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Case Report

Quick Diagnosis: The Key for a Positive Outcome in Malignant Hyperthermia—A Case Report

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ABSTRACT

We report a likely case of malignant hyperthermia triggered by sevoflurane in a 15-year-old male during anesthesia for limb disarticulation surgery. Clinical suspicion was raised with the increasing end-tidal carbon dioxide ($ETCO_2$) and heart rate after induction of general anesthesia. Quick diagnosis, early intervention and teamwork were essential for the positive outcome of this case, preventing the development of more severe complications such as acute kidney injury (AKI) or rhabdomyolysis. Clinical grading score deem this case "*greater than likely*" despite a negative genetic test. Other metabolic derangements related with the primary neoplasm cannot be excluded but there are no reports on the literature describing such an exuberant reaction. The authors wish to highlight the need of prompt diagnosis, which requires a high degree of suspicion, in order to deliver a positive outcome.

Keywords
Anesthesia; Malignant hyperthermia; Patient.

INTRODUCTION

Malignant hyperthermia (MH) is a rare pharmacogenetic condition that causes a hypermetabolic reaction when a susceptible individual is exposed to a triggering agent, namely volatile anesthetics or succinylcholine. Its incidence is hard to estimate with precision, but the prevalence of MH susceptibility varies widely between 1:200-1:3000 although the incidence of clinical MH is much lower, between 1:10.000 and 1:150.000.[1] Sevoflurane can be regarded as a less potent trigger than other anesthetics, but its generic use makes it a relevant causative agent with just as much mortality.[2,3]

Malignant hyperthermia susceptibility is a genetic trait. It can be associated with other myopathies but more often it is the sole manifestation. It is primarily associated with variants in type 1 ryanodine receptor (*RYR1*) intracellular calcium channel (70%), the alpha 1S subunit (CACNA1S) of the voltage-dependent L-type Ca^{2+} (1%) and STAC3 mutation (1%). Despite being heritable, it is not always inherited as some cases have been shown to be due to *de novo* mutation. Furthermore, of those who have a MH crisis up to 30% may not have any of these variants found.[1,4]

In its classic presentation, these drugs interfere with the defective muscle receptor causing an altered flux of calcium in the myocyte. This deregulation of muscle calcium homeostasis leads to generalized muscle contraction, increasing aerobic metabolism leading to hypercarbia as one of the first clinical signs, accompanied by tachycardia and muscle rigidity whereas hyperthermia is a late sign. Finally, rhabdomyolysis due to muscular cells necrosis ensues, causing hyperkalemia, myoglobinuria and acute kidney injury (AKI). Without appropriate treatment, this syndrome has a very high mortality rate, making its early recognition central to the correct management.[5,6]

While MH crisis diagnosis is based on clinical features, definitive diagnosis can be done either with molecular genetic testing or a positive contracture test. Given that molecular genetic tests are not 100% sensitive, MH cannot be excluded based solely on a negative test. In these cases, the physiological gold standard, a caffeine/halothane contracture test should be carried out. Available since the 1970s, this *in vitro* test is based on the measurement of contracture response of a biopsied muscle to graded concentrations of caffeine and the anesthetic halothane. Usually, a 2 g sample from the vastus medialis is taken and is progressively exposed to increasing doses of caffeine and halothane. Once collected, the

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sample has to be processed within 5 h, and since the test is only done in a few specific centers it is not widely accessible. Depending on the degree of contracture to halothane and caffeine expose, it can be excluded or confirmed that the individual is susceptible.[4]

CASE PRESENTATION

We present the case of a 15-years-old male, admitted with an extensive osteosarcoma of the distal femur (33×21 cm). He had no relevant past medical history. Both the patient and direct family members had never been submitted to general anesthesia.

The pre-anesthetic evaluation highlighted cachexia and malnutrition (weight=40 Kg, height=1.58 cm). The physical examination was only evident for the large tumor of the left thigh. Analytical evaluation revealed anaemia (Hb of 7.8 g/dL) and hypoalbuminaemia (2.35 g/dL). He was classified as an American Society of Anaesthesiologists physical status (ASA III) patient.

