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CASE REPORTS / CASE SERIES

Fatal awake malignant hyperthermia episodes in a family with malignant hyperthermia susceptibility: a case series

Épisodes fatals d'hyperthermie maligne sans anesthésie dans une famille souffrant desusceptibilité à l'hyperthermie maligne : une série de cas

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Abstract

Purpose *The present report of two fatal awake malignant hyperthermia (MH) episodes in an MH susceptible (MHS) family is intended to raise awareness among medical personnel and MHS individuals to the possibility of life-threatening non-anesthesia-triggered MH episodes and to provide a strong incentive for development of effective preventive measures.*

Clinical features *Two young athletic males (28 and 16 yr old), members of the same extended family with a history of anesthesia-related MH episodes and deaths, succumbed ten years apart on two different continents, with symptoms unrelated to anesthesia but strikingly similar to typical anesthetic-induced MH. Both suffered an abrupt surge in body temperature, tachycardia, tachypnea, muscle rigidity, hyperkalemia, and respiratory and metabolic acidosis. Despite aggressive resuscitation attempts, both developed cardiac arrest and died shortly upon arrival to hospital emergency departments. Autopsy analyses were negative for drugs, alcohol, or bacterial infection. Individual and familial genetic analyses revealed a novel, potentially pathogenic RYR1 variant (p.Gly159Arg) that co-segregates with the MHS phenotype in the family. Both fatal awake MH episodes are hypothesized to have been triggered by physical exertion compounded with a febrile illness that in one case was due to influenza type A.*

Conclusions *Life-threatening awake MH episodes may develop in some MHS individuals in the absence of anesthetic triggers. Potential triggers can be physical exertion in combination with a febrile illness. Malignant hyperthermia susceptible patients are recommended to be vaccinated against flu and restrict physical activities when febrile, wear an MH alert bracelet, and inform medical personnel of their MH history. Oral dantrolene is suggested to be available to MHS patients for administration with the early signs of awake MH.*

Résumé

Objectif *Ce compte-rendu de deux épisodes fatals d'hyperthermie maligne (HM) survenus en communauté, sans anesthésie, dans une famille susceptible à l'HM*

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(SHM) a pour but premier de conscientiser le personnel médical et les personnes SHM quant au risque d'épisodes d'HM potentiellement fatals et non déclenchés par l'anesthésie. Notre deuxième objectif est d'encourager fortement la mise au point de mesures préventives efficaces.

Éléments cliniques *Deux jeunes hommes sportifs (28 ans et 16 ans), membres de la même famille élargie ayant des antécédents d'épisodes d'HM et de décès liés à l'anesthésie, sont décédés à dix ans d'écart, sur deux continents, de symptômes non liés à l'anesthésie mais présentant une ressemblance frappante à une crise typique d'HM induite par l'anesthésie. Les deux hommes ont souffert d'une hausse rapide de leur température corporelle, de tachycardie, de tachypnée, de rigidité musculaire, d'hyperkaliémie et d'acidose respiratoire et métabolique. Malgré des tentatives vigoureuses de réanimation, les deux sont tombés en arrêt cardiaque et sont décédés peu après leur arrivée à l'urgence. Les analyses d'autopsie étaient négatives en ce qui touchait aux drogues, à l'alcool et aux infections bactériennes. Les analyses génétiques individuelles et familiales ont révélé une nouvelle variante du gène RYR1 potentiellement pathogène (p.Gly159Arg) qui est hérité en co-ségrégation avec le phénotype de SHM dans cette famille. On pense que ces deux épisodes fatals d'HM en éveil ont été provoqués par un effort physique combiné à une maladie fébrile qui, dans l'un des cas, était due à une influenza de type A.*

Conclusion *Des épisodes fatals d'HM en éveil peuvent survenir chez certaines personnes SHM en l'absence de déclencheurs anesthésiques. L'effort physique combiné à une maladie fébrile pourrait constituer un déclencheur potentiel. Les patients susceptibles à l'hyperthermie maligne sont encouragés à se faire vacciner contre l'influenza et à limiter leurs activités physiques lorsqu'ils souffrent de fièvre, à porter un bracelet d'alerte d'HM, et à informer le personnel médical de leurs antécédents d'HM. On suggère que du dantrolène par voie orale soit mis à la disposition des patients SHM afin d'être administré dès les premiers signes d'HM en éveil.*

