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Malignant hyperthermia syndrome: a clinical case report

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CASE REPORT

Malignant hyperthermia is a pharmacogenetic disorder. It manifests as a hypercatabolic skeletal muscle syndrome linked to inhaled volatile anesthetics or depolarizing muscle relaxants. Its clinical signs and symptoms are tachycardia, hyperthermia, hypercapnia, acidosis, muscle rigidity, rhabdomyolysis, hyperkalemia, arrhythmia and renal failure. Mortality without specific treatment is 80% and decreases to 5% with the use of dantrolene sodium.

This article presents the case of a 39-year-old patient admitted to the Intensive Care Unit for malignant hyperthermia after surgery for septoplasty plus turbinoplasty.

INTRODUCTION

Malignant hyperthermia (MH) is an inherited pharmacogenetic disorder of the skeletal musculature, characterized by an anesthesia-related hypermetabolic state (1, 2).

The pathophysiological mechanism is associated with mutation of the RYR1, CACNS1S and STAC3 genes (3, 4), responsible for controlling intracellular calcium homeostasis.

In susceptible individuals, the triggering stimulus causes hyperactivation of the receptors, resulting in uncontrolled release of Ca^{++} from the endoplasmic reticulum (ER) of muscle cells, leading to increased intracytoplasmic Ca^{++}, responsible for enzymatic activation leading to decreased ATP and O_2 consumption and increased anaerobic metabolism, resulting in increased heat and lactic acidosis (5).

Clinical signs and symptoms during the crisis is characterized by tachycardia, hypercapnia, arrhythmia, muscular contracture, cyanosis, metabolic and respiratory acidosis, lactic acidosis, hyperthermia, coagulopathy and rhabdomyolysis (3,6,7).

Mortality without treatment amounts to 80%, decreasing to 5% with supportive measures and effective treatment, which consists of the suspension of halogenated agents, hyperventilation with 100% O_2 and the administration of dantrolene sodium (DS), a muscle relaxant that inhibits the release of Ca^{++} from the ER by acting on RYR1 (2,8,9).

Diagnosis is purely clinical, while post-event confirmation is made by the halothane-caffeine contracture test (CHCT) or genetic study of the mutations of the genes involved (3,10).

CLINICAL CASE

A 39-year-old male patient, with no personal history of interest, was admitted for scheduled surgery for septoplasty plus turbinoplasty.

Anesthetic induction was performed with midazolam, propofol and remifentanil. Neuromuscular relaxation was performed with succinylcholine (100 mg) and rocuronium (50 mg), and hypnosis with desflurane, due to difficult manual ventilation.

The surgery was uneventful and the patient was afebrile. At the end of the surgery, a rapidly progressive rise of EtCO2 (CO_2 at the end of expiration) was observed, reaching values of up to 130 mmHg, tachycardia and axillary hyperthermia 39.5 ºC. When malignant hyperthermia was suspected, desflurane was stopped, physical maneuvers were performed to cool the patient and specific treatment was started with dantrolene sodium, with an initial dose of 250 mg i.v. (2.5 mg/kg), plus continuous perfusion with propofol and cisatracurium. A bladder catheter was placed, diuretics were prescribed and temperature was monitored.

Initial laboratory tests showed mixed acidosis, hyperkalemia, hypocalcemia and renal failure, so calcium bicarbonate, dextrose 5% and insulin were administered, improving $EtCO_2$ and temperature.

Once the patient was stabilized, it was decided to transfer him to the Intensive Care Unit (ICU).

On arrival at the ICU the patient was under the effects of anesthesia, presenting isochoric and normoreactive pupils, muscle hypertrophy, normothermic, tachycardic, good bilateral ventilation, bladder catheterization with myoglobinuria and no edema. He was maintained on mechanical ventilation.

A new analytical control was performed, highlighting: severe hypoglycemia 0.83 mmol/L, hypocalcemia, normalization of hyperkalemia, mild renal failure creatinine 140 **µmol/L** and persistence of acidosis. After 6 hours, a progressive increase in transaminases, lactate dehydrogenase (LDH) and creatinine kinase (CK) was detected,

Table 1 Timeline of laboratory tests

	Basal	6 hours	24 hours	36 hours	2 day	3 day	5 day	6 day	Reference range
Markers of severe metabolic acidosis									
pH	7.05	7.24	7.35	7.37		7.40			7.35 - 7.45
pCO_2 mmHg	84	57	56	48		53			40 - 55
pO_2 mmHg	322	230	55	115		29			
Bicarbonate mmol/L	23.2	24.4	30	27.5		32.4			21 - 26
Base excess mmol/L	-9	-3	2.7	1.8		6.1			-2.5 – 2.5
$SatO_2$ %	99.9	99.7	87	99		55			60 - 85
Lactate mmol/L	5.2	2.2	2.9	1.9		1.9			0.5 – 2
Clinical chemical									
CK U/L		30 930	88 930		112 860		3 460	1 890	46 – 171
LDH U/L		910	1 580			1 114	317	318	120 – 246
ALT (GPT) U/L		150	243		492	529	433	434	10 – 49
AST (GOT) U/L		390	1 023		1 926	1 533	482	279	14 – 35
Creatinine (µmol/L)	150	150	140		140	100	90	90	60 - 100
Potassium (mmol/L)	7.2	5.2	5			4.1	4.2	4.3	3.5 – 5.1
Calcium (mmol/L)	1.67	1.85	1.87		1.95	2.02	2.22	2.12	2.17 –2.59

pCO_2: partial pressure of carbon dioxide (mmHg); pO_2: partial pressure of oxygen (mmHg); SaO2: oxygen saturation; CK: creatinine kinase; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

with a maximum value at 48 hours after the onset of the crisis of 112 860 U/L (Table 1).

