Brazilian Journal of Anesthesiology 2023;73(2):132–137

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Fatigue, depression, and physical activity in patients with malignant hyperthermia: a cross-sectional observational study

Pâmela Vieira de Andrade *, Lívia Maria Valim, Joilson Moura dos Santos, Isac de Castro, José Luiz Gomes do Amaral, Helga Cristina Almeida da Silva

Universidade Federal de São Paulo, Centro de Estudo, Diagnóstico e Investigação de Hipertermia Maligna (CEDHIMA), Disciplina de Anestesiologia, Dor e Terapia Intensiva, São Paulo, SP, Brazil

Received 11 May 2020; accepted 19 July 2021
Available online 6 October 2021

KEYWORDS
Depression;
Physical exercise;
Fatigue;
Malignant hyperthermia

Abstract
Background: Malignant Hyperthermia (MH) is a pharmacogenetic disorder triggered by halogenated anesthesia agents/succinylcholine and characterized by hypermetabolism crisis during anesthesia, but also by day-to-day symptoms, such as exercise intolerance, that may alert the health professional.
Objective: The study aimed to analyze the incidence of fatigue in MH susceptible patients and the variables that can impact perception of fatigue, such as the level of routine physical activity and depression.
Methods: A cross-sectional observational study was carried out with three groups – 22 patients susceptible to MH (positive *in vitro* muscle contracture test), 13 non-susceptible to MH (negative *in vitro* muscle contracture test) and 22 controls (no history of MH). Groups were assessed by a demographic/clinical questionnaire, a fatigue severity scale (intensity, specific situations, psychological consequences, rest/sleep response), and the Beck depression scale. Subgroups were re-assessed with the Baecke habitual physical exercise questionnaire (occupational physical activity, leisure physical exercise, leisure/locomotion physical activity).
Results: There were no significant differences among the three groups regarding fatigue intensity, fatigue related to specific situations, psychological consequences of fatigue, fatigue response to resting/sleeping, depression, number of active/sedentary participants, and the mean time and characteristics of habitual physical activity. Nevertheless, unlike the control sub-group, the physically active MH-susceptible subgroup had a higher fatigue response to resting/sleeping than the sedentary MH susceptible subgroup (respectively, 5.9 ± 1.9 vs. 3.9 ± 2, *t*-test unpaired, $p < 0.05$).

* Corresponding author.
E-mail: pamela.vieira@unifesp.br (P.V. Andrade).

https://doi.org/10.1016/j.bjane.2021.07.038

Conclusion: We did not detect subjective fatigue in MH susceptible patients, although we reported protracted recovery after physical activity, which may alert us to further investigation requirements.

Introduction

Malignant Hyperthermia (MH) is an autosomal dominant pharmacogenetic muscle disorder characterized by a potentially lethal hypermetabolic crisis following exposure to halogenated anesthesia agents and/or succinylcholine.[1,2] MH has genetic heterogeneity, with mutations in the gene for the Ryanodine Receptor 1 (RYR1), reported in 50–70% of susceptible individuals.[2] The in vitro muscle contracture test in response to caffeine/halothane (in vitro Contracture Test: IVCT) is the gold standard to diagnose a MH-susceptible individual.[3] MH susceptibility is also associated with neuromuscular disorders, chiefly Central Core Disease (CCD).[1,2] Thus, patients with MH may be asymptomatic while performing day-to-day activities and present a normal neurological examination. However, they may also present exertion intolerance, generalized muscle hypertrophy or muscle atrophy/weakness.[2–6]

Fatigue is a common symptom in chronic diseases, and it is defined as a decline in performance associated with activity, expressed as persistent and extreme tiredness, lack of energy and physical and/or mental exhaustion.[7–11] Despite a common complaint, fatigue is not always appreciated. At all stages of neuromuscular diseases, fatigue restricts social, family and leisure interactions and impairs patient quality of life.[7–11] Fatigue is an important warning sign for detecting neuromuscular diseases, and requires investigation, especially when it emerges as effort intolerance.[12] Although the combined prevalence of a group of 30 neuromuscular diseases was 160:100,000 individuals, this figure is believed to be underestimated due to subclinical forms and difficulty in reaching a definitive diagnosis due to lack of human/laboratorial resources.[13] This is highlighted by the recent finding of RYR1 and CACNa1S gene variants, linked to MH, in 1 of every 839 individuals in population genomic studies.[14] Furthermore, when there is an association of exercise intolerance with idiopathic increase in Creatine Kinase (CK), up to 60% of individuals are MH susceptible.[12]