Malignant hyperthermia (MH), an inherited disorder of skeletal muscle, presents as a hypermetabolic reaction triggered by volatile anesthetics and/or succinylcholine. Mutations in the *RYR1*, *CACNA1S,* or *STAC3* genes are associated with MH.[1] An uncontrolled release of calcium ions from the sarcoplasmic reticulum into the myoplasm may lead to severe muscle contracture, resulting in excessive heat production, rhabdomyolysis, disseminated intravascular coagulopathy (DIC), cardiac arrest, and death.[2,3] Increased awareness, advances in anesthesia monitoring, and availability of dantrolene, the only drug for the treatment of MH, have substantially reduced the mortality and morbidity of anesthesia-induced MH.[4]

Nevertheless, a growing body of evidence suggests that in some MH susceptible (MHS) patients, the signs of MH may manifest outside of the operating room and in the absence of anesthetic triggers. These potentially fatal episodes are referred to as "awake" MH or MH-like episodes.[5-7] The awake episodes are rare, and present with non-specific symptoms ranging from hyperthermia, muscle cramps, exertional pain, and rhabdomyolysis to a life-threatening hypermetabolic reaction in physically fit and seemingly healthy individuals often without a personal or family history of MH, which makes the diagnosis challenging.[7-10]

We report two fatal cases of awake MH episodes in one extended family with a strong history of anesthetic-induced MH episodes and deaths demonstrating the close connection between anesthesia-induced MH and awake MH episodes. This report is intended to raise awareness among patients and medical personnel (anesthesiologists, emergency department [ED], intensive care physicians, and nurses) to the possibility of life-threatening MH episodes that may develop in MHS individuals in the absence of general anesthesia.

Case description

Informed consent for this report was obtained from the relevant family members.

Case A

A 28-yr-old athletic male (III.2 in Fig. 1) presented to the ED of an Australian hospital in summer 2008 with a sinus tachycardia of 170 beats·min^{-1}, severe bilateral leg weakness, high fever (tympanic temperature, 39.2°C), and diaphoresis. He had a two-day history of a febrile illness with no other significant past medical history. The evening prior to the crisis he had been dancing at a party, where he did not consume any drugs or alcohol (as confirmed on a subsequent toxicology screen). At the ED, adenosine and metoprolol were used to treat the tachycardia with minimal response. He developed what looked like a tonic-clonic seizure with increased muscle tone, which was treated with an intravenous benzodiazepine. With an increase in core temperature to 40.2°C, a drop of systolic blood pressure (BP) from 100 mmHg to 60 mmHg, and a heart rate (HR) of 160 beats·min^{-1}, he progressed to pulseless electrical activity, which was treated according to the Advanced

