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Review

Malignant Hyperthermia in Belgium: 35 years of practice-led research

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Abstract

As of 1986 a laboratory for the diagnosis of Malignant Hyperthermia (MH) was established at the University of Antwerp which since then served as the national reference laboratory for this rare anesthetic complication. Our unit is an accredited lab within the network of the European Malignant Hyperthermia Group and thus has had the chance to attain a solid practical expertise in this disorder, as well as to collaborate in several multicentre studies on MH.

The present review summarizes what collaborative international research has taught us about MH over the last 3,5 decades, and covers evolving insights in such topics as pathophysiology, clinical presentation, treatment, anesthesia for patients with an increased risk of developing MH, molecular genetics, diagnostic work-up and relationship to other myopathies.

Keywords: **Malignant Hyperthermia, anesthetics, muscular diseases.**

Key points

- Malignant Hyperthermia is rare, but fatalities still do occur. Early recognition is the key to a safe outcome.

Mutations in... the genes encoding for the SR 'calcium-release channel complex' induce a prolonged 'open state'. As a result, when subjected to halogenated agents larger than normal amounts of calcium are released from the SR, inducing an MH-crisis.

- A telltale clinical sign is an $ETCO_2$ that continues to rise despite adjusted ventilation.
- The clinical presentation has become more variable than in the halothane/succinylcholine era with insidious presentations, and onset as late as several hours after induction
- Four therapeutic measured should be applied together:
  - eliminate the trigger agent
  - hyperventilate to eliminate CO_2 and correct the acidosis
  - give iv dantrolene 2 mg/kg
  - start active body cooling
- Dantrolene and activated charcoal filters should be available at all locations where general anesthesia is administered.
- Genetic research has demonstrated that changes in the RYR1 genetic code are the most common cause of MH-susceptibility. In less than 1% of patients variants in the regulatory proteins CACNA1S or STAC3-genes are found.
- Reliable familial genetic counseling can be offered in 10 – 20% of families i.e. those with proven pathogenic mutations. In combination with in vitro contracture testing in key individuals this increases to around 50%.
- Before discharge from the hospital, the patient should be informed about the suspected diagnosis of MH, including its implications for her/him and the family.
- Patients at increased risk of developing MH should receive (loco)regional or total intravenous anesthesia. The anesthesia workstation should be

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emptied of trace amounts of volatile anesthetics either by means of prolonged flushing, or (preferably) the use of activated charcoal filters.

Malignant Hyperthermia (MH) is an inherited muscle disease which manifests as an acute rhabdomyolysis during general anesthesia when susceptible individuals are exposed to halogenated anesthetics and/or succinylcholine. Even though the overall mortality dropped from over 70% in the 1970-80s to as low as 5 – 10% nowadays it is still a dreaded complication. Indeed, it most often unexpectedly occurs in children and young adults during 'routine' surgical procedures. Furthermore it is inherited as a dominant disease conferring a risk to a whole family, not only the one individual involved.

Pathophysiology

In what is generally considered to be the first comprehensive description of MH as an anesthesia-induced event entitled 'Anaesthetic deaths in a family' in 1962, it was stated that 'The nature of the anomaly is not known', but 'demonstrates a pattern of inheritance due to an incompletely penetrant dominant gene or genes'[1]. Within the following decade the same authors having found that serum CPK-levels were elevated in many of the family members, postulated that "MH develops in individuals with a myopathy which is inherited"[2].

Based upon further research observations it was stated that a "difference in plasma calcium might represent a fundamental distinction"[3]. The following years it was demonstrated that the primary defect indeed resides in the membrane of the sarcoplasmic reticulum (SR), and that, in patients who are genetically predisposed, halogenated anesthetic agents alter the transporting properties of the SR-membranes. SR stores Ca- ions when muscles are at rest. In response to electrical depolarization, the principal SR-calcium release channel – the 'RYR1 channel' - releases Ca-ions from the SR into the myoplasm. The resulting increase in concentration allows the interaction between actin and myosin, and contraction of the muscle. This process by which electrical signals trigger muscle contraction is called excitation-contraction (E-C) coupling (Figure 1).

