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Masterthesis

Diagnostic Challenges of Malignant Hyperthermia: Diverse Clinical Presentations and Genetic Known Mutations – A Narrative Review

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Abstract

Background: **Malignant hyperthermia (MH) is a life-threatening pharmacogenetic disorder triggered by volatile anesthetics and depolarizing neuromuscular blockers. It is characterized by uncontrolled calcium release in skeletal muscle cells, leading to a hypermetabolic crisis. Despite advances in anesthetic safety, diagnosing MH remains challenging due to its clinical variability and genetic complexity.**

Objective: **This narrative review examines the diagnostic challenges of MH, its diverse clinical presentations, and the implications of genetic mutations. The aim is to enhance perioperative recognition and optimize management strategies**

Methods: **A comprehensive search of PubMed, Scopus, and Web of Science identified studies published between 2005 and January 2025. The review includes case reports, clinical guidelines, expert recommendations, and observational studies addressing MH diagnosis, clinical variability, genetic predisposition, and perioperative management.**

Results: **MH presents with a spectrum of clinical manifestations, from acute crises to delayed-onset forms. The in vitro contracture test (IVCT) remains the diagnostic gold standard, while genetic testing for RYR1 and CACNA1S mutations aids in risk assessment. Emerging evidence suggests broader genetic heterogeneity, complicating diagnosis. Early recognition and timely dantrolene administration are critical for reducing morbidity and mortality. Promising advances in metabolomic profiling and artificial intelligence may enable non-invasive risk assessment.**

Conclusion: **Despite improved diagnostic methods, MH remains a significant perioperative challenge. Enhancing early recognition and broadening genetic testing may reduce adverse outcomes. Future research should focus on non-invasive biomarkers and global standardization of diagnostic protocols.**

Keywords: **Malignant hyperthermia, anesthesia, hypermetabolic crisis, RYR1, CACNA1S, dantrolene, genetic mutations, atypical presentation.**

Introduction

Background

Malignant hyperthermia (MH) is a rare but life-threatening pharmacogenetic disorder triggered by volatile halogenated anesthetics and depolarizing neuromuscular blockers such as succinylcholine. MH is most commonly associated with mutations in the ryanodine receptor 1 (RYR1) gene, although other genes such as CACNA1S may also contribute. This calcium dysregulation triggers a hypermetabolic crisis, leading to hypercapnia, metabolic acidosis, hyperthermia, muscle rigidity, and rhabdomyolysis, which, if untreated, can progress to multiorgan failure and death[10].

MH exhibits an autosomal dominant inheritance pattern with incomplete penetrance, meaning not all genetically predisposed individuals experience a crisis. The estimated prevalence of MH susceptibility is approximately 1 in 400 individuals, while clinical crises occur in 1 in 10,000 to 1 in 250,000 anesthetic exposures[10]. Importantly, not all MH cases are linked to identified mutations, underscoring the need for clinical recognition, even in patients with unremarkable genetic findings.

Dantrolene remains the cornerstone of MH treatment, significantly reducing mortality when administered promptly[16,23]. The 2024 European Malignant Hyperthermia Group (EMHG)

guidelines emphasize the criticality of vigilance, given that MH can occur unpredictably, reinforcing the need for vigilance during every anesthesia[12].

Review Context and Rationale

Despite advances in perioperative monitoring and pharmacologic management, early diagnosis of MH remains challenging. This difficulty arises from the disorder's clinical heterogeneity, delayed or atypical presentations, and overlap with other critical intraoperative conditions. In addition, limited access to diagnostic tools such as the in vitro contracture test (IVCT) and uncertainty surrounding genetic variants complicate the diagnostic pathway. A clear overview of these diagnostic challenges and emerging evidence is needed to guide clinical suspicion, risk stratification, and timely intervention.

