

## CASO CLÍNICO

# Malignant Hyperthermia: A Case Report

## Hipertermia Maligna: Um Caso Clínico

Mara Sousa<sup>1\*</sup>, Rita Peixoto<sup>1</sup>, Rui Silva<sup>1</sup>, Luísa Guedes<sup>1</sup>

### Afiliação

<sup>1</sup>Department of Anaesthesiology, Centro Hospitalar Universitário de São João, Porto, Portugal.

### Keywords

Anesthesia; Dantrolene/therapeutic use; Malignant Hyperthermia; Neuromuscular Depolarizing Agents/adverse effects; Succinylcholine/adverse effects

### Palavras-chave

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## ABSTRACT

Malignant hyperthermia (MH) is a very rare inherited disorder. The incidence of MH is 1: 100 000 although the prevalence of susceptibility to MH is estimated at 1:2000 to 1:3000. MH has a mortality rate of 9.5%. MH is an autosomal dominant disorder and three genes account for the genetic basis of 70% of the patients - RYR1, CACNA1S and STAC3. MH is characterized by an increased body metabolism with hyperthermia, increased carbon dioxide production, skeletal muscle rigidity along with rhabdomyolysis, hyperkalaemia and acidosis with hyperlactacidaemia. These occur when a MH-susceptible individual is exposed to some known triggers such potent volatile anaesthetics and succinylcholine. We present a case report of MH in 22-year-old male ASA II, without any personal or familial MH susceptibility known, admitted to elective dental extraction who suffered a MH crisis. The patient was treated for MH and demonstrated a significant clinical improvement with the administration of dantrolene.

## RESUMO

A hipertermia maligna (HM) é uma doença genética muito rara. A sua incidência é de 1:100000, embora a prevalência de suscetibilidade à doença seja estimada em 1:2000 a 1:3000. A HM tem uma taxa de mortalidade de 9,5%. Trata-se de um distúrbio autossómico dominante e 3 genes são responsáveis por 70% dos casos - RYR1, CACNA1S e STAC3. Caracteriza-se por um aumento do metabolismo corporal com hipertermia, produção aumentada de dióxido de carbono, rigidez músculo-esquelética, rabdomiólise, hipercalemia e acidose com hiperlactacidemia.

A crise de HM acontece quando indivíduos suscetíveis são expostos a determinados *triggers* como os anestésicos voláteis e a succinilcolina. Apresentamos um caso clínico de um doente de 22 anos, sexo

masculino, ASA II, sem história pessoal ou familiar de suscetibilidade à HM conhecida, admitido para cirurgia eletiva de extração dentária, que apresentou uma crise de HM. O doente apresentou melhoria clínica significativa após a administração de dantroleno.

## INTRODUCTION

Malignant hyperthermia (MH) is a very rare inherited disorder with an autosomal dominant transmission pattern.<sup>1</sup> The overall incidence of MH is 1:100 000 although the prevalence of susceptibility to MH is estimated at 1:2000 to 1:3000.<sup>1</sup> Reactions develop more frequently in males than females (2:1) with all ethnic groups being affected.<sup>2</sup> The MH has predominance in children and young people (18.3 years).<sup>2</sup> There are some genes that have been definitely linked to MH susceptibility - RYR1, CACNA1S and STAC3.<sup>1,3,4</sup> Pathogenic variants in those genes are present in 70% of the patients investigated and the majority is found in the RYR1 gene.<sup>3</sup> All of these genes are involved in calcium metabolism at skeletal muscle (RYR1 encodes the skeletal muscle ryanodine receptor type I protein, the CACNA1S gene encodes the alpha-1S subunit of the T-tubular voltage-gated Ca<sup>2+</sup> channel and STAC3 is involved in several processes, including T-tubule organization and regulation of release of sequestered calcium ion into cytosol) so, signs and symptoms of MH are related to an uncontrolled release of intracellular Ca<sup>2+</sup> from skeletal muscle sarcoplasmic reticulum.<sup>1,3</sup> MH is characterized by an increased body metabolism with hyperthermia (heat production), increased oxygen consumption, increased carbon dioxide production, skeletal muscle rigidity (activation of muscle contraction) along with rhabdomyolysis, hyperkalaemia and acidosis with hyperlactacidaemia.<sup>1,2,4</sup> The most consistent signs are

Autor Correspondente/Corresponding Author:

Mara Sousa

Morada: Department of Anaesthesiology, Centro Hospitalar Universitário de São João, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal.

