Sri Lanka Journal of Medicine **SLJM**

Case Report

Citation: Abeysundara A, Rathnayake A, Wijekoon WMPSK, et al. 2024. Malignant Hyperthermia and Dantrolene. Sri Lanka Journal of Medicine, pp 49-52.
DOI: https://doi.org/10.4038/sljm.v33i3.486

Delayed Onset Malignant Hyperthermia in a Child with Previous Uneventful General Anesthesia: A Case Report

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ABSTRACT

Malignant hyperthermia (MH) is a genetic disorder of skeletal muscles which leads to a progressive life-threatening hyperthermic reaction due to the use of Suxamethonium or Inhalational agents in anaesthesia. It is not commonly reported in Sri Lanka. The condition usually manifests in the initial exposure to the causative agents. A 9-year-old male child, who had 2 previous uncomplicated anaesthetic exposure, was admitted for an alveolar bone graft surgery. In the latter part of the surgery, the child developed features of malignant hyperthermia, following exposure to a volatile inhalational agent, isoflurane. Early treatment with dantrolene arrested the disease process and reduced the complications, even though he was treated in intensive care for several days. This case demonstrates that malignant hyperthermia can develop gradually, contrary to the typical rapid onset, even in patients with prior uneventful exposure to triggering agents. Early diagnosis and timely administration of dantrolene are essential to prevent life-threatening complications.

Keywords: Genetic background, dantrolene, malignant hyperthermia, malignant hyperpyrexia

INTRODUCTION

Malignant hyperthermia (MH) is a life-threatening condition with significant morbidity and mortality. This is a condition caused by skeletal muscle hypermetabolism mediated via an abnormal sensitivity of Ryanodine receptors to volatile inhalational anaesthetics. Clinical features include severe muscle rigidity, hyperthermia, hypercapnia followed by myoglobinuria, renal failure and derangements in other organs due to hypoxia. The treatment of choice is dantrolene. The usual presentation is the development of symptoms as soon as the patient is exposed to causative drugs leading to the cancellation of surgeries. This case describes an unusual presentation of MH which was managed successfully.

CASE REPORT

A 9-year-old male, 25 kg child was admitted for an alveolar bone graft of the palate, following a previous cleft palate repair. He was diagnosed with cleft lip and palate at birth and subsequently underwent corrective repair at the age of six and

Received: 2024-04-15 **Accepted revised version: 2024-11-19** **Published: 13-12-2024**

nine months respectively under general anaesthetics, in which volatile inhalational anaesthetic agents had been used without any complications.

His family consists of a father, a mother and two sisters. Only the mother had undergone anaesthesia previously, which was uncomplicated.

This time the child was intubated following induction of anesthesia by propofol and muscle relaxation by atracurium. Anaesthesia was maintained with the volatile agent- isoflurane (MAC 1), oxygen (40%) and air (60%). The surgery lasted about one and a half hours, during which he was on standards of monitoring using non-invasive blood pressure (NIBP), pulse oximetry, ECG, end-tidal Carbon dioxide (EtCO2) and body temperature continuously.

During the latter part of the surgery, it was noted that the core temperature was gradually rising to 38 ^{o}C and then to 42 ^{o}C. Et CO_2 went on rising. Muscles were very stiff. As there was rising suspicion of malignant hyperpyrexia, the patient was removed from the initial anaesthetic machine (which was with isoflurane) and connected to an ICU ventilator with midazolam infusion. Irrespective of various cooling techniques and rapid hydration, the patient continued to have high temperatures. The initial tachycardia proceeded to supra-ventricular tachycardia (SVT) and subsequently fast atrial fibrillations (AF) requiring medical and electrical cardioversion.

Arterial blood gas (ABG) after 30 minutes of starting the hyperpyrexia showed a severe mixed acidosis (PH 7.05, HCO 17 mmol /L, and St HCO of 12 mmol /L) and CO2 of 67mmHg. Lactate was 7.1mmol/L.

The first dose of dantrolene 40mg (2 mg/kg) started in 2 hours followed by another dose of 20mg. Rigidity was subsided, the CO_2 was reduced to 39mmHg and cardiovascular parameters were satisfactory, hence further doses of dantrolene were not given.

