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ORIGINAL INVESTIGATION

Patient suspected susceptibility to malignant hyperthermia: impact of the disease☆

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Abstract
Introduction: Malignant Hyperthermia (MH) is an inherited hypermetabolic syndrome triggered by exposure to halogenated anesthetics/succinylcholine. The lack of knowledge regarding this condition might be associated with the rare occurrence of MH reaction and symptoms.
Methods: This observational study evaluated 68 patients from 48 families with confirmed or suspected MH susceptibility due to medical history of MH reaction or idiopathic increase of creatine kinase or MH-related myopathies. Participants were assessed by a standardized questionnaire and submitted to physical/neurological examination to assess the characteristics of patients with MH, their knowledge about the disease, and the impact suspected MH had on their daily lives.
Results: Suspected MH impacted the daily life of 50% of patients, creating difficulties in performing surgical/clinical/dental treatment and problems related to their family life/working/practicing sports. The questionnaire on MH revealed a correct answer score of 62.1 ± 20.8 (mean ± standard deviation) on a scale 0 to 100. Abnormal physical/neurological examination findings were detected in 92.6% of susceptible patients.
Conclusions: Suspected MH had impacted the daily lives of most patients, with patients reporting problems even before MH investigation with IVCT. Patients showed a moderate level of knowledge about MH, suggesting the need to implement continuing education programs. MH susceptible patients require regular follow-up by a health team to detect abnormalities during physical and neurological examination.

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Introduction

Malignant Hyperthermia (MH) is characterized by hypermetabolism after exposure to volatile anesthetics (halothane/enflurane/isoflurane/sevoflurane/desflurane) and/or succinylcholine. Patients rarely present signs of the condition, such as dysmorphisms, osteoarticular alterations and myopathies, although these are not systematically investigated.[1]

MH susceptibility is an autosomal dominant condition with reduced penetrance/variable expression that is confirmed by a positive *In Vitro* muscle Contracture Test (IVCT).[1,2] While MH reactions occur in 1:10,000 anesthetized children and 1:50,000 anesthetized adults, the incidence of MH susceptible individuals in the population can reach 1:2,000.[2,3] Most of the affected families carry mutations in the type 1 Ryanodine Receptor (*RYR1* gene). On the other hand, few families have mutations in the dihydropyridine receptor and *STAC3* protein genes while several families have no identified responsible gene.[2] *RYR1* gene mutations are also associated with neuromuscular conditions (myopathies) that increase the risk of MH, primarily Central Core Disease and Multiminicore Disease. Therefore, patients with such myopathies and their relatives should be considered MH susceptible until further investigation.[1] Idiopathic Creatine Kinase (CK) increase is another manifestation of *RYR1* mutations.[4] The rarity of MH reaction and symptoms in daily life could be associated with the low level of knowledge about MH and its management, shown both by patients and their treating team. Thus, this study aimed to describe the characteristics of patients referred to a MH referral center in Brazil, the impact suspected MH had on their lives, and their knowledge about MH.

Methods

The present descriptive observational case series study was approved by the Ethics Committee for Research with Human Beings of the institution (0946/06, 0970/2008). After obtaining patients' informed consent, we evaluated consecutive patients referred to MH investigation at a referral center that, since 1997, performs IVCT according to the European MH Group guidelines.[4] Inclusion criteria for MH investigation were past medical history of MH reaction during anesthesia experienced by the patient or patient's first-degree relatives, idiopathic increase in Creatine Kinase (CK), or myopathy possibly related to MH (Central Core Disease or Multiminicore Disease). Data were collected from 2006 to 2016. The initial interview was performed with 68 patients from 48 families. Twelve patients were interviewed only after a positive IVCT result (post-IVCT+ Group) to evaluate whether their knowledge about MH was affected by previous MH diagnosis confirmation by IVCT. The remaining 56 patients were interviewed before IVCT (pre-IVCT Group) and, at the time of the initial interview, they were aware of MH suspicion, but not of the final diagnosis (MH confirmed or ruled out).

