Malignant Hyperthermia

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Abstract

Malignant Hyperthermia (MH), is a rare emergency that happened during General Anesthesia. In Albania, during five last years have three cases diagnosed with Malignant Hyperthermia (MH), and two of them have been fatal finishing with death of two patients. Only one is saved. Malignant hyperthermia (MH), is disease passed down through families that causes a fast rise in body temperature (fever) and severe muscle contractions when the affected person gets general Anesthesia. Malignant hyperthermia's inheritance is Autosomal dominant. The defect is typically located on the long arm of chromosome 19 (19q13.1) involving the ryanodine receptor. More than 25 different mutations in this gene are linked with malignant hyperthermia. In this article I shall represents problems happened when during General Anesthesia, unexpected has e Malignant Hyperthermia. Malignant hyperthermia (MH), occurs in 1 in 5,000 to 50,000 instances (mainly in young people), in which people are given anesthetic gases. The most common triggering agents are volatile anesthetic gases, such as: Halothane, Sevoflurane, Desflurane, Isoflurane, Enflurane, Cyclopropane, Methoxyflurane; The depolarizing muscle relaxants suxamethonium and decamethonium, used primarily in general anesthesia. Other drugs that have been suspected of causing MH include catecholamines, phenothiazines, and monoamine oxidase inhibitors, caffeine. More frequent after ENT (ORL), squint or dental operation due to related with short anaesthetic procedures. -Researchers have described at least six forms of malignant hyperthermia susceptibility, which are caused by mutations in different genes. Variations of the CACNA1S and RYR1 genes increase the risk of developing malignant hyperthermia. Tests about discovering of MH are North American Protocol: Suspicous clinical history for MH, or The standard

procedure is the "caffeine-halothane contracture test", CHCT. Is an invasive test. The fresh biopsy (under local anesthesia), is bathed in solutions containing caffeine or halothane and observed for contraction; under good conditions, the sensitivity is 97%, and the specificity 78%; the use of the "calcium-induced calcium release" test -in addition to the CHCT to make the test more specific. Genetic testing is being performed in a limited fashion to determine susceptibility to MH. In people with a family history of MH, analysis for RYR1 mutations may be useful. Signs and symptoms are:Tachycardia : one of the earliest but a non specific sign,Tachypnea : in spontaneously ventilating patients. Increased sweating, During fulminant acute MH, body temperature may increase at a rate of 1.8–3.6°F (1–2°C) every 5 minutes, Cyanosis, flushing or blanching of skin, Cola coloured urine• masseter spasm or generalised muscle rigidity or both, Capnogram – Gradually increasing EtCO2 not related to other possible causes.. Biochemical parameters: Respiratory with or without metabolic acidosis, Hypercarbia, Hyperkalemia, Hyper calcemia, Hyper phosphatemia, Lacticacidemia, Myoglobinuria, Increase in creatinine kinase: neither a constant feature nor signifies increase muscle metabolism in intra operative period, Abnormal coagulation tests. Diagnostic Criteria are: Muscle rigidity (generalized rigidity including severe masseter muscle rigidity); Muscle breakdown (CK >20,000/L units, cola colored urine or excess myoglobin in urine or serum, potassium above 6 mmol/l); Temperature increase (rapidly increasing temperature, T >38.8°C); Other (rapid reversal of MH signs with dantrolene, elevated resting serum CK levels); Family history (autosomal dominant pattern). Differential Diagnosis ccan be made with: Pheochromocytoma,, Thyrotoxicosis (thyroid storm), Sepsis, Transfusion reactions (acute haemolytic and non haemolytic), Allergic reactions, Central nervous system dysfunction (pontine hge, hypoxic ischemic encephalopathy etc.), Neuroleptic malignant syndrome, Alcohol withdrawal,Drug interactions (MAOI and meperidine), some sort of cronic myopathy. For susceptible patients to MH, must be an special anesthetic procedures and must be ready with use of Dandrolene. Some anesthetic drugs are considered safe.These include local anesthetics (lidocaine, bupivacaine, mepivacaine), opiates (morphine, fentanyl), ketamine, barbiturates, propofol , etomidate, benzodiazepines. The nondepolarizing muscle relaxants pancuronium, cisatracurium, atracurium, mivacurium, vecuronium and rocuronium also do not cause MH. There is mounting evidence that some individuals with malignant hyperthermia susceptibility may develop MH with exercise and/or on exposure to hot environments, Local anaesthetics, Droperidol . Acute Management of MH crisis include:Stop exposure of triggering agents and give 100% O2, notify surgical team to abort intervention, administer 2.5mg/kg Dandrolene (or Azumolene) in repeated doses and 3 gr Mannitol, place the catheter Foley, monitor core temperatre, O2, CO2, urine output, Astrupograme, correct HperKalemi or other biochimic abnormality, correct cardiac problems. Conplications are plenty after Therapy as: Kidney failure,

