Case Report

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Malignant hyperthermia: a case report

Abstract

Malignant hyperthermia (MH) is a rare pharmacogenetic syndrome, which is characterized as a severe hypermetabolic reaction followed by halogenated inhalational anesthetic administration and/or depolarizing muscle relaxants, such as succinylcholine. Therefore, patients at risk of MH need trigger-free anesthesia in order to avoid life-threatening metabolic crises. This report discusses a case of MH in a six-year-old patient, during an Orchidopexy and Urethrocutaneous Fistul's Correction under general anesthesia. Inhalational induction was carried out using Sevoflurane, whereas propofol and fentanyl were afterward administered. During the procedure, the patient developed hypercapnia, significant temperature rise, masseter rigidity, and hyperkalemia. With a diagnostic hypothesis of MH, a protocol guided by the Hotline for MH was applied, leading to a great patient response that made it possible to transfer the child to the Pediatric Intensive Care Unit where dantrolene was administered, allowing good control of the patient's general condition.

Keywords: Malignant hyperthermia, Pediatric anesthesia, Patient Safety, Trigger-free anesthesia, Case report.

Volume 16 Issue 4 - 2024

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Received: July 15, 2024 | **Published:** July 24, 2024

Abbreviations: MH, malignant hyperthermia; creatine phosphokinase (CK); RYR1, ryanodine receptor; CACNA1S, dihydropyridine receptor.

Introduction

Malignant hyperthermia (MH) is a potentially fatal pharmacogenetic disease triggered by the use of muscle relaxants, such as succinylcholine and halogenated anesthetics (halothane, isoflurane, and sevoflurane).[1] This disease is usually characterized by tachycardia, tachypnea, hypercarbia, and muscular rigidity, with a strong potential to progress to hyperthermia, metabolic acidosis, rhabdomyolysis, and death. Its prevalence is more common in children (1:10 000 anesthesia procedures) with half of cases recorded in patients under 15 years.[2] The disease's physiopathology is caused by mutations in dihydropyridine and ryanodine receptor genes that, when exposed to stimulant agents, induce calcium release that leads to local or generalized muscular rigidity. Additionally, when the sarcoplasmic reticulum releases calcium ions beyond physiological levels, the excessive contractures encourage increased oxygen use, excessive CO2 production, hyperthermia (an increase in body temperature of 1 to 2°C per five minutes), and rhabdomyolysis.[2]

Treatment options include prompt cessation of the trigger agents, 100% oxygen delivery, prompt intravenous administration of dantrolene (via rapid intravenous bolus), temperature management, and control and infusing sodium bicarbonate, to minimize death chances.[1] We report the case of a six-year-old patient with a clinical presentation of MH who responded adequately to discontinuation of the inhalational anesthetic infusion, hyperoxygenation, dantrolene (2.5 mg/kg) administered twice, and cold packs application. After being extubated and transferred to the Pediatric Intensive Care Unit and having dantrolene administered every 6 hours followed by hydration, the patient's clinical condition was controlled.

Case report

A six-year-old male was admitted to an Orchidopexy and Urethrocutaneous Fistul's Correction under general anesthesia. An inhalational induction was performed using sevoflurane, and later, propofol and fentanyl were managed. Thus, during the surgical procedure, the patient developed hypercapnia with PCO_2 up to 170. Besides, a significant rise in his temperature was noticed (40.39ºC), along with masseter rigidity and hyperkalemia of 5.7mmol/L. Therefore, a protocol guided by the Hotline for Malignant Hyperthermia was applied, achieving the following outcomes: discontinuation of inhalational anesthetic infusion, hyperoxygenation, following intravenous administration of dantrolene at a dose of 2.5 mg/kg administered twice, and an application of cold packs. The child tolerated the procedure well, exhibiting reduced CO_2 levels, improvement of muscle rigidity, and lowered body temperature. Subsequently, the patient was extubated and transferred to the Pediatric ICU, where he stayed for 24 hours, in ambient air with a central venous catheter that was inserted in the right subclavian vein. In addition, a 20mm gauge peripheral venous catheter was inserted in the right cubital region, and through an indwelling bladder probe, a clear yellow urine could be observed. Maintenance doses of dantrolene were administered every 6 hours, and hydration was maintained with BIC over 24 hours. Among the laboratory findings, the changes related to MH found in the patient were an elevation of muscle enzymes (creatine kinase – CK 7.900U/L in 08/08/2023; Potassium 3,3 mg), highlighting rhabdomyolysis. On the next day (09/08/2023), the patient was transferred to the hospital ward, where the use of dantrolene every 6 hours was continued until the next morning. Thus, on August 10th at 6:00 am, it was given to the patient his last dose of dantrolene, and also new tests were collected to monitoring the patient's overall conditions since it is expected development of acute renal failure.

