Clinical Case Report

Malignant hyperthermia in a young adolescent: A case report

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ABSTRACT
A 15-year-old girl developed symptoms suggestive of malignant hyperthermia during a laparoscopic appendicectomy for acute appendicitis. The triad of masseter spasm, hypercarbia and hyperthermia within 30 minutes of exposure to triggering factors was present and was treated successfully with dantrolene. She is among a handful of cases known locally. The problems faced in the post-acute phase included the development of thrombophlebitis due to dantrolene use in our patient, as well as paucity of testing centres for malignant hyperthermia both locally and in the region. This prevented us from making a definitive diagnosis in our patient.

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INTRODUCTION
Malignant hyperthermia is a rare autosomal dominant pharmacogenetic disorder of variable penetrance usually precipitated by anaesthesia. The first reported case was described by Denborough in 1962 in a young man who came from a family with 10 deaths attributed to anaesthesia. Since then, the understanding of the pathophysiology of this disease and its management has come a long way.

We encountered classical symptoms of malignant hyperthermia after exposure to triggering agents in a previously healthy young girl during an emergency surgery, who responded favourably to dantrolene. She is among a handful of such cases in Singapore. However, due to the lack of a registry as well as testing centres in the region, we are unable to obtain a definitive diagnosis via in vitro contracture testing.

THE CASE
A healthy 15-year-old girl presented for emergency laparoscopic appendicectomy. She was clinically stable and afebrile with normal blood investigations preoperatively.

At the operating theatre, a standard rapid sequence intubation with succinylcholine was performed. Trismus occurred about a minute after administration of the drugs, and additional propofol and succinylcholine was given. She was intubated successfully at the first attempt and mechanical ventilation was started with sevoflurane maintenance. The initial end-tidal carbon dioxide (ETCO₂) reading was 50 mmHg and increased to 60 mmHg over 10 minutes despite multiple adjustments to increase minute ventilation. Her temperature was then measured and it increased by 1 °C to 39.2 °C over the next 10 minutes, during which her ETCO₂ increased to 80 mmHg. At this time, there was no tachycardia or hypotension, but a mixed metabolic and respiratory acidosis was present on blood gas analysis (Table I).

A presumptive diagnosis of malignant hyperthermia was made and our hospital’s code for the condition was activated. An initial dantrolene bolus of 2.5 mg/kg was administered together with the cessation of volatile anaesthetics. Other supportive measures included hyperventilation, active cooling measures and aggressive hydration therapy. She responded favourably within 25 minutes after the dantrolene bolus with normalization of her temperature to 37.4 °C and her ETCO₂ to 45 mmHg, and improvement of her acidosis (Table I). No other adverse sequelae were observed during the acute crisis. She stabilized sufficiently for the surgery to continue. Postoperatively, she was transferred to the paediatric intensive care unit (PICU) for further management.

During her stay at the PICU, she initially had rhabdomyolysis resulting in elevated creatine kinase (CK) and myoglobinuria. These resolved with hydration therapy and her CK levels decreased after a peak at roughly 26 hours after anaesthetic induction, which is consistent with malignant hyperthermia (Fig. 1). Intravenous dantrolene was continued for another 2 days, during which time she did not have any signs of recrudescence, renal impairment or other overt complications of malignant hyperthermia.

During her stay in the general ward, she developed upper limb superficial vein thrombophlebitis corresponding to the dantrolene infusion sites and was seen by the haematologists. She was started on oral cloxacillin but did not require anticoagulation. She was discharged later with minimal functional impairment. A repeat ultrasound scan done 3 months later showed partial recanalization with improvement of clinical symptoms.

Numerous multidisciplinary family discussions were held with her and her parents to explain the disease pathophysiology, impact on her and her family members and further diagnostic work-up. However, as the nearest testing centre was located in Sydney, Australia, it was not feasible to send her and her extended family for testing. She was later discharged with letters to show future anaesthesiologists, information and resources on malignant hyperthermia; and substitutive measures in the form of labelling her as ‘allergic’ to the triggering factors were made in the national drug allergy registry.