Objectives of the Review

This narrative review aims to analyze the diagnostic challenges of malignant hyperthermia (MH), its diverse clinical presentations, and the role of genetic mutations in susceptibility and diagnosis. Specifically, it seeks to:

1. Describe diagnostic challenges, including variability in clinical manifestations, risk of delayed recognition, and overlap with other medical conditions.
2. Characterize the clinical spectrum of MH, from fulminant crises to atypical and delayed-onset cases, to improve early recognition and differential diagnosis.
3. Describe current diagnostic methods, including clinical recognition, in vitro contracture testing (IVCT), and genetic screening, highlighting their advantages and limitations.
4. Describe the role of genetic mutations, particularly RYR1 and CACNA1S variants, in MH susceptibility and risk stratification.
5. Discuss the clinical impact of early recognition and intervention, emphasizing how timely diagnosis and management can reduce morbidity and mortality.

By addressing these objectives, this review aims to enhance clinical awareness, improve diagnostic accuracy, and optimize patient outcomes.

Methods

Study Design

A comprehensive search was conducted across PubMed, Scopus, and Web of Science to identify relevant literature published between 2005 and January 2025. The search was designed to capture:

- Case reports: Illustrating atypical presentations and perioperative challenges.
- Clinical guidelines and expert recommendations: Reflecting current diagnostic and management protocols.
- Systematic and narrative reviews: Providing broader context on diagnostic complexities.
- Original observational studies: Focusing on clinical outcomes, genetic screening, and perioperative strategies.

The following MeSH terms were used:

- Malignant Hyperthermia (D008318)
- Signs and Symptoms (D012711)
- Diagnosis, Differential (D003937)
- Phenotype (D020022)
- Genetic Variation (D044127)

Boolean operators (AND/OR) were applied to optimize search sensitivity. The search was limited to English and French literature.

Study Selection and Data Extraction

Titles and abstracts were screened based on predefined eligibility criteria. Full-text articles of potentially eligible studies were retrieved and assessed for clinical relevance to MH diagnosis, clinical manifestations, or genetic analysis. Key information was extracted using a structured form that included:

- Study design, patient characteristics;
- Clinical presentations;
- Diagnostic approaches and perioperative outcomes;
- Genetic findings (particularly in RYR1 and CACNA1S variants).

Literature Summary

A total of 26 studies were included in the narrative synthesis. The findings were categorized into three dominant themes:

1. Diagnostic complexities in atypical clinical presentations:
   - Highlighting the challenges in recognizing non-classical manifestations of MH, which complicate perioperative diagnosis.
2. Genetic predisposition and associated mutations:
   - Emphasizing the role of RYR1 and other genetic markers in assessing susceptibility and risk stratification.
3. Current clinical management strategies reflected in international guidelines:
   - Illustrating evolving best practices for perioperative care and emergency response to MH crises.

Results

Overview of Included Literature

This narrative review includes 26 studies selected based on clinical relevance to MH diagnosis, presentation, and genetic predisposition. The literature comprises case reports, clinical guidelines, expert consensus documents, and observational studies, offering a broad perspective on current diagnostic challenges.

Case reports illustrate the wide variability of MH presentations, including atypical or delayed-onset forms, and emphasize the importance of clinical vigilance. However, several reports lack standardized confirmatory testing, which may limit diagnostic certainty. Clinical guidelines and expert statements contribute standardized recommendations on diagnosis and perioperative management, including the use of in vitro contracture testing and genetic screening for RYR1 and CACNA1S mutations.

Together, these sources provide complementary insights into the clinical complexity, diagnostic pathways, and evolving strategies for identifying and managing MH across perioperative settings.