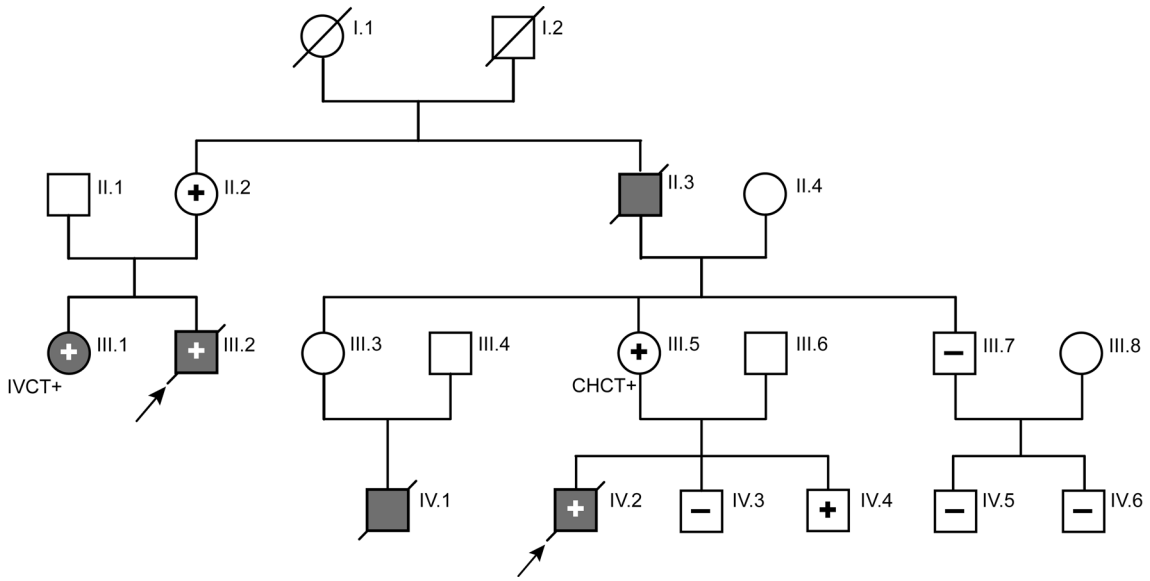

Fig. 1 Pedigree of the malignant hyperthermia (MH) family with two fatal awake episodes. Arrows indicate individuals III.2 and IV.2 who suffered fatal awake episodes. Individuals II.3 and IV.1 developed a fatal MH reaction under general anesthesia. Individual III.1 survived an anesthetic-induced MH episode and was diagnosed MHS by *in vitro* contracture test (IVCT+). Individual III.5 was diagnosed malignant hyperthermia susceptible by caffeine halothane contracture test (CHCT+). Signs in the centres depict individuals who were genetically tested for the p.G159R RYR1 variant. The plus and the minus signs indicate the presence and the absence of the variant, respectively

Cardiovascular Life Support (ACLS) guidelines. He was intubated using succinylcholine (he had not communicated his family history of MH and he was not wearing any alerts) after which increased muscle tone and jaw muscle rigidity were noted. Despite resuscitation attempts, he remained pulseless; a venous blood sample taken three minutes after the cardiac arrest revealed severe acidosis (pH, 6.62; partial pressure of carbon dioxide (P_{CO2}), 217 mmHg; lactate, 25 mmol·L^{-1}; K^+, 7 mmol·L^{-1}; base excess, -28 mmol·L^{-1}; and creatinine kinase (CK), 1392 IU·L^{-1}). He was pronounced dead less than 90 min after ED admission. Post mortem genetic testing revealed a novel heterozygous *RYR1* variant, c.475G>A (p.Gly159Arg).

Seven years later, a similar fatal incident occurred with another family member (case B).

Case B

A 16-yr-old Canadian boy (IV.2 Fig. 1) with a family history of MH presented in December 2016 with fever (rectal temperature, 42.5°C), tachycardia (HR, 220 beats·min^{-1}) and breathing difficulty hours after developing mild flu-like symptoms. The boy was a physically fit soccer player; during the preceding two weeks, he had done vigorous weight lifting exercises. His past medical history included occasional dizziness with headaches, muscle weakness and tachycardia, and two short syncopal episodes at age 12 yr while walking in hot and humid weather, which recurred at age 15 yr during a flu-like illness. Both episodes resolved with rest and hydration, and cardiology assessment revealed no abnormalities.