A search in the Pubmed/Medline database (1960–2021), using the terms MESH malignant hyperthermia AND fatigue (''The state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli''), revealed only 25 articles, with a filter for study in humans. Of these articles, 23 were excluded (9 case reports, 7 unrelated to the topic, 7 reviews), and only two investigated fatigue in MH case series, and reported severe fatigue in 46.6% of patients with gene mutations RYR1[15] and a higher fatigue index in patients with a positive MH contracture test.[6] However, previous experimental studies on fatigue in mice and pigs susceptible to MH have revealed less fatigue than controls after short continuous stimulation, but longer recovery after intermittent stimulation, and less adjustment after training.[16,17] There are no studies on fatigue in the Brazilian population presenting MH.

The present study aimed to investigate subjective fatigue in patients susceptible to MH, as well as factors that interfere with the perception of fatigue, such as depression and habitual physical activity, due to the likelihood that patients with fatigue unconsciously decrease their physical activity. Fatigue could alert health professionals to the presence of neuromuscular disease and the need for further investigation.

Methods

A cross-sectional observational study based on STROBE guidelines and exploratory methodological design was performed at a MH referral center. The project was carried out according to the Code of Ethics of the World Medical Association (Declaration Helsinki) and approved by the Research Ethics Committee (CAAE 04250312.6.0000.5505/2012). All participants expressed agreement by signing an informed consent form. IVCT was performed according to the Protocol of the European Malignant Hyperthermia Group, as described previously.[3] Recruitment of participants took place in person for one year, following the inclusion and exclusion criteria below.

Inclusion criteria

Patients who attended the clinic for investigation/follow-up, showing positive IVCT (MH susceptible or MHS group) and negative IVCT (MH non-susceptible or MHN group) were sequentially included in the study, in addition to a recruited group of individuals without a history of MH (control group). Volunteers in the control group were recruited by the investigator from physicians, residents, undergraduate/graduate students, and other university employees.

Exclusion criteria

Patients with other chronic morbidities and/or neurological disorders, or those under chronic use of medications were excluded from the study.

Participants

The three groups were matched for sex and age using age strata. Age stratification of the patients was calculated based on the age distribution of São Paulo's population. As a result, according to the population distribution of the city of São Paulo reported on the 2010 IBGE census, four strata

were defined: 20–29 years (18% of the sample), 30–39 years (16.4%), 40–49 years (13.9%), and 50–59 years (10.8%), with approximately 50% men and 50% women in all the groups.

Participants of the MH susceptible group were compared to two groups, non-susceptible group and control group to increase reliability, taking into consideration the following aspects: First, control patients with no MH history have a theoretical chance of 1:2,000 of being MH susceptible, due to the estimated frequency of the RYR1 gene mutation in the overall population, and second MH non-susceptible patients may have other subclinical myopathies responsible for MH-like reactions in their families.[2–5]

Study design

Patients were assessed using a clinical-demographic questionnaire, the Fatigue Severity Scale,[18,19] the Baecke Habitual Physical Exercise Scale[20,21] and the Beck Depression Inventory.[22] Due to the magnitude of the assessment, the Baecke Habitual Physical Exercise Scale was applied at a second interview, on 10 MHS patients, 9 MHN patients and 22 controls.

The Fatigue Severity Scale is subdivided into four scales: 1- Fatigue Intensity Scale, 2- Fatigue related to specific situations, 3- Fatigue psychological consequences, and 4- Fatigue response to resting and sleeping.[18,19] Score 4 on the scale is the cutoff point for fatigue intensity.[18]

The Baecke questionnaire analyzes habitual physical activity and is regarded as the best tool to assess physical activity in epidemiological studies due to its low-cost and facility to apply.[20,21] The Baecke scale is subdivided into three subscales: occupational physical activity, leisure physical exercise, and leisure/movement physical activity.[20,21]

The Beck Scale classifies individuals as no depression (0–9 points), mild/moderate depression (10–18), and moderate/severe depression (19–29).[22]

Statistical analysis

To calculate the sample size, we used previously described mean values/standard deviation of perceived fatigue between patients with the RYR1 gene mutation and controls (respectively, 31.7/13.2 and 17.3/10.1).[15] Consequently, to replicate these values with maximum estimation of error of 5%, power of 80% and sample size ratio (control group/MH group) of 2.4, a sample of 9 patients with MH and 22 controls would suffice.