E-mail: maradiva.sousa@gmail.com

the elevation of  $\text{ETCO}_2$  in patients with  $\text{ETCO}_2$  monitoring and muscular rigidity.<sup>4</sup> These symptoms occur when a MH-susceptible individual is exposed to some known triggers such as potent volatile anaesthetics and to depolarizing muscle relaxant, succinylcholine.<sup>4</sup> Desflurane and sevoflurane are considered to be less potent triggers with a slower onset of MH.<sup>5</sup>

The diagnosis involves the *in vitro* contracture test (IVCT) on a muscle biopsy and genetic tests.<sup>3,6</sup> The IVCT is the gold standard for diagnosing MH.<sup>3</sup> This condition has a mortality rate of 9.5%.<sup>2</sup>

## CASE REPORT

We present a case report of a 22-year-old male, ASA Physical Status Classification System II, who was admitted to elective dental extraction. Patient had well-controlled asthma, without crisis within the last 6 months. Neither the patient nor his family had any history of anaesthetic complications or neuromuscular disorder. The routine preoperative laboratory results were within the normal values. In the intraoperative period the ASA standards for basic anaesthetic monitoring were used. Anaesthesia was induced with fentanyl (2  $\mu\text{g}/\text{kg}$ ) and propofol (2  $\text{mg}/\text{kg}$ ). Neuromuscular block was obtained with rocuronium (0.6  $\text{mg}/\text{kg}$ ). Laryngoscopy wasn't difficult and the patient was intubated without complications. Anaesthesia was maintained with 40% of oxygen: 60% of air and sevoflurane (age-corrected MAC 1) with boluses of rocuronium and fentanyl. At the beginning of the surgery there was some difficulty opening the mouth and a bolus of rocuronium was given. One hour after intubation the heart rate of the patient was increased from 60 to 115 beats per minute and we noticed a progressive rising in the end tidal of carbon dioxide ( $\text{ETCO}_2$ ). Initially minute ventilation was adjusted and circuit check and soda lime replacement were done, but  $\text{ETCO}_2$  continued to rise to a maximum of 98 mmHg. Patient auricular temperature also raised with maximum reading of 38.5°C and muscle rigidity was noted. MH was suspected so sevoflurane was stopped, a propofol infusion was started and patient was ventilated with 100% oxygen.

An arterial blood gas analysis was obtained, pH: 7.162,  $\text{PaCO}_2$ : 76.0 mmHg,  $\text{PaO}_2$ : 159 mmHg, lactate: 1.96 mmol/L and the base excess: -4.1 mmol/L. Surgeon was asked to finish surgery as soon as possible. We administered 60 mg (1  $\text{mg}/\text{kg}$ ) of dantrolene, 1g of paracetamol and 8.4% sodium bicarbonate 100 mL for correcting the acidosis. For decreasing the body temperature, active cooling was promptly initiated by applying ice packs on the neck, and axillary area.

We placed a Foley catheter for monitoring the hour urine output, a nasogastric tube and oesophageal temperature probe for continuous monitoring of patient's central temperature. Arterial cannulation was done to continuously monitor

the blood pressure and for the arterial blood gas analysis. One hour after the implementation of the first therapeutic measures the arterial blood gas analysis showed a pH of 7.406, a  $\text{PaCO}_2$  of 46.3 mmHg, a  $\text{PaO}_2$  of 614.4 mmHg and a base excess of 3.1 mM/L, lactate 1.11 mM/L. The central temperature was 37°C, blood pressure and heart rate were within the normal values. After reversal of neuromuscular block with 200 mg of sugammadex the patient was extubated and transferred to the post anaesthesia care unit (PACU). The patient stayed at PACU for 24 hours. Twelve hours after the initial MH crisis a bolus of 60 mg of dantrolene was administered. He complained about myalgia in lower limbs and masseter. Patient's temperature, blood pressure, heart rate and blood gas analysis were normalized during PACU stay. Laboratory data showed an elevation of serum myoglobin to a maximum of >12 000 ng/mL and serum creatinine kinase to a maximum of 39 772 u/L. The patient was discharged from the hospital five days after the onset of MH and sent to genetic study which confirm the pathogenic variant c.487 C>T on exon 6 from the *RYR1* gene.

## DISCUSSION

MH was first described in 1960 by Doctor Michael A. Denborough who investigated a family with a history of deaths related to anaesthesia and presented MH as a familial condition.<sup>7</sup> Since then we can find some MH case reports in literature. The incidence of MH in Portugal is unknown, with very few cases reported. We described the first MH case report in our hospital.

The clinical manifestations of MH vary from patient to patient, and most patients do not develop all signs of MH.<sup>8</sup> Many early signs of a MH crisis can present in various ways and MH may be confused with other medical conditions such as an inadequate depth of anaesthesia, thyroid crisis, pheochromocytoma, anaphylactic reaction, neuroleptic malignant syndrome and serotonin syndrome.<sup>4</sup> We know that the time of onset of a MH crisis can vary from minutes to several hours after induction, in our case it occurred nearly one hour after the induction of anaesthesia.<sup>1</sup> We used propofol, fentanyl, rocuronium bromide and sevoflurane. The first two are not triggers for MH and rocuronium bromide, which is a non-depolarizing muscle relaxant, is also safe for MH.<sup>4</sup> There are some reports of MH during sevoflurane anaesthesia.<sup>5</sup> Desflurane and sevoflurane are considered to be less potent triggers with a slower onset of MH as we could see in this patient.<sup>5</sup>

After recognizing the manifestations of MH, the specific protocol of our institution was put into practice. Sevoflurane was immediately stopped and changed for TIVA with propofol, hyperventilation with 100%  $\text{O}_2$  at high flow and dantrolene was administered.

