Profile of malignant hyperthermia susceptibility reports confirmed with muscular contracture test in Brazil

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Received 10 May 2018; accepted 4 September 2018
Available online 14 January 2019

KEYWORDS
Malignant hyperthermia; Anesthesia; Epidemiology; Brazil

Abstract
Background and objectives: Malignant hyperthermia is an autosomal dominant hypermetabolic pharmacogenetic syndrome, with a mortality rate of 10%–20%, which is triggered by the use of halogenated inhaled anesthetics or muscle relaxant succinylcholine. The gold standard for suspected susceptibility to malignant hyperthermia is the in vitro muscle contracture test in response to halothane and caffeine. The determination of susceptibility in suspected families allows the planning of safe anesthesia without triggering agents for patients with known susceptibility to malignant hyperthermia by positive in vitro muscle contracture test. Moreover, the patient whose suspicion of malignant hyperthermia was excluded by the in vitro negative muscle contracture test may undergo standard anesthesia. Susceptibility to malignant hyperthermia has a variable manifestation ranging from an asymptomatic subject presenting a crisis of malignant hyperthermia during anesthesia with triggering agents to a patient with atrophy and muscle weakness due to central core myopathy. The aim of this study is to analyze the profile of reports of susceptibility to malignant hyperthermia confirmed with in vitro muscle contracture test.

Method: Analysis of the medical records of patients with personal/family suspicion of malignant hyperthermia investigated with in vitro muscle contracture test, after given written informed consent, between 1997 and 2010.

Results: Of the 50 events that motivated the suspicion of malignant hyperthermia and family investigation (sample aged 27 ± 18 years, 52% men, 76% white), 64% were investigated for an anesthetic malignant hyperthermia crisis, with mortality rate of 25%. The most common signs of a malignant hyperthermia crisis were hyperthermia, tachycardia, and muscle stiffness. Susceptibility to malignant hyperthermia was confirmed in 79.4% of the 92 relatives investigated with the in vitro muscle contracture test.

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https://doi.org/10.1016/j.bjane.2018.09.009
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Conclusion: The crises of malignant hyperthermia resembled those described in other countries, but with frequency lower than that estimated in the country. © 2018 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

INTRODUCTION

Malignant hyperthermia (MH) is a potentially fatal autosomal dominant hereditary hypermetabolic syndrome associated with halogenated inhalational anesthetics and/or muscle relaxant (succinylcholine), which was first reported in Brazil in 1975.1-3 MH is the result of mutations in genes linked to intracellular calcium dynamics, particularly the ryanodine (RYR1) and dihydropyridine (CACNA1S) genes, which promote excessive release of calcium into the cytoplasm, lead to skeletal muscle contraction and muscle rigidity, hypermetabolism with increased oxygen consumption and production of carbon dioxide (hypercarbia), increased heat production (hyperthermia) and metabolic acidosis, besides destroying the membrane of muscle fibers, which allows the overflow to the circulation of intracellular constituents, such as potassium, creatine phosphokinase (CK), and myoglobin.2,3 In addition to tachycardia and tachypnea, complications may occur in multiple organs and systems, with arrhythmias, disseminated intravascular coagulation, and renal and hepatic insufficiency.2,3 Survival in MH depends on early recognition, discontinuation of triggering agents, cooling, and support treatment, in addition to the antidote dantrolene sodium, which interrupts the excessive release of calcium at a dose of 2.5 mg.kg−1 intravenous bolus every 5 min until the crisis is controlled.2,3

MH crisis occurs in both sexes, in all ethnicities and regions of the world, with a frequency of one crisis per 10,000 anesthesias in children or 50,000 in adults; this number varies, depending on the population studied and local anesthetic practices.5-9 On the other hand, the frequency of the mutated gene in the population is much higher, it can reach one individual with a mutation in every 2000 people.10-11 Susceptibility to MH can be manifested in