rhabdomyolisis, KID, Respiratory failure, muscular dystrophy. Mortality was greater than 80% when do not put the right diagnosis, but with correct and fast diagnosis and the current management, however, mortality is now less than 5%.

***Key words**: MH- Malignant Hypertherima, CACNA1S - calcium voltage-gated channel subunit alpha1 S, RYR1 genes - ryanodine receptors 1, KID- disseminated intravascular coagulation.*

Objectives

- Describe the pathology- of Malignant Hyperthermia
- Problems of Inheritance and Genetics of Malignant Hyperthermia
- Principles of Treatment and Prevention of Malignant Hyperthermia

Goals

- Review Anesthetic problems during Malignant Hyperthermia
- Pathology-Physiology concepts of Malignant Hyperthermia
- Some characteristic feature of treatment of Malignant Hyperthermia

What is Malignant Hyperthermia

Malignant hyperthermia is disease passed down through families that causes a fast rise in body temperature (fever) and severe muscle contractions when the affected person gets general Anesthesia.

This condition is not the same medical emergencies e as hyperthermia that is due to such as heat Stroke or infection.

Malignant hyperthermia occurs in 1 in 5,000 to 50,000 instances in which people are given anesthetic gases.

Susceptibility to malignant hyperthermia is probably **more** frequent, because many people with an increased risk of this condition are never exposed to drugs that trigger a reaction.

Malignant hyperthermia susceptibility is inherited in an autosomal dominant manner (which means that one copy of the altered gene in each cell is sufficient to increase the risk of the condition).

Causes

The most common triggering agents are volatile anesthetic gases, such as:

Halothane, Sevoflurane, Desflurane, Isoflurane, Enflurane, Cyclopropane, Methoxyflurane

The depolarizing muscle relaxants suxamethonium and decamethonium, used primarily in general anesthesia.

Other drugs that have been suspected of causing MH include catecholamines, phenothiazines, and monoamine oxidase inhibitors, caffeine.

Epidemiology

Incidence is:

- 1:50,000 in adults , 1:15,000 in children incidence varies with triggering agent and geographic location.
- More prevalent in certain areas of a North America.
- Common in young children, but may occur in all age groups from infants in delivery room to 70 years of age.
- Male > female.
- More common in patients with large musculo-sceletal bulk and general anaesthesia after recent exercise.
- More frequent after ENT (ORL), squint or dental operation due to related short anaesthetic procedures.
- susceptible persons may have history of previous uneventful anaesthesia even with triggering agent.

Pathology-Physiology

- In MH susceptible patients the anaesthetic triggering agents cause prolonged opening of RYR1 channel (calcium release channel in muscle), overwhelming the reuptake process, resulting in excess accumulation of calcium intra cellularly.
- The muscle cell is damaged by the depletion of ATP and possibly the high temperatures, and cellular constituents “leak” into the circulation, including potassium, myoglobin, creatine, phosphate and creatine kinase.
- The sustained calcium overload stimulates several metabolic pathways.• Excess demand of ATP
- A hyper metabolic state. It should be remembered that ms mass constitute

30-40 % of body wt. so this hyper metabolic state leads to excess generation of heat.

- The sustained increase in [Ca2+]i leads to muscle contraction without relaxation, i.e. spasm, which, if prolonged, develops into severe contracture.
- The muscle contracture greatly increases the extra vascular resistance to muscle perfusion resulting in ischemia initially locally and eventually systemically.
- The excess oxygen need due to demand for production of extra ATP relative to diminished perfusion due to ischemia lead to metabolic exhaustion, muscle oedema and ultimately result in muscle breakdown.

