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Malignant hyperthermia – what do we know in 2019?

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Malignant hyperthermia (MH) is a life-threatening syndrome caused by sudden, uncontrolled skeletal muscle hypermetabolism in response to inhalation anaesthetics and depolarizing muscle relaxants. MH is related to an abrupt, massive release of calcium from the endoplasmic reticulum. False diagnosis and lack of targeted therapy are associated with high mortality rates; therefore, continuous education and knowledge updating are required. Our aim was to present the most recent data concerning epidemiology, genetics, pathophysiology, clinical course, treatment, and diagnosis of MH.

The search on PubMed database was performed in March 2019, using key words such as: malignant hyperthermia, hyperthermia, ryanodine receptor, dantrolene. Studies published between 2004 and 2019 were selected for this review. Guidelines and recommendations of European Malignant Hyperthermia Group (EMHG) and Malignant Hyperthermia Association of the United States (MHAUS) were also included.

EPIDEMIOLOGY

The estimated incidence of MH is between 1 : 10,000 and 1 : 250,000 anaesthetic procedures [1]. All ethnic groups are affected, all over the world. MH develops more frequently in young individuals and in males than in females [2–4]. The susceptibility to MH is thought to be inherited as an autosomal dominant trait. The prevalence of mutations of genes associated with MH susceptibility ranges from 1 : 2000 to 1 : 3000 [1, 5, 6].

Discrepancies between potential predisposition to MH and its incidence are associated with incomplete penetrance, implying that the genetic defect either requires some additional factors for the phenotype to occur or other factors can prevent its occurrence [6].

In the 70-ties, the mortality after a malignant hyperthermia crisis was 64% [7]. Thanks to the introduction of dantrolene and advances in intraoperative monitoring techniques, the mortality rates significantly decreased. Based on the data of 1987–2006, Larach *et al*. [4] assessed the North America mortality to be 1.4%. In Japan, the mortality was reduced from 40% to 5.9% over four decades [8].

According to the data presented by Mayzner-Zawadzka in 2004, 10 cases of MH were observed annually in Poland [9]. Because reporting episodes of MH is not obligatory, current incidence of MH in Poland is not known.

GENETICS

MH is caused by the mutation in the receptors involved in the mechanism of muscle contraction [1]; the mutation concerns the gene encoding ryanodine receptor 1 (RyR1) on chromosome 19 [6, 10] and the *CACNA1s* gene encoding the a voltage-dependent, L-type calcium channel (the dihydropyridine receptor – DHPR) [11]. In recent years, another mutation has been detected associated with MH susceptibility occurring in one of the North America indigenous tribes, i.e. STAC3, encoding Stac3 protein, which is essential for proper muscle contractions [4, 12].

Mutations within the *RyR1* gene are not only connected with MH but also with numerous RyR1-related myopathies [13, 15], including central core disease (CCD), centronuclear myopathy (CNM), multiminicore disease (MMD), congenital fibre-type disproportion (CFTD) [6, 15]. Some authors have determined that the occurrence of the above myopathies may predispose to the development of MH [1].

PATHOPHYSIOLOGY

There are three RyR isoforms:

- RyR1 – expressed in the skeletal muscles,
- RyR2 – expressed in the myocardium,
- RyR3 – found in the central nervous system (CNS) as well as smooth and skeletal muscles [13].

In the majority of MH cases, the *RyR1* gene mutation is found; therefore, to understand the pathophysiology of MH, it is crucial to know the physiology of muscle contraction.

Normal skeletal muscle contraction is initiated by nervous impulses from the myoneural junction, resulting in the release of acetylcholine from the nerve ending. Acetylcholine activates cation channels leading to the formation of functional potentials and depolarisation of the cell membrane. Depolarisation causes changes in conformation of DHPRs. The altered DHPR shape leads to the activation of RyR1 in endoplasmic reticulum membrane, unblocking the calcium channels and releasing the calcium ions stored in the endoplasmic reticulum; subsequently, actin binds to myosin and the muscle contracts. The muscle relaxes due to the active transport of calcium ions back to the endoplasmic reticulum mediated by the intracellular calcium pumps using the energy of ATP breakdown [1, 13].