PALAVRAS-CHAVE
Hipertermia maligna; Anestesia; Epidemiologia; Brasil

Resumo
Justificativa e objetivo: Hipertermia maligna é uma síndrome farmacogenética hipermetabólica, autossômica dominante, com mortalidade entre 10%-20%, desencadeada por uso de anestésico inalatório halogenado ou relaxante muscular succinilcolina. O padrão-ouro para pesquisa de suscetibilidade à hipertermia maligna é o teste de contratura muscular in vitro em resposta ao halotano e à cafeína. A determinação da suscetibilidade nas famílias suspeitas permite planejar anestesias seguras sem agentes desencadeantes para os pacientes confirmados com suscetíveis à hipertermia maligna pelo teste de contratura muscular in vitro positivo. Além disso, o paciente no qual a suspeita de hipertermia maligna foi excluída pelo teste de contratura muscular in vitro negativo pode ser anestesiado de forma convencional. Suscetibilidade à hipertermia maligna tem manifestação variável, desde indivíduo assintomático que apresenta crise de hipertermia maligna durante anestesia com agentes desencadeantes, até paciente com atrofia e fraqueza muscular por miopatia central core disease. O objetivo deste trabalho é analisar o perfil dos relatos de suscetibilidade à hipertermia maligna confirmados com teste de contratura muscular in vitro.

Método: Análise das fichas de notificação dos pacientes com suspeita pessoal/familiar de hipertermia maligna investigados com teste de contratura muscular in vitro, após assinatura do termo de consentimento, entre 1997-2010.

Resultados: Dos 50 eventos que motivaram a suspeita de hipertermia maligna e a investigação familiar (amostra com 27 ± 18 anos, 52% homens, 76% brancos), 64% foram investigados por crise de hipertermia maligna assintomática, com mortalidade de 25%. Sinais mais comuns da crise de hipertermia maligna foram hipertermia, taquicardia e rigidez muscular. Suscetibilidade à hipertermia maligna foi confirmada em 79,4% dos 92 parentes investigados com teste de contratura muscular in vitro.

Conclusão: Crises de hipertermia maligna assemelharam-se às descritas em outros países, porém com frequência inferior à estimada no país. © 2018 Sociedade Brasileira de Anestesiologia. Publicado por Elsevier Editora Ltda. Este é um artigo Open Access sob uma licença CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).
a variety of ways, ranging from asymptomatic individuals, who present crisis during anesthesia with triggering agents, to patients with atrophy and muscle weakness by central core disease (CCD).1,2,5,7

MH, as an autosomal dominant inheritance, should be investigated in all relatives of suspected patients. The genetic diagnosis encounters difficulties, such as the large size of the RYR1 gene and the presence of several polymorphisms along this gene, in addition to the genetic heterogeneity of MH, where mutations may be present in genes other than RYR1.2,10 The gold standard test for diagnosis of MH susceptibility is the in vitro contracture test (IVCT) performed with skeletal muscle fragments obtained from biopsy of the quadriceps muscle (vastus lateralis or vastus medialis).14 This biopsied muscle is maintained under physiological conditions (37 °C, oxygenation, hydroelectrolytic solution, and glucose) during exposure to increasing concentrations of caffeine and halothane. In patients susceptible to MH, the muscle shows contracture of greater intensity than normal muscles and at lower concentrations of at least one of the two substances used for stimulation.14,15 In Brazil, the MH investigation using IVCT is performed in São Paulo at Cedhima (Center for the Study, Diagnosis and Investigation of Malignant Hyperthermia – http://cedhima.sites.unifesp.br/site/) according to the European protocol, and in Rio de Janeiro according to the American protocol. Cedhima performs IVCT in the context of atypical anesthesia (including anesthetic MH), MH-related neuromuscular diseases, idiopathic hyperCKemia, stress hyperthermia, and severe rhabdomyolysis. When IVCT is positive in a subject, the family investigation is proposed. The determination of susceptibility in suspected families allows the planning of safe anesthesia for patients who are confirmed as susceptible to MH by positive IVCT. Moreover, the patient whose suspicion of MH was excluded by a negative IVCT can be anesthetized in a conventional manner.

In the State of São Paulo, in 2004, the technical standard regarding the guidelines for the diagnosis, treatment, prevention, notification and epidemiological investigation of MH cases was approved within Proprev (State Program for Prevention, Diagnosis and Treatment of Malignant Hyperthermia), under the Coordination of the Secretary of Health.16,17 Proprev-MH also aims at the orientation of susceptible patients and their relatives, with a view to eradicating the number of deaths due to MH syndrome in the State of São Paulo. In this program, laboratory confirmation of MH suspected cases and their relatives is performed by muscle biopsy with muscle contracture test in vitro after exposure to halothano-caffeine. The MH legislation of the State of São Paulo also makes compulsory the supply of dantrolene sodium in health services, in addition to determining the compulsory notification of MH. The federal government does not have similar legislation yet, but the Federal Medical Council mandates the availability of dantrolene and capnography in any anesthesiology service in which MH-triggering drugs are used (Resolution 2174, December 14, 2017 – Diário Oficial da União – Imprensa Nacional).