Clinical Presentations

Malignant hyperthermia (MH) typically manifests as a rapid-onset hypermetabolic crisis triggered by exposure to volatile anesthetics or succinylcholine. Classic features include sudden elevations in end-tidal CO_2, unexplained tachycardia, generalized muscle rigidity, and mixed acidosis. If not treated promptly, the condition may progress to hyperthermia, hyperkalemia, rhabdomyolysis, and ultimately and multiorgan failure[5,10].
Key features of a fulminant MH crisis include:

- Unexplained tachycardia and hypercarbia (elevated end-tidal CO_2).
- Respiratory and metabolic acidosis.
- Rhabdomyolysis with hyperkalemia and elevated muscle enzymes (CPK, transaminases).
- Generalized muscle rigidity.
- Elevated core temperature (>39°C).
- Disseminated intravascular coagulation (DIC) and multi-organ failure[23].

Recognition of these signs is essential for initiating treatment, particularly with prompt dantrolene administration. Evidence shows that mortality decreased from 21% before 1985 to 1.4% between 2000 and 2006 following the implementation of standardized dantrolene protocols and each 30-minute delay in dantrolene increases the likelihood of complications by 1.6 times, underscoring the importance of early intervention[16].

However, not all cases follow this classical pattern and atypical forms of MH pose unique diagnostic challenges and may lead to misinterpretation if clinicians are not vigilant.

Atypical and Delayed-Onset MH (case reports)

Non-obese patients exhibited a higher mean Cmax While fulminant MH crises are well described, some cases present atypically, with symptoms developing gradually or postoperatively. These may arise hours after induction or only upon emergence from anesthesia, particularly following prolonged volatile anesthetic exposure[5,23].

Hyperthermia may appear late or be absent entirely. Early signs can be subtle and misattributed to other causes, and when hyperthermia does occur, alternative diagnoses are often considered first19,23. Because MH does not always follow a textbook presentation, persistent clinical vigilance is essential and recognizing subtle or delayed manifestations can lead to earlier intervention and better outcomes. The following case reports illustrate how delayed or atypical MH can manifest across a variety of perioperative settings.

Delayed-Onset MH After Uneventful Anesthetics

A 16-year-old male undergoing pectus carinatum surgery developed MH five hours after sevoflurane exposure, despite previous uneventful anesthetic procedures. His symptoms included severe rigidity, a $PETCO_2$ of 95 mmHg, and a temperature spike to 40.5°C. The crisis recurred 14 hours later in the ICU, requiring prolonged dantrolene therapy. Genetic testing confirmed an RYR1 mutation (p.Arg2454His)[3].

Postoperative MH: The Importance of Continued Vigilance

A 77-year-old man developed MH 95 minutes after uneventful holmium laser enucleation of the prostate He presented with severe hypertension (220/168 mmHg), hyperventilation, and masseter muscle rigidity, followed by rapid temperature escalation to 39.8°C. Dantrolene administration led to rapid improvement[1].

Intraoperative MH During Single-Lung Ventilation

A 41-year-old patient developed MH during resection of an endobronchial tumor. Symptoms emerged 2.5 hours after induction, including hypercapnia and hemodynamic instability, requiring aggressive dantrolene therapy[8].

MH in Unusual Surgical Settings

A 59-year-old patient with influenza pneumonia

developed MH during ICU sedation with sevoflurane administered via an AnaConDa® device. Five hours into sedation, the patient became unstable, with severe acidosis (pH 7.17), temperature rise from 39.6°C to 40.7°C, and rhabdomyolysis. IVCT confirmed MH susceptibility[2].

MH as not expected during esophagectomy

A 56-year-old man undergoing Lewis-Santy esophagectomy developed MH eight hours after sevoflurane exposure. Comorbidities (COPD, obesity, coronary artery disease) masked early signs. His temperature peaked at 42.5°C, with metabolic acidosis, hyperkalemia, and transient asystole. Genetic testing revealed an RYR1 mutation[11].

These cases illustrate the wide spectrum of MH presentations, from delayed-onset crises to unexpected ICU events. The variability in timing, severity, and clinical settings reinforces the need for ongoing vigilance and prompt intervention. As anesthetic techniques evolve, continued education on MH recognition and management remains essential to ensuring optimal patient safety.