As depicted in the study design flowchart (Fig. 1), the initial interview was performed with the entire sample (68 patients), aiming to describe the characteristics of patients referred to a MH referral center in Brazil, the impact on their lives caused by suspected MH, and their knowledge regarding MH. The initial interview (Supplementary Material Text 1) consisted of a standardized questionnaire collecting the following data: a) Patient identification and demographic questions to describe the patients referred due to suspected MH; b) Past medical history, focusing on patient's neuro psychomotor development and surgical/anesthetic history; c) Family history with emphasis on immigrant ancestry, consanguinity, and comorbidities; d) Patient's MH data (main complaint related to the disease and types of sources of information regarding MH); e) MH suspicion-related problems; and f) Ten questions to assess knowledge regarding MH, with two open and eight closed questions (yes/no or multiple choice), each question worth 10 points, thus total score ranging from 0 to 100 for each participant. Additionally, we registered the correct answer rate per question (how many of the 68 patients got each question right).

In the second phase of the study, we compared MH susceptible versus non-susceptible patients regarding the disorders revealed in the physical/neurological examination. In this second phase, 52 patients were included: 12 patients in the post-IVCT+ group, and 40 in the pre-IVCT group who underwent IVCT (29 resulting IVCT positive and 11 IVCT negative). Therefore, the disorders were compared among 41 patients with a positive IVCT and 11 patients with a negative IVCT. In this second phase, 16 patients from the pre-IVCT group who had not performed IVCT investigation were excluded.

To estimate if a reaction occurring during anesthesia was MH-related, we used a clinical grading scale for MH.[5] Body mass index was classified according to normal values proposed for the Brazilian population.[6]

Based on 247 patients referred for MH investigation by 2010, and on reports of abnormalities in up to 83.3% of Brazilian IVCT+ patients,[4] the size sample estimation established a minimum of 67 patients to replicate this proportion, assuming a maximum estimation error of 5% and confidence level of 80%. After data were classified and analyzed, the Kolmogorov-Smirnov test revealed normal distribution of the variables. Continuous variables with normal distribution are presented as mean ± standard deviation, and categorical variables as absolute and relative frequency. Unpaired *t*-test was used to compare two independent parametric samples. Statistical significance was obtained for p-values < 0.05. GraphPad Prism statistical software, version 3.0 was used for statistical analysis.

Results

Initial interview

The 68 patients had a mean age of 37.82 ± 14.68 years (range 16−78 years). Forty-one patients (60%) were female. Forty-seven (69.1%) defined themselves as Caucasian, 20 (29.4%) as Afro-Brazilian, and 1 (1.5%) as Amerindian. The main reason for MH investigation was a history of anesthetic MH reaction, with a smaller number of families referred due to idiopathic CK increase (hyperCKemia) and myopathy probably associated with MH (prior biopsy showing Central Core Disease or Multiminicore disease) (Table 1). For most of the 31 families with a past medical history of anesthetic MH