The aim of the present study is to analyze data from MH notification records that were confirmed by IVCT, in order to trace the MH profile in our environment, considering the variability of the clinical presentation of MH-susceptibility.

Method
This study was carried out according to the standards required by the Declaration of Helsinki and approved by the Ethics Committee recognized by the National Ethics Committee for Research (Conep), linked to the National Health Council (NHC). Thus, all patients participating in this study previously signed, at the beginning of their investigation, the free and informed consent form (Ethics and Research Committee numbers 0970/08 and 0979/2017).

The evaluation tool was the Proprev-MH record for MH notification (supplementary material online, Fig. 1). From this record, demographic data, clinical history (personal, family, and epidemiological), history of the disease that motivated the investigation, as well as details of the anesthetic technique and clinical and laboratory changes in MH crisis were collected. Data were tabulated and presented as measure of central tendency and dispersion or percentage.

Between 1997 and 2010, 247 patients were referred for IVCT investigation of suspected MH susceptibility, performed as previously described.2,1 One hundred and four patients did not perform muscle biopsy for IVCT and did not have their final diagnosis of MH susceptibility established. The remaining 143 patients comprised 51 patients with suspected MH susceptibility and the members of the respective family group who underwent IVCT. In these 51 families, the IVCT for MH was positive in 50 families and negative in one (one patient who survived the suspected MH crisis had negative IVCT). In 20 of these 50 families susceptible to MH, the patient who motivated the suspicion of MH susceptibility could not undergo investigation with IVCT (death due to suspected MH crisis, aged less than 10 years, or difficulty to attend the diagnostic center). In these 20 cases the confirmation of MH susceptibility occurred with the finding of positive IVCT in relatives. In the remaining 30 families, the patient who motivated the suspected susceptibility to MH could be investigated with IVCT and, after the positive result, the IVCT investigation continued in their relatives. In the present study, the 50 families with IVCT positive for MH were selected for retrospective analysis. These families corresponded to 122 individuals with positive IVCT (30 patients who motivated the suspicion of MH susceptibility and 92 relatives) and 20 individuals who did not undergo IVCT with suspected MH crisis (supplementary material online, Fig. 2).

The malignant hyperthermia research center is active and notifications continued to be made from 2011 to the present time. However, we chose to analyze the period from 1997 to 2010, due to the fact that there was more time to complete the investigation with IVCT in a greater number of relatives. Many patients seen at the malignant hyperthermia research center come from other states and it takes time for their closest relatives to travel to undergo the IVCT, since the biopsy must be done no more than 5h before the end of this test.5
Results

Patients who motivated family investigation

The 50 patients who motivated the investigation in the respective families were aged 27.4 ± 18.9 years (1–70 years) and 24 (48%) were female. Thirty-two patients (64%) were from the State of São Paulo, five (10%) from Minas Gerais, four (8%) from Espírito Santo, two (4%) from Pernambuco, two (4%) from Paraná, one (2%) from Santa Catarina, one (2%) from Rio de Janeiro, and three (6%) had unknown data. Thirty-eight (76%) were classified as whites, nine (18%) as browns, one (2%) as black, and two (4%) as undeclared data. The reasons for MH investigation were:

- Anesthetic malignant hyperthermia: 32 (64%);
- Central core disease: six (12%);
- Idiopathic hyperCKemia: six (12%);
- Human stress syndrome: one (2%);
- Masseter muscle hypertrophy: one (2%);
- Atypical neuroleptic malignant syndrome (NMS): four (8%).

Five (10%) of the 50 patients motivating the investigation had other changes, such as patent ductus arteriosus (one), cerebral aneurysm (one), epilepsy (one), muscular dystrophy (one), and pectus carinatum with scoliosis. One patient referred due to MH during anesthesia had already presented atypical reaction in another previous anesthesia. Significant family history, which could have raised suspicion of MH susceptibility in the 50 patients who motivated the investigation, were present in 14 (28%) of the families: MH during anesthesia (seven), myopathy (four) and typical central core disease (one), atypical NMS (one) in a patient with the same suspicion, unexplained intraoperative death (two).