For the next 24 hours patient was fluid resuscitated with normal saline and Ringer's Lactate to keep the urine output above 50 ml /hour with a sodium bicarbonate infusion to keep the urine alkaline as the urine colour was dark. Lactate slowly came down to normal values in the latter part of the day.

The patient was extubated at 18 hours, as the GCS was 15/15, and cardiovascular and respiratory parameters were satisfactory.

Serum creatinine remained high (peak value of 260µmol/L) in the next 24 hours, irrespective of high urine output. It gradually reduced within the next 3 days. Ultrasound of the Kidney showed a slight increase in echogenicity. AST and ALT and INR started to rise in the 1st 24 hours and peaked (AST 4900 and ALT 1800 IU/L, INR 2.1) in the latter part of the second day. Ultrasonically, the liver was normal and there was no collection of free fluids in the abdomen.

The patient was on N-acetyl cysteine (NAC) and thiamine infusions. The child's CPK level reached 9000µg/L on the 2nd day. Further confirmatory tests for malignant hyperthermia could not be done as they were not available in Sri Lanka. A medical alert card was issued to the patient for future benefits. All other members of the family were tested and had normal CPK levels.

DISCUSSION

Incidence

Malignant hyperthermia is a rare condition with an incidence of 1:10,000 to 1:250,000 anaesthetics. The prevalence of genetic abnormality occurs more frequently (1:400) than incidence. MH affects humans, pigs, dogs and horses (1). This patient was a 9-year-old male. Even though it can affect anyone, most reported reactions have occurred in children and young adults. Males affect more than females (2).

Pathophysiology

Usual muscle contraction occurs following actin and myosin cross-bridging in response to calcium released from the sarcoplasmic reticulum (SR). The receptor involved in releasing calcium is named "Ryanodine 1" (RyR1) (3,4). There are many isoforms of this receptor. RyR1 occupies skeletal muscles while RyR2 occupies cardiac muscles. Calcium release from the SR depends on the coordinated activity of DHPR (dihydropyridine) receptor (which has 4 subunits-Alpha 1, Alpha 2, Delta and Gamma) and RyR1 receptor (3).

Clinical features start from the excessive skeletal muscle contraction following abnormally large amounts of calcium released from the sarcoplasmic reticulum, due to an abnormal response of RyR1 receptor to volatile inhalational anaesthetics or succinylcholine. Sixty to seventy per cent of MH is due to abnormal sensitivity of the RyR1 receptor, while 1% of MH is due to abnormality of DHPR alpha 1 subunit (3,4). Genetical studies reveal RyR1 receptor channel gene is encoded on Chromosome 19(19q13.1), while CACNA1S gene located on chromosome 1(1Q32.1) is responsible for the defect in alpha 1 subunit of DHPR abnormality.

Clinical features

This patient was on isoflurane (0.8 to 1%) from the beginning for about one and a half hours. Succinylcholine was not used as a muscle relaxant. The speed of onset of clinical features depends on the concentration of the volatile agent. Succinylcholine accelerates the onset and reduces the survival rate (2).

Usual initial symptoms include hyperthermia, hypercapnia, tachycardia and unusual muscle rigidity following excessive skeletal muscle metabolism. This child developed tachyarrhythmias (SVT and AF) in the initial stage of MH.

The patient showed features of multiorgan involvement. An increase in serum creatinine and radiological evidence suggested renal involvement, in spite of good urine output. A rise in AST and ALT to a significant amount indicated liver damage. Reduced platelet count and elevated INR may be the features of early DIC. All derangements in the organs were mild to moderate and lasted only a few days.

Management

Early detection and starting dantrolene is imperative to reduce morbidity and mortality of MH to have a better outcome. We were able to start dantrolene in 2 hours. Even Though Initial clinical features completely disappeared after the second dose, there was significant derangement in organ functions evidenced in the following 24-72 hours. This indicated how important it was to start dantrolene early.

