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LETTER TO THE EDITOR

Genetic specification of malignant hyperthermia susceptibility is warranted for assessing fatigue, depression, and exercise intolerance

Dear Editor,

We read with interest the article by de Andrade et al on the prevalence of fatigue, depression, and physical activity in a cohort of 22 patients with Malignant Hyperthermia Susceptibility (MHS) diagnosed by an In Vitro Contracture Test (IVCT), compared with 13 MHS-negative patients and 22 healthy controls.[1] There were no significant differences between the three groups in terms of fatigue intensity, fatigue associated with specific situations, psychological consequences of fatigue, fatigue response to rest/sleep, depression, number of active/sedentary participants, and the mean time and habitual physical activity characteristics, but physically active MHS patients showed a greater fatigue response to rest/sleep than the sedentary MHS subgroup.[1] The study is compelling but has limitations that should be discussed.

A limitation of the study is the design.[1] Patients and controls were assessed using a clinical/demographic questionnaire and scales (fatigue severity scale, Baecke Habitual Physical Exercise Scale (BHPES), and the Beck Depression Inventory (BDI), and were thus based on self-assessment and not on objective findings.[1] The methods also didn't mention whether patients filled out the forms online or in person, and it is unclear if all patients filled out the forms by themselves, or if caregivers or relatives were allowed to answer and respond to the questions.

Another limitation is the diagnosis of MHS.[1] Patients were only diagnosed by IVCT, but no genetic testing was performed.[1] Knowledge of the underlying mutation and the mutated gene is crucial, as different mutations may appear differentially on the scales used. Since MHS can lead to muscle weakness and wasting, cramps, myalgia, hypotonia, fatigue and exercise intolerance, and this is highly dependent on the underlying mutation, it is important to know the causative genetic defect.

Information is also lacking as to why the non-MHS patients underwent IVCT. Have these patients had a history of malignant hyperthermia or malignant hyperthermia-like reaction during anaesthesia, or were these patients' relatives of MHS patients?

Fatigue depends not only on comorbidities and medications, but also on diet, intake of adrenergic substances (caffeine, theophylline, energy drinks, nicotine), subclinical hypothyroidism, pre-diabetes, renal function, and environmental conditions. Therefore, it is crucial to know the results of routine blood tests at the time of the study (how many had subclinical hypothyroidism, pre-diabetes, electrolyte disturbances, untreated arterial hypertension), and what diet the 22 included patients were on.

We disagree that fatigue is the same as effort (exercise) intolerance.[1] There are patients with exercise intolerance but no fatigue and vice versa, and also patients with both, fatigue and exercise intolerance.

We also disagree with the statement in the introduction that MHS is an autosomal dominant disorder.[1] For example, Central Core Disease (CCD) is not only inherited as an autosomal dominant trait but can also follow an autosomal recessive pattern of inheritance.[2] MHS due to an autosomal recessive trait of inheritance has also been reported in patients with mutations in STAC3.[3]

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study. The comparison of MHS patients with non-MHS patients and healthy controls requires homogenous groups with regard to the etiology of MHS, diet, and physical activity, and similar group sizes.

Conflicts of interest

The authors declare no conflicts of interest.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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