The patient was admitted to the operating theatre for lower limb disarticulation. Monitoring with 3-lead electrocardiogram (ECG), non-invasive blood pressure, pulse oximetry, train of four (TOF) and bispectral index (BIS) was ensured and induction with propofol, fentanyl, and rocuronium was achieved. Endotracheal intubation followed without complication. After confirming its correct placement, volume-controlled ventilation was started with adequate volumes, pressures and capnometry (25-30 mmHg). Sevoflurane was started for maintenance of the anesthesia. Five-minutes later, profuse sweating was noticed. Hypoglycemia and insufficient depth of anesthesia were ruled out. Two minutes afterwards, a steady increase in end tidal carbon dioxide ($ETCO_2$) and heart rate were recorded, with $ETCO_2$ values of 70-90 mmHg and heart rate between 150-190 bpm. Minute-ventilation was increased but CO_2 kept scaling, reaching 100-120 mmHg. There was no evident muscle rigidity.

Malignant hyperthermia was promptly suspected, and sevoflurane discontinued. High-flow ventilation with FiO_2 100% was started and the anesthetic technique was changed to a total intravenous anesthesia with propofol. The CO_2 absorbent was replaced. Dantrolene was swiftly prepared by the anesthesia nurse, with the help of another anesthesiologist to confirm the correct dosing and to help dilute it in sterile water. One hundred (100) mg were prepared (diluted in 50 mL syringes) and were administered as soon as they were ready, within the first 10-minutes. An arterial blood gas analysis (ABG) was done, revealing a significant respiratory acidosis (Table 1). An arterial line, central line and urinary catheter were placed, and cooling was started with ice packages. Central temperature monitoring was achieved with an esophageal probe. Maximum temperature registered was 36.3 °C, already during the cooling phase. Additional treatment comprised of: sodium bicarbonate, insulin+hypertonic-glucose and calcium gluconate for impending hyperkalemia. Venous blood samples were obtained and were later found to be within normal references. Furosemide and intravenous crystalloids were liberally administered to assure adequate urine output. This clinical picture resolved with the administration of a single dose of dantrolene and associated support therapy.

Table 1. *Seriated Arterial Blood Gas after Onset of Clinical Picture*

	After Induction	15 min	30 min
pH (7.350-7.450)	7.154	7.489	7.447
pCO_2 (32.0-48.0)	96.2	50.5	49.6
pO_2 (83-108)	468	530	240
HCO_3	27.5	37.5	33
AG (10-20)	11.8	12.7	14.5
BE (-3.2 – 2.7)	5	15	10.2
Hb (11.4-17.5)	8.8	7.2	7.6
Hct	27.1	22.0	23.1
Na (135-145)	138	140	139
K (3.5-4.5)	4.5	2.9	2.7
Ca (1.15-1.29)	1.43	1.15	1.23
Glu (65-95)	118	126	173
Lact (0.4-0.8)	1.7	2.4	3.8

After stabilization the patient was transported to the intensive care unit, where he stayed for 48 h. He was successfully extubated within 24 h and awake ABG was within normal values. No complications were recorded during this period.

The surgical intervention was rescheduled one week later. A combined anesthesia was performed with total intravenous anesthesia and an epidural catheter. Both the anesthesia and the surgery were uneventful.

The patient was referred to a follow-up genetic consultation and deoxyribonucleic acid (DNA) testing (*RYR1* gene sequencing) was negative.

DISCUSSION

Malignant hyperthermia has an estimated incidence of 1:10.000-250.000 per general anesthesia but pediatric patients under 15-years-old make up 50% of the cases and males are affected in a 2:1 ratio.[1] This is in line with our patient's demographics. Sevoflurane was considered responsible for the event.

Most often, the trigger agent is pharmacological, but MH can rarely be caused by vigorous exercise or heat. The timing of the onset of clinical signs varies greatly[5] raging from immediately after administration until in the post-operative phase. In our case, there was no story of any symptoms with exercise of high temperatures and the trigger agent was sevoflurane with an exceptionally fast onset.

