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Episodic RYR1-Related Crisis: Part of the Evolving Spectrum of *RYR1*-Related Myopathies and Malignant Hyperthermia-Like Illnesses

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In this issue of *A&A Practice*, Maryansky et al[1] describe an unusual postoperative complication following endobronchial biopsy of a pulmonary mass. In addition to the mass, the patient had an 8-month history of intermittent fevers and muscle weakness that defied diagnosis. Preoperatively, he reported being "cooled with ice packs" following a distant anesthetic exposure. The authors rightly used that historical fact to choose a trigger-free anesthetic technique (ie, avoidance of anesthetic gases and succinylcholine). About 3 hours after completion of the procedure, the patient developed fever similar to his previous episodes, accompanied by cardiopulmonary failure. On advice from a Malignant Hyperthermia Association of the US (MHAUS) telephone hotline consultant, the patient was administered dantrolene, even though his initial blood gas finding of respiratory alkalosis was not consistent with a diagnosis of malignant hyperthermia (MH).[2] After a second dose of dantrolene, the patient's symptoms appeared to abate, although he required continued intensive care for his heart and lung dysfunction. At first glance, this case description represented sepsis, or some other cause of multiorgan failure in a patient with preexisting comorbidities. A positive response to dantrolene therapy does not confirm an MH diagnosis.

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Subsequent genetic testing on the patient detected a heterozygous *RYR1* variant that is a proven MH susceptible pathogenic variant (www.emhg.org). What should we make of this case? Was this true-true and unrelated? Was this delayed postoperative MH? Or nonanesthesia-related "awake MH"? Or something else altogether? We believe it represented an unusual variant of what we now call "episodic RYR1-related crisis (ERRC)."

Ever since the first descriptions of anesthetic-related MH in the early 1960s, there has been an explosion of knowledge about MH and diagnostic pathogenic variants in the skeletal muscle ryanodine receptor gene (*RYR1*). RyR1 resides at the terminal sarcoplasmic reticulum at the junction between it and the T-tubule (ie, the triad), where it regulates calcium homeostasis between the sarcoplasmic reticulum and the myoplasm. The clinical presentation of MH caused by exposure to anesthetic triggering agents (ie, volatile anesthetic gases and succinylcholine) is now known to represent the "tip of the iceberg" of RYR1-related myopathies (RYR1-RM).[3,4]

RYR1-RMs have a broad clinical spectrum, and are thought to be the most common nondystrophic myopathies, with a potential prevalence of >1/35,000 when including MH susceptibility.[5] Phenotypic presentations can be roughly divided between individuals with persistent weakness (ie, myopathic presentation) and individuals with only dynamic symptoms (eg, MH, exertional rhabdomyolysis, heat-related illness), though many individuals experience both. In terms of congenital myopathies due to *RYR1* mutations, they can be both dominant/de novo or recessive, and can have a very broad range of age of onset and severity. Recessive RYR1-RM is, in general, more severe than dominant RYR1-RM, and includes presentations of severe neonatal hypotonia and weakness. RYR1-RM can also be subdivided by histotype (ie, muscle biopsy findings), with common subtypes including central core disease (usually associated with dominant mutations), multi-minicore disease, centronuclear myopathy, and congenital fiber-type disproportion. Many individuals with myopathy due to *RYR1* mutation may also have susceptibility to MH.[6,7] The presence of a pathogenic *RYR1* variant has been associated with life-threatening and sometimes fatal episodes of rhabdomyolysis caused by heat, exercise, infection, or statin administration.[8,9] The extent to which these dynamic symptoms are relevant concerns for individuals with RYR1-RM is uncertain, as many *RYR1* mutations have not be investigated for potential MH susceptibility and therefore confer an uncertain status. The result is that individuals with RYR1-RM, regardless of mutation, are almost always treated as MH susceptible.

Gronert et al[10] first described the use of oral dantrolene to treat nonanesthesia-related symptomatic patients who began to feel the onset of fever or muscle cramps. Expanding on this, we have successfully managed nonanesthetic dynamic symptoms (eg, myalgias, exercise intolerance) with oral dantrolene in patients with MH susceptibility.[11] Dantrolene has also been used successfully in the management of patients with an *RYR1* variant who developed symptoms perioperatively despite trigger-free anesthetics.[12] Perhaps this could be a potential preoperative treatment option for the patient described by Maryansky et al[1] for future surgeries.

Additional therapies are under development for RYR1-RM. These therapies may address the chronic weakness observed in the myopathic presentations, and/or may ameliorate dynamic

symptoms that are not well addressed with dantrolene. For example, a drug in the class of compounds called RyCals, which have the ability to ameliorate the calcium "leak" seen with some mutations, has recently entered clinical trial.[4,13] Antioxidants have show efficacy in preclinical models, though a recent phase I/II trial of *N*-acetylcysteine in ambulatory RYR1-RM patients failed to reach its primary outcome.

In conclusion, we do not believe that the patient in the accompanying case report had a delayed manifestation of MH, since the patient did not receive an MH-triggering anesthetic, and it occurred 3 hours after his presence in the operating room.[14] We believe the term "malignant hyperthermia," although not exactly descriptive of the true event (which is more likely to represent a "malignant hypermetabolism"), should remain in the pantheon of anesthetic complications as a hypermetabolic syndrome that occurs in susceptible patients when exposed to anesthetic triggering agents. But, if what this patient experienced is not true MH, then what should we call it? Some authors have characterized similar clinical episodes as "awake" or "stress-related" MH,[8,15] but these terms do not encompass the spectrum of additional conditions that contribute to the onset of these episodic RYR1-RM crises that are often characterized by any combination of fever, muscle pain or weakness, and in its most severe form, life-threatening hyperthermia and rhabdomyolysis. We propose a new term called Episodic RYR1-Related Crisis, and suggest that this term encompass the many nonanesthesia-related dynamic symptoms experienced by patients with *RYR1* pathogenic variants. Application of this terminology should provide an important but necessary distinction from "proper" MH, and also enable more direct classification, characterization, and treatment of this very important aspect of the disease.

GLOSSARY

ERRC	episodic RYR1-related crisis
MH	malignant hyperthermia
MHAUS	Malignant Hyperthermia Association of the US
RYR1	ryanodine receptor gene
RYR1-RM	RYR1-related myopathies

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