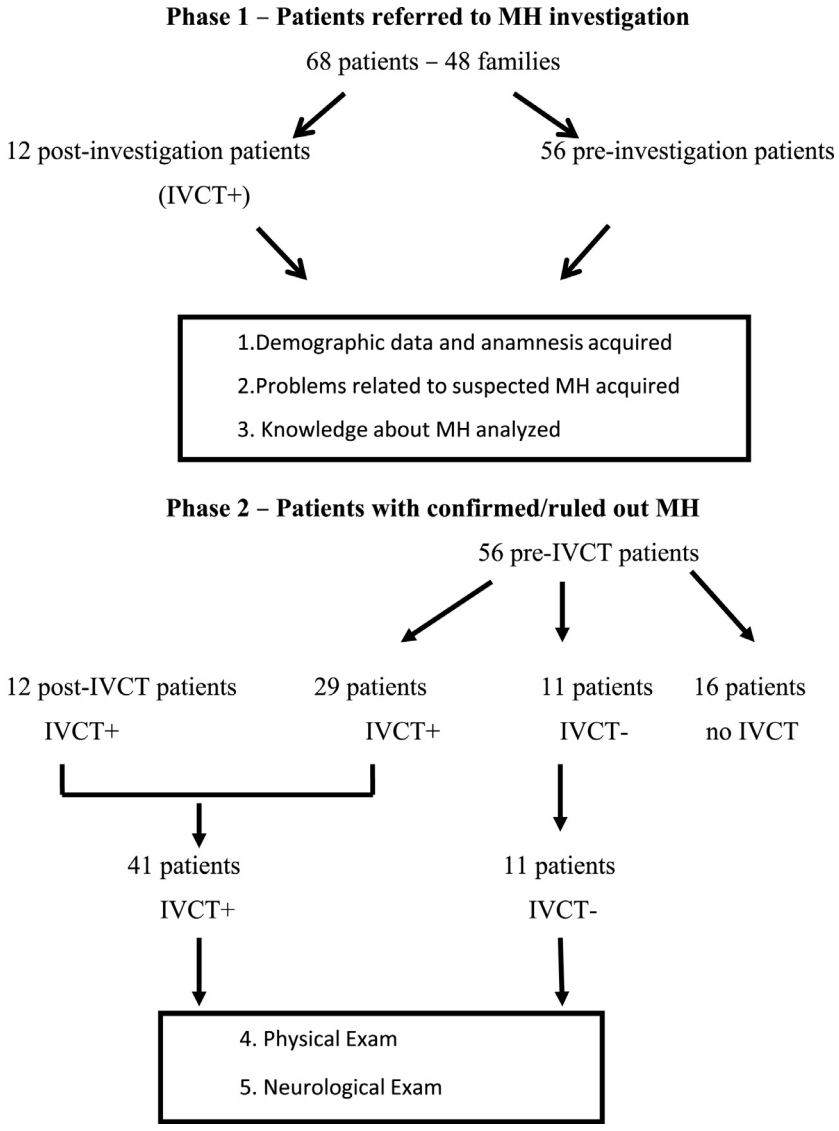

Figure 1 Flowchart illustrating study design.

Table 1 Classification of the 48 families according to testing for MH susceptibility using the *in vitro* contracture test.

48 Families	MH susceptible (IVCT+): n = 29 (60.4%)	MH Non-susceptible (IVCT-): n = 8 (16.6%)	Did not perform IVCT: n = 11 (22.9%)
Anesthetic MH reaction (31 Families – 64.6%)			
12 Families (12 MH reaction survivors tested)[a]	9 (75%)	1 (8.3%)	2 (16.6%)
19 Families (37 first degree relatives tested)[b]	9 (47.4%)	5 (26.3%)	5 (26.3%)
CK level increase 7 Families – 14.6%	6 (85.7%)	1 (14.3%)	0 (0%)
Myopathies 10 Families – 20.8%	5 (50%)	2 (20%)	3 (30%)

MH, Malignant Hyperthermia; IVCT, *In vitro* Contracture Test; CK, Creatine Kinase.
[a] Father was tested for one survivor < 10 years.
[b] 16 MH deaths (11 families) and 8 not tested survivors (8 families).

reaction, only first-degree relatives were evaluated due to death of a patient experiencing MH reaction, to the impossibility of the patient coming for assessment, or a patient too young to perform IVCT, that is ≤ 10 years old (Table 1).

When investigating the health problems of the 68 patients, 32 (47%) denied any disease. None of the patients spontaneously identified MH as a health problem. Conditions recorded as previous personal problems were High Blood Pressure (HBP) (n = 12; 17.6%), Diabetes Mellitus (DM) (n = 6; 8.8%), allergies (n = 6; 8.8%), cardiac disorder (n = 4; 5.8%), myopathy (n = 3; 4.4%), hypothyroidism (n = 2; 2.9%), osteoarthritis (n = 1; 1.5%), ocular toxoplasmosis (n = 1; 1.4%) and migraine (n = 1; 1.5%). Of the 68 patients, 45 reported history of surgery (66%), 58 had been previously anesthetized (85%), with 34 submitted to local anesthesia (58%), 12 to general anesthesia (21%) and 12 did not know the type of anesthesia they received (21%).

We found consanguinity in 4 parental unions (6%) among the 68 patients. Regarding ancestry, 10 patients (14.7%) were not Brazilian descendants, 6 were Portuguese descendants (8.8%), 3 Italian (4.4%), and 1 Polish (1.5%). As for family health problems, HBP occurred in 38 relatives (56%), DM in 28 (41.0%), MH in 18 (26%), undetermined physical deformities in 14 (20%), undetermined mental problems in 12 (18%), cardiac disorder in 10 (15%), myopathies in 6 (9%) − 3 of which Central Core Disease myopathies (4.5%), sudden infant death in 2 (3%), allergic disorder in 1 (1.5%), and neuroleptic malignant syndrome in 1 (1.5%). From the reported 71 causes of death of relatives (33 parents and 38 siblings of respondents), 16 deaths were caused by MH (22.5%), and one by unknown etiology during adenoidectomy (1.4%).

Families referred due to idiopathic hyperCKemia had higher rates of confirmation of MH susceptibility by IVCT, followed by families with myopathies and patients with anesthesia-related MH. Among the 31 families investigated for anesthesia-related MH reaction, there were 36 MH reactions and 16 deaths (42.10%) (Table 1). Three families had more than one death (range 2 to 4) with MH characteristics or perioperative death from unknown causes. Of the 36 MH reactions described, in 34 the surgical procedure could be identified (Table 2).