At the time of admission to the ED, he was unconscious, hyperthermic, and hypotensive (BP, 73/30) with a HR of 200 beats·min^{-1} and an oxygen saturation of 92%. He suffered two tonic-clonic seizures that were treated with lorazepam, and minutes later developed a cardiac arrest (ventricular fibrillation). Resuscitation was initiated according to the ACLS guidelines. The attending anesthesiologist, aware of the MH family history, used rocuronium for intubation; at that time, severe rigidity of abdominal and calf muscles was noted. Despite active cooling with ice packs, cold intravenous fluid, and acetaminophen, his rectal temperature remained 42°C. His cardiac rhythm changed to asystole; blood work showed severe acidosis (pH, 6.75; P_{CO2}, 106 mmHg; partial pressure of oxygen, 41 mmHg; base excess, -17.2 mmol·L^{-1}; K^+, 8 mmol·L^{-1}; lactate, 24 mmol·L^{-1}; phosphate, 3.79 mmol·L^{-1}; CK, 1270 IU·L^{-1}) with onset of DIC with an activated partial thromboplasmin time of 38.1 sec in the presence of fibrin and platelet clumps on blood microscopy. His persistent hyperthermia, muscle rigidity, hemodynamic instability, severe acidosis, and DIC were all suggestive of an awake MH crisis, and about 60 min after initiation of resuscitation, a low dose intravenous dantrolene (20 mg) was administered with no response. The patient died two hours after his admission to the ED, approximately four hours after the onset of the crisis. This

episode can be classified as "almost certain MH" with clinical grading score of 61 if the MH clinical grading scale were applied.[11]

An autopsy showed pulmonary edema and mild to moderate hypoxic-ischemic encephalopathy that correlated with the two cardiac arrests; no other pathologic abnormalities were noted. Toxicology screening was negative for drugs and alcohol. Muscle histology revealed increased number of fibres with internal nuclei (30-35% of fibres) suggestive of an underlying myopathy. Blood and urine cultures were negative for bacterial infection but a nasopharyngeal swab was positive for influenza type A virus. Post mortem genetic screening revealed the same *RYR1* variant, p.Gly159Arg, that was identified in his deceased maternal relative (case A).

His clinically healthy mother was a carrier of the same *RYR1* variant and was diagnosed MHS by caffeine halothane contracture test (CHCT) (4.8 and 4.7 g contracture with 3% halothane and 2 mM caffeine, respectively). Her muscle histology (Fig. 2) showed mild myopathic changes with fibre size variability and internal nuclei in > 15% of fibres, type I fibre predominance, and cores in type I fibres. Despite these findings, she had no muscle-related complaints.

Family history of MH

Figure 1 shows the extended family tree related to the two cases, notable for two fatal (II.3 and IV.1) and one non-fatal (III.1) anesthesia-induced MH episodes. The grandfather of case B, allegedly a healthy man who was a bodybuilder in his youth, died in 1986 at the age of 49 during an operation for hernia repair (using volatile anesthesia). His death was attributed to an adverse reaction to anesthesia, although the diagnosis of MH was not made at the time. He was an obligate carrier of the p.Gly159Arg variant since his descendants (III.3 and III.5 in Fig. 1) as well as his sister (II.2) carried the same variant. Additionally, subject IV.1, a 12-yr-old cousin of case B, developed a fatal MH reaction upon induction for appendectomy in 2008.

The sister of case A (III.1) developed an MH reaction upon induction of isoflurane-based anesthesia for appendectomy in 1997. She developed tachycardia, hyperthermia of 39.2°C, and elevated P_{CO2}. In 2007, she had a positive *in vitro* contracture test (2.3 and 2.5 g contracture with 2% halothane and 2 mM caffeine, respectively) and was found to carry the familial *RYR1* variant, p.Gly159Arg.

Discussion

We describe two fatal cases of awake MH episodes in a family with a strong history of MH susceptibility associated with a potentially pathogenic *RYR1* variant. The clinical symptoms of these episodes—sudden onset of hyperthermia, tachycardia, tachypnea, skeletal muscle rigidity, profound metabolic and respiratory acidosis, and ensuing cardiac failure—reproduced the symptoms of an anesthesia-induced MH reaction[12,13] despite having occured in the absence of any anesthetics. Both awake episodes were triggered by a combination of febrile illness (e.g., influenza type A) and physical exertion—i.e., dancing (case A) and weight lifting (case B). In case A, inadvertent administration of succinylcholine may have exacerbated the initial clinical presentation.

