"The changing face of malignant hyperthermia: Less fulminant, more insidious"

Heytens, Luc ; Forget, Patrice ; Scholtes, Jean-Louis ; Veyckemans, Francis

Abstract
Modern anaesthetic techniques have resulted in the clinical presentation of malignant hyperthermia to be more often indolent and/or insidious than truly fulminant, as previously known in the anaesthetic community. We present four recently referred cases to illustrate this point: one late-onset case, two patients with slowly progressive hypercapnia as the sole sign and a fourth patient with postoperative myalgias and elevated creatine kinase. We also discuss the reasons for the shift in typical clinical presentation. The more insidious character of malignant hyperthermia is most likely due to the lower triggering potency of modern volatile anaesthetics, the mitigating effects of several intravenous drugs (neuromuscular blocking agents, alpha 2 adrenergic receptor agonists, beta-adrenergic blockade) or techniques (neuraxial anaesthesia) and the routine use of end-tidal CO2 monitoring leading to the early withdrawal of triggering drugs. Awareness among anaesthetists of this change in pr...
The changing face of malignant hyperthermia: less fulminant, more insidious

L. Heytens*, P. Forget†, J. L. Scholtès‡, F. Veyckemans§

Summary
Modern anaesthetic techniques have resulted in the clinical presentation of malignant hyperthermia to be more often indolent and/or insidious than truly fulminant, as previously known in the anaesthetic community. We present four recently referred cases to illustrate this point: one late-onset case, two patients with slowly progressive hypercapnia as the sole sign and a fourth patient with postoperative myalgias and elevated creatine kinase. We also discuss the reasons for the shift in typical clinical presentation. The more insidious character of malignant hyperthermia is most likely due to the lower triggering potency of modern volatile anaesthetics, the mitigating effects of several intravenous drugs (neuromuscular blocking agents, alpha 2-adrenergic receptor agonists, beta-adrenergic blockade) or techniques (neuraxial anaesthesia) and the routine use of end-tidal CO₂ monitoring leading to the early withdrawal of triggering drugs. Awareness among anaesthetists of this change in presentation is important since the clinical diagnosis is often more doubtful and, if corroborative evidence is not sought, the diagnosis may be delayed or missed altogether.

Key Words: anaesthetics volatile-halogenated hydrocarbons, complications, malignant hyperthermia, genetic factors, hyperthermia, phenotype

With the aim to provide a comprehensive ‘clinical case definition’, the ‘malignant hyperthermia (MH) clinical grading scale’ lists six indicators of an MH crisis: rigidity, muscle breakdown, respiratory acidosis, temperature increase, cardiac involvement and “other indicators of metabolic derangement not part of a single process”1. In the majority of cases during the era of halothane/succinylcholine use, a combination of most of these signs was reported, resulting in a qualitative likelihood of MH rank 5, ‘very likely’, or 6, ‘almost certain’. Hence, and in view of its then considerable morbidity and mortality, MH became known as a fulminant event. However, changes in the practice of anaesthesia over the last few decades have resulted in more insidious MH patterns, making the immediate clinical diagnosis more difficult to establish. We present four recently referred cases to illustrate this point and discuss the likely reasons for this shift in clinical presentation.

Written informed consent was obtained from all patients for the case descriptions. With the aim to present these cases in a uniform way, we included personal and family anaesthetic history, positive clinical and biochemical findings, in vitro contracture test (IVCT) results, histological and molecular genetic findings and pertinent negative findings. Details on the breathing circuit used are lacking but, since all crises occurred in adults, we assume these to be rebreathing double-limb circuits with CO₂ absorption, fresh-gas flow unknown and minute ventilation as stated. The diagnosis of MH susceptibility was confirmed by IVCT according to the protocol of the European Malignant Hyperthermia Group. This test is considered positive if a contracture of at least 2 mN is obtained at a caffeine concentration of 2 mM or less and/or halothane concentration of 2 Vol% or less. The sensitivity and specificity of this test have been reported to be 99% and 94% respectively2.