Variables were analyzed for normal distribution using the K-S test and expressed as mean/standard deviation for continuous variables with parametric distribution, and for categorical variables as absolute value/percentage.

Differences among groups were calculated using analysis of variance for repeated measures (ANOVA) with Tukey's post-test (parametric data). Unpaired *t*-test was used for intragroup differences. Categorical variables were compared using the Chi-square test (X^2). Results were considered statistically significant for a p-value < 0.05. All tests were performed using Prisma 5.0 statistical software (Graph Pad Prism Statistic Package for Windows; GraphPad Software, 2365 Northside Dr., Suite 560, San Diego, CA 92108, USA).

Results

A total of 57 participants were studied, 22 MH Susceptible (MHS) patients, 13 MH Non-susceptible (MHN) patients, and 22 controls. Of the 22 MHS patients, 13 showed independent positive responses on the IVCT for halothane and caffeine (MHShc), 5 showed positive responses on the IVCT only for halothane (MHSh), and 4 only for caffeine (MHSc).

Mean age showed no significant difference among the three groups (control 36.45 ± 8.18 years, MHS 43.14 ± 15.99 years, MHN 39.44 ± 11.59 years, non-significant p (ns), ANOVA). Gender showed no significant difference between the MHS and control groups (male/female: 11/11 and 12/10, respectively; p ns, X^2), but the MHN group had more female participants (2/11; $p = 0.05$; X^2).

No significant difference was found among the three groups regarding fatigue intensity, occurrence of situation-specific fatigue, fatigue psychological consequences or fatigue response to resting/sleeping (Table 1, Fig. 1). There was a similar number of patients with fatigue in the MHS (n = 5), MHN (n = 3) and control (n = 3) (p ns, X^2) groups.

Table 1 Comparison of level/characteristics of fatigue severity, depression and physical activity among control patients, MH susceptible patients, and MH non-susceptible patients.

	Control (n = 22)	MHS (n = 22)	MHN (n = 13)	p (ANOVA)
Fatigue intensity	2.7 ± 1.3	2.5 ± 1.2	2.7 ± 1.3	ns
Situation-specific fatigue	4 ± 1.7	3.6 ± 1.4	3.4 ± 1.3	ns
Psychological consequences of fatigue	4.6 ± 2.2	4.1 ± 1.5	3.9 ± 1.8	ns
Fatigue response to resting and sleeping	4.7 ± 1.8	4.8 ± 2.1	4.6 ± 2.3	ns
Beck depression scale	5.9 ± 4.2	8.9 ± 7.5	5.8 ± 6.1	ns
Physical exercise mean time (minutes)	120.9 ± 135.2	113.6 ± 191.4	46.15 ± 74.11	ns
	Control (n = 22)	MHS (n = 9)	MHN (n = 10)	p (ANOVA)
Occupational physical activity	2.6 ± 0.5	2.9 ± 0.6	2.6 ± 0.8	ns
Leisure physical activity	2.5 ± 0.9	2.5 ± 0.5	2.3 ± 0.6	ns
Leisure and locomotion physical activity	2.5 ± 0.7	2.2 ± 0.5	2.4 ± 0.8	ns

MH, Malignant Hyperthermia; MHS, MH Susceptible patient; MHN, MH Non-susceptible patient.

