A Rare Occurrence of Suspected Delayed Malignant Hyperthermia in a Young Patient Undergoing an Orthopaedic Surgery

Ortopedik Cerrahi Uygulanan Genç Bir Hastada Nadir Görülen Gecikmiş Malign Hipertermi Şüphesi

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ABSTRACT

Malignant hyperthermia (MH) is a rare but fatal anaesthetic emergency. It is an autosomal dominant (AD) inherited disorder which is characterized by a hypermetabolic response of an individual upon exposure to a certain type of anaesthesia. We report a rare case of desflurane-induced MH in a Malay descent immediately following an uneventful exposure to sevoflurane. The administration of dantrolene in the immediate management successfully treated the patient.

Key Words : Malignant hyperthermia, Desflurane, Malay.

ÖZET

Malign hipertermi (MH) nadir fakat ölümcül bir anestezik acil durumdur. Otozomal dominant (AD) kalıtsal bir bozukluktur ve bir bireyin belirli bir anesteziye maruz kalması üzerine hipermetabolik tepkisi ile karakterize edilir. Sevoflurana sorunsuz bir şekilde maruz kalmanın hemen ardından Malay kökenli nadir bir desfluran kaynaklı MH vakası bildiriyoruz. Derhal yönetimde dantrolen uygulaması hastayı başarıyla tedavi etti.

Anahtar Sözcükler: Kötü huylu hipertermi, Desfluran, Malay.

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INTRODUCTION

Malignant hyperthermia (MH) is an uncommon lethal pharmacogenetic myopathy, which present as progressive hypercapnia, hyperthermia, tachycardia, metabolic/ respiratory acidosis and muscle rigidity upon exposure to anaesthetic agents. Studies have shown that inhalational agents such as isoflurane, enflurane, sevoflurane, and halothane trigger MH. (1,2) Administration of suxamethonium in the absence of volatile anaesthetics may also trigger MH events. Nevertheless, desflurane is a rare trigger for MH. We hereby present a case of a teenage Malay boy who developed MH 90 minutes after being exposed to desflurane during an elective orthopaedic upper limb surgery.

CASE REPORT

A 14-year-old, American Society of Anaesthesiologist (ASA) 1 boy weighing 50 kg, was scheduled for an elective plating of right radius and ulna. Neither the patient nor his family members had prior exposure to general anaesthesia (GA). Informed consent for anaesthesia and surgery was taken from the parents in his presence. The preoperative vital signs and laboratory values were within normal ranges. The patient received no premedication. He was induced with intravenous (IV) fentanyl 2mcg/kg and propofol 3mg/kg in titrated doses, along with sevoflurane 2.5% by mask ventilation in a mixture of oxygen FiO2 1.0. No muscle relaxants were administered. A laryngeal mask airway (LMA) Proseal size 3 was inserted without difficulty. Nasal temperature probe was inserted via the right nostril after LMA insertion. GA was maintained with desflurane 7% in a mixture of oxygen FiO_2 0.5, to achieve Minimal Alveolar Concentration (MAC) of 1.0. Analgesics IV morphine 5mg was administered after induction. Surgery commenced as per usual, and the Heart Rate (HR) ranges between 60 -82 beats per minute, Blood Pressure (BP) ranges 95 – 122/ 63 -90 mmHg and temperature was 36.2- 36.4°C within the first 90 minutes post induction.

After that, the patient was notably becoming tachycardic with a HR of 120 beats per min and BP increased to a range of 130-150/ 70 -85 mmHg. The temperature was 37.5°C. Initial differential diagnosis at that time were inadequate depth of anaesthesia, pain, early sepsis and bleeding. An additional 2mg of IV morphine, along with 1g of IV paracetamol was administered. The patient was deepened further with desflurane to achieve a MAC of 1.2. The surgical drapes revealed minimal blood loss of about 150-200ml. A fluid challenge of 250 milliliters bolus of Hartmann's solution was given as well. Despite those measures, the patient became more tachycardic to a point of 160 beats/minute. There was also a concurrent increase in the end tidal carbon dioxide concentration ($ETCO_2$) from 40mmHg to 70mmHg within 5 minutes despite re-confirmation of LMA placement.