Malignant hyperthermia crisis

Of the 32 patients with MH (12 survivors and 20 without IVCT), ten (31%) had a MH crisis at the first anesthesia, while thirteen (41%) had previously been anesthetized 2.2 ± 2.4 (1–10 times) and in nine patients (28%) this data was unknown by the relatives. The surgeries that required anesthesia were elective in the majority (30 patients: 94%):

- Otorhinolaryngologic surgery in five (16%): adenotonsillectomy in three and associated with septum deviation repair in one and stapledectomy in one;
- Orthopedic surgery in six (19%): congenital crooked foot repair in four, syndactyly repair in one, and fracture in one;
- Hernia repair in four patients (12.5%): hiatus, epigastric wall, umbilical/phimosis, and lumbar disk;
- Other gastrointestinal surgeries in four (12.5%): gastroplasty, colectomy, diverticulectomy, removal of gallstones;
- Oral and maxillofacial surgery in 52 (6%);
- Cryptorchidia repair in two (6%);
- Other neurosurgery in two (6%): lipomyelomeningocele repair, intracerebral tumor exeresis;
- Other surgeries in two (6%): retinoplasty, cervical gland removal;
- Diagnostic procedure in one (3%): microlaryngoscopy;
- Unknown in four (12.5%).

The MH-triggering agent was known in 21 patients: halogenated alone in 13, halogenated associated with succinylcholine in six, and succinylcholine alone in two patients. The halogenated agents used were isoflurane (nine), halothane (six), and sevoflurane (four). In 11 patients, data on the anesthetics used were not known by the patient or relatives, since the patient was referred only with the indication of suspected MH.

Data regarding the interval between the onset of anesthesia and onset of MH crisis were available for six patients (162.5 ± 18.3 min, immediate onset up to 8 h); the MH crisis began in the postoperative period in two patients (both after 3 h). The clinical manifestations during MH crisis, available for 24 patients, are listed in Table 1.

Capnography data were only available for three patients, all with hypercarbia (>55 mmHg with adequate controlled ventilation or >60 mmHg with spontaneous ventilation). Gasometric data, available for eight patients, showed metabolic acidosis (pH < 7.25) in five patients, reduced serum bicarbonate (<20 mEq.L⁻¹) in three patients, reduced base excess (<−8) in two patients, and increased PaCO₂ (>60 mmHg with adequate controlled ventilation) in two patients. Other laboratory tests, available for four patients, showed increase in serum potassium (>6 mEq.L⁻¹) in three patients and CK in two (above 10,000 IU.L⁻¹ without succinylcholine and above 20,000 IU.L⁻¹ with succinylcholine).

The treatment used in the acute phase, reported for 15 patients, included discontinuation of triggering agent (halogenated) in 11 patients, active cooling in nine, hyperventilation with 100% oxygen in seven, administration of sodium dantrolene in five, and diuresis stimulation in two. The management in the late phase of the MH crisis, available for 13 patients, was characterized by ICU monitoring in 11 patients, dantrolene sodium administration for another 24 h in three, CK serum levels monitoring in eight, blood gases monitoring in six, and temperature monitoring in seven. Regarding evolution, eight (25%) patients died due to MH crisis, two (6%) had seque-
lae (myalgia), and 22 (69%) recovered without sequelae. When comparing deaths before (1997–2000) and after (2001–2010) the beginning of implementing specific legislation to fight MH, the frequencies were, respectively, 29% (five in 17 crises) and 20% (three in 15 crises), but still with no statistical difference (Fisher’s test, p non-significant).

In vitro muscle contracture test

In 30 of the 50 patients who motivated the investigation, MH susceptibility was directly confirmed in the patient by positive IVCT, including all patients with atypical NMS, central core disease, idiopathic hyperCKemia, and masseter muscle rigidity, as well as survivors of MH crisis. In most cases there was a positive contractile response to both caffeine and halothane, and they were diagnosed as susceptible to MH with response to halothane/caffeine (MHSc); the minority reacted only to caffeine or halothane and was diagnosed as susceptible to MH with response to caffeine (MHSc) or halothane (MHSh) alone (Table 2).