Serum therapy was increased with resolution of ionic alterations and renal function, but hepatic alterations and muscle destruction persisted for days. A new dose of dantrolene was not required.

The patient had a subsequent good evolution, allowing withdrawal of sedation and extubation at 24 hours. He was discharged from the ICU 48 hours after the crisis, with adequate blood glucose levels.

A genetic study was requested from the reference laboratory, where the c.6856C>G p.(Leu2286Val) mutation in the RYR1 gene was detected. Massive sequencing was used for analysis, using Agilent's CCP17 Sure Select panel. The analysis was performed on the Illumina NextSeq sequencer. This mutation is described in the clinical database of the American College of medical genetics and genomics as a probably pathogenic variant associated with malignant hyperthermia.

DISCUSSION

MH is a pharmacogenetic alteration that manifests as a hypermetabolic response after exposure to inhaled anesthetics (isoflurane, halothane, sevoflurane, desflurane and enflurane), and muscle relaxants such as succinylcholine (1), although it can also be produced by heat, infections, emotional stress, statin therapy and strenuous exercise (3). This reaction occurs in individuals with a certain genetic predisposition. Since susceptible patients do not present phenotypic alterations before anesthesia, it is impossible to diagnose them before exposure or before specific tests are performed.

Anesthetics: nitrous oxide, local anesthetics, propofol, etomidate, thiopental, ketamine, opioids, benzodiazepines, non-depolarizing muscle relaxants are considered safe in MH susceptible patients (2,7,9).

The incidence of MH is 1/50 000 to 1/250 000 in adults and 1/15 000 in children. The actual prevalence is difficult to define because there are patients with no or mild clinical reactions. In addition, the penetrance of the inherited trait is variable and incomplete (1,2).

MH has an autosomal dominant pattern of inheritance. Most of the cases described are due to mutations in three genes: RYR1 (ryanodine receptor type 1), CACNS1S (dihydropyridine receptor), and STAC3. It is estimated that 70% of cases are caused by mutations in the RYR1 gene (1,11,12,13). As discussed above, our patient was heterozygous for the RYR1 gene mutation.

Ryanodine receptors are large (560 kDa) ion channels involved in intracellular calcium release, especially in the sarcoplasmic reticulum. There are three isoforms that are variably distributed in tissues, with the RYR1 isoform predominating in skeletal muscle. In the case of our patient, the mutation described above is associated with a missense-type change that predicts the substitution of an amino acid leucine for valine at position 2286 of the protein.

When the receptor is mutated, it releases excess calcium once activated by anesthetic agents. This results in sustained muscle contraction, altered calcium homeostasis and a hypermetabolic state, especially anaerobic, with lactate production, increased temperature and CO_2 and oxygen consumption. This leads to rhabdomyolysis, hyperkalemia, hypocalcemia, myoglobinuria, elevated CK and hypernatremia (9).

Ionic disturbances are due to loss of function of the cell membrane, on the one hand there is a release of enzymes and electrolytes, especially potassium into the intercellular space. On the other hand, this release is compensated by a flow of water into the cellular interior which causes a state of hypovolaemia in patients, resulting in a haemoconcentration of various analytes such as sodium.

MH may appear early with succinylcholine or late with inhaled anesthetics. In the case described, it was attributed to the mixture of succinylcholine and desflurane. One of the earliest clinical manifestations of MH that should alert the anesthesiologist is increased $EtCO_2$. Hypercapnia is the most specific symptom, being found in 90% of cases (14).

Other associated signs may include cyanosis, metabolic and respiratory acidosis, lactic acidosis and increased CK. Peak CK values are reached hours after the onset of the crisis. In this case, the patient reached values of 112 860 U/L 48 hours after surgery, with a subsequent decrease.

The diagnosis should be confirmed using The Clinical Grading Scale (CSG) for MH developed by Larach (9). A score above 50 classifies the episode as almost certainly malignant hyperthermia, as was the case presented.

Following the European Malignant Hyperthermia Group Guidelines (EMHG) (15), once the condition is diagnosed, treatment should be initiated as soon as possible, progressively decreasing the anesthetic agent. The drug used for MH is dantrolene sodium. Dantrolene is a muscle relaxant that acts at the level of the RYR1 receptor, decreasing intracellular calcium availability and slowing massive skeletal muscle contraction. Initially 2.5 mg/kg should be administered as an intravenous bolus, and this dose should be repeated every 3-5 min. until the signs are controlled, maintaining thereafter the administration of 1 mg/kg every 6 hours to prevent recurrence of crises. In the case presented, only one dose was needed, without presenting subsequent crises. Simultaneously, treatment of hyperthermia, hyperkalemia, acidosis, renal failure and arrhythmias should be started (2,15). Once the crisis has been controlled, the patient should be monitored and transferred to the ICU for at least 24 hours, due to the risk of relapse.

Confirmation of MH is performed by HCT and is indicated when a patient has had a previous suspicious reaction or in patients with a family history (10).

The genetic susceptibility described MH justifies the performance of the genetic study to search for the presence of mutations and subsequent genetic counseling in families with a history (13).

LEARNING POINTS

The laboratory has a key role in early diagnosis for the administration of effective treatment: dantrolene sodium.

The most common clinical manifestations are nonspecific and mild, but associated with exposure to triggering agents, will be sufficient for initial suspicion of MH.

Triggering agents are inhaled anesthetics and depolarizing muscle relaxants.

Confirmation of susceptibility will depend on the result of the halothane-caffeine contracture test (HCTC), indicated three months after the crisis.

The genetic study of the disease aims at a presymptomatic diagnosis, without the need for biopsy, and at assessing new mutations.

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