Case 1

Male, 47 years old, 91 kg

First anaesthetic, scheduled for varicectomy. Personal history: strabismus. Negative anaesthetic family history. Induction of anaesthesia: propofol 200 mg, sufentanil 10 mcg, cisatracurium 12 mg. Maintenance: 2 Vol% sevoflurane in O₂/N₂O mixture. No temperature monitoring, no warming device. Duration of anaesthesia: 150 minutes. During the first hour, end-tidal CO₂ remained between 33 and 38 mmHg but rose steadily thereafter, reaching 50 mmHg after 1.5 hours. Despite increasing ventilation to 14 l/minute, end-tidal CO₂ reached 103 mmHg after 2.5 hours of sevoflurane administration. Arterial blood gases were: pH 7.1, pCO₂ 105.9 mmHg, pO₂ 91 mmHg, bicarbonate 32.3 mmol/l. Blood pressure decreased from 110/65 after induction to 80/45 mmHg at the end of anaesthesia; heart rate increased from 60 to 85 bpm. Rectal temperature was 38°C. No rigidity was noted.
Dantrolene 100 mg was administered 15 minutes after stopping sevoflurane, resulting in the normalisation of end-tidal CO₂ over one hour. The serum creatine kinase (CK) level one hour postoperatively was 390 U/l (normal range 55 to 190 U/l) and peaked at 16,650 U/l after 12 hours. Potassium reached 7 mmol/l. Acute renal failure did not occur. The MH clinical grading scale score was 45—rank 5, ‘very likely’.

Muscle biopsy performed three months later revealed normal histology and an IVCT indicative of MH susceptibility (30 mN contracture at 2 mM caffeine, 23 mN contracture at 2 Vol% halothane). A full c-DNA 106 exon ryanodine receptor 1 (RYR1) Sanger sequencing (gene coding for the ryanodine receptor) did not reveal any variants.

**Case 2**

**Male, 16 years old, 50 kg**

Emergency surgery for a forearm fracture. Personal history: previous general anaesthesia for tonsillectomy without untoward effects. As a well-conditioned athlete he was known to have a sinus bradycardia. Negative anaesthetic family history.

Rapid-sequence induction: propofol 150 mg and succinylcholine 50 mg. Impression of insufficient relaxation of the mandible but endotracheal intubation was successfully achieved at the first attempt and subsequent mechanical ventilation was without any problem. Maintenance of anaesthesia: 3 Vol% sevoflurane in O₂/air mixture supplemented with sufentanil IV; no further muscle relaxant was given. No temperature monitoring was used with no warming device. The duration of exposure to sevoflurane was 30 minutes. End-tidal CO₂ monitoring revealed an increase to 55 mmHg over 30 minutes despite progressive augmentation of minute ventilation to 9.6 l/minute (rate 16 per minute, tidal volume 600 ml). Auricular temperature was 35.1°C. The patient was normotensive and heart rate increased from 40 to 80 bpm. In view of the high end-tidal CO₂ at a minute ventilation of 9.6 l/min and suspicion of MH, anaesthesia was switched to intravenous propofol. Arterial blood gas analysis showed a pH of 7.31, pCO₂ of 51 mmHg and a normal bicarbonate. Dantrolene was not administered. Postoperative serum CK level was not determined. MH clinical grading scale score was 15 (but possibly underestimated as serum CK level was unknown)—rank 3, ‘somewhat less than likely’. Histology was normal. The IVCT showed a contracture of 14 mN at 2 mM caffeine and 22 mN at 2 Vol% halothane. Baseline CK level three months after the event was normal. DNA analysis was not performed.

**Case 3**

**Male, 66 years old, 95 kg**

Urgent laparoscopic appendicectomy for retrocaecal appendicitis. Personal history: two uneventful previous general anaesthetics. Negative anaesthetic family history. In view of previous postoperative nausea and vomiting, rapid-sequence induction and propofol target-controlled infusion were planned.

Induction of anaesthesia: midazolam 2 mg, propofol 300 mg and succinylcholine 100 mg, followed by a continuous infusion of propofol supplemented with sufentanil, rocuronium 50 mg and clonidine 300 mcg. No temperature monitoring was used and no warming device. During the course of anaesthesia no untoward events were noted, there were no signs of hypermetabolism and end-tidal CO₂ remained between 35 and 40 mmHg during the 150-minute procedure. The CK level, measured because of severe myalgias on the first day after surgery, was 20,005 U/l. Renal function remained within normal limits. MH clinical grading scale score was 30—MH rank 4, ‘somewhat greater than likely’. Four months later, his IVCT showed contracture of 4 mN at 2 mM caffeine and 7 mN at 2 Vol% halothane. Histology was normal. DNA analysis was not performed.

