Chapter 8
Malignant Hyperthermia

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8.1 Definition

Malignant Hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscle, a "pharmacogenetics" myopathy [1, 2]. Patients are predisposed to develop a serious state of muscle hypermetabolism during general anaesthesia, such as halogen-containing volatile anaesthetics and/or succinylcholine.

The discovery of a gene-related pathogenesis, particularly if related to mutations in the gene encoding the ryanodine receptor, and possible treatment with a specific antagonist of the ryanodine receptor (Dantrolene), has meant that MH is now a condition which is potentially treatable in Emergency.

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8.2 Epidemiology

MH is prevalent in young male adults. The incidence of episodes of malignant hyperthermia ranges from 1:5000 to 1:50,000/100,000 anaesthesias [2]. The average age ranges from 39 years according to [1] to 23 years according to the Canadian study [3], with a prevalence in the male population [3, 4].

8.3 Pathogenesis

The physiological and biochemical mechanisms that determine malignant hyperthermia are to be found in the regulation of calcium in skeletal muscle. According to recent epidemiological studies, the agents that trigger the disorder of calcium homeostasis are succinylcholine alone or in association with volatile anaesthetics. The latter are hypnotic inhalers used in general anaesthesia, including sevoflurane, desflurane, isoflurane, enflurane and halothane.

MH episodes depend on a functional alteration of the ryanodine receptors which affect uncontrolled release of calcium through the sarcoplasmic reticulum, with an increased concentration of cytoplasmic calcium. This mechanism determines muscle activation with an abnormal increase of cell metabolism and consequent high consumption of oxygen, carbon dioxide production and heat generation.

In the skeletal muscle, calcium channels are regulated by a protein: the ryanodine receptor (RYR1). Cav 1.1 is a voltage-dependent channel that activates RYR1 [5]. Mutations (variations) of genes that encode these two proteins are responsible for the increased susceptibility of some patients to the development of MH. In 70–75% of cases it involves one of the RYR1 gene variant [5, 6]; less frequently a CACNA1S variant is detected which encodes an alpha Cav 1.1. subunit.

Finally, there are cases in which no variant has been identified furthermore, some RYR1 mutations are associated with rare myopathies and some have been described in association with both MH and “central core” myopathies. Given the co-existence

or association of MH with rhabdomyolysis other genes have been identified, which may possibly be involved in the pathogenesis of the disease, such as CPT2, PYGM, ACADM, AMPD1, VLCAD. Next Generation Sequencing (NGS), a technology which allows rapid sequencing of human DNA, will identify new mutations and their correlation with MH [5–7].

Relatives of patients who have an increased susceptibility to MH should not, if possible, be treated with anaesthetics. When the diagnosis is genetic and transmission of the disease is autosomal dominant, children of the affected patients have a 50% chance of developing MH.

An association is frequently found between exercise hyperthermia (exertional heat illness) and MH. The alteration of calcium homeostasis is common to both diseases. Exertional heat illness is a subclinical myopathy that appears after extreme physical exertion.

Some myopathies have an increased susceptibility to malignant hyperthermia: myotonia associated with sodium channels, hypokalemic periodic paralysis, myopathy multiminicore.

8.4 Diagnosis

European Guidelines [8] have been developed in Europe, and there is a US registry [9] with guidance on the diagnosis and management of malignant hyperthermia.

The history is important not only for investigating any previous episodes, but also because there are some associated diseases such as “Central Core” myopathy.

Diagnosis of MH is primarily based on clinical suspicion and on bio-humoral exams.

The main clinical characteristics of the MH patient are muscle rigidity, tachycardia, acidosis, hyperthermia, hyperkalemia and an increased concentration of carbon dioxide (CO_2) at the end of expiration. These parameters, and their importance according to the normal values, are summarized in the Clinical Grading Scale developed in 1994 by Larach et al. [10] (Table 8.1), which allows a certain or possible diagnosis to be reached.