Among the 36 reactions, in nine cases (6 of 12 survivors, 3 of 16 deaths) all the anesthetic data were available. Thus, according to a clinical grading scale for MH, we estimated that the reaction was almost surely related to anesthesia in four patients (score 6), very likely in three (score 5), more than likely in one (score 4), and less than likely in one (score 3). In these nine patients with suspected MH reaction, anesthetic agents used were halothane in 3 (33.3%), isoflurane in 2 (22.2%), sevoflurane in 2 (22.2%), and unknown in 2 (22.2%).

Thirty-four (50%) of the 68 patients reported difficulties related to suspected MH susceptibility status, even before investigation with IVCT. Thirteen (19%) reported difficulty in medical care (difficult access: seven in private and six in public health services), 7 (10%) reported personal life changes, 6 (9%) referred difficulty in finding a job, 5 (7.3%) reported withdrawal from sports, and 3 (4.5%) described refusal from their dentist to apply local anesthetic. Among the 13 patients referring medical care difficulty, 10 (77%) had a problem in surgical care, 2 (15%) in clinical care, and 1 (8%) in clinical/surgical care. Regarding their personal life, patients described fear of situations requiring anesthesia, especially in an emergency; greater concern of relatives regarding risk of accidents requiring emergency anesthesia; sequelae and deaths in relatives who had had a MH reaction; improvement in relationships/conversations among family members.

Table 2 Surgical procedure associated with the 34 cases of suspected MH reaction.

Surgery	n	%
Gastrointestinal	7	20.6
Urological	7	20.6
Orthopedic	4	11.8
Thyroidectomy	4	11.8
Adenoidectomy and/or tonsillectomy	3	8.8
Oral and Maxillofacial	3	8.8
Nodulectomy (two cases in the neck and one in the lung)	3	8.8
Eye surgery	2	5.9
Neurosurgery	1	2.7
Total	34	100.0

The 68 patients obtained a mean ± SD score in the MH questionnaire of 62.1 ± 20.8. There was no significant difference in the MH questionnaire score per patient, when we compared the pre-IVCT+ group (56 patients who did not know whether they were MH susceptible) versus the post-IVCT group (12 patients who already knew they were MH susceptible), 62.5 ± 19.7 versus 60 ± 2 6.3, respectively; unpaired *t*-test, $p = 0.7$ (Supplementary Material figure 1). Regarding the 10 questions, the mean ± SD rate of correct answer per question was 62.1 ± 24.4% (range 28% to 94%) (Table 3).

Comorbidity assessment: physical/neurological examination

Abnormal findings in physical/neurological examination were found in 38 of the 41 MH susceptible IVCT positive patients (93%), and in 10 of the non-susceptible patients (90.9%) (Table 4).

Among the 22 patients with increased weight, 13 (32% of 41) presented overweight (BMI 25 to 29.99), 4 (10%) grade I obesity (BMI 30 to 34.9); 4 (10%) grade II obesity (BMI 35 to 39.9); and 1 (2.5%) grade III obesity (BMI ≥ 40). Muscle hypertrophic changes included calf muscle hypertrophy in 14 (34% of 41) and generalized muscle hypertrophy in 3 (7%) patients. Among patients with dysmorphisms, some had more than one abnormality: 9 (22% of 41) had changes in the ocular musculature (ptosis seven, strabismus one, exophthalmos one), 17 (41.5%) had facial abnormalities (nine presented elevated arched palate, five everted ears, one micrognathia, one prognathism, one facial asymmetry), and 11 (27%) showed spinal/chest/extremity abnormality (five presented kyphosis and/or scoliosis, two pectus carinatum, one genus varus, one genus valgus, one clinodactyly, one brachydactyly). Motor unit syndrome, characterized by muscle weakness with hyporeflexia/hypotonia/hypotrophy, was predominantly proximal and was rarely accompanied by facial diparesis (one patient) or tongue paresis (one

Table 3 MH knowledge questionnaire according to correct answer rate.

