

Malignant Hyperthermia: A Report of a Fatal Case in the Maternal and Pediatric ICU at Hassan II University Hospital, Fes

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Abstract

Review Article

Malignant hyperthermia (MH) is a rare but life-threatening pharmacogenetic disorder triggered by volatile anesthetics and depolarizing muscle relaxants in genetically susceptible individuals. This case report describes a MH crisis in a pediatric and maternal ICU setting at Hassan II University Hospital, Fès. The pathophysiology of MH involves excessive calcium release from the sarcoplasmic reticulum due to mutations in the ryanodine receptor (RYR1) gene, leading to uncontrolled hypermetabolism, muscle rigidity, and severe complications, including hypercapnia, hyperthermia, rhabdomyolysis, and cardiovascular instability. The early clinical sign: hypercapnia, tachycardia, and muscle rigidity warrant immediate recognition and prompt treatment with dantrolene to prevent mortality. Diagnosis relies on clinical presentation, genetic testing, and in vitro contracture testing. The case underscores the importance of perioperative vigilance, early diagnosis, and emergency preparedness in managing MH crises. Advances in molecular diagnostics have improved risk stratification, enabling preoperative identification of susceptible patients. Given the rarity of MH, continued medical education and protocol adherence are critical for anesthesiologists and intensivists. This report aims to enhance awareness and preparedness in anesthesia and critical care settings to mitigate the risks associated with this condition.

Keywords: Malignant hyperthermia, anesthesia complications, RYR1 mutation, dantrolene, hypermetabolism, critical care.

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I. INTRODUCTION

The malignant hyperthermia (MH) crisis is a rare event, and an old adage states that, on average, an anesthetist will encounter it only once during their career. The low incidence of malignant hyperthermia contributes to making this pathology all the more dangerous due to its lack of awareness [1]. This is aimed at maintaining the vigilance of medical and paramedical teams.

Indeed, the administration of all halogenated anesthetics and/or depolarizing neuromuscular blockers: succinylcholine, can trigger a crisis in an apparently healthy individual, a crisis that can lead to death in the absence of sufficiently early diagnosis and treatment. The mechanism of the crisis is a paroxysmal hypercatabolism induced in skeletal striated muscle by halogenated volatile anesthetics and/or depolarizing neuromuscular blockers, in individuals suffering from a genetic mutation.

The designation "MH" has persisted although hyperthermia is a late symptom of the crisis. This pharmacogenetic disorder of skeletal muscle is generally associated with mutations in the ryanodine receptor calcium channel (RyR1) of the sarcoplasmic reticulum (SR). MH crises triggered by anesthesia are observed not only in humans but also in other species, particularly certain breeds of pigs. The existence of this animal model has facilitated the understanding of the mechanism of the crisis, the discovery of an effective treatment (dantrolene), and the localization of the responsible genetic anomalies [2, 3].

II. PATHOPHYSIOLOGY:

a. Physiological excitation-contraction coupling [5]

The propagation of the action potential along the motor nerve to the endings of the nerve fibers leads to the release of acetylcholine at the neuromuscular junction, which acts on the postsynaptic receptors and causes depolarization of the sarcolemma (plasma membrane of the muscle cell). The depolarization is

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transmitted to the T-tubules, invaginations of the sarcolemma where the calcium mobilization complexes are located.

These complexes, also known as triads, are formed by the juxtaposition of a T tubule and two terminal cisternae of the sarcoplasmic reticulum (SR). The two ion channels responsible for excitation-contraction coupling are located in the triad, the dihydropyridine receptor (DHPR) in the plasma membrane of the T tubules and the ryanodine receptor (RYR1) in the membrane of the SR. The DHPR is a voltage-dependent calcium channel. Membrane depolarization causes its opening and the activation of the RYR1 receptor through physical and functional interaction with the DHPR.

The opening of the activated RYR1 channel allows the release of calcium contained in the sarcoplasmic reticulum, which leads to an increase in intracellular calcium levels that will be responsible for muscle contraction. When the muscle fiber is at rest, the interactions between the two contractile proteins, actin and myosin, are inhibited by the troponin complex. The increase in intracellular calcium concentration causes a lifting of this inhibition, the relative sliding of actin and myosin filaments, and the shortening of the sarcomeres that leads to muscle contraction. Relaxation occurs when the nerve stimulation stops, the calcium channels close, and calcium ions are reabsorbed into the sarcoplasmic reticulum by calcium-dependent ATPases (SERCA). The energy required for muscular work comes from three sources: creatine phosphate under the action of creatine phosphokinases (CPK).