**Case 4**

**Male, 18 years old, 74 kg**

General anaesthesia for emergency osteosynthesis of a traumatic femoral fracture. Negative personal history. Negative anaesthetic family history.

Induction of anaesthesia: femoral nerve block with ropivacaine, followed by induction of general anaesthesia with propofol 200 mg, sufentanil 25 mcg, atracurium 40 mg. Maintenance of anaesthesia: 2 Vol% sevoflurane in O₂/air mixture supplemented with sufentanil IV. No temperature monitoring, nor forced air warming. Duration of exposure to sevoflurane: 80 minutes. After 60 minutes of anaesthesia, end-tidal CO₂ increased from 42 to 60 mmHg over 10 minutes. Minute ventilation in the meantime had been increased to 14 l/min (rate 22/minute, tidal volume 650 ml). Rectal temperature 36.8°C. The patient remained normotensive but heart rate increased from 70 to 100 bpm. Rigidity was not noted. An MH crisis was suspected on the basis of inappropriate hypercapnia. Sevoflurane was stopped and anaesthesia was converted to intravenous propofol. The arterial blood gas analysis showed a pH of 7.32, pCO₂ of 49 mmHg, pO₂ of 283 mmHg and bicarbonate 25 meq/l. Dantrolene was not administered. Postoperative serum CK level was 1200 U/l and the potassium was 4.8 mmol/l. MH clinical grading scale score: -15—rank 3, ‘somewhat less than likely’. The IVCT one year later showed a contracture of 18 mN at 2 mM caffeine and 40 mN at 2 Vol% halothane. Light microscopy was normal. DNA analysis was not performed.

**Discussion**

MH is a pharmacogenetic disorder of skeletal muscle, transmitted as an autosomal dominant trait and manifests as
hypermetabolism during anaesthesia when susceptible individuals are exposed to volatile anaesthetics and/or succinylcholine. The clinical presentation reflects disturbed calcium homeostasis as a result of defects in the genes coding for the proteins involved in excitation-contraction coupling—the dihydropyridine-ryanodine receptor complex—which serves as the main calcium-release channel in striated muscle. The ensuing sarcoplasmic calcium overload induces sudden, potentially lethal rhabdomyolysis.

MH has most often been described as a clinically fulminant phenomenon, e.g. it is assumed that, upon exposure to triggering agents, MH-susceptible patients will typically present with a combination of rapidly evolving hypercapnia, haemodynamic instability, rigidity, hyperthermia and signs of rhabdomyolysis. Over the last decade however, the number of cases referred with only subtle clinical signs has increased. In view of the small numbers reported to our centre covering a population of only 11 million inhabitants, a true statistical analysis from our data is not possible. But as there is a paucity of literature on this topic, we present a series of four cases, out of a total of six investigated probands over 18 months, with an insidious clinical pattern. During the same period, only one case was fulminant (MH clinical grading scale 3—rank 6, ‘almost certain’); one clinically suspicious but insufficiently documented episode of MH was negated by IVCT.

The large spectrum of manifestations from subclinical to fulminant has always been reported but even a recent retrospective analysis of the characteristics of the index of adverse anaesthetics does not report this shift in clinical presentation. However, studies of this magnitude are hampered in their data interpretation by the lack of a uniform reporting system, limited data availability and variability in diagnostic and management protocols. Therefore, in this study the 44.2% of patients with a ‘less than likely’ or ‘unlikely’ clinical grading scale score are attributed to limitations in data collection rather than incomplete phenotypic presentation. On the other hand, one recent article by Schuster et al does address the difficulty in diagnosing abortive courses.