During MH crisis, the calcium channels are rapidly activated after the exposure to triggers. Substantial amounts of calcium ions are released, which leads to muscle contraction. Muscle rigidity results from the inability to restore the concentration of free calcium below the value activating the contraction. The calcium concentration can be reduced when the activity of channel pumps is intensified; to achieve this, the production of ATP needs to be increased, which results in the production of considerable amounts of thermal energy, leading to hyperthermia. Hypermetabolism of skeletal muscles results in specific metabolic chaos. The demand for oxygen, its consumption and the production of carbon dioxide increase. Aerobic metabolism changes to anaerobic metabolism. Moreover, the production of lactates increases, and acidosis enhances. Finally, the production of ATP is no longer feasible, and the temperature is high, leading to the destruction of the muscle cell (rhabdomyolysis) [1, 13].

TABLE 1. Safe and prohibited medications for patients with the diagnosis or suspicion of malignant hyperthermia susceptibility [1, 2, 13, 14]

Triggers	Safe drugs
• Ether	• Propofol
• Halothane	• Ketamine
• Enflurane	• Etomidate
• Isoflurane	• Benzodiazepines
• Sevoflurane	• Barbiturates
• Desflurane	• Opioids
• Succinylcholine	• Nitrous oxide
	• Non-depolarising muscle relaxants
	• Local anaesthetics

TRIGGERING FACTORS

MH event can occur already after the first exposure to triggering agents. The triggers include all halogenated inhalation anaesthetics and depolarising muscle relaxants (succinylcholine). The remaining anaesthetics, local anaesthetics, opioids, benzodiazepines and non-depolarising muscle relaxants are considered safe.

Table 1 lists the most common anaesthetics considered possible MH triggers and those that can safely be used in patients with the diagnosis or suspicion of MH susceptibility [1, 2, 13, 14]. It should be emphasised that prior exposure to MH triggers does not exclude the MH development during the next anaesthetic procedure.

The on-going debates are focused on stress and exercise as possible triggers of MHE, as well as its connection with exertional heat illness (EHI) and exertional rhabdomyolysis (ER). The above three hypermetabolic conditions are characterised by the development of RYR1-related rhabdomyolysis [15]. However, no direct correlation between MH susceptibility and an increased risk of EHI/ER has been demonstrated. There are some reports describing positive in vitro muscle contracture tests, yet it is difficult to assess their sensitivity and specificity in patients. Noteworthy, in 70% of patients with EHI/ER, the detected RyR1 variants are of no clinical importance. Nevertheless, patients with MH-related mutations should be considered MH susceptible, until exclusion [6].

Importantly, there is no exercise-induced MH. Despite many similarities, MH is inseparably connected with inhalation anaesthetics and succinylcholine. The lack of these triggers excludes the diagnosis of MH [1].

SYMPTOMS AND CLINICAL COURSE

MH reaction may occur at any time during general anaesthesia as well as in the postoperative period [1, 2, 14, 16]. Its course may be extremely abrupt, or its signs and symptoms may develop slowly and atypically. Early diagnosis and targeted therapy can save patient's life [14].

During MH crisis, the end-tidal carbon dioxide ($etCO_2$) concentration suddenly and unproportionally increases with normal ventilation parameters maintained. In patients breathing spontaneously, tachypnoea is of importance. The administration of succinylcholine may cause maseter spasm followed by generalised muscle rigidity, which results in rhabdomyolysis. Heat produced due to hypermetabolism, caused by massive muscle contraction, is responsible for a substantial elevation in body temperature. Beside increased concentration of $etCO_2$, the relevant symptoms of MH include tachycardia, arrythmias

and instability of arterial pressure [1, 2, 14]. The above symptoms may be interpreted as a result of inadequate depth of anaesthesia.

In fully symptomatic MH crisis, the body temperature abruptly increases, even above 44°C. It may increase by 1–2°C every 5 minutes [1]. Unless timely diagnosed, MH leads to severe rhabdomyolysis and multiple organ failure. Secondarily to myoglobinuria, the patient can develop acute kidney injury (AKI). Moreover, disseminated intravascular coagulation (DIC) can be observed. The following are likely to be detected in laboratory testing, mixed respiratory and metabolic acidosis, elevated creatine kinase (CK) concentration, even above 20,000 IU L^{-1}, hyperkalaemia, and increased myoglobin levels [3]. The most common symptoms of MH are presented in Table 2.