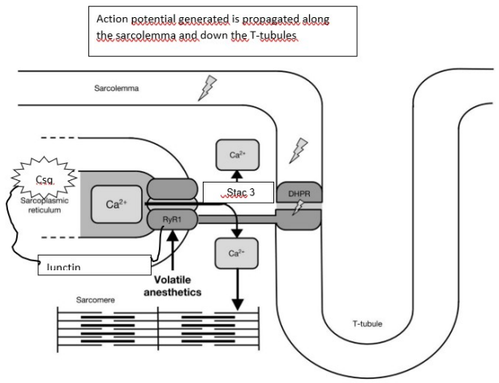

Fig. 1 — Functional implication of RYR1/DHPR receptor mutations after exposure to volatile anesthetics: the action potential generated in the motor endplate is propagated along the sarcolemma and down the T-tubules, to be captured by the voltage sensitive dihydropyridine receptor. The depolarization-induced conformational change in turn leads to the opening of the RYR1 calcium-channel, and calcium release from the SR into the myoplasm. Ca-interaction with actin and myosine results in contraction. Mutations in the RYR1-DHPR complex, and potentially in associated proteins such as junctin, Stac 3, upon exposure to inhalational aneshtetics lead to a 'longer open state' of the channel, with massive calcium release from the SR, inducing an MH reaction.

In 1990 McLennan concluded from linkage studies that MH was likely to be caused by mutations in the RYR1-gene[4]. Since then, this finding has been confirmed and resulted in the concept that RYR1-mutations lead to a prolonged 'open state' of the Ca-release channels. As a result, when these patients are subjected to halogenated agents, enormous amounts of Ca are released from the SR inducing an MH-crisis by a number of metabolic derangements summarized in Figure 2, and commented upon in the 'clinical presentation'[5].

Clinical presentation

Monitoring during anesthesia in the 1960-80s was solely based on clinical observation of physical signs (absence of movement, blood pressure, heart rate, respiratory rate, peripheral perfusion) and without today's pulse oximetry and capnography. The clinical features of the MH-reactions were originally therefore described as tachycardia, hemodynamic instability, sweating and progressive hyperthermia possibly leading to death. The 'malignant' part of the name has proved useful in emphasizing the potentially fatal outcome of MH. However, with the changing over time of anesthetic technique and monitoring, the 'hyperthermia' component has become less useful as nowadays fever >39°C more often than not identifies a relatively late feature of a reaction in which expeditious intervention is important. To consider an early diagnosis Hopkins therefore suggested to think of MH as 'malignant hypermetabolism'[6]. Indeed, the earliest clinical features (rising $ETCO_2$, tachycardia) point at the metabolic nature of the reaction, following the triggered Ca-release. One very useful dictum by TCK Brown states: "the most useful clinical sign of MH is an $ETCO_2$ that continues to rise despite increasing ventilation"[7].

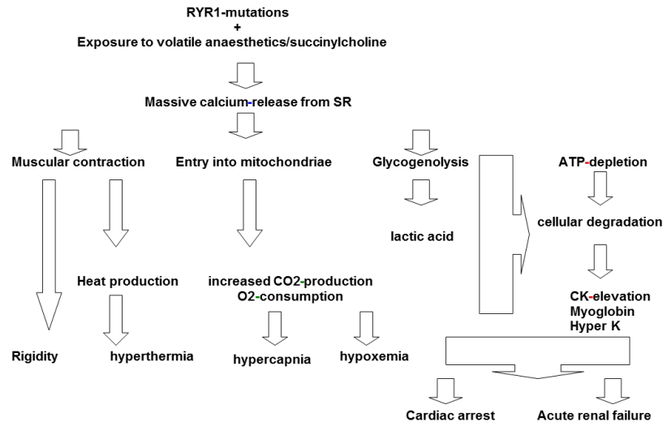

Fig. 2 — Main metabolic processes involved in an MH-crisis.

As is true for the hyperthermia, the amount of muscle damage (rhabdomyolysis) in the early stage of the crisis is limited, and there is considerable overlap between peak CPK levels in patients suspected of having had a non-sustained/early treated MH episode and CPK changes occurring after surgery, certainly surgeries having substantial tissue damage.