Genetics

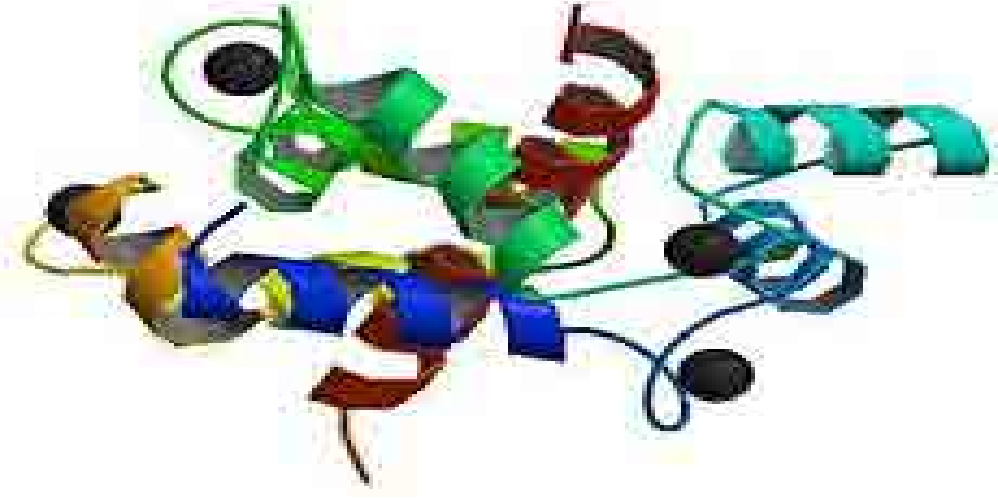
- Malignant hyperthermia's inheritance is Autosomal domiant.
- The defect is typically located on the long arm of chromosome 19 (19q13.1) involving the ryanodine receptor.
- More than 25 differen t mutations in this gene are linked with malignant hyperthermia.
- These mutations tend to cluster in one of three domains within the protein, designated MH1-3. MH1, MH2, are located in the N-terminus of the protein, which interacts with L-type calcium channels and Ca2+. MHS5
- MH3 is located in the transmembrane forming C-terminus.
- Chromosome 7q and chromosome 17 have also been implicated. It has also been postulated that MH and Central Core Disease may be allelic and thus can be co-inherited.
- Researchers have described at least six forms of malignant hyperthermia susceptibility, which are caused by mutations in different genes. Variations of the CACNA1S and RYR1 genes increase the risk of developing malignant hyperthermia.
- The genetic causes of several other types of malignant hyperthermia (MHS2, MHS4, and MHS6) are still under study.
- A form of the condition known as MHS3 has been linked to the CACNA2D1 gene.
- MHS5- An important gene associated with Malignant Hyperthermia Susceptibility Type 5 is CACNA1S.

(Note: CACNA1S-"calcium channel, voltage-dependent, L type, alpha 1S subunit", RYR1 - Ryanodine receptor 1 also known as skeletal muscle calcium release channel.)

Muscle contractions are triggered by the flow of certain charged atoms (ions) into muscle cells. The proteins produced from the *RYR1* and *CACNA1S* genes are involved in the movement of calcium ions within muscle cells.

- In response to certain signals, the CACNA1S protein helps activate the RYR1 channel, which releases stored calcium ions within muscle cells. The resulting increase in calcium ion concentration inside muscle cells stimulates muscle fibers to contract.
- An overabundance of available calcium ions causes skeletal muscles to contract abnormally, which leads to muscle rigidity in people with malignant hyperthermia.
- An increase in calcium ion concentration within muscle cells also activates processes that generate heat (leading to increased body temperature) and produce excess acid (leading to acidosis).

FOTO: Abnormalities in the Ryanodine receptor 1 gene are commonly detected in people with have experienced an episode of malignant hyperthermia, and may be used to determine the risk of episodes in their relatives



Susceptibility to MH is often inherited as an autosomal dominant disorder, for which there are at least 6 genetic loci of interest, most prominently the ryanodine receptor gene (*RYR1*).