In the remaining 20 patients, the suspected MH susceptibility was indirectly confirmed after a relative has had positive IVCT. The relatives underwent the investigation because the patient who motivated the investigation had died (eight families) or was below the minimum age/weight of 10 years/20 kg established by the IVCT protocol (10 families), or was unable to undergo investigation (two families). The choice of relative to be initially biopsied included the first-degree closest relatives of (parents, children, siblings) and, within this group, those with muscular complaints (myalgia, cramps, exercise intolerance), changes in physical examination (hypertrophy or muscular atrophy, dysmorphisms) or increased CK. Of the 92 relatives of patients who were the subjects of the study, most of them were represented by first-degree relatives (mothers, fathers, siblings, and children), followed by more distant relatives (uncles, nephews, cousins, and grandchildren). Most relatives were susceptible to MH, and were subclassified as MHSc, with a smaller number of MHSh or MHSc (Tables 2 and 3).

Non-investigated patients

The 104 non-investigated patients were aged 25 ± 18.7 years (8 months–77 years), 52% female, and were referred for personal/family history of anesthetic-induced MH (59 patients, 56%), central core/multiminicore (11 patients, 10.5%), atypical NMS (7 patients, 7%), atypical anesthetic reaction (4 patients, 4%), undefined myopathy (4 patients, 4%), idiopathic hyperCKemia (2 patients, 2%), atypical anaphylactic shock (2 patients, 2%), exercise intolerance (1 patient, 1%), muscle stiffness (1 patient, 1%), and inadequate reason (13 patients, 12.5%). Among the 91 non-investigated patients, but with possible anesthetic risk, 31 of them were below the minimum age/weight required for investigation and their relatives refused to undergo investigation; other impeding factors were the distance between domicile-hospital and refusal of surgery.

Discussion

This study has as limitation the absence of detailed anesthesia information for all patients presenting with MH crisis. Even in the State of São Paulo, where notification is mandatory, there are patients without detailed report of the event. When the patient is directed to a referral center, reports are requested from the original hospitals and health care professionals involved in the care. However, many services were disabled and medical records were not available. It is crucial that patients receive detailed reports to protect the entire family, prevent further deaths in operating rooms and postoperative intensive care units, and allow better characterization of MH in Brazil. According to current legislation, the epidemiological investigation of MH suspected cases follows the investigation steps of notifiable diseases in general, with completion of the Malignant Hyperthermia Investigation Form of the Center for Epidemiological Surveillance and laboratory confirmation of suspected cases.16,17

The average age of the cases that motivated the investigation reveals a predominance of young men and women, as recorded in other countries.4,5,10,19 The concentration in São Paulo is explained by the location of the Brazilian
Table 3  Degree of kinship and outcome of IVCT in 92 relatives investigated.

| Kinship       | n  | MHS | MHSh | MHSc | MHN |
|---------------|----|-----|------|------|-----|
| Mother        | 10 | 4   | 4    | 0    | 2   |
| Father        | 11 | 7   | 4    | 0    | 0   |
| Brothers      | 26 | 14  | 7    | 3    | 2   |
| Children      | 10 | 4   | 1    | 0    | 5   |
| Uncles        | 7  | 5   | 1    | 1    | 0   |
| Nephews       | 15 | 3   | 7    | 2    | 3   |
| Cousins       | 12 | 2   | 0    | 3    | 7   |
| Grandchild    | 1  | 1   | 0    | 0    | 0   |
| Total (%)     | 92 | 40  | 24   | 9    | 19  |

MHN, non-susceptible to malignant hyperthermia; MHS, susceptible to malignant hyperthermia with response to halothane and caffeine; MHSc, susceptible to malignant hyperthermia with response only to caffeine; MHSh, susceptible to malignant hyperthermia with response only to halothane; n, number; IVCT, in vitro contracture test in response to halothane and caffeine.

MH Hotline and the referral center for investigation, as well as the mandatory notification of MH in São Paulo. Since 1990, the MH Hotline has guided health professionals about MH 24 h a day via telephone (+55-11-55759873). Most of the cases requiring investigation had a MH crisis, either during or within 3 h after the end of the anesthesia. It is worth noting that there is a wide variation between the onset of anesthesia and the onset of the HM crisis, a cause for concern since the delay in diagnosis/treatment is associated with increased morbidity and mortality. MH crises had similar characteristics to that described, with the exception of the low rate of notification of hypercarbia, due to the absence of routine monitoring with capnography during anesthesia at these events.