Aerobic metabolism is highly efficient, producing 36 molecules of ATP for 1 molecule of glucose, and leads to a significant and immediate increase in oxygen consumption and carbon dioxide release. A percentage of the energy is dissipated as heat, resulting in an increase in body temperature. If the energy production by aerobic metabolism is insufficient, due to either excessively high muscle activity (sprinting) or prolonged activity (marathon), anaerobic metabolism is "engaged." It is much less efficient, producing only 3 molecules of ATP per molecule of glucose and releasing lactic acid [5].

A crisis of malignant hyperthermia occurs in individuals who most often present a genetic mutation of

the ryanodine calcium receptors or, more rarely, a mutation of the dihydropyridine receptors present on the sarcoplasmic reticulum of myocytes. These mutations (of which more than 40 are currently described) are responsible for excessive opening of calcium channels when exposed to triggering agents. The usual use of sevoflurane and desflurane in modern anesthesia often leads to a delayed clinical presentation compared to halothane and isoflurane, which were used previously. Currently, patients susceptible to malignant hyperthermia have already been exposed on average three times to triggering agents without clinical manifestation [8-10].

Patients at risk of malignant hyperthermia are considered to be those with congenital core myopathies and related myopathies associated with the RYR1 gene, individuals with unexplained chronic elevation of CPK, severe exercise-induced hyperthermia, or severe exercise-induced rhabdomyolysis. A history of neuroleptic malignant syndrome does not constitute a risk situation for anesthetic malignant hyperthermia [6].

b. Diagnosis [13].

The genetic mechanisms of MH sensitivity are primarily associated with pathogenic variations (mutations) in the RYR1 gene (encoding the ryanodine-sensitive Ca²⁺ channel of the sarcoplasmic reticulum) and, much more rarely, in the CACNA1S gene (encoding the voltage-dependent Ca²⁺ channel sensitive to dihydropyridine). Screening of the RYR1 gene can be performed on DNA extracted from peripheral blood either on targeted regions or on the entire exons.

Alternatively, the search for mutations can be conducted on the entire RYR1 transcript from a muscle fragment. RYR1 explorations show numerous variations that involve the replacement of one amino acid with another (missense), an event whose molecular consequences are difficult to predict, even with the assistance of software dedicated to predicting the pathogenicity of genetic variants. The European Malignant Hyperthermia Group (EMHG) has consequently issued recommendations on the interpretation of RYR1 variants (website www.emhg.org/genetics/). A list of recognized mutations responsible for MH is available on this website.