If an MH-reaction is allowed to proceed unchecked, the metabolic overactivity will lead to pronounced respiratory acidosis with $ETCO_2$ often attaining 100 mm Hg, hyperthermia, muscle rigidity, hyperkalemia, acidosis and hypoxia. Later, as demands on the homeostatic mechanisms become overwhelmed, and ATP-supply becomes insufficient, membrane potentials cannot be maintained and the permeability of the cell membrane increases entailing a loss of H+, phosphate, Mg++, K+., myoglobin and creatine kinase into the bloodstream. A change to anaerobic metabolism and production of lactate worsens acidosis. Massive rhabdomyolysis is associated with muscle swelling and may lead to a compartment syndrome and/or acute renal injury. Diffuse intravascular coagulation may develop as a consequence of pronounced hyperthermia.

The combination of respiratory acidosis, sympathetic stimulation, and hyperkalemia is highly arrhythmogenic, and cardiac arrest should be anticipated unless the process still can be reversed by dantrolene.

The increasing body temperature in itself accelerates the metabolic process. Oyama et al demonstrated that the mutants of RYR1 are temperature-hypersensitive compared with the receptors not carrying mutations, thus leading to accelerated heat-induced Ca-release further aggravating the process[8]. Therefore early temperature management is important even when the degree of fever in itself is not life-threatening.

Clinical variability: In the halothane/succinylcholine era of anesthesia reactions tended to occur soon after the administration of the triggering agents with clinical signs becoming apparent within minutes, hence the adjective 'malignant'.

However, over the last 2 decades several insidious cases of MH with onset as late as several hours after induction have been reported[9,10,11,12]. We therefore nowadays know MH to have a highly variable clinical presentation. This is true for both the timing of onset (early versus late), as well as the magnitude of the clinical signs (fulminant versus insidious).

In a collaborative study of six participating centres we also found a wide histopathological spectrum in patients with MH and rhabdomyolysis due to RYR1-mutations. In only 10% of patients, and even though these patients carried a pathogenic mutation, the histological analysis was normal. In the other 90% myopathic features were found ranging from an increase in the number of fibres with internal nuclei (60%), centralized nuclei (36%), increased fibre size variation (88%), type-I-fibre predominance (26%), unevenness on oxidative staining (48%) to central cores (14%) and multiple minicores (6%)[13].

The variability in clinical presentation of MH is due to genetic -, as well as anesthesia-related factors[12]. Moreover, external conditions such as preexisting fever, pain and stress and previous muscle damage can influence the severity of the reaction[14].

Genetic factors: to date over 400 different RYR1 variants have been reported to be potentially linked to MH-susceptibility. In vitro experiments have clearly demonstrated that some of these mutations have more profound functional consequences than

others: an experiment by Carpenter in 2009 showed that different RYR1-variants are consistently associated with more or less pronounced in-vitro responses to test drugs, and serum CK-level[15]. They concluded that different mutations confer a differential calcium-conductance to the Ca-channel. To some extent this depends on the location of the variant in the channel structure, with mutations in the pore region inducing more severe effects than in the peripheral regions.

Anesthesia-related factors:The particular inhalation anesthetic used has an influence on the clinical course as the relative potency of the inhalation agents in this respect varies considerably: halothane > isoflurane > sevoflurane > desflurane. This has been shown by studying the time interval between induction of anesthesia and the development of signs of MH. A statistically significant faster onset of the MH reaction was found with halothane versus enflurane versus sevoflurane[16].

The incremental contracture response of MH-muscle seen after in-vitro exposure to increasing concentrations of halothane provides evidence that triggering is dose-dependent. This is felt to explain why MH is more prevalent and more fulminant in children who are exposed to higher concentrations during inhalation induction, whereas adults are only exposed to the lower maintenance concentrations following iv induction. The extent to which hypermetabolism develops is also time-dependent and therefore short procedures, or withdrawal of volatile agents early in the course of the reaction, result in too short an exposure to fully develop the syndrome. Symptoms may very well abate when exposure to the triggering agents is ended, even without the administration of dantrolene. In this sense it can be hypothesized that the generalized use of $ETCO_2$-monitoring since the 1990s has played a crucial role in the more timely diagnosis of MH, the subsequent early withdrawal of triggering drugs and therefore its less frequent fulminant presentation.
IV anesthetic agents may either enhance or protect against the development of an MH-crisis. Succinylcholine clearly enhances the clinical response as in combination with a volatile agent it triggers an earlier and more severe reaction compared with a volatile agent alone.

