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MALIGNANT HYPERTHERMIA: A CASE REPORT

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ABSTRACT

Malignant hyperthermia manifests clinically as a hypermetabolic crisis when a malignant hyperthermia-susceptible individual is exposed to a volatile anesthetic such as halothane, isoflurane, enflurane, sevoflurane, or desflurane or depolarizing muscular blockers such as succinylcholine. The condition shows autosomal dominant inheritance with reduced penetrance, and is mostly associated with mutations resulting in abnormal ryanodine receptor type 1 or, more rarely, dihydropyridine receptors. Exposure to triggering agents may lead to unregulated passage of calcium from the sarcoplasmic reticulum into the intracellular space, resulting in an acute malignant hyperthermia crisis. Mortality from malignant hyperthermia in the United States was 16.9% in 2001 and 6.5% in 2005, but it is characterized by high morbidity. Therapy is based on suspension of the triggering agent and administration of dantrolene. Diagnosis is possible by biopsy using in vitro contraction tests or DNA screening for malignant hyperthermia. The authors present a case of malignant hyperthermia during myocardial revascularization through off-pump coronary artery bypass graft.

Keywords: *malignant hyperthermia, anesthesia, skeletal muscles, volatile anesthetic*

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Introduction

Malignant hyperthermia (MH) manifests clinically as a hypermetabolic crisis when an MH-susceptible individual is exposed to a volatile anesthetic such as halothane, isoflurane, enflurane, sevoflurane, or desflurane or depolarizing muscular blockers such as succinylcholine[1]. Brady et al. reported a prevalence of MH due to anesthesia in surgical patients as approximately 1:100000 surgical procedures in New York State[2]. However, the real incidence of MH is unknown. This figure is probably underestimated because unrecognized, mild, or atypical reactions occur because of variable penetrance of the inherited trait.

According to Rosero et al. mortality rates from MH in the United States were 16.9% in 2001 and 6.5% in 2005[3].

Episodes of anesthesia-induced MH are more common in men than in women (2:1)[4]. Approximately one third of the patients who develop acute MH have a previous uneventful exposure to triggering agents[5]. MH is one of the risk situations detailed in the Declaration of Helsinki on Patient Safety in Anesthesiology, so it is important that protocols should be put in place to manage this syndrome if it arises[6]. Here the authors present a case of MH during myocardial revascularization through off-pump coronary artery bypass graft (OPCABG).

Case Presentation

A 68-year-old man was hospitalized with a diagnosis of critical triple vessel coronary heart disease. His medical history was positive for prior

acute myocardial infarction, chronic obstructive pulmonary disease, and L4-L5 discopathy for which he had undergone a laminectomy a few years earlier. Allergies were not reported. At admission, the following parameter values were recorded: creatinine: 1.08 mg/dL (0.80-1.30), aspartate aminotransferase: 23 U/L (15-85), and alanine transaminase: 47 U/L (30-65). It was determined that the patient should undergo myocardial revascularization by OPCABG. To accomplish this, total balanced anesthesia was performed.

The following premedication was administered 30 min before intervention: cefazolin (1 g i.v.), midazolam (1 mg i.v.), ranitidine (50 mg), and trimeton (10 mg). For the induction phase, propofol (2 mg/kg bolus), midazolam (5 mg), continuous infusion of propofol (3 mg/kg/h), and sevoflurane (minimum alveolar concentration: 0.7) were used. For curarization, the following were administered: succinylcholine (1 mg/kg) and cisatracurium in continuous infusion at 1.5 gamma/kg/min. Finally, for analgesia, remifentanil (0.15 g/kg/min), acetaminophen (1 g) and ketorolac (30 mg) were used. During induction, curarization, ventilation, and intubation phases, no complications associated with anesthesia were detected and the patient maintained good respiratory and hemodynamic parameters. Mechanical ventilation was performed in volumetric mode (fractional inspired oxygen concentration: 65%, tidal volume: 600 mL, 15 breaths per min). Approximately 90 min after the start of surgery, significant alterations in the respiratory state were observed, with mechanical and manual ventilation being extremely difficult. High peak pressure (48 cm H_2O), high end-tidal carbon dioxide (70 mmHg), and low tidal volume (200 mL) suggested severe respiratory acidosis related to hypercarbia (pH 7.2, partial pressure of oxygen: 200, partial pressure of carbon dioxide: 86).

During this phase the patient maintained a good hemodynamic profile and a temperature of about 37.2°C. Physicians considered decurarization resulted in bronchospasms and administered cisatracurium, methylprednisolone, adrenaline s.c., theophylline, and magnesium sulfate without improvement. The possibility of MH was then considered.

The patient was administered dantrolene i.v. (2 mg/kg), sevoflurane was suspended, and respiratory circuits were replaced. A slow and gradual improvement in respiratory parameters was observed and less difficult mechanical ventilation with a tendency towards normalization of arterial blood gas analysis values were obtained until the end of the intervention. Progression in the immediate postoperative period was characterized by phases of mild respiratory acidosis with partial increase in lactates, for which dantrolene (1 mg/kg) was given. Muscle enzymes were re-evaluated, some of which exhibited very high values (myoglobin: 7866 ng/mL, creatinine kinase: 1365 U/L).