The earliest symptoms include the masseter spasm, hypercapnia and tachycardia. Hypercapnia can be considered the most specific symptom, which occurs in more than 90% of cases. Noteworthy, despite its name connected with an increase in body temperature, hyperthermia is present only in about 60% of patients. Only in 8% of cases, hyperthermia is one of the earliest symptoms; therefore, it is not the symptom necessary for MH crisis diagnosis [2, 3].

The time between the exposure to triggers and development of symptoms varies, depending on the anaesthetic used. When the inhalation anaesthetic is administered together with succinylcholine, this time is shorter. The symptoms develop most quickly after halothane. There was no significant difference found in MH symptoms comparing sevoflurane and desflurane. MH event may also occur after succinylcholine as the only trigger used [3, 17].

Moreover, the first symptoms may occur in the postoperative period. Litman *et al*. [16] analysed 528 MHE in North America. Ten of the analysed cases occurred in the postoperative period, up to 40 minutes after the completion of general anaesthesia. In none of the cases, hyperthermia was the first symptom.

Despite the treatment provided, recrudescence of MH symptoms is observed in 20% of patients in the postoperative period, 80% of which appear within 16 hours following the first symptoms. This length of time was found to be correlated with the half-life of dantrolene. The incidence of recrudescence is higher in patients with higher muscle mass, longer action of the anaesthetic before the first symptoms and in patients who developed elevated body temperature during the MH crisis [18].

The initial MH diagnosis can be confirmed using The Clinical Grading Scale (CGS) for Malignant Hyperthermia developed by Larach. The scale assesses six groups of symptoms of MH: muscle rigidity, muscle breakdown, respiratory acidosis, tem-

TABLE 2. Early and late symptoms of malignant hyperthermia eposide according to the European Malignant Hyperthermia Group (EMHG) recommendations [14]

Early	Late
• Increased $etCO_2$ • Tachypnoea (spontaneous breathing) • Tachycardia, ventricular arrythmias • Masseter spasm after succinylcholine • Muscle rigidity • Elevated skin temperature • $\downarrow SaO_2$ • Arterial pressure fluctuations • Hyperhidrosis • Marmorated skin • Metabolic and respiratory acidosis	• Hyperkalaemia • Elevated body temperature > $1^{o}C$/5 min • ↑ CK activity • ↑ myoglobulin level • Myoglobinuria • DIC

TABLE 3. The Clinical Grading Scale (CGS) for malignant hyperthermia [19]

Parameter	Score
Muscle rigidity	
Generalized muscular rigidity	15
Masseter spasm following succinylcholine	15
Muscle breakdown	
CK > 20 000 IU L^{-1} 1 with succinylcholine	15
CK > 10 000 IU L^{-1} without succinylcholine	15
Cola coloured urine in the perioperative period	10
Myoglobin in urine > 60 µg L^{-1}	5
Myoglobin in serum > 170 µg L^{-1}	5
Potassium > 6 mEq L^{-1}	3
Respiratory acidosis	
$etCO_2$ > 55 mm Hg with appropriately controlled ventilation	15
$PaCO_2$ > 60 mm Hg with appropriately controlled ventilation	15
$etCO_2$ > 60 mm Hg mm Hg with spontaneous ventilation	15
$PaCO_2$ > 65 mm Hg Hg with spontaneous ventilation	15
Inappropriate* hypercapnia (in anaesthesiologist's judgment)	15
Inappropriate* tachypnoea	10
Temperature increase	
Inappropriate* rapid increase in temperature (in anesthesiologist's judgement)	15
Inappropriate* temperature increase > 38.8°C in the perioperative period	10
Cardiac involvement	
Inappropriate sinus tachycardia	3
Ventricular tachycardia or ventricular fibrillation	3
Others	
Arterial blood BE < –8 mEq L^{-1}	10
Arterial blood < 7.25	10
Quick subsidence of symptoms after dantrolene	5

*Inappropriate in a given clinical situation or/and in the anaesthesiologist's judgement.
CK – creatine kinase, $etCO_2$ – end-tidal carbon dioxide concentration, $PaCO_2$ – partial concentration of carbon dioxide in arterial blood, BE – base excess

TABLE 4. Interpretation of CGS score [19]

Score	Grade	MH likelihood
0	1	Almost never
3–9	2	Unlikely
10–19	3	Less than likely
20–34	4	More than likely
35–49	5	Very likely
≥ 50	6	Almost certain