Some intravenous anesthetics on the other hand oppose the triggering. Non-depolarizing neuromuscular blockers have been shown to consistently delay the onset of MH in susceptible pigs, and are associated with a significantly increased onset time and lower postoperative CK concentration in human MH. Centrally acting sympatholytic drugs such as clonidine and dexmedetomidine, more frequently used than 10 years ago, will blunt adrenergic reactivity such as tachycardia and hypertension. The use of drugs that reduce sympathetic heart rate responses (beta-blockers, remifentanil, high-dose opioids), will also suppress the clinical signs, at least in an early phase.

Even with this in mind it is clear that the observation that some MH-susceptible individuals may have been repeatedly but uneventfully exposed to halogenated agents before eventually developing an MH-reaction suggests the variable presence of additional modifying factors.

These include severe pain and stress (e.g. from fractures), increased baseline body temperature due to intercurrent infection, the recent intake of recreational drugs, and intense exercise in the days preceding the anesthesia[14].

The current point of view therefore is that MH is a multifactorial event, determined by genotype, the combined administration of halogenated agents/IV drugs, and additional circumstances that may exert a synergistic or antagonistic effect.

Therapy

According to a North American clinical study MH has a morbidity rate of 20-30%[10]. Their analysis also provides solid evidence that better patient outcomes are associated with an early diagnosis and treatment.

The European Malignant Hyperthermia Group (EMHG) already published recommendations on the treatment of MH in 2010 entitled "Recognition and management of a malignant hyperthermia crisis"[17]. The only change in this guideline over the last decade was the implementation of activated charcoal filters as a means to promote the wash-out of volatile agents.

The mainstay of therapy consists of four simultaneous measures:

- eliminate the trigger agent by
  - immediately halting the administration of volatile agents (turn off and remove vaporiser from breathing circuit)
  - applying activated charcoal filters (Vapor Clean^R) in both in- and expiratory limb of the breathing circuit
- hyperventilate (minute volume x 2-3) to eliminate CO_2 and correct the respiratory acidosis
- give loading dose of iv dantrolene 2 mg/kg actual body weight (response on $ETCO_2$, heart rate and temperature can be anticipated in a few minutes)
- start body cooling: IV administration of cold crystalloid , place ice packs

Other recommended measures to be taken:

- Call for help
- Revert to TIVA if surgery needs to be continued
- Repeat dantrolene 1 mg/kg dose every 10 min until the reaction subsides

Treatment goals are

- $PaCO2 < 6$ kPa or 45 mm Hg with normal minute ventilation
- temp < 38,5°C

- Treat arrhythmias according to local instructions (but avoid calcium channel blockers).
- Look for corrobative evidence with documentation of events in the anesthesia file
- Obtain laboratory studies: arterial blood gas, electrolytes, coagulation profile, muscle enzymes during/shortly after the event, and repeat after 12-24 hrs.
- It is clearly advized that before discharge from the hospital the patient be informed about the suspected diagnosis of MH, including its implications for patient and family.

Dantrolene is a direct-acting muscle relaxant shown to inhibit RYR1-dependent Ca_{2+}- transients, thereby serving to decrease resting Ca_{2+} in the myoplasm. It does not inhibit RYR_2-receptors present in the myocardium which explains why the drug has no negative inotropic effects.

The compound is highly lipid soluble, and water insoluble. Mannitol and sodium bicarbonate help to solubilize dantrolene but the resulting alkaline solution is irritating to peripheral veins.

Overdosing with dantrolene results in CNS-depression, hypotension, vomiting and muscle weakness which lasts for up to 72 hours. Dantrolene may interact with, and potentiate other drugs e.g. Ca-channel blockers, non-depolarizing neuromuscular blockers as well as the sedative action of benzodiazepines or other CNS-depressants.

There is general agreement that dantrolene should be stocked wherever halogenated anesthetics are used. The EMHG advised in 2020 that "36 vials of dantrolene should be immediately available with a further 24 vials available within 1 h"[18].

The 2019 revision of the Belgian standards for patient safety in anesthesia state that "a minimum of 240 of Dantrolene (20 vials) must be immediately available, at all times"[19].

The discussion about how much dantrolene should be stocked is a long-standing one. The efficacy of dantrolene is not doubted but it is considered too expensive for the rare instances it is used. The actual hospital price in belgium is close to 70 euros/20 mg which means that 36 vials entail a cost of 2520 euro for a shelf life of 2,5 years, or a cost of 1000 euro/y.