Challenges in MH Diagnosis

The clinical features of malignant hyperthermia (MH) often overlap with other perioperative emergencies, making early diagnosis particularly difficult. Intraoperative signs such as tachycardia, hypercapnia, and rigidity are non-specific and can mimic a range of more common conditions. Furthermore, the absence or delayed onset of hyperthermia may divert attention from MH as a potential diagnosis[10].

In some cases, MH occurs postoperatively, increasing the risk of misdiagnosis as another metabolic disorder[1]. Adding to the complexity, some MH-susceptible patients undergo multiple uneventful anesthetics before experiencing a crisis, giving a false sense of security[16].

Because MH lacks specific early signs, it shares clinical similarities with several perioperative emergencies, making differential diagnosis essential:

- Neuroleptic Malignant Syndrome (NMS) – shares muscle rigidity, metabolic acidosis, hyperthermia, and rhabdomyolysis, though it is associated with antipsychotic use;
- Thyrotoxic Crisis – includes hyperthermia and tachycardia;
- Pheochromocytoma Crisis – features severe hypertension and tachycardia due to catecholamine excess;
- Sepsis– Includes fever, cardiovascular instability, and metabolic acidosis but usually has an identifiable infectious source;
- Anaphylaxis and Drug Reactions – lead to intraoperative instability, bronchospasm, or hypotension;
- Hyperkalemic Cardiac Arrest – occurs after succinylcholine, mimics MH but lacks rigidity and hyperthermia[10,14].

Malignant Hyperthermia Clinical Grading Scale (CGS)

To support perioperative recognition, the Malignant Hyperthermia CGS was developed. This tool assigns points to key clinical features, such as unexplained hypercarbia, rigidity, rhabdomyolysis, and temperature elevation to estimate the likelihood of MH, assigning a cumulative score that reflects the probability of MH[10]. While not definitive, it offers a structured method for early decision-making, particularly in atypical cases.

When MH is suspected, confirmation requires specialized testing. The IVCT remains the gold standard but is invasive and available only in select centers[12]. Genetic testing offers a non-invasive alternative but is limited by incomplete penetrance and variants of uncertain significance[17,19].

The most effective diagnostic approach is multimodal, combining clinical assessment, structured scoring tools, and confirmatory testing to ensure accurate diagnosis and patient safety.

Genetic Mutations Associated with MH

Malignant hyperthermia (MH) is a pharmacogenetic disorder caused by mutations affecting calcium regulation in skeletal muscle cells, leading to uncontrolled hypermetabolism. Understanding these genetic variants is essential for risk assessment, diagnosis, and prevention[21].

The RYR1 gene, located on chromosome 19q13, encodes the ryanodine receptor, a calcium-release channel in skeletal muscle. Mutations in RYR1 account for approximately 70% of MH cases, with over 400 identified variants, though only a fraction have been validated as pathogenic[21]. Additional factors, including post-translational modifications and regulatory protein interactions, may further influence susceptibility[17]. Although RYR1 is the most common genetic determinant, other genes also contribute to MH risk. CACNA1S mutations, found on chromosome 1q32, have been implicated in ~1% of cases[10]. STAC3 mutations, primarily identified in the Lumbee Native American population, have further expanded the genetic landscape of MH susceptibility[21].

MH follows an autosomal dominant inheritance pattern, meaning that first-degree relatives of affected individuals have a 50% chance of inheriting susceptibility. However, incomplete

penetrance means that some individuals with mutations may never develop MH, even after multiple anesthetic exposures. The estimated prevalence of MH susceptibility is approximately 1 in 10,000, though the true figure may be higher due to variable expression and underdiagnosis[10].