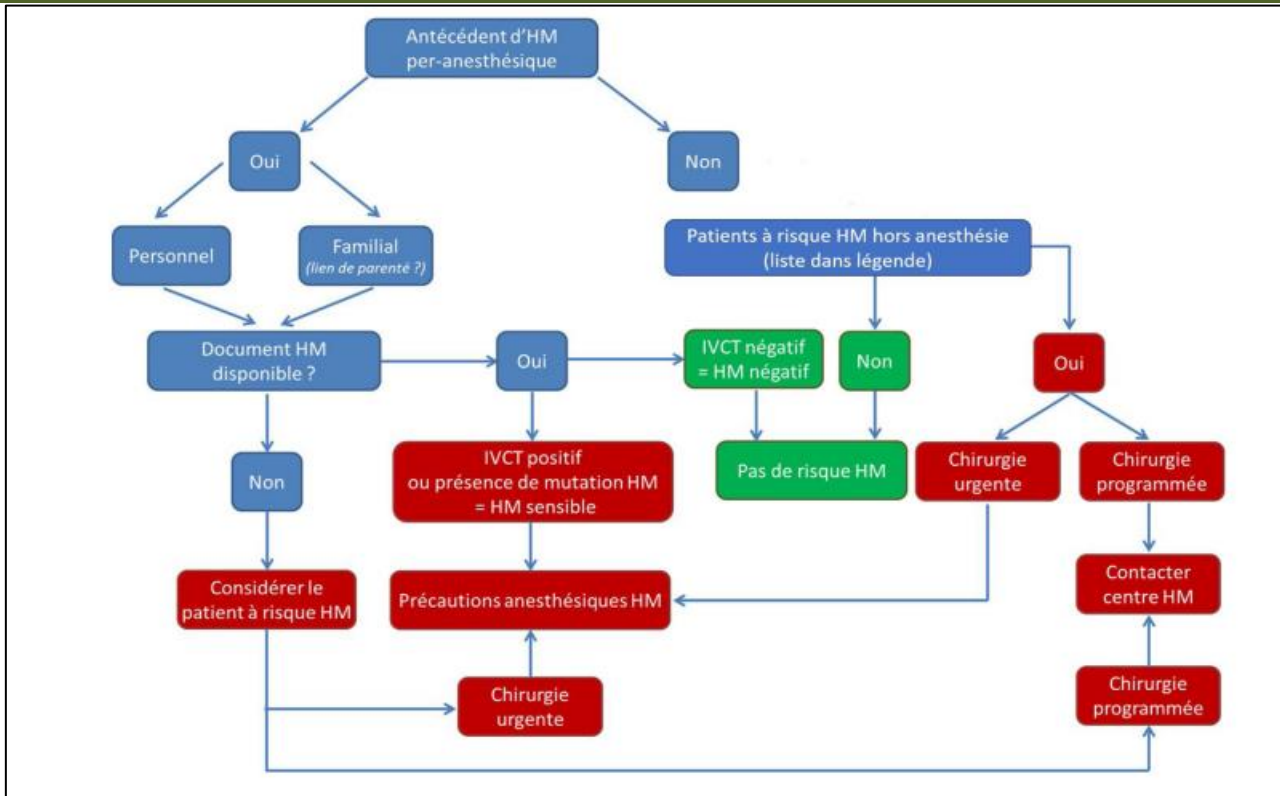


Figure 1: Screening for the risk of malignant hyperthermia in anesthesia consultation

HM: Hyperthermie Maligne; IVCT: In Vitro Contracture Tests

III. CLINICAL SIGNS OF MALIGNANT HYPERTHERMIA CRISIS [7]

Three groups of symptoms are observed indicating hypermetabolism, muscle rigidity, and muscle distress (rhabdomyolysis). The interval between anesthetic induction and the appearance of the first signs is highly variable. It is less than one minute in cases of induction with halogenated agents and succinylcholine. The interval can extend to several hours. It seems unlikely that a malignant hyperthermia crisis would begin in the postoperative period, after the cessation of the triggering agents.

1. Hypercapnia

The first sign of hypermetabolism is a significant increase in PetCO₂ observed on the capnograph. The increase in VO₂ is suggested by the decrease in FetO₂. The MH crisis does not cause early desaturation of arterial blood, due to the high level of FIO₂ used during anesthesia. Tachypnea may be indicative in a spontaneously ventilating patient, in response to hyperproduction of CO₂. Acidosis is initially hypercapnic, then progresses to mixed acidosis due to lactic acid accumulation. This is a sign of severity.

2. Tachycardia/ventricular arrhythmias

Tachycardia is almost constant but trivial, especially in pediatric anesthesia, and therefore non-specific. Ventricular arrhythmias, often associated with

hyperkalemia from rhabdomyolysis, are common but not constant. Signs of circulatory failure are late, as at the onset of the crisis, cardiac output is high in proportion to hypermetabolism.

3. Hyperthermia

Hyperthermia is usually delayed. It occurs earlier in children with lower body mass. The body temperature can reach 43 °C in fulminant forms just preceding death.

4. Muscle rigidity

Muscle rigidity is a specific but late and inconsistent sign. It is first observed at the level of the masseters (masseter spasm), as these muscles are very powerful and the limitation of mouth opening does not escape the anesthetist at the time of tracheal intubation. The rigidity then extends to the entire body. In the fulminant MH crisis, it is impossible to bend the arms and especially the legs, as this rigidity resists curarization.

5. Elevation of CPK

The signs of rhabdomyolysis must be systematically sought: early hyperkalemia, severe but transient; red urine due to the presence of myoglobin with a peak in blood between 2 and 4 hours; elevation of CPK levels in the blood with a maximum between 12 and 24 hours. The CPK level varies according to the duration and severity of the crisis and can reach up to 2000 times the normal value. Consideration must be given to the type of surgery, position, and any potential traumatic

context. It is essential to repeat the measurement during the first 48 hours, as a continued increase may reflect a delayed resumption of the MH crisis.