MH susceptibility is phenotypically and genetically related to central core disease (CCD), an autosomal dominant disorder characterized both by MH symptoms and myopathy.

Suscebility Testing

The main candidates for testing are those with a close relative who has suffered an episode of MH or has been shown to be susceptible.

- The standard procedure is the "caffeine-halothane contracture test", CHCT. Is an invasive test.
- The fresh biopsy (under local anesthesia), is bathed in solutions containing caffeine or halothane and observed for contraction; under good conditions, the sensitivity is 97%, and the specificity 78%.
- The use of the "calcium-induced calcium release" test -in addition to the CHCT to make the test more specific.

Non invasive test is:

- Intramuscular injection of halothane 6 vol% has been shown to result in higher than normal increases in local pCO2, among patients with known malignant hyperthermia susceptibility.
- Intramuscular injection of caffeine was followed by local measurement of the pCO2; those with known MH susceptibility had a significantly higher pCO2 (63 versus 44 mmHg).

Genetic testing:

- is being performed in a limited fashion to determine susceptibility to MH. In people with a family history of MH, analysis for RYR1 mutations may be useful.

Indications for Muscle Biopsy Testing for MH

- Suspicious clinical history for MH,
- First degree relative of a proband (index case) with a clinical history of MH if the proband cannot be tested (e.g, too young, too old, MH death, not willing to undergo the muscle biopsy, no test centre available),
- Family history of MH where genetic testing is negative for mutation,
- Severe masseter muscle rigidity after succinylcholine administration that is associated with myoglobinuria and/or marked CK elevation ,

Possible Indications:

- Unexplained rhabdomyolysis during or after surgery (may present as sudden cardiac arrest due to hyperkalemia),
- Moderate to mild masseter muscle rigidity with evidence of rhabdomyolysis,
- Exercise-induced rhabdomyolysis Probably Not Indicated Sudden unexpected cardiac arrest during anesthesia ,or early postoperative period not associated with rhabdomyolysis.
- Age less than 5 years or weight less than 40 pounds (insufficient muscle mass)
- Neuroleptic malignant syndrome

North-American Protocol

- Sensitivity of 97% specificity of 85 %• a contracture of ≥ 0.5 g (force) in response to exposure to halothane is considered positive, and a contracture of ≥ 0.3 g in response to 2 mm caffeine is considered positive
- Based on this test, a patient can be categorized as one of the following:MHS -- muscle contracture occurs with both halothane and caffeine; MH-equivocal -- muscle contracture occurs with caffeine or halothane, but not both; or M H-negative -- muscle contracture does not occur with either agent.
- Attempts to enhance the sensitivity, such as measuring the muscle contracture response to ryanodine and to chloro- cresol, have been introduced, and these agents have been somewhat successful in clarifying equivocal cases.
- CHCT (Caffeine Halothane Contracture test)…This is a compilation of a response to 3% halothane taken from an MH patient.
- Three pieces of muscle are shown.
- The muscle is stimulated every 10 seconds and the contraction force is measured and displayed as a quick upstroke.
- When halothane is introduced, a sustained increase in muscle tension is noted, termed a contracture.
- In the top bundle, a 1.2-g contracture is noted.
- A normal response is a contracture of less than 0.5 g
- CHCT• Also positive in central core disease and hypokalemic periodic paralysis.

Clinical Picture of Malignant Hyperthermia

- First clinical case published in 1960 in LANCET, by Denborough and Lovell.
- Association with porcine stress syndrome and malignant hyperthermia

described in early 1970 – the clinical picture of which resembles with malignant hyperthermia in animal model when potent triggering agent is administered.

Clinical picture:

- A hyper metabolic disorder of skeletal muscle.
- Clinical presentation is highly variable and it depends on species, breed, genetic make up, and triggering agents.
- Time of onset : unpredictable, varying from within minutes to several hours of induction; it may even occur in post operative period in the recovery room.
- The most potent triggering agent appear to be induction of anaesthesia with halothane followed by administration of succnylcholine.
- The symptoms appear almost immediately.Presentation is gradual and delayed in onset after the induction with new halogenated anaesthetic agents.

