVs were identified in the index cases of 14 families and also in some relatives with mild or no symptoms. MHS status was confirmed by IVCT in 2 families with *RYR1* SVs, while there had been suspected MH events and a history of sudden unexpected deaths in other two families, respectively. Some of the *RYR1* SVs identified by Dalmini et al. [7] have also been reported in MHS individuals; moreover, the RyR1 channel with the Lys1393Arg substitution, identified in two unrelated ER families, has been demonstrated previously to be hypersensitive to the pharmacological (4-chloro-m-cresol) activation, indicating a disease-causing role for this mutation [8]. Furthermore, phenotypic variability associated with some *RYR1* SV has been found, even in patients/subjects of the same family with the same SV, and more than one SV occurred

in some patients/families [3,7], suggesting a possible composite modulating effect. Although functional studies are required to define the pathogenic effects of some SVs and to assess if they are the cause of non-anesthetic MH events in patients, the results of Dlamini et al. [7] expand the spectrum of *RYR1* SVs associated with these events and potentially with MHS. In conclusion, it may be advisable to provide non-MH triggering anesthesia to patients with otherwise unexplained ER or stress-induced MH events until definitive diagnostic IVCT can be performed. Considering the phenotypic variability associated with some *RYR1* SVs, a careful assessment of family members is also advised. Moreover, *RYR1* SVs should be considered in the investigation of these patients and of family members in order to identify individuals at potential risk for MH reactions.

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