III.A Differential diagnosis

It presents with isolated signs suggesting MH. An isolated hypercapnia may indicate an accumulation of CO₂ following difficult intubation, CO₂ insufflation for laparoscopy, a circuit issue, or peri- or postoperative hypoventilation. An isolated hyperthermia prompts the investigation of excessive warming due to a warming blanket, particularly in children, or an infectious syndrome. An isolated rhabdomyolysis diagnosed in the presence of red urine, postoperative myalgias, and elevated CPK may be related to posture, the duration of the procedure, and a traumatic context.

III.B Anesthesia of a patient at risk of malignant hyperthermia

Outpatient hospitalization is possible. Scheduling the patient in the first position is desirable to avoid volatile anesthetic vapors in the operating room. The preparation of the ventilator depends on the model. The purging with a flow of 10 L/min of gas in an open circuit must be carried out for a duration varying between

10 and 50 minutes depending on the type of ventilator, to take into account the absorption possibilities of halogenated agents in complex internal circuits. The evaporators are removed to avoid a handling error. The risk of malignant hyperthermia will be included in the checklist. Prophylaxis with dantrolene orally or IV is currently not indicated.

The anesthetic technique can utilize all local anesthetics (including those with vasoconstrictors), all intravenous hypnotics, morphine derivatives, non-depolarizing neuromuscular blockers. Monitoring in the post-anesthesia care unit should focus on urine color and body temperature. There has been no published occurrence of proven malignant hyperthermia crisis while adhering to these guidelines. An early preoperative and postoperative CPK dosage may be informative for patient follow-up. The rapid diagnosis and administration of Dantrolene can reduce mortality below 5% [12].

IV. MANAGEMENT OF MALIGNANT HYPERTHERMIA IN PEDIATRICS: Carried out in 2019 by CAMR and ADARPEF, updated in 2023

HYPERTHERMIE MALIGNEN EN PEDIATRIE


<p>SUSPECTER (y compris à distance de l'exposition)</p> <ul style="list-style-type: none"> <input type="checkbox"/> Halogénés / succinylcholine <input type="checkbox"/> PEtCO₂ élevée / tachypnée <input type="checkbox"/> Tachycardie / marbrures <input type="checkbox"/> Hyperthermie / sueurs/trismus / Rigidité <input type="checkbox"/> Myoglobulinurie, acidose, élévation des CPK post-opérateur <input type="checkbox"/> Terrain favorisant (myopathie, ...) 	<p>ELIMINER</p> <ul style="list-style-type: none"> <input type="checkbox"/> Anesthésie trop légère <input type="checkbox"/> Hypoventilation <input type="checkbox"/> Insufflation de CO₂ – anomalie circuit
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APPEL A L'AIDE / chariot urgence
 Obtenir Dantrolène
 Arrêt procédure ?


TRAITER

- Arrêter les halogénés → Relais IV : kétamine, midazolam
- Hyperventiler en FiO₂ 100 % - circuit ouvert haut débit gaz frais (2 à 3 fois ventilation minute du patient) et si disponibles avec des filtres à charbon actif
- Prélever Gaz du sang + kaliémie
- Poser 2^{ème} VVP
- Monitorer température centrale et PetCO₂
- Dantrolène injectable:** [tel pharmacie/lieu de stockage]
 - 2,5 mg/kg IVD (flacon 20 mg à diluer dans 60ml d'eau stérile, ex: 20 kg = 50 mg = 2,5 flacons, voir abaque verso).
 - Si échec (quelques min) répéter par dose de 1 mg/kg IVD toutes les 10 minutes
 - Jusqu'à 10 mg/kg au total (ex: 20 kg = 10 flacons)
- Refroidir par voie externe +/- interne jusqu'à 38°C
- Traiter Hyperkaliémie: 0,1 UI/kg d'insuline dans 10 mL/kg de G10 % sur 15 minutes, Gluconate de Ca (0,5 mL/kg max 2 g) si troubles du rythme
- Traiter Acidose métabolique (grave pH < 7,2) : Bicarbonate de sodium 1 mEq/Kg soit 2 mL/kg de Bicarbonates 4,2 %
- Surveiller diurèse : si oligurie → Remplissage NaCl 0,9 %


1. Prélever 60 ml d'EPPI par flacon



2. Utiliser le trocart




3. Agiter



APRÈS

- Surveillance Réa min. 24 h : GDS, CPK, kaliémie, Myoglobine (sang + urine), coagulation
- Dantrolène: 1 mg/kg toutes les 4 heures tant que persistent signes cliniques
- Prélèvement génétique / biopsie musculaire / adresser centre référent
- Rappel: contre-indication de l'association Dantrolène - inhibiteurs calciques



Abaques DANTROLENE

Dilution standard: 1 flacon de 20 mg à diluer dans 60 ml d'eau stérile.

