



Case Report

Malignant hyperthermia in a young man: A case report

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ABSTRACT

Introduction and Importance: Malignant hyperthermia (MH) is a hypermetabolic reaction caused by exposure to halogenated volatile anesthetics or succinylcholine. Symptoms include unexplained elevations in end-tidal carbon dioxide and body temperature, muscle rigidity, hemodynamic instability, and electrolyte disturbances. Delayed diagnosis and treatment end up with detrimental consequences.

Case presentation: A 19-year-old healthy patient with a negative surgical history for anesthesia complications presented for an elective otolaryngology surgery. Following a smooth induction of general anesthesia and while maintained on sevoflurane, the patient started having elevation in end-tidal carbon dioxide and body temperature followed by hemodynamic instability. MH reaction was suspected. Dantrolene was directly administered intravenously along with cold physiologic saline. Consequently, body temperature as well as end tidal CO₂ gradually decreased; the patient improved hemodynamically. The surgery was completed, and the patient was transferred to the intensive care unit for continuity of care.

Clinical discussion: MH is challenging for both anesthesia and surgical teams as well as for hospitals in general. Although symptoms are non-specific, the diagnosis of MH reaction and the subsequent initiation of treatment with dantrolene should be prompt. As such, hospitals should be logistically prepared for such scenarios. Furthermore, the treating medical team should be trained in advance in order to avoid any possible delay that might result in catastrophic consequences on the patient.

Conclusion: Early recognition and initiation of treatment are important for survival in MH. This can be achieved by proper staff education along with logistical preparedness.

1. Background

Malignant hyperthermia (MH) is an emergent hypermetabolic disorder in individuals exposed to succinylcholine and/or volatile anesthetics, except for xenon and nitrous oxide [1]. MH was first described in 1960. Its incidence ranging from 1:10000 to 1:22000 [2], has dropped over the past years, due to a decrease in the use of succinylcholine [3]. Higher incidence of MH is noted in the pediatric population and in males as compared to females. The exact cause of this predominance is not yet clear [4]. Multiple genes increase the susceptibility to MH; they include RYR1, CACNA1S and STAC3 [3,5]. In MH, the classical sign is generalized skeletal muscle contraction which leads to a state of hypermetabolism. As a result, the body's use of ATP increases which leads to an increase in the production of CO₂ and lactic acid. This leads to metabolic acidosis and CO₂ retention. The resulting rhabdomyolysis causes hyperkalemia which can sometimes cause life-threatening arrhythmias if left untreated. Another unfortunate consequence is the development

of renal failure due to myoglobinuria resulting from the breakdown of skeletal muscle cells [1]. Rare cases of MH were reported in non-anesthesia settings. Potential triggers are heat stress, emotional stress, vigorous exercise [6] and extensive physical activity in combination with febrile infections in patients with either a personal history or a family history of MH. Such a type of MH is labeled awake MH [7]. Although fever is one of the key aspects of MH, there have been reported cases of MH without fever in the young population [8,9]. In this population, dantrolene is effective in reversing the fatal symptoms of MH as well. It acts on decreasing the interaction between actin and myosin within the sarcomere of a skeletal muscle cell [10].

2. Case presentation

We present the case of a 19-year-old healthy Caucasian male patient weighing 95 kg, with a past surgical history of tonsillectomy at the age of 2 years without any anesthetic complications, scheduled for an elective

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rhinoplasty. The center was not equipped with a specialized intensive care unit. The patient is known to have allergy to ibuprofen; he had developed generalized edema following previous administration. His family history is negative for any adverse events related to anesthesia. Earlier that same day, his sister underwent an uneventful rhinoplasty under general anesthesia (GA). After pre-medicating with 75mg of intramuscular meperidine, an intravenous (IV) line was inserted. Induction of GA was made using midazolam (1.5 mg), fentanyl (150 µg), lidocaine (100 mg), propofol (200 mg) and cisatracurium (12 mg). The patient was easily intubated. Dexamethasone (8 mg) and amoxicillin/clavulonate (1.2 g) were given. The patient was maintained on volatile anesthetics (sevoflurane and nitrous oxide) along with IV remifentanyl infusion at a rate of 0.1 µg/kg/min. Thirty minutes later, the end-tidal carbon dioxide (ETCO₂) started to gradually increase from 40 mmHg, reaching a peak of 130 mmHg as illustrated in Fig. 1. The patient developed sinus tachycardia and oxygen desaturation reaching 110 beats per minute and 95%, respectively. He was also found to have muscle rigidity. His esophageal temperature increased to 39.4° Celsius. Arterial blood gas analysis (ABGs) was done, showing a pH of 7.06 and a pCO₂ of 123 mmHg (Table 1). An MH reaction was high on the differential.