TABLE 5. The management guidelines in cases of suspected malignant hyperthermia eposide according to the European Malignant Hyperthermia Group (EMHG) [14]

Treatment	Symptomatic treatment
• Discontinue the anaesthetic • Hyperventilation 100% O_2 > 10 L min^{-1} • Get help • Discontinue the surgical procedure • Convert to non-trigger anaesthesia (e.g. TIVA) • Remove a vaporiser • Do not waste time changing the breathing circuit/machine • **Dantrolene 2 mg kg^{-1} (max. 10 mg kg^{-1})**	• External cooling • Correction of hyperkalaemia • Correction of acidosis • Treatment of arrythmias • Forced diuresis **Monitoring** • ECG, SpO_2, $etCO_2$, BP, RR • Temperature • Arterial blood gases • CK, myoglobin, glycaemia • Coagulogram • Urine output • Central venous access, arterial line

perature increase, cardiac involvement, and some others, e.g. reversibility of symptoms after the use of dantrolene. The score 50 and above evidences MH (Tables 3 and 4) [19].

MANAGEMENT

According to the European Malignant Hyperthermia Group (EMHG) Guidelines, after recognizing an MH crisis, appropriate treatment should be introduced as soon as possible:

1. Immediately discontinue all drugs that may trigger MH reaction.
2. Call for help.
3. Start hyperventilation (increase minute ventilation 2–3 times normal) with 100% oxygen at high flow.
4. If possible, discontinue surgery; otherwise, convert to non-trigger anaesthesia (e.g. TIVA).
5. Do not waste time changing breathing circuit in the anaesthetic machine; a vaporiser should be removed.
6. Administer dantrolene as quickly as possible [14].

The essential elements of management and treatment of MH crisis are presented in Table 5.

CAUSAL TREATMENT – DANTROLENE

Dantrolene [tradenames: Dantrolene (Europe), Dantrium (Europe, USA), Revonto (USA), Ryanodex (USA)] is the most important element of causal treatment of MH crisis and is the only agent that enables quick reduction of MH symptoms by decreasing the release of calcium from the endoplasmic reticulum [20]. Depending on sources, the initial dose of dantrolene is 2–2.5 mg kg^{-1} [5, 13, 21]. The dose recommended by EMHG is 2 mg kg^{-1} [14]. The dose should be repeated every 5 min until the patient's condition is stabilised [13, 21]. The max. dose is 10 mg kg^{-1} 24 h^{-1}. According to the MHAUS guidelines, the use of higher doses is permissible, if necessary [21]. Whenever the symptoms do not subside after the dose exceeding 10 mg kg^{-1}, an alternative diagnosis should be considered [1].

Dantrolene is available in 20 mg vials; the content of each should be dissolved in 60 mL of sterile water (usually attached) to obtain the concentration of 0.33 mg mL^{-1}. Dantrolene should not be dissolved in 0.9% solution of sodium chloride [14, 20, 21]. For an adult patient, even 35–50 vials can be required [2, 14]. Each vial of dantrolene also contains 3 g of mannitol, which ought to be considered during further symptomatic treatment [20].

In the United States, Ryanodex is available, which is a concentrated formula of dantrolene. One vial contains 250 mg of dantrolene; to dissolve the drug, only 5 mL of sterile water is needed (the concentration obtained is 50 mg mL^{-1}) [1], which facilitates and accelerates the administration of the first dose. The above preparation is not available in Europe.

In Poland, dantrolene is imported as a life-saving drug (target import) and temporally authorised for

TABLE 6. Symptomatic treatment of malignant hyperthermia eposide according to the European Malignant Hyperthermia Group (EMHG) and Malignant Hyperthermia Association of the United States (MHAUS) recommendations [14, 21]

Hyperthermia • Cold i.v. fluids: 2–3 L 0.9% NaCl 4°C • Ice packs over the neck, groins and under armpits • Gastric, bladder, rectum lavage with cold fluids • Therapeutic hypothermia • Stop cooling at temp. < 38.5°C	**Hyperkalaemia** • Infusion of glucose with insulin • $CaCl_2$ 10 mg kg^{-1} *i.v.* • Dialysis/CRRT	**Acidosis** • Hyperventilation • Bicarbonates at pH < 7.2
	Arrythmias • Amiodarone 300 mg *i.v.* • β-blocker • Calcium channel blockers must not be used	**Forced diuresis > 2 mL kg^{-1} h^{-1}** • Furosemide 0.5 mg kg^{-1} • Mannitol 1 g kg^{-1} • Crystalloids

sale (no permission based on the Regulation of the Minister of Health of 2001 is required).

