Malignant Hyperthermia, Exertional Heat Illness, and RYR1 Variants: The Muscle May Not Be the Brain

To the Editor:

Fiszer *et al.*[1] identified the novel *RYR1* and *CACNA1S* variants in two cohorts of subjects with the history of malignant hyperthermia (MH) and exertional heat illness (EHI), respectively. Searching for similar mutations in MH and EHI implies that there is a link between the two conditions. Impaired calcium homeostasis is the apparent common factor between the two conditions. This was hypothesized by Wingard and Gatz[2] in the late 1970s, given the clinical and biological similarities between exertional heat stroke (EHS) and the most severe forms of EHI and MH, including hyperthermia and rhabdomyolysis. EHS is viewed as a subclinical myopathy triggered by strenuous exercise. This view was supported by a porcine model of MH in which the triggers were hyperthermia and stress.[3] At first glance, the unexpectedly high prevalence of subjects with EHI susceptible to MH found by Fiszer *et al.* (12 of 28, 43%) also substantiates this hypothesis.

However, this assertion is likely to be incorrect. Linking MH and EHI raises two possibilities: either subjects with the history of MH are prone to exhibit EHI when exposed to strenuous physical exercise or subjects with the history of EHI are prone to MH when exposed to volatile anesthetics. The former hypothesis is supported by one single case report to date. The later assertion would require the determination of MH status before the onset of EHI, which is ethically unacceptable because it involves an invasive procedure, the *in vitro* contracture test (IVCT), to diagnose MH susceptibility (MHS) among asymptomatic subjects.

In the French armed forces, driven by the same assumptions, the MHS trait was investigated by IVCT among soldiers with the history of EHS until 2013. Using the European protocol, 17.2% (78 of 454) of the subjects were found to exhibit MHS, which is much higher than the 1.48% frequency reported in a control population.[4,5] Of note, subjects with EHS who were susceptible to MH neither had a higher risk of recurrence nor had a greater EHS severity. Furthermore, they exhibited a significantly less important IVCT response than MH control subjects. These findings raise the following question: what is the implication of the presence of a high MHS trait or *RYR1* variants among subjects with EHI? A low specificity of both IVCT and RYR1 sequencing could be hypothesized. For *RYR1*, Fiszer *et al.* cautiously concluded that *RYR1* and *CACNA1S* polymorphisms were of "uncertain significance," meaning that they cannot be considered risk factors for MH or EHI without further studies. Of note, there were more *RYR1* variants (5 of 16, 31%) among subjects with EHI who were nonsusceptible to MH than those with EHI who were susceptible to MH (2 of 12, 17%), but the difference was not significant (Fischer exact test = 0.66). Furthermore, EHI encompasses a wide range of unrelated disorders, ranging from physiological states, cramps, and exhaustion to life-threatening states like EHS. Therefore, the EHI group is not homogeneous and may resemble the general population. Among patient with EHS, an MHS response in IVCT may reflect an impaired calcium homeostasis that will not necessarily trigger MH but may result in an increased heat production during strenuous exercise. This hypothesis could account for different thermolysis profiles among individuals submitted to a standardized endurance test and constitute a predisposing risk factor for EHS.

Finally, the authors should be congratulated for their outstanding contribution. It has been four decades since the link between EHS and muscle was established. Is it time to seek for further links between EHS and brain function to clarify where "exercise starts and stops"?[6]

Competing Interests

The author declares no competing interests.

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References

1. Fiszer D, Shaw MA, Fisher NA, Carr IM, Gupta PK, Watkins EJ, Roiz de Sa D, Kim JH, Hopkins PM: Next-generation sequencing of RYR1 and CACNA1S in malignant hyperthermia and exertional heat illness. Anesthesiology 2015; 122:1033–46
2. Wingard D, Gatz E: Some observations on stress susceptible patients, The Second International Symposium on Malignant Hyperthermia. Edited by Aldrete J, Britt F. New York, Grune and Stratton, 1978, pp 363–72
3. Harrison GG: Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. Br J Anaesth 1975; 47:62–5
4. Sagui E, Montigon C, Abriat A, Jouvion A, Duron-Martinaud S, Canini F, Zagnoli F, Bendahan D, Figarella-Branger D, Brégigeon M, Brosset C: Is there a link between exertional heat stroke and susceptibility to malignant hyperthermia? PLoS One 2015; 10:e0135496
5. Ording H, Brancadoro V, Cozzolino S, Ellis FR, Glauber V, Gonano EF, Halsall PJ, Hartung E, Heffron JJ, Heytens L, Kozak-Ribbens G, Kress H, Krivosic-Horber R, Lehmann-Horn F, Mortier W, Nivoche Y, Ranklev-Twetman E, Sigurdsson S, Snoeck M, Stieglitz P, Tegazzin V, Urwyler A, Wappler F: *In vitro* contracture test for diagnosis of malignant hyperthermia following the protocol of the European MH Group: Results of testing patients surviving fulminant MH and unrelated low-risk subjects. The European Malignant Hyperthermia Group. Acta Anaesthesiol Scand 1997; 41:955–66
6. Kayser B: Exercise starts and ends in the brain. Eur J Appl Physiol 2003; 90:411–9

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