

Malignant Hyperthermia- Review ArticleAlaa Sabbahi, MD^{1*}, Dania Abdulelah Sabbahi, BDS, MSc, PhD²¹Department of Anesthesiology and Intensive Care, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia²Department of Dental Public Health, Faculty of Dentistry, King Abdulaziz University, Jeddah, Saudi Arabia**Review Article*****Corresponding author**

Alaa Sabbahi

Article History

Received: 15.12.2018

Accepted: 23.12.2018

Published: 30.12.2018

DOI:

10.36348/sjimps.2018.v04i12.013



Abstract: The malignant hyperthermia is a rare autosomal dominant disease of the skeletal muscles. Triggered by volatile anesthetics and succinylcholine which leads to excess release of calcium from sarcoplasmic reticulum that leads to hypermetabolic status of the body and it could be fatal. The incidence between 1:10000 and 1:250000 anesthetics. It is more common in males than females, and the young more than old people. MH cause by mutation in RYR1, CACHA1S or STAC3 genes. Symptoms of MH are muscle rigidity, tachycardia, hypercapnia, hypoxemia and hyperthermia. The symptoms of MH could be mistaken by other conditions and therefore delay the treatment. Treatment is by stopping the triggering agent, symptomatic treatment to prevent complications and the only pharmacological agent that reverses the MH is Dantrolen. IVCT is the gold standard to diagnose MH but it is invasive. Genetic testing is less invasive and also help in diagnosis of MH and identification of the affected gene, but it does not replace IVCT.

Keywords: malignant hyperthermia, anesthesia, volatile anesthetic, succinylcholine, RYR1 receptor, Dantrolen.

INTRODUCTION**Definition**

Malignant hyperthermia (MH) is a rare autosomal dominant disease of the skeletal muscles, where there is a defect in intracellular calcium regulations that triggered by volatile anesthetic agents and succinylcholine, results in uncontrolled release of calcium from the sarcoplasmic reticulum (SR) which leads to hypermetabolic status of the body and death if not treated [1].

Prevalence

The incidence is between 1:10000 and 1:250000 anesthetic. MH can occur at first exposure to the triggering agents or even after multiple exposures (patient require average 3 anesthesia exposure before triggering). It can be found in all ethnic groups, and it is more common in males than females 2:1, children more than adults and young more than the old people [2, 3].

Pathogenesis

It is an autosomal dominant disease which is caused by mutation of RYR1, CACNA1S or STAC3 genes. In UK, the RYR1 variants were found in 76% of independent MH families. Some of the families have more than one variant gene [4].

Pathophysiology

In normal myocyte, when the action potential arrive the sarcolemma, it propagates it into the T tubules. The DHPR located in T tubules, sense the action potential and activates it. The RYR1 receptor located in the SR near the DHPR receptor. Which is also activated and release calcium from the SR to the sarcoplasm [5]. The calcium then binds to troponin

which activates the myofibrils that need ATP to initiate the contraction. The contraction ends when calcium ions are pumped back to the SR which also needs ATP, allowing the muscle to relax [6].

In MH with mutation in RYR1 receptor, rapidly uncontrolled release of calcium into the sarcoplasm results in increase in calcium level which leads to excessive energy expenditure due to Ca-ATPase pump activation as it attempts to counteract the SR Ca leak. The continuous stimulation of the myofibril by the excess calcium in the sarcoplasm leads to excessive use of ATP and then ATP depletion.

To compensate the excessive ATP use, the cell uses O₂ to produce ATP, CO₂ and H₂O. When the O₂ is depleted, ATP is produced by anaerobic fermentation which also produces lactic acid. Then depletion of ATP result in loss of cellular integrity and Cell break down which leads to the release of cell content into the blood stream [3].

Triggering agents

MH triggered by pharmacological agents. These are succinylcholine which is a depolarizing muscle relaxant and all volatile anesthetic like halothane, sevoflurane, desflurane, isoflurane and others except for nitrous oxide and xenon [7, 8].

Exercise and heat could be a trigger for MH. In many case, the reports they found were correlation between patients who developed hyperthermia and rhabdomyolysis after exercise of exposure to heat and MH, in which those patients has a RYR1 variant or positive IVCT [9,10].

Clinical presentation

It can occur anytime during anesthesia up to 1 h after discontinuing volatile anesthesia in post-operative period.

The course of MH could range between mild, moderate to severe MH crises [11]. Basically, the symptoms occur when the myocytes lose its wall integrity and expel all its content into the blood stream.

