Malignant Hyperthermia

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Abstract

Malignant hyperthermia (MH) is an uncommon, life-threatening pharmacogenetic disease, triggered by halogenated volatile anesthetics and the depolarizing muscle relaxant succinylcholine. Pediatric intensive care specialists may be confronted with MH in various circumstances: (i) intensive care treatment of a patient presenting with an acute episode of MH, (ii) intensive care treatment of a patient with known MH susceptibility or a suspected history for MH susceptibility, (iii) differential diagnosis of patients presenting with hypermetabolic disorders and/or rhabdomyolysis. Although the triggering mechanisms of MH are not yet fully elucidated, it is well known, that various single point mutations in genes involved in excitation-contraction (EC) coupling of skeletal muscle are causative for MH susceptibility. The most important genetic locus is the RYR1 gene encoding the protein for the calcium channel of the sarcoplasmic reticulum. If MH susceptible individuals are given volatile anesthetics and/or succinylcholine, MH may be triggered. These triggering agents may cause a loss of intracellular calcium control in skeletal muscle, leading to skeletal muscle hypermetabolism, causing metabolic and respiratory acidosis and various consecutive life threatening symptoms if treatment is not initiated immediately. Corner stones of a successful therapy are (i) immediate cessation of triggering agents, (ii) application of dantrolene and (iii) symptomatic treatment of additional clinical and laboratory findings seen during an MH episode. After any clinical MH episode the patient, and in case of a positive finding his or her relatives, must undergo a systematic MH diagnostic workup. Individuals and family members with MH susceptibility should get appropriate information and a warning card for MH. It may be postulated that any loss of myoplasmic calcium control is causing hypermetabolism in various diseases different from MH (e.g. exercise hypermetabolism, heat stroke, sepsis) and thus, similar therapeutic approaches to MH treatment may be applied.

Keywords

Malignant hyperthermia • Dantrolene • Pharmacogenetics • Skeletal muscle • Volatile anesthetics

Malignant hyperthermia (MH) is an uncommon, life-threatening pharmacogenetic disease, triggered by halogenated volatile anesthetics and the depolarizing muscle relaxant succinylcholine. The first description of MH was published 1960 by Denborough and Lovell, which suggested MH to be an inherited disorder [1]. Indeed, subsequent investigation of the family tree by these same authors showed a dominantly inherited genetic disorder published in a second paper with the full description of the case and the family history [2]. The observation that freshly biopsied muscle strips from patients having survived MH were more sensitive

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to caffeine and halothane in vitro compared to muscle strips from individuals with no history of MH, allowed the development of diagnostic protocols for the investigation of MH susceptibility [3–5]. Screening of suspected MH susceptible individuals and their family members led to the identification of MH causative genetic mutations and non-invasive genetic screening of families with identified MH mutations.

In 1990, the genetic locus for MH susceptibility was identified on human chromosome 19 (RYR1-gene encoding the ryanodine receptor protein or calcium channel of the sarcoplasmic reticulum in skeletal muscle) [6, 7]. However, several researchers demonstrated heterogeneity of MH susceptibility [8]. Thus, it became clear that MH is not a monogenic disorder, even if one single point mutation in many families may be identified and then be used for the non-invasive diagnosis in these MH families [9, 10]. Evidence for alternative genetic loci in addition to RYR1 in humans was demonstrated on chromosomes 3, 7 and 17, whereas causative mutations were localized in the alpha 1-subunit of the human dihydropyridine-sensitive L-type calcium-channel receptor in skeletal muscle on chromosome 7q [11–13]. An actual list of causative mutations for MH is available on the website of the European Malignant Hyperthermia Group [14].

The pathophysiology of MH is explained by the loss of myoplasmic calcium control in skeletal muscle of MH susceptible individuals. Trigger agents (all halogenated volatile anesthetics and the depolarizing muscle relaxant succinylcholine) may increase the myoplasmic calcium concentration in MH susceptible individuals causing an increase of skeletal muscle metabolism [15]. MH may be life threatening if not immediately diagnosed and correctly treated. The most important components of a successful treatment include [16] early diagnosis (unexplained increase of endtidal CO_2, metabolic acidosis), immediate cessation of trigger agents, and dantrolene treatment (Fig. 8.1).