Three of the four cases presented had a rank 3 or 4 on the MH grading scale, i.e. a qualitative likelihood of ‘somewhat less than likely’ to ‘somewhat greater than likely’. The first case had a likelihood of ‘very likely’ but a very slow onset pattern. Subsequent IVCTs in all cases were indicative of MH susceptibility. Identifying a known MH causative mutation would have corroborated the in vitro diagnosis of MH in these patients, but as our health authorities only recently started to support Sanger sequencing in RYR1-myopathies, these results are not available yet (apart from Family 1). On the other hand, at least one more family member has been diagnosed with MH susceptibility by IVCT, indirectly substantiating the diagnosis in the probands.

Case 1 presented with both clinical and biochemical signs of perioperative rhabdomyolysis, which was, in retrospect, sufficiently indicative of MH susceptibility. Because of the slow onset of the signs, a presumptive diagnosis of MH was only considered after two hours of anaesthesia and for some time even felt to be an argument against MH by the attending anaesthetist. This pattern is more common than generally assumed, as evidenced by several similar reports over the last few years. Regarding the more ‘indolent character’ of MH, a recent paper provides, for the first time, statistical evidence that the MH median onset time was significantly shorter for the cases that occurred before 1998, compared to the cases that occurred later.

The absence of RYR1 mutations upon sequencing is unfortunate as it excludes genetic diagnosis in this family. It is certainly not an argument against MH susceptibility, as it is well known that an RYR1 mutation is found in only 70% of patients with a positive IVCT. CACNA1S cDNA sequencing is now being considered as two mutations in the gene CACNA1S on chrom1 (encoding the main subunit of the dihydropyridine receptor) are consistent with presumed pathogenicity in current databases. The assessment of the pathogenicity of most of these variants, however, remains challenging.

Cases 2 and 4 presented with ‘inappropriate hypercapnia’ as the sole disturbing finding. The anaesthetist was alerted by the progressive hypercapnia, which could not be corrected by increasing minute ventilation to more than twice the minute volume expected to be sufficient for maintaining normocapnia under anaesthesia. Also, in these two cases the abatement of the symptoms without having administered dantrolene created doubt about the diagnosis. Case 3 was highly atypical: biochemical evidence of rhabdomyolysis was detected because the patient reported major myalgias the day after the administration of succinylcholine as a unique MH-triggering agent.

The large variability in clinical presentation of MH is partly due to genetic, and partly due to anaesthesia-related, factors. Regarding differences in genotype, about 400 different RYR1 mis-sense mutations have been reported to be potentially linked to MH susceptibility to date, but only a small minority have been convincingly shown to be ‘causative of MH’ (see www.emhg.org). Apparently, some of these mutations have more profound functional consequences than others. This was demonstrated by Carpenter et al in 2009, who showed that different RYR1-variants are consistently associated with significant differences in IVCT response and serum CK level. They concluded that different mutations confer a differential calcium-conductance to the calcium channel. Besides this, several anaesthesia-related factors are important. The particular inhalational anaesthetic used has an influence on the clinical course. Every inhalational agent, except nitrous oxide and xenon, has been implicated as a trigger, but the relative potency of the inhalational agents in this respect varies considerably. This has been shown by in vitro effects during
contracture testing, by in vivo comparison in susceptible swine and by studying the time interval between induction of anaesthesia and the development of signs of MH in humans. In the latter study, a statistically significant faster onset of the MH reaction was found with halothane (median 20 minutes, range 5 to 45 minutes) versus enflurane (median 55 minutes, range 20 to 480 minutes) versus sevofluurane (median 60 minutes, range 10 to 210 minutes). Data analysis from the North American Malignant Hyperthermia Registry showed a faster MH onset after halothane exposure than isoflurane, but not when compared to sevofluurane. Since halothane is only rarely used in human anaesthesia in Western countries, nowadays a slower onset pattern should be anticipated with the currently used volatile agents.

The extent to which MH develops is said to be time-weighted and therefore short procedures, or withdrawal of volatile agents early in the reaction, result in too short an exposure to fully develop the syndrome. Symptoms may abate when exposure to the triggering agents ends, even when dantrolene is not administered. In this sense it can be hypothesised that the widespread use of end-tidal CO₂ monitoring since the 1990s has played an important role in the more timely diagnosis of MH, the subsequent early withdrawal of triggering drugs and, therefore, its less frequent full-blown presentation.