Discussion

We are reporting on the case of a pediatric patient who had a clinical presentation of MH, during a surgical procedure, after being given sevoflurane anesthesia in order to perform an Orchidopexy and Urethrocutaneous Fistul's Correction.[1]

Malignant Hyperthermia incident episodes during anesthesia are between 1:10,000 and 1:250,000, specifically in pediatric patients.[2] Even though MH may be triggered after first exposure to anesthesia with known agents, on average, these patients require three exposures to such anesthetics before it is triggered. Male patients are most affected at a 2:1 ratio. In addition to that, pediatric patients under

15 years old make up 52% of reported cases. This is an autosomal dominant genetic disease with mutation mainly in the gene for the ryanodine receptor (RYR1) and the dihydropyridine receptor (CACNA1S), that manifests as a hypermetabolism of the skeletal muscle crises associated with some anesthetics. These mutations promote the excessive and prolonged release of calcium into the cytoplasm, causing a hypermetabolism of skeletal muscle and muscle rigidity. The muscle disease causes collapse of the muscle fiber and acute and generalized necrosis, triggering rhabdomyolysis.[2]

The hypermetabolism due to the increased oxygen consumption and production of CO_2 leads to metabolic acidosis and destroy the membrane of muscle fibers, and, because of that, the test results show elevated myoglobin, as well as prothrombin time, creatine phosphokinase (CK) and potassium. Besides that, more complications can occur in other organs and systems, for instance, tachypnea, cardiac dysfunction, acute pulmonary edema, acute renal failure, hepatic dysfunction, cardiac arrest, disseminated intravascular coagulation, and coma.[2]

In addition, it is crucial to be attentive to the possibility of developing risk of acute renal failure. In rhabdomyolysis, there is a release of intracellular constituents, such as myoglobin, oxidative injury associated with myoglobin, and toxic vasoactive substances, which can be transformed into hematin in the kidneys. This substance is toxic to the kidneys, increasing the risk of ischemia due to renal vasoconstriction and tubular toxicity. Additionally, hemoglobin crystals can be formed, further reducing renal flow.[2] There are molecular studies that can assess the occurrence and recurrence's risk of MH episodes. However, the genetic test isn't available for all patients because of its high cost and technical difficulty. As a result, the definitive diagnosis of MH susceptibility depends solely on caffeine-halothane contracture testing internationally. As an essential tool for MH's screening, pre-anesthetic evaluation is extremely important to consider patients with a suspected family and personal history of MH. So, beyond investigating the history of the classic clinical presentation and familial deaths related to anesthesia, it is necessary to check for previous episodes of postoperative fever, rhabdomyolysis, and myoglobinuria among others.[3]

The treatment consists of Dantrolene's administration, which works by increasing the RYR protein's affinity for Mg2+. In that way, the Mg2+ blocks the RYR protein's capacity to release calcium and stops the uncontrolled cascade that causes the hypermetabolic state of MH. In addition, as prophylaxis, treatment for susceptible patients is no longer routinely recommended. This is due to the improbability of severe HM episodes without prior exposure triggering agents, besides dantrolene not being completely free of significant side effects.[1,3,4] Furthermore, it's important to highlight how the early identification of initial signs of MH allows for a swift management of the condition and, as a result, an improved prognosis. In this context, hypercarbia, sinus tachycardia, localized muscle rigidity, and hyperthermia are the initial crisis indicators, and the symptoms worsen over time and depending on the type of medication used. Once the condition is identified, it's crucial to immediately halt anesthetic medications and initiate the patient care protocol, seeking assistance, normalizing ETCO2 values, administering dantrolene, and treating the patient's temperature and hypercalcemia.[3] As for the postoperative period, it is decisive to observe the patient in ICU for at least 24 hours due to the risk of recurrence. Dantrolene's administration every 4 or 6 hours can be indicated (0,25 $mk.kg^{-1}.h^{-1}$), besides performing frequent arterial blood gas analysis and intermittent CK monitoring every 6 or 8 hours to observe vital, and signs and laboratory indicators.[1,4]

Finally, it is part of good medical practice to guide the patients and their families about HM and future precautions, as well as refer patients above 20 kg to the nearest biopsy center for best monitoring and diagnostic confirmation.[5]