His body temperature also shot up suddenly to 39.8°C. However, no changes in muscle tone was detected. Judging by these evidences, a high suspicion of MH was made and an anaesthetic emergency was declared. The surgeon was informed, and the surgery was withheld. Additional help was obtained and the suspected triggering agent desflurane was immediately discontinued. The breathing circuits were changed to an external oxygen supply, using bag-valve mask ventilation, where the patient was hyperventilated with FiO2 1.0. Anaesthesia was maintained with targeted concentration infusion (TCI) of propofol of 3-6mcg/ml and remifentanil 3-7 ng/ml. Active cooling was initiated immediately with ice packs over the patient's chest, abdomen and bilateral axillae. One pint of cold saline was administered rapidly. A 16 G cannula was inserted on the patient's right foot where IV dantrolene 2.5mg/kg (total 120 mg) was administered over 30 minutes. Arterial cannulation was done to monitor intra-arterial blood pressure and for serial arterial blood gases (ABG). A Foley's catheter was inserted, and the urine was clear. The initial ABG showed severe respiratory acidosis with pH 7.141, $PaCO_2$ of 70.5 mmHg, PaO_2 of 89.6 mmHg, bicarbonate of 19.4 mmol/L and a base excess of -4.8 mmol/L. The patient was then electively intubated with a size 7.5 cuffed endotracheal tube with no difficulty. A tall tented T wave was seen at the cardiac monitor signifying hyperkalemia; thus, a bolus dose of lytic cocktail composing intravenous calcium gluconate 10 mmol/L, insulin 10 units and dextrose 50% 50 milliliters were given immediately.

Around 20-30 minutes post dantrolene administration, there was a dramatic improvement of heart rate down to 100 beats per minute, $ETCO_2$ improved to 35mmHg and temperature normalized to 37.2°C. Surgery was allowed to resume and completed at the 60th minute after the onset of MH. Post operatively, patient was transferred to the post-anaesthesia care unit (PACU) for close monitoring. ABG before transfer to PACU was pH 7.428, $PaCO_2$ of 32.8 mmHg, PaO_2 of 292 mmHg, bicarbonate of 22.6 mmol/L and a base excess of -2.4 mmol/L.

Immediate post-operative blood investigations showed severe hyperkalemia of 7.3 mmol/L with mild acute kidney injury (AKI) (serum creatinine of 79 µmol/L). Creatinine kinase was slightly elevated to 217 U/L. Nevertheless, there was no myoglobinuria (clear-coloured urine) and hyperkalemia resolved after the initial single dose of lytic cocktail. Blood investigations repeated 8 hours later showed resolved AKI (serum creatinine 55 µmol/L). Throughout observation at PACU, patient remained stable. No further dose of dantrolene was required. Patient was extubated in PACU after 12 hours post operation. He was sent back to the orthopaedic ward and been discharged home well at day three post operation.

The gold standard of caffeine - halothane - contracture test (CHCT) and muscle biopsy for evaluation of MH susceptibility was unable to be offered to our patient as it is not available in our Malaysian setting. However, he underwent a detailed genetic blood testing, 3 weeks after being discharged. The results showed negative detection of mutational change at CACNA1S and RYR1 genes, however a variant of uncertain significance was identified in RYR1 (Fig 1).

Gene	Variant	Zygosity	Variant Classification
RYR1	c.11969G>C (p.Gly3990Ala)	heterozygous	Uncertain Significance
The following genes were evaluated for sequence changes and exonic deletions/duplications: CACNA1S, RYR1			
Results are negative unless otherwise indicated			

Fig 1 : The DNA analysis and report of our patient, which showed variant of uncertain significance identified in RYR1.