Signs and symptoms

- Tachycardia : one of the earliest but a non specific sign.
- Tachypnea : in spontaneously ventilating patients.• Increased sweating.
- Increased body temperature : late and serious sign of MH and may not be present at the time of the diagnosis.
- During fulminant acute MH, body temperature may increase at a rate of 1.8–3.6°F (1–2°C) every 5 minutes.
- Cyanosis, flushing or blanching of skin.
- Cola coloured urine• masseter spasm or generalised muscle rigidity or both.
- Capnogram – Gradually increasing EtCO2 not related to other possible causes.
- The earliest , the most sensitive and specific sign of M.H Excessive heating and rapid exhaustion of CO2 absorber.
- Other possible causes: Hypoventilation Other causes of Hyper metabolism,
- Partial airway obstruction Absorption of CO2 from exogenous source equipment malfunction.
- Biochemical parameters..
- Respiratory with or without metabolic acidosis.– Hypercarbia– Hyperkalemia– Hyper calcemia– Hyper phosphatemia.– Lacticacidemia.– Myoglobinuria.
- Increase in creatinine kinase: neither a constant feature nor signifies increase muscle metabolism in intra operative period– Abnormal coagulation tests ,

Outcome

- Mortality un acceptably high.
- Mostly due to failure to recognize the syndrome in the early phase.Earlier death rates were 80%
- Now come down to < 5% after introduction of dandrolene sodium.
- There is 25% recrudescence rate in 1st 24- 36 hrs.
- Even after successful treatment there may be prolonged muscle pain and weakness (chronic slowly progressive myopathy) for which physical rehabilitation may be necessary.
- Dysarrythmia from markedØDeath results from…. sympathetic stimulation and Severe spasm makingØHyperkalemia intubation and ventilation Myoglobinuric renal failure¬impossible Ø Disseminated intravascular coagulation.Ø(acute tubular necrosis).
- Multi organ failure when core temperature is¬Neurological damage. elevated beyond critical temperature (>43 deg c).

Diagnosis

Tests that may be done include:

Blood clotting studies (PT, or prothombin time; PTT, or partial thrombloplastin time)

Chem-20, including CPK (creatinine phosphokinase, a muscle protein destroyed during the acute illness)

Genetic testing to look for defects in the RYR1 gene

Muscle biopsy

Urine myoglobin (muscle protein) determination

- Muscle rigidity (generalized rigidity including severe masseter muscle rigidity),
- Muscle breakdown (CK >20,000/L units, cola colored urine or excess myoglobin in urine or serum, potassium above 6 mmol/l),
- Temperature increase (rapidly increasing temperature, T >38.8°C),
- Other (rapid reversal of MH signs with dantrolene, elevated resting serum CK levels),
- Family history (autosomal dominant pattern).

Diagnosis of an Attac During Anesthesia

The earliest signs are:

- early Masseter Muscle Contracture following administration of Succinylcholine,
- a rise in End-Tidal Carbon Dioxide Concentration (despite increased minute ventilation),
- unexplained Tachycardia,
- muscle Rigidity,
- tachypnea (in a spontaneously breathing patient),
- cyanosis,
- hypertension,
- cardiac dysrhythmias ,
- Hyperthermia -Temperature increase (rapidly increasing temperature, T >38.8°C)

So, Core body temperatures should be measured in any patient undergoing general anesthesia longer than 20 minutes. Blood Tests shows:

- Hyperkalemia- above 6 mmol/l
- increased Phosphate (leading to decreased Calcium) and—if determined—raised Myoglobin;
- Metabolic acidosis and Respiratory Acidosis
- a raised Creatine Kinase level (CK >20,000/L units)
- Muscle breakdown (CK >20,000/L units),
- cola colored Urine or excess myoglobin in urine or serum,
- Severe Rhabdomyolysis may lead to acute renal failure, so kidney function is generally measured on a frequent basis.