Dose initiale 2,5 mg/kg							
Poids (kg)	5	10	15	20	30	40	50
Dose (mg)	12,5	25	37,5	50	75	100	125
Nb de flacons	0,6	1,25	1,9	2,5	3,7	5	6,25
Nb de ml de la solution	40	75	110	150	220	300	375

Dose complémentaire 1 mg/kg							
Poids (kg)	5	10	15	20	30	40	50
Dose (mg)	5	10	15	20	30	40	50
Nb de flacons	0,25	0,5	0,75	1	1,5	2	2,5
Nb de ml de la solution	15	30	45	60	90	120	150

11. Framework: RPP hyperthermia malignancy SFAR 2019 <https://sfar.org/download/rpp-hyperthermie-maligne/> Consensus guidelines on perioperative management of malignant hyperthermia suspected or susceptible patients from the European Malignant Hyperthermia Group. Rüffert and Al. BJA 2021. RPP: Référentiel des Pratiques Professionnelles.

According to the recommendations of experts for the risk of Malignant Hyperthermia in anesthesia and resuscitation SFAR - CRC September 12, 2013, it is recommended to have a poster in all locations where general anesthesia is performed, describing the diagnosis and treatment of the MH crisis, as well as clear and precise information on immediate access to the stock of DANTROLENE and the preparation procedure for intravenous injection.

Clinical Case Report

This is a 5-year-old patient, being followed for vesico-ureteral reflux with the following history:

- Medical history: recurrent urinary infection due to a pyelocaliceal junction syndrome.
- Surgical history: never operated.

The patient was admitted to the operating room for a correction of vesico-ureteral reflux.

The preoperative evaluation shows a conscious patient, stable in terms of hemodynamics and respiration, with a cardiac and pleuropulmonary examination without abnormalities. The preoperative assessment shows a

hemoglobin level of 11g/dl, normal renal function, normal hemostasis assessment, and a blood type of O+.

A patient's admission to the operating room:

- Installation, standard non-invasive monitoring and warming
- Establishment of two venous access points with pre-filling using 0.9% saline
- Antibioprophylaxis with Keflin
- Pre-oxygenation
- Induction performed with: 40 micrograms of fentanyl, 100mg of propofol, and 10mg of rocuronium.
- Easy intubation with a size 4.5 tube with cuff
- Maintenance with Sevoflurane and propofol bolus
- The patient was ventilated in volume-controlled mode, with a tidal volume of 150ml, a respiratory rate of 24 breaths per minute, and an FiO₂ of 50%
- The procedure lasted 3 hours and involved a correction of the VUR

At the end of the procedure, the patient presented with symptoms of hyperthermia, rigidity, sweating, and hypercapnia. Given this clinical condition, the diagnosis of Malignant Hyperthermia was made, leading to the decision to discontinue halogenated agents, hyperventilation with 100% FiO₂, vascular filling, and cooling of the patient.

➤ **DANTROLENE NOT AVAILABLE AT THE HOSPITAL.**

The patient was transferred to the Maternal and Pediatric ICU Department for additional care.

In the department: Intubated patient, ventilated sedated under the effects of drugs, tachycardia at 180 Bpm, hypotensive 74/35 mmHg, electrical signs of hyperkalemia (VENTRICULOGRAM), saturating correctly in controlled volume mode (hyperventilation - 100% fio2), rigid with profuse sweating and hyperthermia at 42°C.

The evolution was marked by the worsening of the clinical picture with hyperkalemia at 8 Meq/l with lactic metabolic acidosis (8 mmol/l) on arterial gas, CPK level 15 times the normal value. The management focused on continuing the hypokalemic measures (infusion of bicarbonates, 1g of calcium, lasilix 60mg, glucose serum + insulin). the patient has installed a cardiocirculatory arrest such as ventricular fibrillation, hence the initiation of external cardiac massage, with delivery of an External Electric Shock at 4Kj/kg, without improvement. administration of a second bolus of calcium gluconate and bicarbonate with continuation of external cardiac massage and EES. The patient did not recover despite the resuscitation measures taken (for 45 minutes).

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