Since sevoflurane was suspected to be the triggering agent, volatile anesthetics were directly turned off. The patient was placed on 100% oxygen. A bolus of 240 mg IV dantrolene was given (2.5 mg/kg; 12 vials of 20 mg). Sodium bicarbonate was given as well. Ice packs were applied on the head, shoulders, and chest. The patient was well hydrated with cold physiologic saline. A urinary catheter was placed with good diuresis. Following the initial dose of dantrolene, ETCO₂ levels and body temperature started to gradually drop over a period of 1 h. The patient was kept intubated and was maintained on a continuous infusion of midazolam, fentanyl and propofol. His serum creatine phosphokinase (CPK) was 1830 U/L. One hour later, repeat ABGs showed a pH of 7.43 and a pCO₂ of 31 mmHg (Table 1). Six hours later, a second dose of IV dantrolene (100 mg) was given as per the published guidelines [11,12]. The patient had to be transferred by ambulance to a larger hospital 30 km away where an intensive care bed was reserved. Basic monitoring of SPO₂, blood pressure and heart rate was applied during transportation. He remained hemodynamically stable and was extubated 24 hours later. Before discharge, he was advised to undergo further diagnostic testing and investigation to confirm the diagnosis of MH susceptibility. Moreover, proper education on the possibility of occurrence of MH to his family members was provided. However, upon later follow-up, he informed us that he will not be undergoing any diagnostic tests as per his physician's recommendations. He was only advised to wear a necklace or bracelet identifying his predisposition to MH. As for the patient's experience, he described it as frustrating, especially when he recalled the moment when he woke up in the intensive care unit, intubated, unaware of what happened to him. He also described having generalized weakness and fatigability, lasting for almost three months following the

incident. Our work has been reported in line with the SCARE 2020 criteria [13].

3. Discussion

Although the exact mechanism of malignant hyperthermia is not fully understood, various experimental evidences has shown that it is attributed to an exaggerated release of free cytoplasmic calcium from the sarcoplasmic reticulum upon exposure to the previously mentioned triggering agents [1,14]. The released calcium binds to troponin C leading to the movement of tropomyosin away from the myosin binding sites, causing muscle contractions [4]. This fulminant release of calcium outweighs the cellular capacity of restoring homeostasis via aerobic and anaerobic mechanisms; this leads to a sustained muscular contraction and depletion of the ATP reserves [4]. Subsequently, this will generate a high mechanical stress on the muscular cells causing a loss of integrity of the cellular membrane, leakage of ions and electrolyte disturbances, most commonly hyperkalemia. Larger molecules including creatinine kinase and myoglobin are also lost from the muscles [3].

MH manifests differently among individuals; variable signs exist with different times of onset and duration. The most common sign of MH is an unexplained increase in ETCO₂, uncontrollable by modification of the ventilatory parameters [3,15]. Cardiovascular signs include sinus tachycardia, often mistaken for light level of anesthesia. Additional possible cardiovascular signs include cardiac arrhythmias and unstable blood pressure. Muscular features include generalized muscle rigidity, mostly involving the masseter muscle. Late signs include hyperthermia and electrolyte disturbances, notably hyperkalemia. The duration after which signs and symptoms occur varies from one patient to another. For instance, in the case presented by Ndikontar et al., the first sign was an elevation of temperature which occurred after 105 minutes [16]. In our case, MH was suspected 30 minutes after induction when the ETCO₂ started to rise. The sequelae immediate effects of MH are rhabdomyolysis manifesting as elevated creatine kinase, myoglobin levels and myoglobinuria. In contrast to other reports where patients developed acute kidney injury requiring hemodialysis [16,17], our patient did not develop renal complications. As it can be noticed, none of the signs and symptoms are specific for malignant hyperthermia; thus, other differential diagnoses such as neuroleptic malignant syndrome, serotonin syndrome, exertional rhabdomyolysis, exertional heat stroke, thyrotoxicosis, pheochromocytoma and intoxications must be ruled out [5].

Early recognition and initiation of treatment of MH is crucial. The initial step is to discontinue all the possible triggering agents and remove the vaporizers. The patient must be placed on 100% oxygen at high flow. Minute ventilation must be increased 2–3 times the normal rate to reverse respiratory acidosis and hypoxemia. Activated charcoal filters can be added to the inspiratory and expiratory limbs of the circuit [3]. The only approved medication to treat MH is dantrolene, which is a specific ryanodine receptor antagonist. Dantrolene must be available wherever volatile anesthetics and succinylcholine are used [18]. The loading dose of dantrolene is 2.5 mg/kg of actual body weight; repeated every 5 min with a maximum dose of 10 mg/kg. When the clinical signs subside and the acute crisis is controlled, it can be given at a dose of 1 mg/kg every 4–6 hours or a drip of 0.25 mg/kg/hour for 24 hours [13, 19]. If the cumulative dose is achieved without clinical improvement, other differential diagnoses should be considered. According to the European malignant hyperthermia group guidelines, it is recommended to store at least 36 vials which serve the patient for around 20–30 minutes, with the possibility to further obtain additional vials (at least 24 vials) [20] within 30 minutes in hospitals where MH triggering medications are used. The initiation of the use of dantrolene for the treatment of MH has resulted in a significant decrease in MH-related mortality rate from 70–80%–10% [4]. Additional key points in the management include monitoring of blood gases, correction of electrolyte disturbances, correction of cardiac arrhythmias, maintenance of good hydration and initiation of active body cooling whenever body temperature is