Differential Diagnosos

- Pheochromocytoma,
- Thyrotoxicosis (thyroid storm)
- Sepsis
- Transfusion reactions (acute haemolytic and non haemolytic)
- Allergic reactions
- Central nervous system dysfunction (pontine hge, hypoxic ischemic

encephalopathy etc.)
- Neuroleptic malignant syndrome,
- Alcohol withdrawal,
- Drug interactions (MAOI and meperidine)
- Differential Diagnosis- Thyrotoxicosis Pheochromocytoma :MH -MH Thyrotoxicosis -Pheochromocytoma↑ ETCO2 (End Tidal CO2)↑ ETCO2 +++ +++ ++ ++ ++ ++↑ HR↑ HR +++ +++ +++ +++ +++ +++↑ BP↑ BP + + ++ ++ +++ +++RigidityRigidity ++ ++ +/- +/- --AcidosisAcidosis +++ +++ -- + +

Diseases associated with MHS

- Central core disease.
- Multicore myopathy or Evan's myopathy or MH myopathy.
- King Denborough syndrome.
- Rhabdomyolysis, but not- MH,
- Brody's disease
- Deficient calcium adenosine triphosphatase
- McArdle's disease
- Myophosphorylase B deficiency
- Dystrophinopathies and other abnormalities of the structural proteins in the muscle membrane there is chronic elevation of CK indicating chronic rhabdomyolysis,
- Post operative myoglobinurea may be the only sign of M.H without any other sign of increased muscle metabolism,- But d/d (day doses) of post operative myoglobinurea is large.

Anesthesia for the Patints Susceptible to MH

- Patients susceptible to MH can be safely anesthetized using non triggering agents• primary regional anaesthetic technique is also appropriate when feasible, all local anaesthetic are considered safe.
- Core temperature and minute ventilation should be monitored closely in all patients.
- To "clean" the anaesthesia machine and ensure that the patient will not be exposed to trace anaesthetic gases.
- To use fresh anaesthetic circuit..and use of vaporizer free machine if possible.
- Flushing the anaesthesia machine with high-flow oxygen (at least 10 L/

minute) for 20 minutes,
- Placing tape over the vaporizer canisters to avoid accidental administration
- The re breathing bag should be attached to the distal end of the ventilator circuit with at least 5 ventilator cycles per minute during the 20- minute flushing.
- The CO2 absorber should be replaced with a fresh absorber
- Dantrolene is not required prophylactically but should be readily available.
- Postoperative observation for 4 hours is recommended for patients

Anesthetic Protocol of different Myopathy or Myotonic Disorders

- The anaesthetic protocol of different myopathy or myotonic disorders and M.H are more or less same.
- But what differs….is that..:
- The implications of a diagnosis of X-linked myopathy, myotonia, or autosomal-dominant ryanodine receptor mutation that are quite different for the rest of their family.

A very much related condition

- Masseter muscle rigidity (MMR).• Defined as jaw ms rigidity along with limb ms flaccidity after administration of succinylcholine (scch) impeding intubation and persisting for > 2 mins.
- MMR may be the first sign of MH, or it can develop during an MH episode. However, it may also occur as an exaggerated response to succinylcholine (scch) in normal individuals.
- Slow tonic fiber of masseter and lateral pterygoid ms responds to depolarising ms relaxant with contracture, the reason of development of MMS (masseter muscles spasm).
- May occur even after pretreatment of defasciculating dose of NDMR (non depolarising muscle relaxant).
- The most common response to succinylcholine is "jaw stiffness" that is subclinical and can only be detected using special measuring devices. This is a normal response to succinylcholine and is considered to be of no prognostic significance with respect to MH.
- A greater increase in masseter spasm (MMS) is called "jaw tightness that interferes with intubation." This group may be quite large (1–2%) in children who are administered halothane and succinylcholine.

- A small but unknown number of these patients are at risk for MH.
- The most severe form of masseter muscle spasm has been characterized as "the mouth could not be opened" or "jaws of steel." This group is documented to have an increased incidence of fulminant MH and increased mortality if the triggering agents are continued.
- MMS may occur in normal persons. 30% of patients with MMS prove to be MH susceptible. Additional signs increase likelihood of MH 50 – 60% if metabolic signs present, 70 – 80% if muscle signs present,
- May be the first indication of previously unsuspected muscle disease particularly myotonic conditions..
- If possible abandon surgery
- Otherwise choose to MH safe technique,
- Allow 15 min to get the patient stabilised..monitor ETCO2, temperature, and consider arterial line,
- Investigate: blood for CK within 24 hr period, and first voided urine for myoglobin
- But the scale lacks sensitivity and early termination of crisis would not yield sufficient score indicative of malignant hyperthermia.
- Patients rated D6 are encouraged to go for ms biopsy test.