![Creatine kinase levels](image)

Fig 1. Trend of creatine kinase levels
DISCUSSION

Malignant hyperthermia is a rare pharmacogenetic disorder with an autosomal dominance inheritance pattern of variable penetrance. The prevalence of malignant hyperthermia varies greatly according to geographical location with the European Malignant Hyperthermia group quoting a 1:10 000 prevalence of genetic susceptibility to malignant hyperthermia while a Japanese study showed a diagnostic prevalence of 1:73 000. Currently, there have been no studies on the incidence of malignant hyperthermia in Singapore. There is also a 2:1 male preponderance and the majority of cases of malignant hyperthermia occur in children and young adults. Malignant hyperthermia occurs due to defective ryanodine receptors that trigger an acute rise in calcium levels when exposed to succinylcholine or volatile anaesthetic agents. This leads to sustained muscle contraction with an exponential increase in metabolic demands. Excessive heat and carbon dioxide production, as well as the onset of anaerobic respiration give rise to the classical symptoms of hyperthermia, hypercarbia and metabolic acidosis. Rhabdomyolysis leads to acute myoglobin-induced renal failure, as well as hyperkalaemia and associated arrhythmias.

Survival from a crisis of malignant hyperthermia is dependent on its early recognition and prompt therapeutic action, with dantrolene being the mainstay of treatment. Our patient presented with the classical symptoms but due to the rarity of the syndrome, trismus was initially attributed to reduced efficacy of succinylcholine or transient increase in masseter muscle tone after succinylcholine. Only after the onset of hypercarbia and hyperthermia was the diagnosis made, after which dantrolene was administered rapidly, resulting in resolution of the crisis and a good overall outcome for the patient. Intravenous dantrolene should be administered at a dose of 2.5 mg/kg, with adult and paediatric dosing being identical, and continued until symptoms abate or the maximal cumulative dose of 10 mg/kg is reached. In the post-acute phase, dantrolene should be continued for at least 24 hours to prevent recrudescence, a serious and potentially fatal condition.

The development of thrombophlebitis in our patient is likely due to the intravenous dantrolene. With dantrolene’s highly alkaline nature (pH 9.5) and insolubility, phlebitis has been mentioned as the second most common side-effect after muscle weakness, with an incidence of 9%–10%. In addition, accidental extravasation of the infusion can also cause severe tissue necrosis.

The biggest challenge posed by this episode was that of confirming the diagnosis. The muscle contraction test is considered to be a definitive test and two protocols exist: the North American Malignant Hyperthermia Group (NAMHG) caffeine–halothane contracture test and the European Malignant Hyperthermia Group (EMHG) in vitro contracture test. There are no testing centres in Singapore or Southeast Asia and the nearest centre is in Sydney, Australia.

Genetic testing requires known familial malignant hyperthermia causative mutation genes in the family. In addition, negative results for a familial malignant hyperthermia mutation has to be followed by contracture testing to confirm or exclude susceptibility to malignant hyperthermia.

Our patient scored 70 points on the Larach clinical grading scale, placing her in the ‘almost certain’ group. Based on this clinical grading and her response to dantrolene, the consensus was that she did have malignant hyperthermia. Her presumptive diagnosis is further substantiated by the fact that only 20.4% of patients present with classical signs or laboratory findings that are representative of all the possible types of presentation, namely respiratory acidosis, metabolic acidosis and muscular signs.

There are plans to set up a local registry for patients in Singapore. Hopefully with advances in technology and DNA sequencing, alternative tests to the in vivo contracture testing will be developed and allow a possible avenue for the work-up of patients with possible malignant hyperthermia.

Conclusion

This case is among the handful reported from Singapore. Prompt diagnosis and rapid treatment resulted in a favourable outcome in our patient. However, due to the rarity of the condition, we do not have a local protocol for further diagnostic work-up and management of such patients and their families. The development of such facilities in the region will help investigate such patients and their families.

Consent. The patient’s mother gave consent for the publication of this case report.

REFERENCES