Table 8.1 MH diagnostic tool

Item	Score
Rigidity	
Generalized muscular rigidity (in absence of shivering due to hypothermia, or during or immediately following emergence from general inhalational anaesthesia)	15
Masseter spasm shortly following succinylcholine administration	15
Muscle breakdown	
Elevated creatine kinase >20,000 IU after anaesthetic that included succinylcholine	15
Elevated creatine kinase >10,000 IU after anaesthetic without succinylcholine	15
Cola colored urine in perioperative period	10
Myoglobin in urine >60 μg/L	5
Myoglobin in serum >170 μg/L	5
Blood/plasma/serum K+ >6 mEq/L (in absence of renal failure)	3
Respiratory acidosis	
$PETCO_2$ > 55 mmHg with appropriately controlled ventilation	15
Arterial $PaCO_2$ > 60 mmHg with appropriately controlled ventilation	15
$PETCO_2$ > 60 mmHg with spontaneous ventilation	15
Arterial $PaCO_2$ > 65 mmHg with spontaneous ventilation	15
Inappropriate hypercarbia (in anaesthesiologist's judgment)	15
Inappropriate tachypnea	10
Increase in temperature	
Inappropriately rapid increase in temperature (in anaesthesiologist's judgment)	15

Table 8.1 (continued)

Item	Score
Inappropriately increased temperature >38.8 °C (101.8?F) in the perioperative period (in anaesthesiologist's judgment)	10
Cardiac involvement	
Inappropriate sinus tachycardia	3
Ventricular tachycardia or ventricular fibrillation	3
Other indicators that are not part of a single process. (These should be added without regard to double-counting)	
Arterial base excess more negative than ?8 mEq/L	10
Arterial pH <7.25	10
Rapid reversal of MH signs of metabolic and/or respiratory acidosis with I.V. dantrolene	5

The Canadian study reports that the most frequent symptoms are: hyperthermia (>38.8) (66.7%), sinus tachycardia (>120 bpm) (62%), hypercapnia (51.9%), rigidity of the masseter muscle (34.9%) and generalized muscle stiffness in 25.6% of the patients.

The symptoms may occur during anaesthesia or in the postoperative period. The rise in temperature can be transient (lasting 20 min) or late, in which case body temperature must be carefully monitored in the ICU. The hyperpyrexia can reach 44°. The temperature may increase by 1–2° every 5 min in patients with a poor prognosis. This condition causes increased oxygen consumption, high CO_2 production due to dysfunction of vital organs, and an increased risk of DIC (disseminated intravascular coagulation). These parameters (metabolic/respiratory acidosis, oxygen and carbon dioxide) can be evaluated on an arterial level by hemogasanalysis (HGA).

Clinical Grading Scale for IM: raw score

Interpreting the raw score: MH rank and qualitative likelihood

Raw score range	MH rank	Description of likelihood
0	1	Almost never
3–9	2	Unlikely
10–19	3	Somewhat less than likely
20–34	4	Somewhat greater than likely
35–49	5	Very likely
50+	6	Almost certain

Hypermetabolism and hypoxia lead to widespread muscle damage. Among the bio-humoral diagnostic tests, the Guidelines suggest that the creatinine-kinase (CK) value test is one of the bio-humoral diagnostic tests to be carried out. The persistence of increased values of CK, even higher than 10,000–20,000 IU/L, is shown in association with a greater susceptibility to MH. There are numerous pathological conditions that can determine an increase in CK; the test therefore has low sensitivity and specificity.

If muscle damage is extensive it is also possible to detect myoglobinuria, which causes renal failure.The in vivo contracture test (IVCT) is a validated and useful method for diagnosis. Two modes of execution and interpretation of results have been developed by the European Group for the Study of Malignant Hyperthermia (EMHG) [8] and the North American group for Malignant Hyperthermia (NAMHG). Both protocols are based on muscle response to halothane and caffeine, both with induction of muscle contraction properties.

The EMHG protocol distinguishes four diagnostic laboratory groups: MHShc (malignant hyperthermia susceptible to halothane and caffeine), MHSh (malignant hyperthermia susceptible to halothane), MHSC (malignant hyperthermia susceptible to caffeine) and MHN unchanged (normal: no susceptibility to caffeine or halothane). NAMHG considers as positive those patients with an abnormal response to both (halothane and caffeine) and negative those patients whose tests are both negative.