Symptoms divided into early and late. Early symptoms include tachycardia, hypercapnia, hypoxia, combined metabolic and respiratory acidosis, generalized muscular rigidity and masseter spasm (more with succinylcholine). Late symptoms include hyperthermia, rhabdomyolysis, acute renal failure, cardiac arrhythmia, hypotension and shock [11].

When lactic acid is released into the bloodstream, acidosis stimulates the sympathetic nerves which lead to tachycardia and arrhythmias. Potassium release also leads to arrhythmias [12]. Hypercapnia occurs gradually despite normal to increase minute ventilation or abruptly after succinylcholine use. Patients may exhibit tachypnea in spontaneous breathing. Masseter muscle spasm usually occurs after succinylcholine use and generalized muscle rigidity is also an early symptom. Hyperthermia is a late sign of MH, it increases gradually and core temperature may increase 1-2 C every 5 min in fulminant MH. Hypoxia and cyanosis is due to uncontrolled hypermetabolism which leads to increase oxygen requirement. Rhabdomyolysis may occur later which leads to the release of creatine phosphokinase (CK), myoglobin and potassium into the blood stream and it may lead to renal failure [11].

Deferential diagnosis

Any conditions that mimic the symptoms of malignant hyperthermia could delay the diagnosis and treatment of MH.

Light anesthesia, sepsis, thyroid storm, pheochromocytoma, neuroleptic malignant syndrome, serotonin syndrome and cocaine overdose.

Diagnosis of MH in Acute Setting

Blood tests may support the diagnosis of MH in acute crisis to help us initiate the treatment. Blood gas analysis will show a combined metabolic and respiratory acidosis, hypercapnia, hypoxemia and excess base. Hyperkalemia, hypercalcemia, Increase CK and myoglobin in blood. Dark urine indicated myoglobinuria.

Management and Treatment

After MH recognition, the treatment should be commenced immediately without any delay. First thing to do is to stop the triggering agent, for example, volatile anesthesia and call for help. Give the patients 100% oxygen and switch the anesthesia from volatile to intravenous sedatives or opioids. Increase the minute ventilation and increase the gas flow to the maximum [11] the only pharmacological treatment for MH is Dantrolene. Dantrolene interfere with the calcium release from the SR through RYR1 [13]. Bolus of 2.5 mg/kg should be given immediately and repeated in 5 minutes interval until the symptoms of MH subside. If the repeated bolus dose reached 10 mg/kg, then the diagnosis of MH should be reconsidered [14]. Symptomatic treatment of MH is also important to prevent complications. Metabolic acidosis should be treated with sodium bicarbonate. Increase minute ventilation to treat respiratory acidosis. Correct hyperkalemia. Cardiac arrhythmia is usually treated when hyperkalemia and acidosis are corrected but sometimes antiarrhythmic drugs might be needed. Amiodaron is the first drug of choice and also beta blocker can be given. Avoid calcium channel blocker in the presence of Dantrolene because it may worsen hyperkalemia [15]. Insert Foley catheter and monitor urine output and urine color. Dark urine color indicates myoglobinuria. Insert large IV and hydrate the patient to keep urine output above 1-2 ml/kg/h and prevent renal failure, give frusemide, mannitol or bicarbonate if necessary. Cool the patient by giving him cold IV normal saline at 4 C and ice pack to all exposed area and stop cooling when temperature reach 38.5 C. DIC may occur in fulminant MH, so prophylactic heparin must be considered [14,16].

After stabilization, the patient should be transferred to the ICU and monitored for 48 – 72 h, insert an arterial line and continue giving dantrolene either 1mg/kg IV q 4-6 h or 0.25 mg/kg/h for at least 24h or even longer if clinically indicated.

Diseases related to Malignant Hyperthermia

Patients with skeletal muscle diseases that associated with RYR1 mutation could be susceptible to MH like central core disease [17], Multiminicore disease [18], King-Denborough syndrome [19].

Extensional heat stroke (EHS) is an elevated core temperature associated with signs of organ failure due to hyperthermia and rhabdomyolysis and it occurs during physical activity [20].

Patients who develop severe myopathy after statin use could be also MHS. Patients presented with severe myopathy and rhabdomyolysis and genetic testing was positive for RYR1 and CACNA1S variation. Nevertheless, they have positive IVCT [21, 22].

DIAGNOSIS

The clinical grading scale is used to aid the recognition of malignant hyperthermia but it is not a diagnostic tool by itself. With the clinical grading scale, we can estimate the qualitative likelihood that an adverse anesthetic event is a clinical MH which is based on points assigned to specific abnormal signs and blood testing. The points are then summed to produce a score. The clinical grading scale also estimates a subject's qualitative likelihood of MH susceptibility when the subject has family history of MH. The clinical indicator of the family history is also added to the score. The final score shows us the MH risk of the patient, ranging from almost never to almost certain [23].