Avoidance of causative agents, proper cooling techniques to reduce temperature, and mechanical ventilation to evade a rise in CO_2 are indicated as initial measures. Sodium bicarbonate and insulin-dextrose solutions are indicated in the event of developing hyperkalemia. Calcium gluconate to stabilise the heart in hyperkalemia should be avoided as it may further precipitate muscle contractions.

Renal failure can be developed following dehydration and myoglobinuria. Hydration with adequate fluids and bicarbonate infusions to make urine alkaline may help.

The child was kept intubated for several hours due to practical reasons. Early awakening gives the patient the added advantage of detecting the development of compartment syndrome early (5). If a patient develops myoglobinuria, he can develop compartment syndrome. Clinical evaluation is more important as the peak level of CPK may not reach until 24 hours (5).

Patients should be nursed in an Intensive care as 10-20% of patients may develop recrudescence within 24 hours (6).

Dantrolene

The only drug which has convincing results is dantrolene. Unfortunately, as this is a rare disease, dantrolene is not freely available in many centers. The first dose should be given immediately to prevent high rates of mortality and morbidity. The dose is calculated on the actual body weight. 2- 2.5 mg/kg for the initial dose (7). The majority of patients do not need further doses. However, subsequent doses are indicated every 10 minutes, provided the clinical features are persistent, even exceeding 10 mg/kg of the maximum total dose recommended (4).

Excessive amounts of dantrolene may cause dose-dependent muscle weakness leading to difficulties in weaning from the ventilator. There are reported high incidences of thrombophlebitis following dantrolene infusions.

CONCLUSION

Malignant hyperthermia is a rare entity following exposure to volatile inhalational anaesthetics or succinylcholine. It can develop in subsequent exposures to the causative agents, even with uncomplicated previous exposures. Early diagnosis and treatment with dantrolene may prevent high morbidity and mortality.

Author declaration

Acknowledgement
Sincere appreciation should go to the parents of the child for being very cooperative with us in giving all necessary details and consent for the publication.

Authors' contributions:
Conceptualization and Design: AA, AR, SDBJ; Data Collection and Patient Care: AA, AR, WMPSKW; Literature Review: AA, AR, SDBJ; Manuscript Writing: AA, SDBJ; Critical Review and Editing: AA, AR.

Conflicts of interest:
The authors declare that there is no financial or non-financial conflict of interest.

Funding statement:
Self-funded.

Ethics statement:
Written informed consent was obtained from the patient before they participated in the case, ensuring their understanding of the purpose, procedures, and potential implications involved.

Statement on data availability:
All data generated during this study are included in this published article.

REFERENCES

1. Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. Orphanet J Rare Dis. 2015 Aug 4;10(1):1–19. https://doi.org/10.1186/s13023-015-0310-1
2. Amare M, Wilson M. Malignant hyperthermia. Vol. 21, Anaesthesia and Intensive Care Medicine. Elsevier Ltd; 2020. p. 368–72.
3. Pathirana, C. (2008) 'Malignant hyperthermia', Sri Lankan Journal of Anaesthesiology, 16(2), p. 101-103. https://doi.org/10.4038/slja.v16i2.357
4. Gregory, Haili PharmD, BCPS; Weant, Kyle A. PharmD, BCPS, BCCCP, FCCP. Pathophysiology and Treatment of Malignant Hyperthermia. Advanced Emergency Nursing Journal 43(2):p 102-110. https://doi.org/10.1097/TME.0000000000000344
5. Glahn KPE, Bendixen D, Girard T, Hopkins PM, Johannsen S, Rüffert H, et al. Availability of dantrolene for the management of malignant hyperthermia crises: European Malignant Hyperthermia Group guidelines. Br J Anaesth. 2020 Aug 1;125(2):133–40.
6. Hopkins PM, Girard T, Dalay S, Jenkins B, Thacker A, Patteril M, et al. Malignant hyperthermia 2020: Guideline from the Association of Anaesthetists. Anaesthesia. 2021;76(5).
7. Hopkins PM. Recrudescence of malignant hyperthermia. Anesthesiology. 2007 May;106(5):893–4.. https://doi.org/10.1097/01.anes.0000265144.63696.af