Since the place where the episode occurred (stomatology

department) is not located in the main operation room, dantrolene was not immediately available. Nonetheless it was made available 15 minutes after the incident. This finding is extremely relevant since it is known that dantrolene should be administered as soon as possible because, although there is no defined maximum time interval for its administration, the risk of complications resulting from a MH crisis doubles at every 30 minutes of delay in its administration.<sup>9</sup>

We also provide symptomatic treatment, such as surface cooling strategies, acidosis treatment with hyperventilation and sodium bicarbonate administration. It has been reported that dantrolene infusions should be repeated until the cardiac and respiratory systems are stabilized and patients should be kept under clinical observation and monitored in the ICU or in a recovery unit for at least 24 hours.<sup>10</sup> In this case, with apparent clinical improvement and hemodynamic stability, it was decided to extubate the patient and transfer him to the PACU (levels 2 and 3 of care available), where he remained for 24 hours.

Prompt recognition of an MH crisis with immediate implementation of treatment is the key to a safe outcome,<sup>4</sup> therefore we reinforce the importance of the existence of an institutional protocol based on guidelines published by The European Malignant Hyperthermia Group (EMHG), for the detection and handling of an MH crisis. It is also important to mention that the Portuguese Society of Anaesthesiology recommends the existence, in all operating rooms, on a specific location accessible by all professionals, of standardized sets for the management of MH with performance flowcharts.

According to the EMHG report is of utmost importance that once a case of MH is suspected, the patient and their relatives should always be referred to a national MH centre for further investigation. Also, patients suspected of being MH-susceptible should undergo diagnostic testing using IVCT at a designated MH-laboratory.<sup>10</sup> Our patient was submitted to a molecular genetic screening test to detect a mutation in the *RYR1* gene, according to the indication of the genetic consultant. An anaesthesiology appointment was scheduled for the patient, where he was informed again about his condition and warned to always mention it, in order to avoid future events. We also registered the occurrence of this event on the internet database created by EMHG. In Portugal there is no identical database.

The authors conclude that the rarity of these events and the scarcity of reported cases are a limitation in the way this condition is managed. Early identification and treatment of MH are crucial for a better outcome. It is also important to develop effective measures promptly available in the context of the operating room. These measures could be applied at a national level and a notification system should be implemented.

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#### ORCID

Mara Sousa  <https://orcid.org/0000-0002-9573-7472>

Rita Peixoto  <https://orcid.org/0000-0001-7257-2655>

Rui Silva  <https://orcid.org/0000-0001-7921-2441>

Luísa Guedes  <https://orcid.org/0000-0001-5257-9550>

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## REFERENCES

1. Brandom BW, Callahan PM. Malignant Hyperthermia An Update. *Adv Anesth*. 2015; 33:113-28.
2. Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia: a review. *Orphanet J Rare Dis*. 2007;2:21.
3. Litman RS, Griggs SM, Dowling JJ, Riazzi S. Malignant hyperthermia susceptibility and related diseases. *Anesthesiology*. 2018;128:159-67. doi: 10.1097/ALN.0000000000001877.
4. Gupta PK, Hopkins PM. Diagnosis and management of malignant hyperthermia. *BJA Educ*. 2017;17:249-54.
5. Lee YS, Kim WY, Lee SH, Baek SM, Ok SJ, Kim JH, et al. A case of malignant hyperthermia during anesthesia induction with sevoflurane - A case report. *Korean J Anesthesiol*. 2010;59 Suppl(Suppl):S6-S8. doi: 10.4097/kjae.2010.59.S.S6.
6. Hopkins PM, Ruffert H, Snoeck MM, Girard T, Glahn KP, Ellis FR, et al. European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. *Br J Anaesth* 2015; 115:531-9. doi: 10.1093/bja/aev225.
7. Denborough MA, Forster JFA, Lovell RRH, Maplestone PA, Villiers JD. Anaesthetic deaths in a family. *Br J Anaesth*. 1960;34:395
8. Kim DC. Malignant hyperthermia. *Korean J Anesthesiol*. 2012; 63:391-401.
9. 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. doi: 10.1213/ANE.0b013e3181c6b9b2.
10. Glahn KP, Ellis FR, Halsall PJ, Müller CR, Snoeck MM, Urwyler A, et al. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. *Br J Anaesth*. 2010;105:417-20. doi: 10.1093/bja/aeq243.