IVCT (in vitro contracture test) is the gold standard for diagnosis of MH. There are two protocols developed for the IVCT, one developed by the European Malignant Hyperthermia group (EMHG) and another one developed by North American Malignant Hyperthermia group (NAMHG) and its called caffeine/halothane contracture test (CHCT) [24]. In Japan, they use the calcium induced calcium release test (CICR) but it is not internationally standardised [25].

A muscle biopsy is taken from the patient under anesthesia from the vastus lateralis or medialis. This muscle biopsy then exposed to halothane or caffeine and caused to contract by electrical stimuli. The isometric contracture is measured [26]. If the halothane and caffeine tests were positive then the individual is MH susceptible (MHS_{hc}). If both halothane and caffeine tests were negative then the individual is not MH susceptible (MHN). If only halothane test is positive then the individual is considered susceptible (MHS_h) and if only caffeine test is positive then the individual is also considered susceptible (MHS_c) [27]. The sensitivity is 99% and the specificity is 94% [28]. 97% sensitivity and 78% specificity following the NAMHG protocol [29]. The IVCT is invasive and it is done only in specialized centers. The minimum age for the test is 4 years old according to the EMHG and 10 years old in NAMHG.

A less invasive way to diagnose MH is molecular testing and DNA analysis, which require

only blood sample. Molecular testing still doesn't replace IVCT [30].

REFERENCES

1. Hosokawa, Y., Casa, D. J., Rosenberg, H., Capacchione, J. F., Sagui, E., Riazi, S., ... & Lee, E. C. (2017). Round table on malignant hyperthermia in physically active populations: meeting proceedings. *Journal of athletic training*, 52(4), 377-383.
2. Rosenberg, H., Pollock, N., Schiemann, A., Bulger, T., & Stowell, K. (2015). Malignant hyperthermia: a review. *Orphanet journal of rare diseases*, 10(1), 93.
3. Kushnir, A., Wajsberg, B., & Marks, A. R. (2018). Ryanodine receptor dysfunction in human disorders. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, 1865(11), 1687-1697.
4. Miller, D. M., Daly, C., & Gargner, L. (2018). Genetic epidemiology of malignant hyperthermia in UK. *British Journal of Anaesthesia*, 121(4), 944-952.
5. Franzini-Armstrong, C. (1999). The sarcoplasmic reticulum and the control of muscle contraction. *The FASEB Journal*, 13(9002), s266-S270.
6. OpenStax. 2013. Anatomy and Physiology. OpenStax CNX. <https://opentextbc.ca/anatomyandphysiology/chapter/10-3-muscle-fiber-contraction-and-relaxation/>
7. Gronert, G. A., & Milde, J. H. (1981). Hyperbaric nitrous oxide and malignant hyperpyrexia. *BJA: British Journal of Anaesthesia*, 53(11), 1238-1238.
8. Froeba, G., Marx, T., Pazhur, J., Baur, C., Baeder, S., Calzia, E., ... & Georgieff, M. (1999). Xenon does not trigger malignant hyperthermia in susceptible swine. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, 91(4), 1047-1047.
9. Bendahan, D., Kozak-Ribbens, G., Confort-Gouny, S., Ghattas, B., Figarella-Branger, D., Aubert, M., & Cozzone, P. J. (2001). A noninvasive investigation of muscle energetics supports similarities between exertional heat stroke and malignant hyperthermia. *Anesthesia & Analgesia*, 93(3), 683-689.
10. Thomas, J., & Crowhurst, T. (2013). Exertional heat stroke, rhabdomyolysis and susceptibility to malignant hyperthermia. *Internal medicine journal*, 43(9), 1035-1038.
11. Schneiderbanger, D., Johannsen, S., Roewer, N., & Schuster, F. (2014). Management of malignant hyperthermia: diagnosis and treatment. *Therapeutics and clinical risk management*, 10, 355.
12. Ørding, H. (1989, January). Pathophysiology of malignant hyperthermia. In *Annales francaises*