SYMPTOMATIC TREATMENT

Once causal therapy of MHE has been implemented, symptomatic treatment must be initiated (Table 6). Active cooling is essential: cold *i.v.* fluids, gastric and bladder lavage with 0.9% NaCl solutions of low temperature, cold compresses, therapeutic hypothermia. Cooling should be discontinued at central temperature of 38.5°C to prevent unintended hypothermia. The disorders of electrolytes and acid-base imbalance should be corrected. In order to prevent acute kidney injury, the urinary output > 2 mL kg^{-1} h^{-1} should be maintained [14]. While treating arrythmias, antagonists of calcium channels are contraindicated (e.g. verapamil, diltiazem) – used with dantrolene, they may significantly increase hyperkalaemia [1].

Given the different etiopathogenesis of hyperthermia and fever, antipyretics are not recommended for treating MH crisis. Fever results from an increase in temperature secondarily to changes in the set point of the hypothalamic thermoregulatory system, most commonly due to the action of pyrogens. Thus, in fever the system of thermoregulation is intact but acts at a higher level, as opposed to hyperthermia in which the core temperature increases, yet the set point is normal. In hyperthermia, the temperature cannot be reduced with antipyretics.

MONITORING

After MH crisis, the affected patient should be monitored in the ICU for at least 24 hours [1, 5], due to the patient's condition and possible recrudescence of symptoms. Standard monitoring should be provided (arterial pressure, heart rate, respiratory rate, core temperature, urine output, capnometry) and mechanical ventilation continued. Every 6–8 hours, monitoring should involve parameters of acid-base balance in arterial blood, activity of creatine kinase, presence of myoglobin in urine and clotting disturbances; moreover, appropriate symptomatic treatment should be initiated. Dantrolene should be continued. The MHAUS recommends administering dantrolene in a dose of 1 mg kg^{-1} every 4–6 hours or in continuous infusion (0.25 mg kg^{-1} h^{-1}) for 24 h or longer, depending on the patient's condition.

The discontinuation of dantrolene or prolonged intervals between doses can be considered when the following criteria are met [21]:

- metabolic stability for 24 h,
- core temperature < 38°C,
- decreasing CK levels,
- no myoglobinuria detected,
- no muscle rigidity detected.

TABLE 7. Syndromes and diseases which should be considered in differential diagnosis of malignant hyperthermia according to the European Malignant Hyperthermia Group (EMHG) recommendations [14]

Differential diagnosis	
• Inadequate anaesthesia and analgesia	• Heat stroke
• Improper lung ventilation	• Chromaffin tumour
• Equipment defects	• Cocaine, *ecstasy*/drug toxicity
• Overheating during surgery	• Neuromuscular diseases
• Malignant neuroleptic syndrome	• Rhabdomyolysis
• Thyroid crisis	• Sepsis

Each MH-suspected patient should be referred for further diagnostic to determine the susceptibility to MH. Each MH event should be registered in the anonymous EMGH database registry at www.mh-event.emhg.org [22].

COMPLICATIONS

Complications after MH crisis occur in about 20–30% of patients. The most common disorders involve the myocardium, kidneys and consciousness. In addition, pulmonary oedema, DIC, liver dysfunction, and compartment syndrome may develop. An early administration of dantrolene reduces the risk of MH complications. Every 30 minutes of delay since the first symptoms almost doubles while each increase in core temperature by 2°C almost triples the risk of complications [2, 3]. The risk of DIC increases with an elevation of core temperature to about 40–41°C [1, 2]. The incidence of complications is higher in patients with the CGS > 35 [3].

DIFFERENTIAL DIAGNOSIS

Malignant hyperthermia is rare, and its symptoms are not pathognomic. Therefore, MH should be differentiated from other anaesthesia-associated clinical situations or other diseases (Table 7).

IDENTIFICATION OF MALIGNANT HYPERTHERMIA-SUSCEPTIBLE PATIENTS

Medical history is essential for identification of MH-susceptible patients. Special attention should be paid to unexplained deaths in the family during anaesthetic procedures or symptoms of rhabdomyolysis related to exercise or stress. Moreover, a variety of diseases is associated with an increased risk of MH, including King-Denborough syndrome, central core disease [1].