The concept that MHS individuals may develop life-threatening hypermetabolic reactions in the absence of anesthesia was first introduced over 40 years ago with reports of sudden unexplained non-anesthesia-related deaths in some MH families.[14,15] While different diagnoses may be possible in some of those cases, a link between awake MH episodes and anesthesia-induced MH reactions has been supported by further reports on exercise

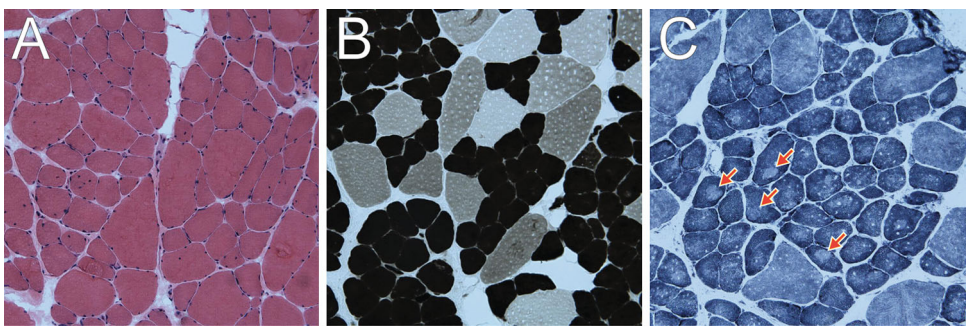

Fig. 2 Histologic stains of muscle biopsy samples from the family member III.5. A) Hematoxylin and Eosin staining reveals fibre size variability and multiple internalized nuclei in many fibres. B) ATPase assay (pH 4.2) shows type I fibre predominance (dark fibres) and type II fibre hypertrophy (light-stained fibres). C) Nicotinamide adenine dinucleotide-tetrazolium reveals cores (arrows) in type I fibres. Scale bar, 30 μm

and heat induced rhabdomyolysis and deaths, associated with *RYR1* variants.[6-8,16,17] The awake MH episodes are predominantly observed in children or physically fit young men who have been exposed either to excessive heat, extreme and unaccustomed exercise, flu-like illnesses, alone or in combination.[9] Of the above triggers, influenza A presents a particular concern as it has a highly aggressive onset with fast surge in the body temperature, accompanied by rhabdomyolysis.[18-20] Awake MH episodes are sporadic and in the majority of cases, the MH status of the patients was deduced retrospectively; only few hitherto published cases concerned individuals with personal or family history of MH.[16,17]

In contrast to previous reports, where the link between MH crises and awake MH episodes was difficult to prove, the cases reported here confirm the close connection between MH and the awake MH episodes. The novel *RYR1* variant, c.475G>A (p.Gly159Arg), identified in this family is a strong candidate for a causative MH mutation. It co-segregates across three generations with the MHS phenotype in the extended family and is also implicated in both fatal awake MH episodes. The variant is novel (only reported in this family) and is absent from human genetic variation databases. It results in the substitution of the highly conserved uncharged glycine 159 with a positively charged arginine. It is predicted to be damaging by *in silico* prediction tools. Moreover, the p.Gly159 amino acid residue maps to the highly conserved region of the N-terminal domain crucial for the RyR1 channel function. Functional studies and high-resolution modeling of RyR1 showed that the MH-associated mutations adjacent to p.Gly159Arg render the RyR1 channels more sensitive to agonists and lessen thermal stability of the RyR1, thereby conferring a temperature-sensitive phenotype to mutation carriers.[21,22]

As *RYR1*-related awake MH episodes share genetic changes with anesthetic-induced MH,[23] dantrolene may be of value for their treatment. Dantrolene stabilizes the closed state of the RyR1 channel, thereby inhibiting excessive Ca^{2+} release via RyR1 and averting a potential hypermetabolic reaction.[24] Oral dantrolene has successfully been used off-label for many MHS patients and has been shown to be effective in preventing or diminishing the severity of muscle-related symptoms.[8,17,25,26] Dantrolene has also effectively been used in the treatment of conditions symptomatically similar to MH, such as neuroleptic malignant syndrome,[25] exercise-induced rhabdomyolysis and muscle pain,[8,27] exertional heat stroke,[28] and alcohol and drug intoxication.[9,29]

Successful management of MH relies on early diagnosis and aggressive treatment.[30] In case B, ineffectual use of dantrolene can be explained by the fact that it was administered at the advanced stages of the crisis (after the second cardiac arrest), emphasizing once again the need for early awake MH diagnosis and rapid dantrolene access and administration.