Item	Question	Correct answer n (%)	Incorrect answer n (%)	Not answered n (%)
A	What are signs of an MH reaction?	25 (36.77%)	15 (22.05%)	28 (41.18%)
B	What is the cause of MH?	56 (82.36%)	8 (11.76%)	4 (5.88%)
C	When does MH reaction occur?	55 (80.89%)	6 (8.82%)	7 (10.29%)
D	How is MH treated?	40 (58.83%)	9 (13.23%)	19 (27.94%)
E	Who is at risk for MH?	46 (67.65%)	13 (19.12%)	9 (13.23%)
F	How can MH be avoided?	32 (47.06%)	27 (39.71%)	9 (13.23%)
G	Can a MH susceptible patient undergo surgery?	64 (94.12%)	3 (4.41%)	1 (1.47%)
H	Can a patient with MH receive local anesthesia during dental treatment?	61 (89.71%)	2 (2.94%)	5 (7.35%)
I	Does a MH susceptible individual have any restrictions regarding medication?	24 (35.29%)	28 (41.18%)	16 (23.53%)
J	Does a MH susceptible individual have any restrictions in daily or professional activities?	19 (27.94%)	43 (63.24%)	6 (8.82%)

patient). Patients with altered tactile sensitivity referred medical history of arthropathy or previous surgery at the symptomatic site.

Discussion

In this sample of patients referred to our MH reference center to perform MH susceptibility investigation, most participants were in the fourth decade of age and females. Demographic characteristics of different samples of MH patients vary depending on the inclusion criteria adopted for performing MH investigation with IVCT. Until 2003 our MH reference center had adopted 14 years as the minimum age for investigating MH with IVCT. From 2004 onwards the inclusion age criterion changed to 10 years.[4]

Both MH reactions and positivity in IVCT are more common in males.[7] Female participant predominance in our study could be explained by the greater demand from female patients for our MH service. Supporting this hypothesis, data revealed that 70% of patients attending general outpatient clinics in Brazil are women, perhaps reflecting a greater concern of the female population regarding health issues.[8] Our sample included participants of several ethnicities (Caucasian, Afro-Brazilian, Amerindian), confirming the occurrence of MH in all ethnic groups.[9]

Table 4 Findings detected during physical/neurological examination of 41 MH susceptible and 11 MH non-susceptible patients.

Clinical/Neurological findings	MH susceptible IVCT+:n = 41	MH negative IVCT-:n = 11
BMI < 18.5	1 (2.4%)	0 (0%)
BMI > 24.9	22 (53.6%)	5 (45.4%)
Hypertension	9 (21.9%)	4 (36.3%)
Neurological findings		
Dysmorphisms	19 (46.3%)	6 (54.5%)
Muscle hypertrophy	17 (41.5%)	3 (27.2%)
Motor unit syndrome	15 (36.6%)	5 (45.4%)
Cranial nerve abnormalities	5 (12.2%)	1 (9.1%)
Tactile hypoesthesia[a]	5 (12.2%)	0 (0%)

[a] Compression neuropathies related to anatomical deformities or previous surgeries.

Overall, the participants in our sample did not regard MH as a personal health problem. Explaining this finding is difficult, considering the fatality associated with MH reaction. As an alternative, it is likely that patients do not perceive MH as a disease because they do not notice changes in their daily health status that are specifically MH-related and do not feel regular follow up at a health service is required, which would lead to MH care neglected throughout life. Thus, perhaps MH is perceived by the patient as a risk, not a disease. Among the health conditions associated with MH, Central Core Disease myopathy stands out, albeit the condition usually shows a slow and benign clinical progress and may go unnoticed by patients.[1] Regarding personal medical history, the incidence in our sample was lower than expected among Brazilians for HBP (versus 36.0% of Brazilians over 40 years of age), hypothyroidism (versus 12.3% to 19.1% of elderly Brazilians), osteoarthritis (versus 6% to 12% of adult Brazilians), migraine (versus 15% of female and 5% of male), and drug allergies (versus 10% of patients).[10–14] These low incidences may be explained given our sample was younger than the population age ranges in which those health conditions are most prevalent. This hypothesis is supported by the higher frequency of HBP reported by family members.

Our sample showed a higher than expected incidence among Brazilians for DM (versus 5.7% of adults and nearly 18% of elderly Brazilians) and cardiac disorder (versus 3.6% of the Brazilian population).[10,15] These data, not previously described in our country, may be a fortuitous association resulting from overweight/obesity present in more than half of our sample, while overweight/obesity is present in 18% of the Brazilian population.[16] However, recently, Tammineni

et al. described the incidence of hyperglycemia in 42% of a Canadian MH susceptible sample due to decreased muscle glucose storage, resulting from intracellular calcium leakage.[17]

Most of our sample had a history of prior surgery/anesthesia, attesting that absence of MH reaction during previous anesthesia does not imply MH non susceptibility because MH penetrance/expressiveness varies.[2] The majority of patients in our sample had Brazilian parents or parents of unknown nationality, whereas the minority had European ancestry. Additionally, because of Brazilian population miscegenation, mutations from Indigenous and African populations must be considered.