According to the EMGH recommendations, the diagnostic procedures for MH susceptibility should be carried out in the following situations [23]:

- MH in family history,
- unclear events/complications during or up to 60 minutes following anaesthesia with triggers,

- unexplained intraoperative deaths in the family,
- postoperative rhabdomyolysis after myopathies have been excluded,
- exertional rhabdomyolysis, recurrent rhabdomyolysis, idiopathic hyperCKemia,
- exertional heat stroke requiring hospitalisation,
- myopathy and detection of a non-characteristic, rare RyR1 variant.

DIAGNOSTIC METHODS

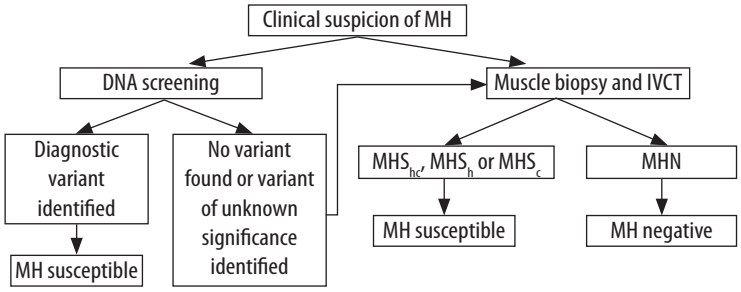
The "gold standard" for diagnosis of MH is an *in vitro* contracture test (IVCT) [1]; its sensitivity is 99% and specificity 94%. The procedure is invasive and involves muscle biopsy (most commonly – quadriceps femoris) under local anaesthesia or other anaesthesia without MH triggers. The test should be carried out in an accredited laboratory within 5 hours since biopsy. The EMGH guidelines define precise dimensions, thickness and weight of a biopsy specimen as well as its storage and transport conditions. The specimen is exposed to halothane and caffeine under the defined conditions, according to the EMGH protocol [23]. Alternatively, ryanodine or 4-chloro-m-cresol can be used. The protocols are available at the EMGH website [22]. In North America, the caffeine-halothane contracture test (CHCT) is used, according to the protocol accepted. The protocols used in Europe and North America differ in terms of the methods applied. The European model is more sensitive and specific. The major limitation of the contracture tests is its expensiveness and poor availability [1]. Currently, only 15 accredited laboratories perform IVCT worldwide. Their list is available at www.emhg.org/accredited [22]. IVCT is not available in Poland.

An alternative to muscle biopsy is genetic testing using next-generation sequencing (NGS). NGS is recommended for family members of individuals with confirmed MH susceptibility [22]. About 70% of MH cases are associated with RyR1 gene mutations. More than 700 variants of RyR1 mutations have been discovered [24]. According to the data of March 2019, available at the EMHG website, 48 RyR1 mutations and 2 CACNAIS mutations are accepted as diagnostic mutations for MH [22].

When the MH-related mutation is detected in genetic testing, the patient is considered MH-susceptible. However, the absence of such mutations does not exclude susceptibility and requires further diagnosis, i.e. IVCT [23] (Figure 1).

Noteworthy, in about 50% of probands with positive IVCT results confirming MH susceptibility or in those with the history of MHE, no RyR1 and CACNAIS mutations are detected and the genetic basis of MH susceptibility remains unknown [6].

Genetic testing is less specific than IVCT [22]. Its major asset is higher availability [1]. Moreover, genetic testing is less expensive, as compared to IVCT and its costs are likely to decrease when such examinations become widespread. Therefore, there is a chance for genetic tests to become screening tests in the population at risk of MH.



MH – malignant hyperthermia; IVCT – *in vitro* contracture test; MHS$_{hc}$ – a caffeine threshold (as defined earlier) at a caffeine concentration of 2.0 mmoL L^{-1} or less in at least one caffeine test, and a halothane threshold concentration at 0.44 mmoL L^{-1} or less in at least one halothane test; MHS$_h$ – a halothane threshold concentration at 0.44 mmoL L^{-1} or less in at least one halothane test and a caffeine threshold at a caffeine concentration of 3 mmoL L^{-1} or more in all caffeine tests; MHS$_c$ – a caffeine threshold at a caffeine concentration of 2.0 mmoL L^{-1} or less and a halothane threshold concentration above 0.44 mmoL L^{-1} in all halothane tests; MHN – a caffeine threshold at a caffeine concentration of 3 mmoL L^{-1} or more in all caffeine tests and a halothane threshold concentration above 0.44 mmoL L^{-1} in all halothane tests.