DISCUSSION

This case report is very significant in several aspects. Firstly, there is only a limited number of cases of MH reported in individuals of Malay descent globally. In addition, it is very rare for desflurane-induced MH to occur. Thirdly, the patient received inhalational induction using sevoflurane without complications just prior to changing to desflurane for maintenance of anaesthesia.

Multiple large-scale studies had been conducted to evaluate the prevalence of MH but they were mostly limited to a few Western high-income countries. Although reported prevalence of MH is estimated about 1:10000 to 1:250000, it has been predominantly described in Caucasians and occasionally Black Americans. (1,5) Moreover, epidemiological research on MH is lacking in Malaysia and only a handful of such cases have been reported so far. (6-8) The implication is low index of suspicion among clinicians due to lack of awareness and unfamiliarity with MH, which can contribute to the increased morbidity and mortality related to it. Therefore, it is important to note that MH affects all ethnicities in many parts of the world. (1)

MH-susceptible individuals have genetic abnormalities associated with ryanodine receptor (RYR1) resulting in excessive accumulation of myoplasmic calcium, which manifests as a hypermetabolic crisis and leads to multiorgan failure. (3,4) Susceptibility to MH is inherited in an autosomal dominant fashion and the associated mutations form the basis of the caffeine-halothane-contracture test (CHCT) and genetic test.

Studies have shown that desflurane is a trigger of MH in swine but only a few cases have been documented in humans. (9-10) In most cases, suxamethonium, which is also a widely known triggering agent, were administered. (11-13) In several case reports, increased end-tidal carbon dioxide unrelated to inadequate ventilation or rebreathing was the first sign with or without tachycardia and hyperthermia. (5,13-15) However, no muscle rigidity was reported, most probably because suxamethonium was not the primary triggering agent. (16) Despite being reported as less potent than other volatile agents, MH in almost all cases exposed to desflurane were of the same severity as in cases receiving potent triggers and required treatment with dantrolene. Only one case described elimination of the MH episode with discontinuation of desflurane. (15)

In our patient, the development of MH can be attributed to sevoflurane. However, it was very unlikely that it was the trigger in this case because complete washout of sevoflurane following its use for inhalational co- induction was achieved within the first 5 minutes and intraoperative vital signs were normal in the first 90 minutes of the surgery. MH presenting more than one hour after discontinuation of a particular trigger is rare and warrants an investigation of other diagnoses. Additionally, onset of MH patients exposed to sevoflurane is much shorter than that of desflurane. (17) Work by Allen et al. demonstrated that MH presentation with desflurane anaesthesia is often delayed (53 -380 minutes) and other reports agree with this, including one case that was diagnosed seven hours after induction. (5,14-16)   This is probably because desflurane induces small release of calcium from the sarcoplasmic reticulum in skeletal muscle fibres. (18)

Our patient did not undergo a caffeine-halothane-contracture test as is not available in our Malaysian setting and only underwent detailed genetic blood testing which revealed no mutations associated with MH. Therefore, it cannot be concluded with absolute certainty that he was experiencing MH. However, according to the MH clinical grading scale, the patient attained a score of 46 and thus, was very likely to be experiencing an episode of MH. (19) Other diagnoses were promptly excluded, allowing early and accurate diagnosis of MH. Subsequently, our patient responded positively towards dantrolene followed by resolution of abnormal parameters without recrudescence, further suggesting that it was a true MH crisis.

CONCLUSION

The prevalence of malignant hyperthermia in Malays globally and specifically in Malaysia is underdiagnosed and underreported. Previous uneventful anaesthetic exposure does not rule out susceptibility to MH in the future.

Rapid administration of dantrolene plays a crucial role in the immediate management of MH and it saves valuable lives. Clinicians must have high index of suspicion for a diagnosis of delayed-onset MH with the use of desflurane.

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