Genetic Testing and Clinical Implications

Genetic testing plays an increasingly important role in MH diagnosis but cannot replace functional tests such as the in vitro contracture test (IVCT)[17]. Targeted sequencing of RYR1 and CACNA1S helps identify pathogenic mutations, while next-generation sequencing (NGS) has broadened genetic screening by detecting novel variants, though many remain of uncertain significance[25]. Whole-exome sequencing (WES) provides a more comprehensive analysis but cannot fully exclude MH susceptibility, reinforcing the necessity of functional testing[17]. A confirmed RYR1 or CACNA1S mutation allows for preoperative risk assessment and anesthetic planning. Patients with a known genetic predisposition should avoid volatile anesthetics and succinylcholine, with total intravenous anesthesia (TIVA) as a safer alternative[21]. Given its hereditary nature, MH susceptibility warrants genetic counseling to assess the risk in family members[25]. Beyond anesthetic-induced crises, RYR1 mutations have been linked to neuromuscular conditions, including central core disease, exertional hyperthermia, and rhabdomyolysis, necessitating a broader clinical evaluation in affected individuals[10].

Future Directions in MH Genetic Research

Advancements in genomic analysis and biomarker research are improving MH risk assessment. Functional studies continue to refine genotype-phenotype correlations, providing deeper insights into how specific RYR1 variants influence clinical outcomes[17]. Biomarkers and metabolomic profiling are being explored as non-invasive diagnostic alternatives, with recent evidence indicating distinct metabolomic signatures in MH-susceptible individuals, such as alterations in long-chain acylcarnitines, diacylglycerols, and oxidative stress markers. These findings suggest potential for early detection and risk stratification through non-invasive methods[26]. Artificial intelligence-driven genomic analysis holds promise for enhancing risk prediction and personalized patient management[25]. Despite these advances, MH remains a complex disorder, requiring an integrated approach that combines genetic screening, clinical evaluation, and perioperative risk management.

Discussion

Malignant hyperthermia (MH) remains a significant diagnostic challenge due to its unpredictable onset, clinical variability, and genetic complexity. Early recognition is critical but often complicated by nonspecific early signs like tachycardia, hypercapnia, and muscle rigidity, which overlap with other perioperative emergencies[5,10].

The 2024 EMHG Guidelines emphasize standardized diagnostic protocols to improve patient safety and perioperative outcomes. Diagnosis primarily relies on IVCT for definitive confirmation, while genetic testing aids in risk stratification and family screening. Clear referral criteria, including family history and adverse anesthetic reactions, are outlined to optimize patient evaluation[12].

Despite improvements in diagnostic strategies, atypical MH presentations continue to pose significant challenges. Delayed-onset and milder hypermetabolic responses are frequently misdiagnosed, increasing the risk of complications. Enhanced perioperative vigilance, coupled with prompt cessation of triggering agents and early administration of dantrolene, remains crucial for preventing severe outcomes. Evidence shows that prompt administration of dantrolene significantly reduces mortality and complication rates[16].

Emerging research into metabolomic profiling and non-invasive biomarkers shows promise for improving early detection and risk stratification of MH[26]. Advances in artificial intelligence may further enhance diagnostic precision, allowing for better perioperative risk assessment[25]. Moving forward, efforts should prioritize global standardization of diagnostic protocols, broader access to genetic testing, and the integration of non-invasive technologies into clinical practice.

Conclusion

Malignant hyperthermia (MH) remains a significant diagnostic challenge due to its unpredictable onset and complex genetic background. Early recognition and timely intervention are crucial to prevent severe complications, yet the variability in clinical presentations often leads to delayed diagnosis. This highlights the need for better perioperative monitoring and more accessible, non-invasive screening methods.

A comprehensive approach combining clinical suspicion, functional testing, and genetic analysis remains essential for accurate diagnosis.

Looking forward, promising research in metabolomic profiling and non-invasive biomarkers

may offer new pathways for early detection of MH, making it easier to identify at-risk patients before a crisis occurs[26]. Advances in artificial intelligence also hold the potential to improve diagnostic accuracy and predict patient susceptibility with greater confidence[23].

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The author agrees to share the data supporting the findings of this review upon reasonable request. Requests should be directed to the corresponding author via the contact information provided on the title page.

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