MH crises were treated according to current guidelines, except for administration of the specific antidote dantrolene. Its registration with ANVISA (Brazilian Health Regulatory Agency) occurred in 1997 and, despite the Brazilian Federal Medical Council recommendation for its availability in places where halogenates/succinylcholine are used, the obligation is regulated by law in few Brazilian states. The mortality in Brazil, up to one-fourth of patients, is still high compared to other countries, despite the reduction (not significant) in the number of deaths after the beginning of the legislation. A study of MH with the members of the Brazilian Society of Anesthesiology (SBA) in 1989 reported 49 cases of MH, with 51% mortality (none of them received dantrolene) and referral of only six of the 24 survivors for investigation.

Among the phenotypic changes of cases requiring investigation, we highlight osteoarticular alterations and dysmorphisms (pectus carinatum, scoliosis, crooked foot, umbilical hernia, cryptorchidism), also described in other series and that may increase MH suspicion. In almost a third of the cases there were personal/family history that would raise suspicion of MH and indicate the non-administration of triggering agents during anesthesia. In addition, previous anesthesia without complications, present in one-third of the sample requiring investigation, does not exclude MH susceptibility.

Among the cases that motivated investigation, there were patients with CCD myopathy (central core disease) who are usually monitored by neurologists/neuropediatricians and should be regarded as susceptible to MH and anesthetized with all precautions to avoid contact with triggering agents, including washing out residual halogenated agents from the anesthetic machine. Among the cases requiring investigation, idiopathic hyperCKemia also occurred, which is usually detected by clinicians and has several differential diagnoses. The so-called human stress syndrome, or awake MH, would correspond to the occurrence of hypermetabolism symptoms suggestive of MH in situations of stress (infection, physical exertion, high ambient temperature), even without contact with triggering halogenated and succinylcholine agents. Muscle hypertrophy without apparent reason may be one of the MH susceptibility expression forms. Normally, NMS is not related to MH, its pathophysiology is linked to decreased cerebral dopamine as proven by neuroleptics. However, rare patients with NMS have recurrent crises and neuromuscular complaints, such as myalgia and cramps, and have characterized atypical presentations that may be related to associated underlying diseases.

IVCT – in vitro contracture test

The gold standard IVCT investigation showed positivity of nearly 100% in patients requiring investigation, with only one patient in whom MH susceptibility was excluded. This may be due to the fact that only patients with a more severe/typical clinical condition are referred for investigation and/or detailed/multidisciplinary evaluation of each patient referred before IVCT, which allowed the exclusion of suspected MH in almost 10% of referrals. Among the relatives investigated, almost 80% had positive tests for MH, above the 60% described in Europe, which could result from the selection of first-degree relatives with muscular complaints/dysmorphisms. The frequency of Ryanodine gene mutation may be higher in Brazil, a fact corroborated by the greater frequency of recessive forms of CCD myopathy in Brazil and a higher frequency of MH crisis in a
However, MH is still underreported in Brazil: even considering the lowest frequency of MH reported in other countries (1:50,000 anesthesia in adults), Silva et al. estimated at least 77 crises/year in Brazil in 2009.28 A greater number of notification and disclosure of MH in Brazil is required, with training of surgical center teams to attend to this emergency.

The presence of a contracture above the 0.2 g threshold in IVCT, either for halothane or caffeine, or the two substances used independently, has a positive response and susceptibility to MH, indicating avoidance of halogenates and succinylcholine. The importance of discriminating patients with a IVCT response to the two substances (halothane and caffeine) is due to the fact that these patients are preferentially chosen for genetic study in search of new genes or binding studies.3 In addition, the threshold and intensity of contracture in response to caffeine showed a correlation with the presence of mutations in the ryanodine gene.1,2

Conclusion

MH crises resembled those described in other countries, but with a frequency lower than that estimated.

Funding

Research protocol 90/95 FMUSP; CEP 0970/08 Unifesp; Fapesp, Capes – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Brasil – financing code 001. CNPq.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2018.09.009.

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