This is considered a waste of money certainly when the dantrolene remains unused and expires. However when compared to the cost of the several defibrillators many hospitals permanently deploy - rightfully considered a necessary emergency tool - but seldomly use, dantrolene is in fact inexpensive when prorated.

In 2014 a nanosuspension of dantrolene was commercialized in North America (Ryanodex^R). The 20 ml vials contain 250 mg of dantrolene. This formulation requires significantly less IV-fluid to reconstitute and the loading dose can be administered significantly faster than Dantrium^R (1-2 min versus 10–15 min). The cost of Ryanodex^R is about thrice that of Dantrium^R. This formulation is not commercialized in Europe.

Anesthesia for patients with an increased risk of developing MH

Patients who are known or suspected to be MH-susceptible can safely be anesthetized with (loco) regional anesthesia regardless of the class of local anesthetic drugs.

If general anesthesia or sedation is required, the triggering volatile agents and succinylcholine must be avoided at all times. In order to also avoid trace amounts of volatile agents present in the anesthesia workstation the breathing circuit including the reservoir bag and soda lime canister should be changed for uncontaminated ones, and the anesthesia machine should be flushed with a fresh gas flow of 10L/min for at least 60 min. In case there is insufficient time for this: install an uncontaminated breathing circuit, flush with air with maximum flow rate for 90 seconds and insert activated charcoal filters (VaporClean^R) in both inspiratory and expiratory limbs. These filters have to be changed after 12 hours of use.

A logical choice of anesthesia regimen in these patients is TIVA with propofol, morphinomimetic and if necessary, a non-depolarizing muscle relaxant. Pretreatment with dantrolene is not advised in view of its side-effects (thrombophlebitis, muscle weakness, potentiation of muscle relaxants)[20].

The EMHG also has developed recommendations to provide a safe anesthesia technique in parturients and their offspring (www.emhg.org/recommendations).

Genetics

Genetic research has convincingly demonstrated that changes in the RYR1-genetic code are the most common cause of MH-susceptibility, with variants being found in up to 70% of families[21]. To date, more than 400 variants have been identified, but based on experimental and/or clinical evidence, thusfar only 48 of these are considered to be truly pathogenic (www.EMHG.org/genetics). Only when one of these pathogenic variants is identified,

can MH-susceptibility in an individual be confirmed and can genetic testing be extended to family members. All members of the family carrying this specific variant should be considered MH-susceptible On the other hand, individuals who do not carry this familial variant unfortunately cannot be ruled out to be MH-susceptible because of the possibility of more than one variant being present in a particular family. Therefore patients without the familial muations should be offered contracture testing to confirm their MH-negative status.

This also implies that the vast majority of code sequence changes still are considered 'variants of unknown significance (VUS's)' as it remains unknown whether they truly induce an increased Ca-release from the SR, and translate into an MH-reaction. The detection of one of these therefore remains of doubful diagnostic value.

In a publication in 2019 in the AAB we summarized the results of RYR1-sequencing in a cohort of 34 Belgian families with proven MH-susceptibility. Eighteen different variants were detected in 25 families. Ten of these were considered pathogenic, 8 were variants of 'uncertain significance'. The most frequent mutation was p.Gly341Arg found in 7 different families. Like many other recent reports a high number of different variants was found, the vast majority of which in only a few, or even single families[22].

Two recent insights have to be emphasized:

Excitation-contraction coupling and Ca-release from the SR are highly complex processes. The core of the Ca-release channel is the RYR1 derived protein structure physically spanning the junctional space and interacting with tetrads composed of four voltage-activated subunits of the dihydropyridinereceptor within the T-tubule membrane. The Ca-release is the result of bidirectional signaling and tightly regulated functions of both channels.

Moreover, the Ca-release is also subject to regulation by several other proteins within the triad junction, amongst which: STAC3 (regulatory protein thought to stabilize the DHPR-RYR1 complex (www.emhg.org)), triadin, junctin, calsequestrin, calmodulin,…

Over the last ten years several variants have been found in the genes encoding some of these proteins with the same 'gain-of-function' effect on Ca-release: CACNA1S encoding the alpha 1-subunit of the dihydropyridine receptor (DHPR) and STAC3.