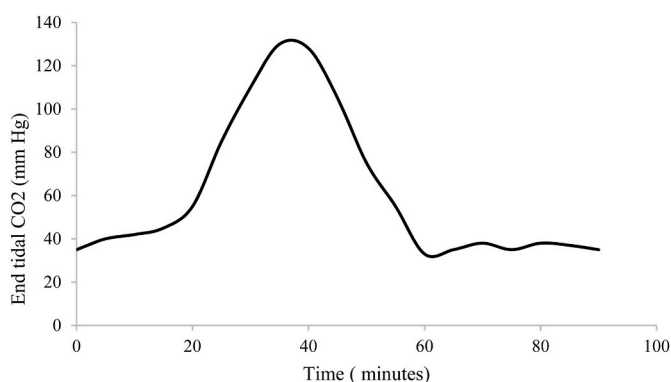


Fig. 1. End tidal CO₂ trend over time in mmHg as measured by the capnogram.

Table 1
Intraoperative ABGs and CPK values.

	pH	pCO2 (mm Hg)	pO2 (mm Hg)	Potassium (meq/L)	Bicarbonate (meq/L)	Oxygen saturation (%)	CPK (U/L)
30 minutes post induction	7.06	123	417	4.8	34	100	1830
1 hour post initiation of treatment	7.43	31	338	5.9	20	100	1859
6 hours post initial event	7.35	39	255	4.2	21	100	2010

pCO2: partial pressure of carbon dioxide (mmHg); pO2: partial pressure of oxygen (mm Hg); CPK: Creatine phosphokinase (U/L).

above 38.5° Celsius [3]. After stabilization, the patient should be monitored in the intensive care unit for at least 24 hours [3], and even 36–48 hours due to an elevated risk of recrudescence of MH [4], which happens in 23% of patients [4,7].

The available tests for the diagnosis of MH susceptibility are: muscle biopsy with the caffeine-halothane contracture test and genetic testing. The former test is the gold standard given its high sensitivity and specificity [21,22], but it is considered an invasive procedure since it requires a surgical biopsy in specific centers. In patients with suspected MH it is indicated to be done 3 months following the event. As for genetic testing, even though it is easier and more accessible for patients, it is relatively less sensitive for the assessment of MH susceptibility and expensive [23]. For the latter reasons, our patient and his family members did not undergo diagnostic testing despite being counseled to do so. Moreover, diagnosis of MH is possible with The Clinical Grading Scale developed by Larach [14,24]. A raw score above 50 is equivalent to having almost certainly malignant hyperthermia (Table 2). In our case, the patient scored 58 points. Likewise, a 14-year-old patient undergoing general anesthesia for testicular torsion had a score of 63 [25].

Finally, in our case, proper identification of suspected MH was possible. Dantrolene immediately reversed the serious complications. Our patient didn't have a history of anesthetic complications and his family history was negative for MH. Despite this, MH episode was encountered. Similarly, in the case presented by Magistris et al., MH occurred despite the patient having undergone uneventful general anesthesia on multiple occasions [17]. Although rare, proper staff education regarding the disease should be available and instructions for preparation of dantrolene should be provided.

4. Conclusion

Our case report highlights that the successful management of MH does not only rely on its rapid recognition by the anesthesiology team but also on the ability to logistically have access to a sufficient amount of dantrolene and properly administer it in a timely manner. Since MH is

Table 2
Larach et al.'s Clinical Grading Scale for MH susceptibility.

Clinical finding (Maximum score)	Manifestation
1. Muscle rigidity 15 points	Generalized rigidity, severe masseter spasm after succinylcholine administration
2. Muscle breakdown 15 points	Creatine Kinase above 20000 U/L Cola colored urine Excess urine/serum myoglobin Potassium > 6mEq/L
3. Respiratory acidosis 15 points	ETCO2 > 55 mmHg PaCO2 > 60 mmHg
4. Metabolic acidosis 10 points	Base deficit >8 mEq/L, pH < 7.25
5. Temperature increase 15 points	Rapidly rising temperature; T > 38.8 °C
6. Family History 15 points	Positive MH family history in first degree relative
7. Cardiac involvement 3 points	Unexplained sinus tachycardia; ventricular tachycardia or fibrillation
8. Other indicators	Rapid reversal of metabolic/respiratory acidosis with IV dantrolene (5 points), elevated resting creatine kinase (10 points)

extremely rare, anesthesiologists might not encounter it during their careers. Proper training should be implemented such as simulation sessions or drills in order to improve their confidence and preparedness in the rare case of an MH crisis [26].

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Consent

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Author contribution

All authors equally contributed in the preparation of the manuscript. All authors read and approved the final manuscript.

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The corresponding author accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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The following information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijso.2023.100675>.

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List of abbreviations

ABGs	Arterial blood gas analysis
CACNA1S	Calcium voltage-gated channel subunit alpha1 S
CPK	Creatine phosphokinase
DIC	Disseminated intravascular coagulation
ETCO ₂	End-tidal carbon dioxide
GA	General anesthesia
IV	Intravenous
MH	Malignant hyperthermia
RYR1	Ryanodine receptor 1
STAC3	SH3 And Cysteine Rich Domain 3

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