On the first postoperative day, the course was characterized by unstable hemodynamics, a febrile peak with a maximum temperature of 38.2°C, and difficulty in weaning from the ventilator with the need in the immediate post-extubation period of non-invasive ventilation with a continuous positive airway pressure helmet. On the fourth postoperative day, there were high values for muscle enzymes and significant increases in transaminases (aspartate aminotransferase: 4188 U/L, alanine transaminase: 2611 U/L, lactate dehydrogenase: 3462 U/L, creatinine: 3.9 mg/dL) with oliguria, so high doses of diuretics i.v. were administered. In the following days, the patient responded positively to therapy with normalization of hemodynamic, respiratory, diuresis, and hematochemical parameters. At discharge, the patient was advised to go to the MH center to undergo in vitro contracture test. The test conducted according to European Malignant Hyperthermia Group guidelines for the investigation of MH susceptibility[7] gave a positive result.

Discussion

MH-susceptible patients have genetic skeletal muscle receptor abnormalities, allowing excessive calcium accumulation in the presence of certain anesthetic triggering agents. Very little is known about the specific mechanisms by which anesthetics interact with these abnormal receptors to trigger an MH crisis. However, MH-susceptibility, which is autosomal dominant with reduced penetrance, is mostly associated with mutations that result in abnormal ryanodine receptor type 1 or, more rarely, dihydropyridine receptors[8]. Exposure to triggering agents in these patients may lead to unregulated passage of calcium from the sarcoplasmic reticulum into the intracellular space, resulting in an acute MH crisis. Such susceptibility, as in the current case, can be investigated in the patient and family through a biopsy in vitro contracture test or DNA screening for MH[9]. In any case, it is crucial to identify patients with possible susceptibility to the

preoperative phase by asking whether there is a family history of MH, whether there have been unexpected deaths or complications from anesthesia in any blood relative, if the patient has a muscular disorder, or if the patient has had episodes of high fever after surgery. However, some patients have previous uneventful exposures to triggering agents[8].

The timing of the onset of clinical signs varies, usually 45-55 min after exposure to triggering agents[1]. During an episode of MH, clinical manifestations are due to cellular hyper-metabolism, leading to sustained muscular contraction and breakdown (rhabdomyolysis), anaerobic metabolism, acidosis, and their sequelae. Early manifestations are metabolic (elevated end-tidal carbon dioxide, increased oxygen consumption, hyperkalemia after succinylcholine, respiratory acidosis, sweating), cardiovascular (muscular rigidity), muscular (masseter spasm), and cardiac arrhythmias (unstable arterial pressure). Late manifestations are hyperkalemia, a rapid increase in core body temperature, grossly elevated blood creatine phosphokinase, grossly elevated blood myoglobin, dark-colored urine due to myoglobinuria, severe cardiac arrhythmias, cardiac arrest, and disseminated intravascular coagulation[1,10].

According to European Malignant Hyperthermia Group guidelines, management of an MH crisis should immediately focus on stopping all trigger agents, hyperventilating with 100% oxygen at high flow, changing to a non-trigger anesthesia, asking the surgeon for termination/postponement of surgery, and disconnecting the vaporizer (10). A useful drug is dantrolene (2 mg/kg i.v.; 20 mg ampules are mixed with 60 mL sterile water). The patient should be monitored (oxygen saturation, ECG, non-invasive arterial pressure, temperature, potassium, creatinine kinase, arterial blood gases, myoglobin, glucose, and renal and hepatic functions) (10). Rosero et al. reported that mortality from MH in the United States was 16.9% in 2001 and 6.5% in 2005[3].

However, it is important to highlight that morbidity from MH, such as muscle pain, prolonged intensive care admission, neurological injury, renal injury, and cardiac rhythm abnormalities, is still very high and a full recovery from an MH episode could take many months. From a medico-legal point of view, cases of MH can be complex. Assessment usually focusses on the health of the deceased prior to death, or if the patient has survived, examination of the outcome as well. With regard to medical responsibility, consideration should be given to the fact that, although rare, MH is a predictable pathology, but the predictability of the disease must be assessed on a case-by-case basis.

References

1) Brandom BW, Callahan PM. Malignant hyperthermia. An Update. Advances in Anesthesia 2015; 33: 113-128.
2) Brady JE, Sun LS, Rosenberg H, Li G. Prevalence of malignant hyperthermia due to anesthesia in New York State, 2001 - 2005. Anesthesia & Analgesia 2009; 109(4): 1162-1166.
3) Rosero EB, Adesanya AO, Timaran CH, Joshi GP. Trends and Outcomes of Malignant Hyperthermia in the United States, 2000 to 2005. Anesthes 2009;1 10(1):89-94.
4) Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. Orphanet J Rare Dis 2015; 10: 93.
5) Bendixen D, Skovgaard LT, Ording H. Analysis of anaesthesia in patients suspected to be susceptible to malignant hyperthermia before diagnostic in vitro contracture test. Acta Anaesthesiol Scand 1997; 41: 480-484.
6) Kollmann-Camaiora A, Alsina E, Dominguez A, del Blanco B, Yepes MJ, et al. Clinical protocol for the management of malignant hyperthermia. Rev Esp Anestesiol Reanim 2017; 64(1): 32-40.
7) Hopkins PM, Rüffert H, Snoeck MM, Girard T, Glahn KPE, et al. European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. Br J Anaesth 2015; 115 (4): 531-539.
8) Green Larach M, 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. Anesthes 2008;108(4):603-611.
9) Halsall PJ, Ellis FR. Malignant hyperthermia. Anaesthesia and Intensive Care Medicine 2005; 6(6): 192-194.
10) Glahn KPE, Ellis FR, Halsall PJ, Muller CR, Snoeck MMJ, et al. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. BJA 2010; 105(4): 417-420.

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