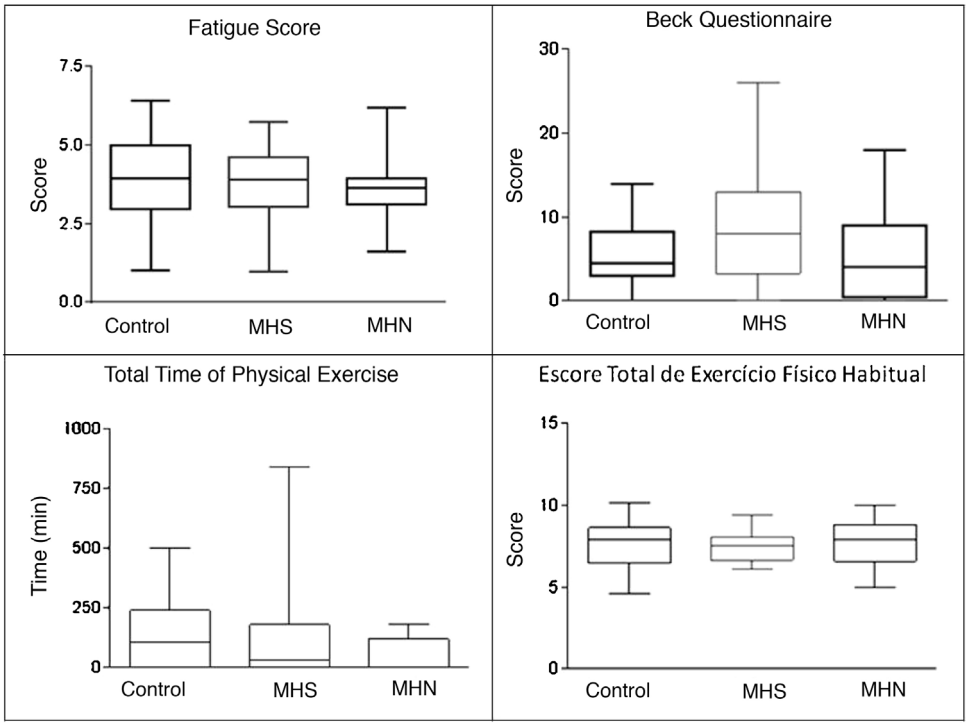

Figure 1 Comparison of fatigue, depression (Beck questionnaire) and habitual physical exercise scores, in addition to total exercise time, among control, MH susceptible and non-susceptible patients. MH, Malignant Hyperthermia; MHS, MH Susceptible patients; MHN, MH Non-susceptible patients; min, minutes.

Table 2 Intragroup analysis of the MHS group and control group regarding active versus sedentary patients.

Fatigue response to resting and sleeping	Actives	Sedentary	p^a
MHS	5.9 ± 1.9 (n = 11)	3.9 ± 2 (n = 11)	0.02
Control	4.2 ± 1.9 (n = 10)	5.1 ± 1.8 (n = 12)	ns

MHS, MH Susceptible patients.
[a] Non-paired *t*-test.

No significant difference was found among the three groups regarding the degree of depression (Table 1, Fig. 1). Considering the individual classification of each participant according to the Beck scale, it was possible to classify participants mainly as with no depression (12 MHS, 11 MHN, 18 controls), followed by mild/moderate depression (8 MHS, 2 MHN, 4 controls) and moderate/severe depression (2 MHS), but no significant difference among the three groups was found (p ns, X^2).

There was no difference in the mean weekly physical exercise time among the three groups. The Baecke Habitual Physical Exercise Questionnaire showed no difference among the three groups in the scores for occupational physical activity, leisure physical exercise, and leisure and locomotion physical activity (Table 1, Fig. 1).

There was no difference in the number of sedentary individuals in the three groups (50% MHS, 69% MHN and 54.5% control, p ns, X^2). Comparison of sedentary patients in the three groups did not reveal differences regarding fatigue, depression, and Baecke habitual physical activity (p ns, ANOVA).

Active/sedentary subgroup analysis

Comparison of sedentary versus active MHS subgroups revealed no differences regarding fatigue intensity, situation-specific fatigue, fatigue psychological consequences, and depression. However, fatigue response to resting/sleeping was higher in the active MHS subgroup than in the sedentary MHS subgroup (Table 2). Comparison of sedentary control versus active control subgroups showed no differences in fatigue intensity, situation-specific fatigue, fatigue psychological consequences, fatigue response to resting/sleeping, and depression (Table 2). Furthermore, no difference was found between active MHS and active controls, as well as between sedentary MHS and sedentary controls (Table 2).

Discussion

The present study did not detect higher intensity/frequency of fatigue among MH susceptible patients compared to con-

trols and MH non-susceptible patients, nor differences in the occurrence of depression or in the pattern of physical activity among the three groups. Furthermore, we analyzed active/sedentary patients in each group, aiming to assess the unconscious reduction in physical activity due to fatigue. Our findings revealed that physically active MH-susceptible patients had a greater impact of resting/sleeping on fatigue recovery than sedentary MH-susceptible patients. This finding, absent in the comparison of active controls with sedentary controls, may reflect the delay in recovery after physical activity in MH, as well as the difficulty to adapt to exercise, described in animal models.[16,17]