Table 1 Diagnosis X Associated Problems - Based on Hotline Hm Brazil

Signs of MH	Unexpected Sudden Cardiac Arrest in a Young Patient	Trismus/ Masseter Muscle Spasm with Succinylcholine
ETCO2 increase	Presume hyperkalemia and initiate treatment	Early signs of HM in many patients
Trunk or global rigidity	Monitor CPK, myoglobin, and arterial blood gas until values normalize	If limb rigidity, initiate dantrolene
Tachycardia and Tachypnea	Consider Dantrolene's use	For emergency procedures,continue with non-triggered agents, assess and monitor the patient, and also consider Dantrolene treatment
Mixed Acidosis (metabolic and respiratory)	Search for hidden myopathy	Measure CPK and urinary myoglobin levels for 36 hours
Temperature increase	Resuscitation can be difficult and time-consuming	Check CPK immediately and every 6 hours until it normalizes
Myoglobinuria	-	Monitor for dark or cola-colored urine. If present, initiate fluid resuscitation and measure myoglobin levels

Created by the authors

Table 2 Criteria used for Grading Malignant Hyperthermia ScaleFrom Larach et al.,[5] Rosenberg et al.,[7] Raut et al.[8]

Clinical Finding[1]	Indicators[2]	Score
Respiratory acidosis	ETCO2 > 55 mm Hg, PaCO2 > 60 mm Hg	15
Cardiac involvement	Unexplained sinus tachycardia, ventricular tachycardia, or ventricular fibrillation	3
Metabolic acidosis	Base deficit > 8mEq/L, pH< 5	10

Citation: Alito MFR, Fagundes, MEMC, Valente ACA, et al. Malignant hyperthermia: a case report. *J Anesth Crit Care Open Access.* 2024;16(4):96–100. DOI: 10.15406/jaccoa.2024.16.00598

Table 2 Continued..

Clinical Finding[1]	Indicators[2]	Score
Muscle rigidity	Generalized rigidity, severe masseter muscle rigidity	15
Muscle Breakdown	Serum creatine kinase concentration > 20,000/L units, cola-colored urine, excess myoglobin in urine or serum, plasma [K+] > 6 mEq/L	15
Temperature increase	Rapidly increasing temperature, T> 38.8°C	15
Family history	Consistent with autosomal dominant inheritance	15
Other	Rapid reversal of MH signs with dantrolene (score = 5), elevated resting serum creatine kinase concentration (score=10)	-
SCORE	RISK	RATING
0	Risk 1	Almost impossible
3-9	Risk 2	Unlikely
10-19	Risk 3	Less than likely
20-34	Risk 4	More than likely
35-49	Risk 5	Fairly likely
50 or >	Risk 6	Almost certain

1- Clinical findings are in order of relative importance (except family history)

2- Signs occurring during or shortly after general anesthesia in the untreated individual.

Table 3 Test Results

Description	Normal Range	08/08 10:02am	08/08 10:20 am
pH	8-May	6.87	7.24
pCO2	38 - 50	> 115 mmHg	50 mmHg
pO2	35 - 40	188 mmHg	509 mmHg
Na+	136 - 147	139 mmol/L	132 mmHg
K+	3,4 - 4,7	5.3 mmol/L	6.0 mmol/L
Ca+	1,12 - 1,32	1.27 mmol/L	1.00 mmol/L
Glic	< 100	124 mg/dL	100 mg/dL
Lac	< 18	23 mg/dL	13 mg/dL
Hct	33 - 44	37%	32%
		08/08 3:28 pm or 15:28	08/08 10:01 pm or 22:01
Myoglobin	25-58	1941	557
CPK	20 - 180	5913	7939

Created by the authors

Table 4 Patient Clinical Indicators Based on the Rating Scale Created by the authors

Clinical Finding	Score
1- Respiratory acidosis	15
2- Muscle rigidity	15
3- Muscle breakdown	15
4- Temperature increase	15
5- Fast reversal after dantrolene	5
TOTAL SCORE	65
CATEGORY	Risk for Malignant Hyperthermia: 6 - almost certain

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Table 5 Lab Test Result from day 08/08 to 10/08