The vast majority of variants involve RYR1, only approximately 1% involve variants in CANCA1S or STAC3[21]. Further potential candidates are variants in the ASPH gene (encoding junctin which functions as a regulator of EC-coupling) and the TRPV1-channel who was also demonstrated to have a role as an SR Ca_{2+} channel[23,24].

With this complexity in mind it is clear why even with the currently available whole exome screening programs, in about one quarter of families no genetic variants can be detected neither in RYR1 or in any genes encoding for the auxiliary proteins.

Further complicating genetic counseling is that more and more evidence demonstrates that it is not uncommon for some MH-families to harbour more than one genetic factor – eg multiple mutations in RYR1[25], or a mutation in RYR1 plus sequence changes in other myopathy- associated genes that play important roles in muscle function. The conclusion is that MH-susceptibility at least in a significant minority of families is genetically heterogeneous.

This means that at present MH genetic testing has not attained the anticipated level in sensitivity and specificity. In only in 10 – 20% of families can genetic techniques be used on their own, eg those with the true pathogenic mutations. When combined with a muscle biopsy in the proband of the family however genetic counseling appears to be feasible in about 50% of families overall[21].

Diagnostic work-up

A family's disposition to MH is identified by a clinical MH-episode in the proband. Epidemiological studies have shown that MH most often is transmitted in an autosomal dominant way; therefore all family members are at risk with first degree family members having a 50% risk.

Because MH is both life threatening and preventable, it is of paramount importance to accurately diagnose susceptibility and thus effectively manage the MH-patient during procedures requiring general anesthesia.

Since the late 1980 the gold standard for the detection of MH-susceptibility is the in vitro contracture testing (IVCT) with caffeine and halothane in which muscle tissue is exposed to incremental doses of these drugs, and the contracture response is measured.

This test has been standardised across Europe by the European Malignant Hyperthermia Group and shows a high degree of sensitivity (99%) and specificity (93.5%): (http://www.emhg.org).

The test is considered abnormal (MH-susceptible) if a sustained contracture of at least 2 mN (0.2 gr) is obtained at caffeine concentrations of 2 mM or less, and halothane concentrations of 2 Vol% or less. Normal individuals (MHN) do not react at the threshold concentrations of either agent.

The currently employed diagnostic work-up of a clinical diagnosis of an MH-crisis in a proband in our laboratory is as follows: the decision to commence by either muscle biopsy or genetic analysis is based on the available clinical information. Convincing evidence of an MH-crisis allows for first line RYR1-sequencing whereas a doubtful episode first requires IVCT either corroborating the clinical diagnosis, or negating it. Further family counseling is based upon a combination of IVCT data and genetic analysis.

Since the start of our diagnostic MH-lab over a 1000 patients have been investigated by either IVCT or genetic tests, roughly 40% of which showed evidence for MH-susceptibility. In 2019 we published an overview of the then available DNA-analysis in our population[22].

We noticed a significant change in the referral indications for in vitro contracture testing over the last few years: the proportion of patients referred without a history of MH but because of variants of unknown significance in RYR1 has signficantly increased from 0% 5 years ago to half of the referrals in 2022. These class 3 variants are being detected during the diagnostic workup of single or recurrent episodes of rhabdomyolysis, or chronic aspecific signs of a myopathy such as pronounced muscle cramps, myalgia or muscle weakness. Close to 40% of this group of patients have an abnormal IVCT, and therefore have to be considered at risk to develop an MH-crisis when exposed to triggering agents[26].