Malignant hyperthermia diagnosis was based on sudden tachycardia and escalating $ETCO_2$, despite compensatory ventilatory adjustments. Obviously, due to its rarity, there are other conditions, some more frequent, that can mimic MH and should be considered in the differential diagnosis namely thyroid storm, malignant neuroleptic syndrome, serotonin syndrome, pheochromocytoma, sepsis, faulty equipment with rebreathing, endotracheal tube migration, iatrogenic overheating.[4,5] Most of these options were excluded given the medications that were administered and

patient history. Correct placement of the endotracheal tube was confirmed multiple times with auscultation, ventilatory settings adjusted and ventilator pressures checked. Despite not apparent pathological finding and an increase in minute ventilation, $ETCO_2$ kept rising.

Treatment must be initiated when diagnosis is reasonable and in the absence of an alternative, such as this case. Based solely on clinical score that predicts the likelihood of MH, our setting scored 33 (greater than likely).[7]

Dantrolene is the life-saving treatment, but its preparation can be challenging given the low solubility in water. In our centre, it is always available in the operating theatre, in a specially designated MH car located at post-anesthesia care unit (PACU). Fortunately, it was quickly fetched, and we had 2 people readily available to prepare it, which contributed to how fast it was diluted and administered. MH should respond to dantrolene, even though multiple doses may be required. In our case, the clinical signs only resolved with the quick administration of a single dose of dantrolene, supporting our diagnostic hypothesis. Should Dantrolene not be available, we would have provided support therapy, ensuring the wash out of sevoflurane and controlling further manifestations. This would most likely result in a more symptomatic and worse prognosis case, as mortality without dantrolene can be as high as 80%.[5]

Concerning temperature control, active cooling was started as soon as MH was considered. Since continuous temperature monitoring was only initiated afterwards and as hyperthermia is usually a late clinical sign, we could not confirm an increase in core temperature.

Other supportive therapies are frequently necessary in these cases. Despite the ABG showing a borderline potassium (4.5 mmol/dL), given the risk of an exponential increase and to prevent malignant arrhythmias, treatment was preemptively started which resulted in a slight hypokalemia. We also initiated vigorous fluid therapy with furosemide, which resulted in a urine output great than 2 ml/Kg/h, in order to promote the wash out of metabolic products and myoglobin and therefore prevent AKI. Calcium gluconate administration is debatable, given that on the one hand it further contributes to calcium overload but on the other hand can be helpful in the prevention of arrhythmogenesis.[6]

If not quickly controlled, MH evolves into rhabdomyolysis with laboratory findings of myoglobinuria and AKI, none of which were present in our case. The severity of muscle degradation and temperature rise could be correlated with the muscle mass of the individual. Given that our patient was a teenager with a clear poor nutritional status we were not expecting a great increase in myoglobinemia. Additionally, lack of these manifestations can also be attributed to the quick administration of effective treatment stopping the process of cellular destruction at its core.

As mentioned, clinical score deemed our case likely however definitive diagnosis requires genetic testing or muscle biopsy after an acute event. In favor of our hypothesis we have the sudden start of suggestive symptoms when sevoflurane was administered, the apparent resolution with dantrolene, the absence of these same symptoms when the surgery was rescheduled and anesthetic management was changed. Nevertheless, *RYR1* sequencing was negative for our patient which could potentially be explained by another gene being at the origin. This finding has also forced us to consider other metabolic imbalances related to the primary sarcoma as the cause of this clinical picture. However, we could not find any literature to support this hypothesis, nor does it explain the lack of symptoms in the second anesthetic approach.

Finally, given the clinical likelihood of HM, muscle biopsy for caffeine-halothane will be the next step to confirm this diagnosis. It is worth noting, however, there might be some discrepancies between genetic testing and phenotypical manifestations: as mentioned, up to 30% of patients with clinical episode of MH have no known causative gene identified, even if they have a positive contracture test and clinical manifestations. On the other hand, even when a mutation is found, there is only around 40% chances that they will develop symptoms when exposed to a trigger agent (incomplete penetrance). This represents the lack of understating we still have about this condition but also the lack of reliable high sensitivity and specificity tests.[8]

CONCLUSION

Given the low incidence of MH, a high index of suspicion is crucial for early recognition and initiation of treatment, even without all the clinical manifestations. Dantrolene administration should be a priority as it is the only directed therapy available. Treatment requires a solid protocol well-known by all intervening members that act together towards the common goal, the patient.

CONSENT

The authors have received written informed consent from the patient.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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