Awake MH episodes should be included in differential diagnosis in the ED and intensive care unit care of patients with hemodynamic instability and hypermetabolism, especially if the patients are members of MH families. Considering that most awake MH episodes are exercise and/or heat-related, and in the face of the growing popularity of outdoor sports, increased number of heat waves due to global warming, and recurrent influenza A and B pandemics, such episodes may occur more frequently. Failure to devise effective preventive measures may come at a high cost to human lives.

Malignant hyperthermia susceptible patients are recommended to i) get vaccinated against influenza type A and B, ii) be aware of symptoms of exertional myalgia when engaged in physical activities in hot and humid weather, and avoid very strenuous and prolonged physical exercise, particularly in a hot environment, and iii) wear a medical alert bracelet and inform medical personnel of MH family history. Additionally, to prevent further fatalities caused by inevitable delays in administration of dantrolene, oral dantrolene supplies may be offered to MHS patients and their relatives, so that it can be administered at the earliest possible time should an awake MH episode be suspected.[26-28] It is our hope that these case reports will help reverse the view on MH exclusively as an "anesthetic" disorder and provide a strong incentive for developing efficient guidelines aimed at early recognition and treatment of awake MH episodes.

Conflicts of interest None declared.

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References

1. *Riazi S*, *Kraeva N*, *Hopkins PM*. Malignant hyperthermia in the post-genomics era: new perspectives on an old concept. Anesthesiology 2018; 128: 168-80.