Rodents carrying the RyR1Y522S/wt mutation in the ryanodine gene were able to run without experiencing MH crises or rhabdomyolysis, if body temperature did not increase excessively.[16] However, after strenuous physical training for six weeks, these rodents did not show an increase in oxidative capacity and endurance as normal rats and, in addition, ran a 42% shorter distance. Studies with MH-susceptible pigs revealed left-shifted force-frequency ratio, increasing the contraction force/tetanus ratio, and provoking less fatigue after continuous short stimulation (150 Hz for 10 seconds). On the other hand, there was a reduction in tetanic potentiation after continuous stimulation and lengthier recovery after intermittent stimulation (100 Hz for 500 ms, 0.5 second/stimulus train), which could be explained by excitation-contraction decoupling.[17]

Fatigue is a complaint that should be valued, as it is an important symptom in several neurological disorders, such as demyelinating disease of the central nervous system, Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Parkinson's disease, in addition to several neuromuscular diseases and Chronic Fatigue Syndrome.[8–10,19] Fatigue affects 80–90% of patients with MS, impairing cognitive and functional capacity, and restricts daily activities due to the extreme sensation of mental and physical fatigue, which is intensified by high room temperature.[8,9] Fatigue is poorly understood in ALS, even though it is a frequent symptom not linked with physical disability, and is often mistaken for depression and muscle weakness.[19] In ALS, fatigue occurs in up to 83% of patients, isolated or associated with other symptoms, and thus, can intensify them.[19] Fatigue is an early Parkinson's disease symptom and as the disease progresses, it affects more than 58% of patients.[9] Fatigue is found in up to 60% of patients presenting neuromuscular diseases, such as facioscapulohumeral dystrophy, myotonic dystrophy and hereditary neuropathies.[10]

Chronic Fatigue Syndrome includes cognitive dysfunction, sleep disturbances, psychological changes, and fatigue, that occurs in 6.9% to 33% of affected men, and 10.9% to 42% of affected women.[8] Diagnosis of Chronic Fatigue Syndrome requires exclusion of other illnesses that can promote fatigue. Thus, the evaluation of 20 patients with chronic post-viral fatigue revealed that 15 (75%) showed positive in vitro muscle contracture tests, and two presented variants in the ryanodine receptor gene previously associated with MH.[23] As MH susceptibility may be associated with chronic complaints of muscle pain, cramps and exercise intolerance, it is understandable that this can be mistaken for Chronic Fatigue Syndrome.[2,3,5] However, data from our study suggest that MH susceptible patients do not have a greater perception of fatigue (subjective fatigue) than non-susceptible individuals, despite the difficulty in recovering and adapting to physical exertion.

Thompson et al.[6] objectively evaluated fatigue and found that MH susceptible patients had lower ATP production via the oxidative pathway, lower aerobic and anaerobic capacity, and lengthier recovery time when compared to controls. According to these authors, these changes indicate a deficit in production of energy during intense exercise and impaired fatigue endurance during exercise and may explain exercise intolerance shown by some MH susceptible patients. This apparent discrepancy between the subjective fatigue findings in our study and the objective fatigue findings of the Canadian group may be due to a difference in genetic characteristics between the samples of the two studies, in addition to environmental differences related to the temperature to which patients are adapted in Canada and Brazil. Furthermore, although Thompson et al.[6] excluded patients unable to perform strenuous physical activity, their MH-susceptible group showed a significantly lower level of physical activity than the control group. Another possible explanation for this disagreement would be that the fatigue scale can measure not only physical fatigue, but also mental fatigue and the social consequences of fatigue.[9] Moreover, there is an intrinsic limitation to all scales, as they all require patients to remember accurately from past events. It would be interesting to investigate whether patients susceptible to MH presenting objective findings of fatigue would also have a higher perception of subjective fatigue compared to controls matched by degree of physical activity.

Recently, a study revealed that patients with diseases related to the ryanodine gene showed more fatigue severity perception and motivation problems than controls, with no difference between permanent (myopathies) and episodic (malignant hyperthermia, hyperkalemia/rhabdomyolysis) phenotypes, but milder findings in latter group.[15] However, patients with episodic phenotype of ryanodine gene mutations did not exhibit more activity fatigue than controls. Besides using a distinct fatigue detecting tool, the Individual Strength Checklist, that study was based on a spontaneous response to a questionnaire sent by email, with an overall response rate of 72/139 (52%), which could have selected patients presenting more symptoms, while our study comprised a sample of consecutive patients.[15]

Conclusion

Our analysis, based on in-person administration of validated fatigue questionnaires, differed from an earlier clinical study as it has not detected an increase in the intensity/frequency of subjective perception of fatigue in MH susceptible patients versus controls, concurring with previous experimental studies in MH susceptible animals that used objective methods to assess peripheral physiological fatigue. However, active MH susceptible patients had a delay in recovery from fatigue after physical activity compared to sedentary MH susceptible patients. This characteristic, which can be expressed as effort intolerance in physically active patients and may be a symptom of MH, can alert health professionals to the need for further investigation.