- d'anesthesie et de reanimation* (Vol. 8, No. 5, pp. 411-416). Elsevier Masson.
13. Bannister, R. A. (2012). Dantrolene-Induced Inhibition of Skeletal L-Type Current Requires RyR1 Expression. *BioMed research international*, 2013.
 14. Malignant Hyperthermia Association of United State. Managment a Crisis. <https://www.mhaus.org/healthcare-professionals/managing-a-crisis/>
 15. Rubin, A. S., & Zablocki, A. D. (1987). Hyperkalemia, verapamil, and dantrolene. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, 66(2), 246-248.
 16. Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin. (2018). Leitlinie zur Therapie der Malignan Hyperthermie. *Anästhesiologie und Intensivmedizin*, 59, 204-208
 17. Quane, K. A., Healy, J. M. S., Keating, K. E., Manning, B. M., Couch, F. J., Palmucci, L. M., ... & Bendixen, D. (1993). Mutations in the ryanodine receptor gene in central core disease and malignant hyperthermia. *Nature genetics*, 5(1), 51.
 18. Guis, S., Figarella-Branger, D., Monnier, N., Bendahan, D., Kozak-Ribbens, G., Mattei, J. P., ... & Pellissier, J. F. (2004). Multimimicore disease in a family susceptible to malignant hyperthermia: histology, in vitro contracture tests, and genetic characterization. *Archives of neurology*, 61(1), 106-113.
 19. D'Arcy, C. E., Bjorksten, A., Yiu, E. M., Bankier, A., Gillies, R., McLean, C. A., ... & Ryan, M. M. (2008). King-denborough syndrome caused by a novel mutation in the ryanodine receptor gene. *Neurology*, 71(10), 776-777.
 20. Casa, D. J., DeMartini, J. K., Bergeron, M. F., Csillan, D., Eichner, E. R., Lopez, R. M., ... & Yeargin, S. W. (2015). National Athletic Trainers' Association position statement: exertional heat illnesses. *Journal of athletic training*, 50(9), 986-1000.
 21. Guis, S., Bendahan, D., Kozak-Ribbens, G., Figarella-Branger, D., Mattei, J. P., Pellissier, J. F., ... & Cozzone, P. J. (2003). Rhabdomyolysis and myalgia associated with anticholesterolemic treatment as potential signs of malignant hyperthermia susceptibility. *Arthritis Care & Research: Official Journal of the American College of Rheumatology*, 49(2), 237-238.
 22. Isackson, P. J., Wang, J., Zia, M., Spurgeon, P., Levesque, A., Bard, J., ... & Vladutiu, G. D. (2018). RYR1 and CACNA1S genetic variants identified with statin-associated muscle symptoms. *Pharmacogenomics*, 19(16), 1235-1249.
 23. Larach, M. G., Localio, A. R., Allen, G. C., Denborough, M. A., Ellis, F. R., Gronert, G. A., ... & Ording, H. (1994). A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology*, 80(4), 771-779.
 24. Larach, M. G. (1989). Standardization of the caffeine halothane muscle contracture test. *Anesthesia & Analgesia*, 69(4), 511-515.
 25. Endo, M., Yagi, S., Ishizuka, T., Horiuti, K., Koga, Y., & Amaha, K. (1983). Changes in the Ca-induced Ca release mechanism in the sarcoplasmic reticulum of the muscle from a patient with malignant hyperthermia. *Biomedical Research*, 4(1), 83-92.
 26. Rosenberg, H., Sambughin, N., & Dirksen, R. (1993). Malignant hyperthermia susceptibility, GeneReviews. edited by Pagon RA, Bird tD, Dolan CR, Stephens K, Seattle WA. Seattle, University of Washington,
 27. Hopkins, P. M., Rüffert, H., Snoeck, M. M., Girard, T., Glahn, K. P. E., Ellis, F. R., ... & Gillies, R. (2015). European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. *BJA: British Journal of Anaesthesia*, 115(4), 531-539.
 28. Ørding, H., Brancadoro, V., Cozzolino, S., Ellis, F. R., Glauber, V., Gonano, E. F., ... & Kozak-Ribbens, G. (1997). In vitro contracture test for diagnosis of malignant hyperthermia following the protocol of the European MH Group: Results of testing patients surviving fulminant MH and unrelated low-risk subjects. *Acta Anaesthesiologica Scandinavica*, 41(8), 955-966.
 29. Allen, G. C., Larach, M. G., & Kunselman, A. R. (1998). The Sensitivity and Specificity of the Caffeine-Halothane Contracture Test A Report from the North American Malignant Hyperthermia Registry. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, 88(3), 579-588.
 30. Girard, T., Treves, S., Voronkov, E., Siegemund, M., & Urwyler, A. (2004). Molecular genetic testing for malignant hyperthermia susceptibility. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, 100(5), 1076-1080.