FIGURE 1. Diagnostic tests for malignant hyperthermia susceptibility based on the European Malignant Hyperthermia Group (EMHG) guidelines [23]

Reprinted from *European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility*. P.M. Hopkins, H. Rüffert, M.M. Snoeck, et al. Br J Anaesth 2015; 115: 531-539, with permission from Elsevier.

ANAESTHESIA OF PATIENTS DIAGNOSED WITH MALIGNANT HYPERTHERMIA SUSCEPTIBILITY

The risk of MH and the measures provided to limit its risk should be discussed with patients in detail. There are no special contraindications for premedication [22]. Prophylactic administration of dantrolene before anaesthesia is not recommended [1, 21, 22]. Nevertheless, dantrolene should be at hand. Each centre that uses MH-triggering factors is recommended to have 36 vials of dantrolene, 20 mg each, or 3 vials, 250 mg each (Ryanodex). Dantrolene should be available within 5 minutes since the suspicion of MH crisis [21].

Non-triggering anaesthesia (without inhalation anaesthetics and succinylcholine) should be performed. Regional anaesthesia can be used. No non-standard laboratory tests are needed prior to or after the anaesthetic procedure in MH susceptible patients [22]. It is not recommended to determine CK before anaesthesia to assess the risk of MHE or MH susceptibility [1, 25]. An elevated serum level of CK may evidence muscle pathology yet has no connection with MH susceptibility [30]. In patients with persistently idiopathically elevated CK levels in blood (hyperCKemia), MH susceptibility should be tested [23].

The anaesthesia machine should be prepared according to one of the following options [21, 22, 26]:

1. Use the vapour-free workstation or

2. Flush the standard machine with 100% oxygen or air at high flow, according to the manufacturer's instructions. The procedure may take 10 to over 90 minutes. It is recommended to disconnect vaporisers and to change breathing circuit and soda lime canister or

3. Use the activated charcoal filters (ACFs).

Before attaching ACFs, the anaesthesia machine should be flushed with 100% oxygen at max. flow for 90 seconds. The EMHG recommends placing ACFs on both inspiratory and expiratory limb of the breathing circuit. The filters can be applied for max. 12 hours.

According to the MHAUS guidelines, the use of an ICU ventilator that has never been exposed to volatile anesthetic agents is also acceptable.

During anaesthesia, standard intraoperative monitoring should be provided, and core temperature determined [22]. Standard temperature monitoring is advocated in all patients undergoing general anaesthesia longer than 30 minutes and in patients subjected to surgical procedures longer than 1 hour [27]. The above rule is of importance as whenever MH occurs during general anaesthesia, lack of temperature monitoring increases the risk of death by 13 times and higher and is associated with the 30% mortality. Measurement of skin temperature instead of core temperature increases the risk of death during MH crisis almost 10 times due to delayed diagnosis and treatment [28].

After the anaesthetic procedure, ICU hospitalisation is not necessary; standard postoperative care should be administered [22, 29]. Anaesthesia without MH-triggering drugs provides protection against MH.

NEW RESEARCH STUDIES

A systematic review and meta-analysis assessing the incidence of MH are now under preparation; the data from all the countries will be analysed for the first time. The analysis is to involve the subgroups according to geographic region, age, race, gender and triggering factor [30].

The on-going study at the Children's Hospital Medical Center in Cincinnati aims at determining the factors conditioning penetrance of the mutations that are known to cause MH. The authors are to determine how genetic mutations in connection with non-genetic factors affect the MH risk in children undergoing general anaesthesia with triggering factors [31].

SUMMARY

Malignant hyperthermia is a challenge for anaesthesiologists and those responsible for health care organisation. Appropriate preparation of institutions providing medical services as well as anaesthesiologists and intensivists ensures a significant reduction in MH mortality. The Polish Society of Anaesthesiology and Intensive Therapy (PTAiIT) was a signatory to the Helsinki Declaration concerning the safety of patients in anaesthesiology; one of the assumptions was to have the procedure for MHE designed [32]. The Section of Paediatric Anaesthesiology and Intensive Therapy of the PTAiIT issued the statement that dantrolene should be available in any centre anaesthetising children. It seems, however, that this recommendation is not observed in all such places. Another issue is that the *in vitro* contracture test cannot be performed in Poland while genetic testing is available.