Who ansthetic drugs are safe?

Other anesthetic drugs are considered safe. These include local anesthetics (lidocaine, bupivacaine, mepivacaine), opiates (morphine, fentanyl), ketamine, barbiturates, propofol , etomidate, benzodiazepines. The nondepolarizing muscle relaxants pancuronium, cisatracurium, atracurium, mivacurium, vecuronium and rocuronium also do not cause MH. There is mounting evidence that some individuals with malignant hyperthermia susceptibility may develop MH with exercise and/or on exposure to hot environments.

- Local anaesthetics
- Droperidol

Acute management of an MH crisis

1. Declare crisis: Call for help, MH cart
2. Notify surgical team: Determine best time to abort procedure, assist with active cooling of patient,
3. Stop exposure to triggering agents: Discontinue volatile agents, hyperventilate

with high fresh gas flows using 100% oxygen. termination of use of volatile anaesthetics and succinylcholine. removal the **vaporizer** and use of new circuit.• flushing the anaesthesia machine with high-flow oxygen (at least 10 L/minute) for 20 minutes,

4. Do not change anesthesia machine.
5. Switch to nontriggering anesthetic technique: total IV anesthesia.
6. Administer 2.5 mg/kg of dantrolene in repeated doses based on clinical and laboratory response.
7. Each vial contains 20 mg of Dantrolene and 3 g of Mannitol.
8. Mix with only preservative-free sterile water.
9. Obtain additional peripheral or central venous access, as indicated.
10. Place arterial catheter for continuous monitoring of hemodynamics and vascular access for frequent blood sampling.
11. Place Foley catheter to monitor urine output.
12. Initiate and continue active cooling of patient as indicated.
13. Address metabolic and electrolyte derangements.
14. Transfer to intensive care unit for further treatment and continuation of dantrolene.

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Treatment with Dandrolene

1. Dantrolene sodium was first introduced in 1979 as an injectable antidote for acute MH. Prior to that time, the drug was available in an oral formulation for use as an adjunct in the treatment of muscle spasticity associated with spinal cord injury or cerebral palsy,
2. Dantrolene sodium inhibits the release of calcium from the SR (sarcoplasmatic reticulum) by binding to RYR1 and reverses the effects of MH i.e uncouples depolarisation with contraction. Fast contracting twitch ms are affected more than slow contracting antigravity ms (musculo-sceletical).
3. Administration of 2-3 mg/kg dantrolene intravenously. Repeat every 5 –10 min up to 10 mg/ kg , till metabolic symptoms are controlled,
4. After initial stabilization, Continue intravenous dantrolene for at least 24

h after control of initial episode (approximately 1 mg/kg q 6 h). Watch for recrudescence by monitoring in an intensive care unit (ICU) for 36 h. Recrudescence occurs in about 25% of MH cases,

5. Dose : 2- 3 mg /kg initially.. To be repeated every 5 – 10 min upto 10 mg/kg to control clinical signs of hypermetabolism,
6. To continue upto 24- 48 hrs to prevent recrudescence and worsening of rhabdomyolysis.,
7. Generally safe in clinically recommended dose,
8. Has no effect on cardiac or smooth muscle,
9. Side effects include:
   - nausea, malaise, light headedness,
   - muscle weakness,
   - irritation and phlebitis at the intravenous site due to the high pH of the drug,
   - Hepatotoxicity after long term oral use of the drug,
   - Respiratory muscle weakness may occur when large doses are used or whenadministered to patients with an neuromuscular disorder.

Azumolene

- Is a 30-fold more water-soluble analogue of dantrolene that also works to decrease the release of intracellular calcium by its action on the ryanodine receptor.
- In MH susceptible swine, Azumolene was as potent as Dantrolene.
- It has yet to be studied in vivo in humans, but may present a suitable alternative to dantrolene in the treatment of MH.
- Azumolene has also been shown to be as effective as dantrolene at preventing and reversing contracture in in vitro experiments with human skeletal muscle.
- Furthermore, elucidating earlier ideas on the pathogenesis of malignant hyperthermia, researchers point out that it may be “as much a syndrome of exaggerated Ca2+ entry as it is of exaggerated Ca2+ release.