Test	Normal Range	10/08 12:13 AM	09/08 7:25 AM	09/08 5:09 PM	08/08 10:01 PM	08/08 3:28 PM
URINE						
Nitrite	-	negative	negative	-	negative	negative
Density	1015 - 1025	**1010**	**1030**	**-**	**1030**	**1025**
Red blood cells	~ 4	8	3	-	2	1
White blood cells	-	3	2	-	5	1
Crystals	-	negative	negative	-	negative	negative
Cylinder	-	negative	negative	-	negative	Negative
Epithelial cells	-	(+)	+	-	(+)	(+)
Yeast	-	negative	negative	-	negative	negative
Mucus filament	-	sparse	+	-	sparse	sparse
Venous blood gas analysis						
pH	7,32 - 7,43	7,42	7,39	-	7,33	7,35
pO2	35 - 40	37	37	-	38	39
pCO2	38 - 50	44	44	-	44	40
HCO3	22 - 29	28,5	26,6	-	23,2	22,1
Total CO2	23 - 30	29,9	28	-	24,6	23,3
%SO2C	60 -75	72	70	-	67	70
BE	0 - 2	**3,6**	1,3	-	**-2,8**	**-3,3**
Urea	0,3 - 0,7	0,47	0,36	-	0,35	0,47
Phosphorus	2-6	4,4	-	-	-	4,5
Sodium	136 - 145	136	-	-	**134**	**132**
Myoglobin	25 - 58	35	-	-	**557**	**1941**
Uric acid	2,6 - 6	**1,9**	-	-	-	-
PAT	25 - 40	25,8	31,9	-	-	-
EAS urine						
Bilirubin	-	negative	negative	-	negative	negative
Urobilinogen	0,1 - 0,1	normal	normal	-	normal	Normal
Ketone bodies	-	negative	negative	-	80 mg/dL	negative
Glucose	0 - 99	negative	negative	-	negative	negative
Proteins	~ 0,1	negative	negative	-	negative	negative
Hemoglobin	-	**positive**	negative	-	negative	negative
pH	5-8	6,5	5,5	-	5,5	5
Nitrite	-	negative	negative	-	negative	negative
Density	1015 - 1025	**1010**	**1030**	**-**	**1030**	**1025**
Red blood cells	~ 4	8	3	-	2	1
CK	20 - 80	**2650**	**5647**	**5690**	**7939**	**5913**
Ionized calcium	1,12 - 1,32	1,13	1,15	-	1,15	1,18
Potassium (saline solution)	3,4 - 4,7	3,5	**3,3**	-	4,3	4,6
Manganese	1,6 -2,7	1,6	-	-	-	2,1
Urea (saline solution)	10-38	17	14	-	17	24
PCR	0,01 - 4,99	**17,55**	**13,27**	-	-	3,81
Complete Blood Count						
Red blood cells	4 - 5,5	4,02	**3,96**	-	4,23	4,56
Hemoglobin	11 - 14, 5	11,4	11	-	12	12,5
Hematocrit	33 - 44	33,5	33	-	35,2	37,7
MVC	74 - 94	83,3	83,3	-	83,2	82,7
MCH	26 -32	28,3	27,9	-	28,3	27,4
MCHC	31,5 - 36	34	33,4	-	34,1	33,2
RCDW	11 - 14,5	13,8	**15**	-	14,4	14,5
White blood cells	4000 - 12000	6300	8200	-	**12350**	**12590**
Neutrophil	6000 -26000	**51**	**67**	**-**	**87**	**80**
Segmented neutrophil	30 -50	**51**	**67**	**-**	**87**	**80**

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Table 5 Continued...

Test	Normal Range	10/08 12:13 AM	09/08 7:25 AM	09/08 5:09 PM	08/08 10:01 PM	08/08 3:28 PM
Eosinophils	1-5	**6**	**1**	**-**	**0**	**1**
Basophil	0 -2	0	0	-	0	0
Lymphocyte	40 - 70	**35**	**23**	**-**	**9**	**14**
Monocytes	3-14	8	9	-	4	5
Platelets	140 - 400	248	225	-	244	288
Band neutrophils	-	0	0	-	0	0
Atypical lymphocyte	-	0	0	-	0	0

Conclusion

It can be concluded that Malignant Hyperthermia is a serious disease for risk patients that manifests as hypermetabolism of the skeletal muscle crises associated with some anesthetics. Considering how fast it can evolve to a worse scenario, such as hyperthermia, metabolic acidosis, circulatory collapse, and death, it is essential to know how to act in these cases and what is the best treatment for the quick handling of the patient, which demands a correct training and knowledge of the professionals in this area. In that way, a well-done pre-anesthetic evaluation is essential to recognize signs and symptoms and prevent morbidity and mortality from the disease. Also, it is crucial for the survival of these patients to the immediate use and maintenance of dantrolene for a period of minimum duration of 48 hours.

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