There is also evidence that the triggering is dose-dependent. This can be deduced from the incremental contracture response of MH muscle seen after in vitro exposure to increasing concentrations of halothane. This is felt to be a contributing factor to MH being 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 an intravenous induction.

Intravenous anaesthetic agents may either enhance or protect against the development of MH. Succinylcholine enhances the clinical response as the combination of succinylcholine with a volatile agent triggers an earlier reaction compared with a volatile agent alone, and survival rates appear to be lower. Other intravenous anaesthetics oppose the triggering. Experiments in susceptible pigs have shown that thionepentone delays the onset. This has not been shown with propofol. Likewise, non-depolarising neuromuscular blocking agents such as pancuronium have been shown to consistently delay its onset in MH-susceptible pigs. Young et al reported that the administration of non-depolarising neuromuscular blocking drugs was associated with a significantly increased onset time and lower postoperative CK concentration in human MH. Barbier et al described a slow-onset case of MH under sevofluurane anaesthesia combined with a mid-thoracic epidural anaesthesia. Part of the explanation may be the sympatholytic effect of the epidural blockade.

Clonidine, an alpha-2 agonist with central sympatholytic action, may blunt adrenergic reactivity and thereby the expected tachycardia and hypertension. The newer dexmedetomidine attenuates sympathetically mediated responses to perioperative and thermal stress. Likewise, although beta-adrenergic blockade does not completely prevent halothane-induced MH in the porcine model, the signs are clearly delayed.

Several cases have recently been published during which the diagnosis of MH was complicated in laparoscopic surgery because the increase in end-tidal CO₂ and mild tachycardia induced by the CO₂ in the pneumoperitoneum confounded their clinical interpretation. However, the extra amount of CO₂ absorbed through the peritoneum is modest compared to the overall CO₂ production in the body. Measurements of the systemic absorption of CO₂ with a metabolic monitor indicate an increase in carbon dioxide production of 15% for peritoneal laparoscopy, and 40% to 60% in patients undergoing retroperitoneoscopy, and end-tidal CO₂ could easily be maintained within normal limits by adjustment of minute ventilation. Therefore, the increase in minute volume needed to correct the hypercapnia is rarely >50%. In case 4, however, even doubling minute volume could hardly correct the hypercapnia and it is exactly this inappropriateness that points at hypermetabolism and a possible MH crisis. Therefore, we entirely agree with the dictum by Brown that “the most useful clinical sign of MH is an end-tidal CO₂ that continues to rise despite increasing ventilation.”

Although asymptomatic increased CK levels have, for years, been considered not to be a reliable predictor of MH suscepti-
tibility, leading to the abandonment of the serum CK level as a screening test for MH\(^{39}\), in our opinion a watchful eye is still advised. Indeed, RYR1 mutations such as c.1021G>C (Gly341Arg) and c.487C>T (Arg163Cys) can be a specific cause of chronically elevated CK activity in patients with strictly normal histological findings\(^{30,31}\). Postoperative rhabdomyolysis, certainly if CK is more than 10,000 U/l without, and more than 20,000 U/l with, the use of succinylcholine, is very suspect and either points at an underlying myopathy or MH susceptibility. The exception may be morbidly obese patients who undergo prolonged procedures leading to a crush and/or compartment syndrome\(^{35}\).

The interactions of drugs and techniques with the presentation and/or the diagnosis of MH are summarised in Table 1.

**Conclusion**

Although MH can still present as a fulminant event in the true sense of the word, anaesthetists should be aware of the increasing proportion of insidious presentations. Whereas fulminant MH is characterised by a combination of rapidly evolving signs of hypermetabolism (hypercapnia, tachycardia, hypertension, hyperthermia), muscular symptoms (masseter spasm, rigidity) and rhabdomyolysis, more and more attenuated presentations occur. We therefore recommend that in our current practice sufficient attention be paid to the following signs or measures, even when occurring as a sole abnormality:

- foremost: persistent, unexplained and difficult-to-correct hypercapnia,
- rapidly increasing and/or inappropriately elevated body temperature,
- masseter spasm following the administration of succinylcholine and
- clinical or biochemical evidence of rhabdomyolysis: increased postoperative CK level, voiding of cola-coloured urine (myoglobinuria), with or without hyperkalaemia.

**References**