RYR1 and CACNAIS molecular genetic diagnosis should be indicated as diagnostic tests confirming the predisposition to MH. The European Guidelines [8] indicate a possible parallel diagnostic path which includes both DNA screening and muscle biopsy, with the contracture test in vivo. The decision as to which procedure to follow depends on the characteristics of the patient's condition, the characteristics of the hospital where he or she is under treatment, and the urgency with which test results are awaited (e.g. the patient is awaiting surgery).In urgent cases, the mainstay of diagnosis is clinical suspicion based on the signs and symptoms reported by the patient.

Patients with a persistent increase in CK, or patients symptomatic for possible muscle pain, should undergo a neurological evaluation which includes an electromyographic examination as part of the diagnostic tests to rule out myopathy, before the administration of anaesthesia agents that may cause malignant hyperthermia.

Results which suggest the patient is suffering from myopathy, to be looked for in the proximal muscles of the four limbs, are: CMAP amplitude and reduced duration associated with a recruiting interference at submaximal contraction, and sometimes in the presence of spontaneous fibrillation activity and positive slow waves. In myopathic forms there may be some bizarre high-frequency discharges.

8.5 Differential Diagnosis

There are several conditions that can mimic MH during anaesthesia: sepsis, anaphylaxis, thyroid dysfunction, serotonin syndrome, pheochromocytoma, increased iatrogenic temperature, cocaine overdose, neuroleptic malignant syndrome.

8.6 Management and Treatment

Prognosis of an MH crisis depends on how early treatment is started.

Crisis management of malignant hyperthermia should be rapid: it consists of interrupting exposure to a trigger (succinylcholine and/or volatile anaesthetics), administration of a specific therapy (Dantrolene) and adoption of supportive and prevention measures against possible complications [11].

When exposure to trigger agents is interrupted, anaesthesia must be ensured through I.V. administration of sedatives or opioids.

Hyperventilation with 100% O_2 must be carried out until end-tidal CO_2 values decrease and become normal.

Dantrolene, a derivative of hydantoin, acts as a specific antagonist of the ryanodine receptor by inhibiting the release of calcium from the sarcoplasmic reticulum. Side effects are rare, but there have been reports of prolonged breathing problems, tissue necrosis after accidental extravascular injection, nausea, vomiting, headache and dizziness.

Dantrolene dosage varies, depending on the patient's clinical response or the amount needed to alleviate symptoms. The dosage must return the monitored parameters to a standard range. A dosage of 5 mg/kg of Dantrolene over 24 h is recommended if the initial loading dose was of 2.5–5 mg/kg. A higher dose is recommended over the 24 h (10 mg/kg) if the initial dose is 7.5–10 mg/kg. The maximum cumulative dose is 20 mg/kg [11].

If there is hyperthermia, ice packs can be placed on the groin, under the armpits and on the neck, or nasogastric lavage can be performed with iced solutions. If there is arrhythmia, calcium channel blockers must not be administered.

It is important to perform blood tests with blood count, blood gas analysis, serum CPK, myoglobinaemia, myoglobinuria with clotting profile every 6–12 h. If hyperkalemia is detected, continue hyperventilation and correct blood glucose with insulin (if necessary).

Use diuretics and mannitol to achieve the following diuresis value: 2 mL/kg/h.

DIC occurs when body temperature exceeds 41°.

Despite treatment with Dantrolene, the syndrome may recur; therefore the patient must be monitored in an intensive care unit for at least 36 h.

8.7 Outcome and Mortality

The main complications that can lead to death are: renal failure, heart failure, DIC, pulmonary edema and compartment syndrome. Renal failure is reported in some studies [3] as the most frequent complication; on the contrary, in the American registry Larach et al. report altered state of consciousness and cardiac dysfunction as the main consequences of malignant hyperthermia [4].

An unfavourable outcome is associated with either a delay in the administration of Dantrolene [3] or inadequate monitoring of hyperthermia [9].

Mortality, which in the past could reach 42.3% [12], currently ranges from 6.5 to 15% according to the most recent studies [1–12].

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