Financial support

This study was performed with the support provided by the Coordination for the Improvement of Higher Education Personnel-Brazil (CAPES) – Financing Code 001.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Denborough MA, Lovell RRH. Anaesthetic deaths in a family (letter). Lancet. 1960;276:45.
2. Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. Orphanet J Rare Dis. 2015;10:93.
3. Almeida Silva HC, Almeida CS, Brandão JCM, et al. Hipertermia Maligna no Brasil: análise da atividade do Hotline em 2009. Rev Bras Anestesiol. 2013;63:20–6.
4. Schieren M, Defosse J, Böhmer A, Wappler F, Gerbershagen MU. Anaesthetic management of patients with myopathies. Eur J Anaesthesiol. 2017;34:641–9.
5. Litman RS, Griggs SM, Dowling JJ, Riazi S. Malignant Hyperthermia Susceptibility and Related Diseases. Anesthesiology. 2018;128:159–67.
6. Thompson SJ, Riazi S, Kraeva N, et al. Skeletal Muscle Metabolic Dysfunction in Patients With Malignant Hyperthermia Susceptibility. Anesth Analg. 2017;125:434–41.
7. Allen DG, Lamb GD, Westerblad H. Skeletal muscle fatigue: cellular mechanisms. Physiol Rev. 2008;88:287–332.
8. Whitehead L. The Measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J Pain Symptom Manage. 2009;37:107–28.
9. Friedman JH, Alves G, Hagell P, et al. Fatigue rating scales critique and recommendations by the movement disorders society task force on rating scales for Parkinson's Disease. Mov Disord. 2010;25:805–22.
10. Kalkman JS, Zwarts MJ, Schillings ML, van Engelen BGM, Bleijenberg G. Different types of fatigue in patients with facioscapulohumeral dystrophy, myotonic dystrophy and MHSN-I. Neurol Sci. 2008;29:S238–240.
11. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue - A practical guide for clinicians and researchers. Journal of Psychosomatic Research. 2004;56:157–70.
12. Santos JM, Andrade PV, Galleni L, et al. Idiopathic hyperCK-emia and malignant hyperthermia susceptibility. Can J Anaesth. 2017;64:1202–10.
13. Mungunsukh O, Deuster P, Muldoon S, O'Connor F, Sambughin N. Estimating prevalence of malignant hyperthermia susceptibility through population genomics data. Br J Anaesth. 2019;123:e461–463.
14. Deenen JC, Horlings CG, Verschuuren JJ, Verbeek AL, van Engelen BG. The Epidemiology of Neuromuscular Disorders: A Comprehensive Overview of the Literature. J Neuromuscul Dis. 2015;2:73–85.
15. van Ruitenbeek E, Custers JAE, Verhaak C, et al. Functional impairments, fatigue and quality of life in RYR1-related myopathies: A questionnaire study. Neuromuscul Disord. 2019;29:30–8.
16. Rouviere C, Corona BT, Ingalls CP. Oxidative capacity and fatigability in run-trained malignant hyperthermia-susceptible mice. Muscle Nerve. 2012;45:586–96.
17. Balog EM, Enzmann NR, Gallant EM. Malignant hyperthermia: fatigue characteristics of skeletal muscle. Muscle Nerve. 2000;23:223–30.
18. Schwartz JE, Jandorf L, Krupp LB. The Measurement of fatigue: a new instrument. J Psychosom Res. 1993;37:753–62.
19. Ramirez C, Piemonte MEP, Callegaro D, Da Silva HCA. Fatigue in amyotrophic lateral sclerosis: Frequency and associated factors. Amyotroph Lateral Scler. 2007;9:75–80.
20. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. 1982;36:936–42.
21. Florindo AA, Latorre MRDO. Validation and reliability of the Baecke questionnaire. Br J Sports Med. 2003;9:129–35.
22. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561–71.
23. Timmins MA, Rosenberg H, Larach MG, Carly S, Kraeva N, Riazi S. Malignant hyperthermia testing in probands without adverse anesthetic reaction. Anesthesiology. 2015;123:548–56.