Pediatric intensive care specialists may be confronted with MH in various circumstances. For example, pediatric intensive care specialists may be called upon to provide intensive care treatment of a patient presenting with an acute episode of MH, e.g. after MH is diagnosed during or after induction of anesthesia using trigger agents. Anesthesiologists should alert the intensive care team and be available for assistance with ongoing treatment in the ICU. Tables 8.1, 8.2, and 8.3 present detailed information on the early and late clinical symptoms of MH, differential diagnosis, and concepts for appropriate treatment [16]. Modern digital electronic devices, such as iPhone or iPad applications are now available, which may be helpful for a systematic approach [17, 18]. Following a suspected MH episode, the patient should be referred to a MH diagnostic center for a diagnostic workup. A list of centers in Europe is presented on the website of the European Malignant Hyperthermia Group (www.emhg.org). Similarly, a list of centers in the United States is presented on the website of the Malignant Hyperthermia Association of the United States (www.mhaus.org). The patient and his family should get appropriate genetic counseling and a warning card about MH.

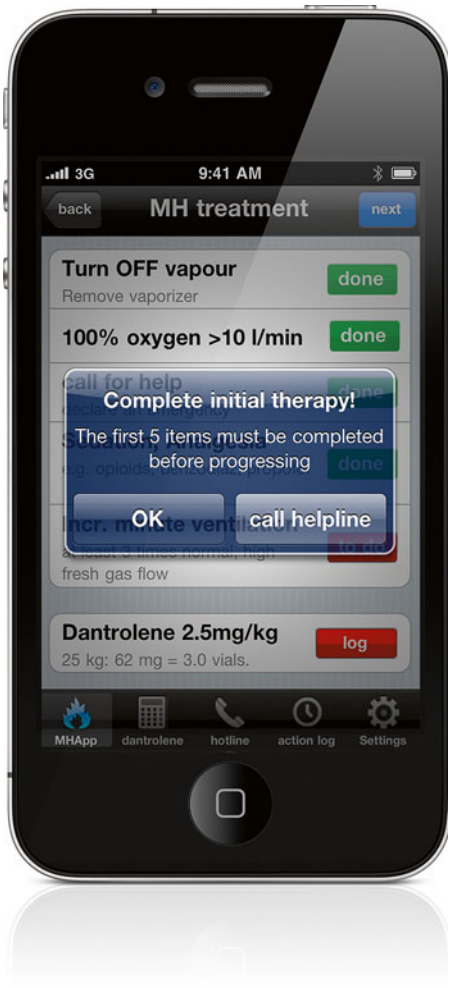

Fig. 8.1 Treatement screen of iPhone application MHApp. This application might be used for training, teaching and treatment of MH episodes

Alternatively, if a patient with known or suspected MH susceptibility is treated for any reason in the ICU, trigger agents (all volatile anesthetics and succinylcholine) must be strictly avoided. Whether some patients without MH susceptibility may develop an MH-like hypermetabolic syndrome has not been systematically proved. However, it may be speculated, that a genetic predisposition with minor degree of abnormal myoplasmic calcium regulation may develop an MH-like syndrome, which may be treated according to effective MH therapy. Selected myopathies, i.e. central core disease (CCD), multi minicore disease (mMD), nemaline myopathy and King-Denborough myopathies are associated