2. *Larach MG*, *Brandom BW*, *Allen GC*, *Gronert GA*, *Lehman EB*. Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006: a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. Anesthesiology 2008; 108: 603-11.
3. *Jones PM, Allen BN, Cherry RA, et al*. Association between known or strongly suspected malignant hyperthermia susceptibility and postoperative outcomes: an observational population-based study. Can J Anesth 2018; DOI: https://doi.org/10.1007/s12630-018-1250-8.
4. *Riazi S*, *Kraeva N*, *Muldoon SM*, *et al*. Malignant hyperthermia and the clinical significance of type-1 ryanodine receptor gene (RYR1) variants: proceedings of the 2013 MHAUS Scientific Conference. Can J Anesth 2014; 61: 1040-9.
5. *Denborough M*. Malignant hyperthermia. Lancet 1998; 352: 1131-6.
6. *Brown RL*, *Pollock AN*, *Couchman KG*, *et al*. A novel ryanodine receptor mutation and genotype-phenotype correlation in a large malignant hyperthermia New Zealand Maori pedigree. Hum Mol Genet 2000; 9: 1515-24.
7. *Lavezzi WA*, *Capacchione JF*, *Muldoon SM*, *et al*. Case report: Death in the emergency department: an unrecognized awake malignant hyperthermia-like reaction in a six-year-old. Anesth Analg 2013; 116: 420-3.
8. *Potts LE*, *Longwell JJ*, *Bedocs P*, *et al*. Improving awareness of nonanesthesia-related malignant hyperthermia presentations: a tale of two brothers. A A Case Rep 2014; 3: 23-6.
9. *Dlamini N*, *Voermans NC*, *Lillis S*, *et al*. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. Neuromuscul Disord 2013; 23: 540-8.
10. *Butala B*, *Brandom B*. Muscular body build and male sex are independently associated with malignant hyperthermia susceptibility. Can J Anesth 2017; 64: 396-401.
11. *Larach MG*, *Localio AR*, *Allen GC*, *et al*. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology 1994; 80: 771-9.
12. *Larach MG*, *Gronert GA*, *Allen GC*, *Brandom BW*, *Lehman EB*. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. Anesth Analg 2010; 110: 498-507.
13. *Riazi S*, *Kraeva N*, *Hopkins PM*. Updated guide for the management of malignant hyperthermia. Can J Anesth 2018; 65: 709-21.
14. *Wingard DW*. Letter: Malignant hyperthermia: a human stress syndrome? Lancet 1974; 2: 1450-1.
15. *Britt BA*. Combined anesthetic- and stress-induced malignant hyperthermia in two offspring of malignant hyperthermic-susceptible parents. Anesth Analg 1988; 67: 393-9.
16. *Tobin JR*, *Jason DR*, *Challa VR*, *Nelson TE*, *Sambuughin N*. Malignant hyperthermia and apparent heat stroke. JAMA 2001; 286: 168-9.
17. *Groom L*, *Muldoon SM*, *Tang ZZ*, *et al*. Identical de novo mutation in the type 1 ryanodine receptor gene associated with fatal, stress-induced malignant hyperthermia in two unrelated families. Anesthesiology 2011; 115: 938-45.
18. *Wakabayashi Y*, *Nakano T*, *Kikuno T*, *Ohwada T*, *Kikawada R*. Massive rhabdomyolysis associated with influenza A infection. Intern Med 1994; 33: 450-3.
19. *Ayala E*, *Kagawa FT*, *Wehner JH*, *Tam J*, *Upadhyay D*. Rhabdomyolysis associated with 2009 influenza A(H1N1). JAMA 2009; 302: 1863-4.
20. *Molenaar JP*, *Voermans NC*, *van Hoeve BJ*, *et al*. Fever-induced recurrent rhabdomyolysis due to a novel mutation in the ryanodine receptor type 1 gene. Intern Med J 2014; 44: 819-20.
21. *Kimlicka L*, *Lau K*, *Tung CC*, *Van Petegem F*. Disease mutations in the ryanodine receptor N-terminal region couple to a mobile intersubunit interface. Nat Commun 2013; 4: 1506.
22. *Murayama T*, *Kurebayashi N*, *Yamazawa T*, *et al*. Divergent activity profiles of type 1 ryanodine receptor channels carrying malignant hyperthermia and central core disease mutations in the amino-terminal region. PLoS One 2015; 10: e0130606.
23. *Kraeva N*, *Sapa A*, *Dowling JJ*, *Riazi S*. Malignant hyperthermia susceptibility in patients with exertional rhabdomyolysis: a retrospective cohort study and updated systematic review. Can J Anesth 2017; 64: 736-43.
24. *Krause T*, *Gerbershagen MU*, *Fiege M*, *Weisshorn R*, *Wappler F*. Dantrolene–a review of its pharmacology, therapeutic use and new developments. Anaesthesia 2004; 59: 364-73.
25. *Bamaga AK*, *Riazi S*, *Amburgey K*, *et al*. Neuromuscular conditions associated with malignant hyperthermia in paediatric patients: a 25-year retrospective study. Neuromuscul Disord 2016; 26: 201-6.
26. *Scalco RS*, *Voermans NC*, *Piercy RJ*, *Jungbluth H*, *Quinlivan R*. Dantrolene as a possible prophylactic treatment for RYR1-related rhabdomyolysis. Eur J Neurol 2016; 23: e56-7.
27. *Timmins MA*, *Rosenberg H*, *Larach MG*, *Sterling C*, *Kraeva N*, *Riazi S*. Malignant hyperthermia testing in probands without adverse anesthetic reaction. Anesthesiology 2015; 123: 548-56.
28. *Larner AJ*. Dantrolene for exertional heatstroke. Lancet 1992; 339: 182.
29. *Russell T*, *Riazi S*, *Kraeva N*, *Steel AC*, *Hawryluck LA*. Ecstacy-induced delayed rhabdomyolysis and neuroleptic malignant syndrome in a patient with a novel variant in the ryanodine receptor type 1 gene. Anaesthesia 2012; 67: 1021-4.
30. *Riazi S*, *Larach MG*, *Hu C*, *Wijeysundera D*, *Massey C*, *Kraeva N*. Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands. Anesth Analg 2014; 118: 381-7.