Although MH episodes are incidental, the MH knowledge among anaesthesiologists should be continuously updated; the present paper is to serve this purpose.

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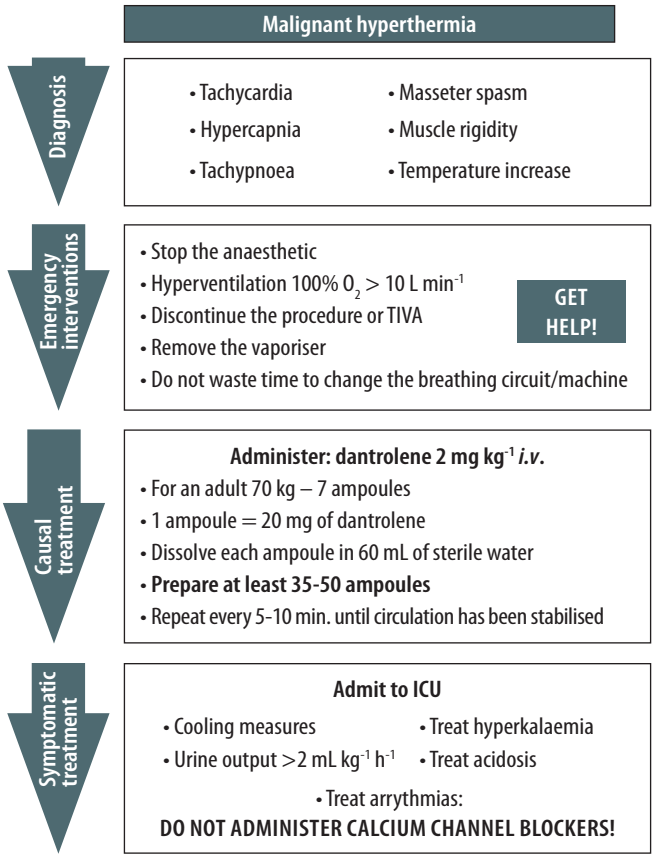

Malignant hyperthermia			
1. Diagnosis	• Increased end-tidal CO_2 • Tachypnoea, if breathing spontaneously • Tachycardia, ventricular arrythmias • Masseter spasm after succinylcholine • Muscle rigidity • Enhanced skin temperature	• Decreased saturation • Arterial pressure fluctuations • Hyperhidrosis • Marmorated skin • Metabolic and respiratory acidosis	
2. Action **GET HELP!**	• Stop the anaesthetic • Hyperventilation 100% O_2 > 10 L min^{-1} • Discontinue the procedure or TIVA • Remove the vaporiser • Do not waste time to change the breathing circuit/anaesthetic machine		
3. Treatment Monitoring	**DANTROLENE 2mg/kg** • For an adult 70 kg –7 ampoules • 1 ampoule = 20 mg of dantrolene • Dissolve each ampoule in 60 mL of sterile water • Prepare at least 35-50 ampoules • Repeat every 5-10 min until the circulation has been stabilised	**MONITORING** • ECG, SpO_2, $etCO_2$, BP • Temperature • Arterial blood gases • CK, myoglobin, glycaemia • Coagulogram • Urine output • Central access • Arterial line	
4. Symptomatic treatment **ICU admission**	**HYPERTHERMIA** • Cold fluids *i.v.*: 2–3 L of 0.9% NaCl 4°C • Ice packs over the neck, groins, under armpits • Gastric, bladder, rectum lavage with cold solutions • Therapeutic hypothermia • Stop cooling at < 38.5°C	**HYPERKALAEMIA** • Infusion of glucose with insulin • Glycaemia – every hour • $CaCl_2$ 10 mg kg^{-1} *i.v.* • Dialysis **ARRYTHMIAS** • Amiodarone 300 mg *i.v.* • β-blocker • No calcium channel blockers!	**ACIDOSIS** • Hyperventilation • Bicarbonates 1–2 mEq kg^{-1} **FORCED DIURESIS** • >2 mL kg^{-1} h^{-1} • Furosemide 0.5–1 mg kg^{-1} • Mannitol 1g kg^{-1} • Crystalloids

Description: lek. Agnieszka Cieniewicz