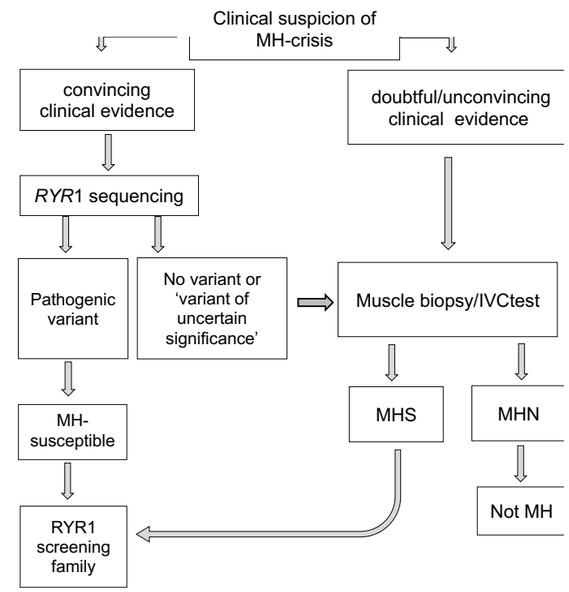

Fig. 3 — Flowchart of the currently used diagnostic work-up of a clinical suspicion of an MH-crisis in a proband. The decision to start by either muscle biopsy or molecular genetic analysis is based on the available clinical and biochemical information: convincing evidence allows for first-line RYR1 sequencing in the hope of finding a diagnostic RYR1 mutation, whereas a doubtful episode first requires in vitro contracture testing either corroborating the clinical diagnosis, or negating it. Further family counseling is based upon a combinaton of IVCT data and molecular genetic analysis.

Relationship to other myopathies

Until about a decade ago it was thought that many different disorders of the musculoskeletal system predisposed to MH-susceptibility. This has been the case amongst others for osteogenesis imperfecta, Noonan syndrome, CPTII deficiency, Brody disease, myotonia congenita, Duchenne and Becker dystrophy, the core diseases, hypokalemic periodic paralysis, metabolic myopathies such as McArdle's disease, etc..

The (in)significance of this 'association' has been the cause of a long debate for several reasons: the clinical signs of an MH episode such as hyperther-

mia/tachycardia/respiratory acidosis are aspecific, the clinical documentation and appropriate investigations were often absent, and last but not least the invasive nature of confirmatory tests of MH-susceptibility does not simplify the distinction between MH-susceptibility and systemic and/or neuromuscular complications from other causes.

The spectrum of complications in dystrophic patients to react adversely to anesthetic agents including life-threatening rhabdomyolyis most resembles an MH-crisis and has been reported repeatedly, including fatal cases. This however is primarily based on 'toxic' effects of the anesthetic drugs – certainly succinylcholine, more rarely volatile anesthetics - on a fragile sarcolemma. Therefore the term 'anesthesia induced rhabdomyolysis' has been coined to this complication, which is now considered to be a different entity than the rhabdomyolysis on the basis of RYR1-mutations. As a preventive measure however prolonged administration of volatile anesthetics, and certainly succinylcholine, should be avoided.

Other neuromuscular disorders may also predispose to anesthesia-related complications in their own right but a definite increased risk for MH only appears to exist for the so-called 'congenital myopathies'. Affected patients usually present from birth or infancy with non- or slowly progressive generalized hypotonia and muscular weakness. Motor milestones are delayed while intelligence is normal.

These individual entities include central core disease, multiminicore disease, centronuclear (myotubular) myopathy, congenital fibre-type proportion, and King-Denborough syndrome. These diseases are genetically heterogenous with over 20 genes being involved, often in combination with RYR1-gene mutations, and therefore called 'RYR1 myopathies". These patients are considered to be at risk for MH.

Detailed recommendations for the anesthetic management of patients with neuromuscular disorders in general, and specific recommendations for 1)the neuromuscular junctions disorders, 2)the nondystrophc myotonia and periodic paralysis, 3)myotonic dystrophy types 1 and 2, 4)muscular dystrophy, 5)congenital myopathies and congenital dystrophies and 6) mitochondrial and metabolic myopathies have been published recently in a consensus document by the European Neuromuscular centre[27].

For quite some years and in view of their similar clinical presentation an association has been suggested between heatstroke, exertional rhabdomyolysis and MH[28,29,30]. All tree present with variable combinations of hyperthermia and rhabdomyolysis but are triggered by either streneous physical activity, abnormal environmental conditions or general anesthesia. The initial evidence was based on the finding of abnormal IVCT's in these patients. In one large study 45,6% of 466 subjects showed a result indicative of MH-susceptibility[30]. A problem however is that the IVCT has been validated in the diagnosis of MH-susceptibiliy, but not for these other entities. More recently evidence for an association is also suggested by genetic studies finding a high prevalence of RYR1-variants in these patients. One study published in 2013 in 39 unrelated identified 9 RYR1-mutations/variants in 14 families, 5 of them previously associated with MH31. Although it is clear that heatstroke and exertional rhabomyolysis again show a wide genetic spectrum in nature, patients who have presented with such an episode should be considered to carry a higher risk for MH than the overall population risk.

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