ICU Treatment (Reanimation Room Treatment)

1. Monitor core temperature, electrocardiogram, arterial blood pressure, and urine output.

2. Active surface cooling , naso gastric and rectal lavage with cold saline but avoid overcooling to body temp < 38 deg. c
3. Adequate Hydration with saline preferably cold.•
4. Management of acidosis with i.v bicarbonate 1-2 meq/kg iv if not rapidly improved with dantrolene.•
5. Maintenance of urine output with mannitol (0.25 gm/kg iv) and loop diuretics (frusemide 1 mg/kg iv). Forced alkaline diuresis.
6. Correction of Hyperkalemia with glucose-insulin, and calcium.
7. Cardiac dysarrhythmia usually responds to correction of Hyperkalemia acidosis. Persistent **arrhythmias** may be treated with standard anti arrhythmic like procainamide or lidocaine,
8. CCB s (Calcium Channel Blocker) should not be preferably used,
9. Continue intravenous dantrolene for at least 24 h after control of initial episode (approximately 1 mg/kg q 6 h),
10. Watch for recrudescence by monitoring in an intensive care unit (ICU) for 36 h. Recrudescence occurs in about 25% of MH cases,
11. Ensure adequate urine output by alkaline diuresis because myoglobinuria is common,
12. Follow coagulation profile watching for the occurrence of disseminated intravascular coagulation (DIC),
13. Measure creatine kinase (CK) every 6 h until falling then at least daily until normal. CK may remain elevated for 2weeks. To be kept in mind that baseline CK may be elevated in some patients post operatively,
14. Counsel patients and families regarding testing and future anaesthetics.

Possible Complications

- Amputation
- Breakdown of muscle tissue (rhabdomyolysis)
- Compartment syndrome (swelling of the hands and feet and problems with blood flow and nerve function)
- Death
- Disseminating intravascular coagulation (abnormal blood clotting and bleeding)
- Heart rhythm problems
- Kidney failure
- Metabolic acidosis
- Respiratory dysfunction (fluid buildup in the lungs)
- Weak muscles (myopathy) or muscular dystrophy (deformity)

Prognosis

Prognosis is poor if this condition is not aggressively treated. In the 1970s, mortality was greater than 80%; with the current management, however, mortality is now less than 5%. Repeated episodes or untreated episodes can cause kidney failure. Untreated episodes can be fatal.

Prevention

- If you or anyone in your family has malignant hyperthermia it is very important to tell your doctor, especially before having surgery with general anesthesia.
- Using certain medications can prevent the complications of malignant hyperthermia during surgery.
- Avoid stimulant drugs such as cocaine, amphetamine (speed), and ecstasy. These drugs may cause problems similar to malignant hyperthermia in people who are prone to this condition.
- Genetic counseling is recommended for anyone with a family history of myopathy, muscular dystrophy, or malignant hyperthermia.

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Her2 In Gastric Cancer In Albania

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General background

Gastric cancer (GC) is the fourth most common cancer in Albania. HER2-positivity rates in GC are reported with a wide range. There is no data for it in Albania.

Materials and method

A total of 192 patients, with primary GCs was retrospectively analyzed for HER2 overexpression by IHC. Dual SISH, was used in only 20 GCs with equivocal results. We dispersed HER2 results by: gender and age, histopathological diagnosis and stage, type of the specimen. The results were compared.

Results

We examined by IHC 73.4% (141 cases) surgical and 26.5% endoscopic biopsies: 18.4% (26 cases) and 15.7% (8 cases) HER2 3+, respectively. HER2 overexpression (3+) was detected in 17.7% (34 cases). HER2 equivocal (2+) was detected in 24.5% (47 cases). 17.8% , 14%, 4.7% were respectively intestinal type, diffuse, signet ring and the rest adenocarcinoma NOS. GC prevailed in the group age of 61-70 yrs