We reported physical deformities in one fifth of the families and in nearly half of the patients, supporting the reports of increased frequency of congenital malformations and osteoarticular disorders associated with MH, comprising congenital clubfoot, dislocated patella, cryptorchidism, ptosis/strabismus, cleft palate, micrognathia, scoliosis, pectus carinatum/excavatum, and King Denborough syndrome.[18] Existing physical abnormalities and/or deformities enhance the likelihood of patients undergoing repair surgery and, consequently, the risk of developing MH reaction.

MH reactions and perioperative deaths from unknown causes were responsible for one fifth of the deaths of family members, with the aggravating factor of the occurrence of more than one death in the same family. This suggests lack of information sharing among relatives and/or lack of awareness of MH reaction severity, as well as not realizing the need to report MH reaction to health professionals before receiving anesthesia. Our sample registered modest scores on the MH questionnaire suggesting that information provided during the consultation and investigation may not be sufficient. Another possibility is that information should be reinforced regularly, as suggested by the lack of difference between scores registered by patients still awaiting investigation and by patients already with a positive IVCT result at the time of evaluation. These findings are even worse if considering the elevated MH reaction mortality rates still observed in these families, which is considerable higher than the 1.4% reported in the United States between 1987—2006.[19] On the other hand, the mortality rate found in our sample may be overestimated, as it is possible that only more severe reactions had been reported/referred for investigation.

There is no scientific evidence supporting contraindication of local anesthesia for dental care because using local anesthetics is safe, as the only drugs triggering MH reaction are halogenated agents and succinylcholine. The lack of confidence of patients on the level of knowledge on MH of health professionals is noteworthy, a finding in agreement with the study by Simões et al., which revealed that 50% of anesthesiologists correctly answered to questions regarding the indication of muscle biopsy and pharmacology of dantrolene, and 90% to the question related to MH diagnosis and treatment.[20]

Nearly all patients with MH susceptibility confirmed by positive IVCT presented abnormal findings in the physical/neurological examination. The most common abnormality, presented in almost 50% of those patients, was trophic syndrome characterized by muscle hypertrophy, formerly described in MH patients, and possibly resulting from chronically high levels of calcium in muscle fibers.[1,2] Muscle weakness with hyporeflexia/hypotonia/hypotrophy is a characteristic clinical sign of the myopathy which, like MH susceptibility, could be explained by *RYR1* mutations.[1] Due to the slowly progressive characteristic, the weakness may remain unnoticed by patients, who adapt themselves to the functional loss. Some patients presented sensory cranial nerve involvement that usually is not related to MH (I – olfactory, VIII – auditory), what may be an accidental association.

This study has limitations because of unavailability of data related to MH reactions, as most patients/families were not provided with comprehensive reports on atypical reactions during anesthesia. Additionally, the effort to recover these data at the hospital the patient had attended was unsuccessful because many services had shut down, or the medical charts had been discarded. It is vital that families be fully informed/warned to prevent new MH reactions in the patient/family. Moreover, MH reactions must be reported to a MH referral center for diagnostic confirmation of suspected MH susceptibility.

Another limitation of the study was that, in the second phase, some patients were excluded because they did not perform IVCT. However, if the sample size calculation considers our finding of 92.6% IVCT+ patients presenting changes, the minimum sample number would be 39 patients, which is consistent with the number of patients showing abnormalities in the physical/neurological examination who were analyzed in the second phase of the study. Conversely, this sample size may not have been sufficient to detect differences between the susceptible/non-susceptible groups. The preliminary data presented here should support larger future studies, including control groups with patients without suspected MH.

In response to the need for continuing education of MH susceptible patients and health professionals, our reference center began to publish information electronically through the website https://cedhima.unifesp.br/ and created a Facebook page for better interaction with/between patients (https://www.facebook.com/HipertermiaMaligna/).

Conclusion

The impact of suspected MH is relevant in our environment and is translated by difficulties described by patients even before performing IVCT investigation. Patients showed an intermediate level of knowledge about MH, suggesting the need to implement continuing education programs. Abnormalities detected by physical/neurological examination highlight the need for regular monitoring of patients susceptible to MH by health professionals.

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Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2021.10.021.

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