Table 8.1 Clinical signs of MH

Early signs
Metabolic
Inappropriately elevated CO_2 production (raised end-tidal CO_2 on capnography, tachypnea if breathing spontaneously)
Increased O_2 consumption
Mixed metabolic and respiratory acidosis
Profuse sweating
Mottling of skin
Cardiovascular
Inappropriate tachycardia
Cardiac arrhythmias (especially ectopic ventricular beats and ventricular bigeminy)
Unstable arterial pressure
Muscle
Masseter spasm if succinylcholine has been used
Generalized muscle rigidity
Later signs
Hyperkalemia
Rapid increase in core body temperature
Grossly elevated blood creatine phosphokinase levels
Grossly elevated blood myoglobin levels
Dark-colored urine due to myoglobinuria
Severe cardiac arrhythmias and cardiac arrest
Disseminated intravascular coagulation

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Table 8.2 Differential diagnosis of MH

Inappropriate anesthesia, analgesia, or both
Infection or septicemia
Insufficient ventilation or fresh gas flow
Anesthetic machine malfunction
Anaphylactic reaction
Pheochromocytoma
Thyroid crisis
Cerebral ischemia
Neuromuscular disorders
Elevated end-tidal CO_2 due to laparoscopic surgery
Ecstasy or other dangerous recreational drugs
Malignant neuroleptic syndrome

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with malignant hyperthermia [19]. Triggering agents must be avoided in these patients. Other myopathies, such as muscular dystrophies and mitochondrial myopathy seem not to be associated with MH [19], although succinylcholine should be avoided in all myopathic patients.

Finally, there are several disorders mimicking MH-like symptoms (see Table 8.2). The differential diagnosis can be quite challenging. With the exception of a fulminant MH episode, diagnosis of MH is frequently difficult. Treatment with dantrolene should be initiated even if there is no clear

Table 8.3 MH Treatment

Stop all trigger agents immediately
Hyperventilate (use a minute volume 2–3 times normal) with 100 % O_2 at high flow
Declare an emergency and call for help
Change to non-trigger anesthesia (TIVA)
Inform the surgeon and ask for termination/postponement of surgery
Disconnect the vaporizer—do not waste time changing the circuit/anesthetic machine
Dantrolene
Give dantrolene 2–2.5 mg/kg i.v. (ampoules of 20 mg are mixed with 60 ml sterile water)
Obtain dantrolene from other sources, for example, pharmacy/nearby hospitals—at least 36–50 ampoules may be needed for an adult patient
Dantrolene infusions should be repeated until the cardiac and respiratory systems stabilize
The maximum dose (10 mg/kg) may need to be exceeded.
Monitoring
Continue routine anesthetic monitoring (SaO_2, ECG: Electrocardiogram, NIAP: Non invasive arterial pressure, ETCO2: End-tidal CO2)
Measure core temperature
Establish good i.v. lines with wide-bore cannulas
Consider inserting an arterial and central venous line, and a urinary catheter
Obtain samples for measurement of K+, CK, arterial blood gases, myoglobin, and glucose
Check renal and hepatic function and coagulation
Check for signs of compartment syndrome
Monitor the patient for a minimum of 24 h (ICU: Intensive care unit, HDU: high-dependency unit, or in a recovery unit)
Symptomatic treatment
Treat hyperthermia
Chilled 0.9 % saline i.v.
Surface cooling: wet, cold sheets, fans, and ice packs placed in the axillae and groin
Other cooling devices if available
Treat hyperkalemia
Dextrose/insulin
Dialysis may be required
Treat acidosis
Hyperventilate to normocapnea
Give sodium bicarbonate i.v. if pH <7.2
Treat arrhythmias
Amiodarone
Beta-blockers (e.g. propranolol/metoprolol/esmolol)—if tachycardia persists
Maintain urinary output >2 ml/kg/h
Furosemide 0.5–1 mg/kg
Mannitol 1 g/kg

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Consult your local Malignant Hyperthermia Investigation Unit about the case

Patients suspected of being MH-susceptible should undergo diagnostic testing using in vitro contracture testing (IVCT) at a designated MH-laboratory (United States: www.mhaus.org; Europe: www.emhg.org)

MH diagnosis, as delayed treatment can be deleterious. Due to the mode of action dantrolene can lead to muscle weakness. The drug is hyperosmotic and can provoke phlebitis.

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