Malignant hyperpyrexia: A dread complication
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A thorough discussion of malignant hyperpyrexia is provided, including its incidence, theoretical considerations, diagnosis and clinical management, along with suggestions for its prevention. A step-by-step treatment chart is also included.

We are, indeed, fortunate in the Anesthesia Department at North Carolina Baptist Hospital to have an excellent supply of equipment. Yet, we are guilty, at times, of failing to take full advantage of it. A prime example is the temperature probe, a valuable aid in the diagnosis of malignant hyperpyrexia. In fact, it is so important that failure to monitor body temperature during anesthesia may have medical-legal implications.

Consider for a minute that you have a limited supply of temperature monitoring probes. You must be selective of each patient that is to have his temperature monitored. How thorough can you be in your pre-operative screening of that patient? Which patient is to be suspected of possibly developing malignant hyperpyrexia? Is it the 50-year-old or the 2-year-old? The purpose of my paper is to try to answer these questions and others.

Historical background
In 1937, the first reference to hyperpyrexia as a reaction to anesthesia was made by Dr. Arthur Guedel in a monograph on Inhalational Anesthetics. Three years later, another reference appeared in Anesthesiology. Slowly, in the early and middle 1960's, several case reports began to generate interest and awareness of this phenomenon, which became known as malignant hyperpyrexia.

It soon became evident that fever associated with anesthesia was not rare and, in severe cases, was quite frequently fatal. As late as August, 1973, however, only 300 cases of malignant hyperpyrexia have been reported as such in the world's literature.1

Incidence
The highest incidence of malignant hyperpyrexia occurs in healthy children, adolescents, and young adults. The condition is rare in the elderly, but it has been described in patients up to 78 years-of-age. Until recently, it was thought that infants were not affected, but a case has now been reported in a child of 3 months. The previous lowest age had been 18 months. It is more common in adult males than females, which may be due to the male's greater muscle mass.2,8 Racial predilection is varied.2

This disease is frequently observed in patients with myopathies or muscle-related conditions, such as strabismus, ptosis, hernia, or orthopedic abnormalities. Myopathic signs include abnormal or absent reflexes, pelvic or shoulder girdle weakness, or wasting of thigh musculature.4
Denborough and associates have noted malignant hyperpyrexia in a number of young boys ages 10-13 with the following characteristic features: small for age, undescended testes, lumbar lordosis, thoracic kyphosis, pectus carinatum, and unusual facial appearance with a small chin and low set ears.

This dread complication is observed more frequently than halothane hepatitis. In the anesthetized population, malignant hyperpyrexia occurs in about one in 15,000 children and in about one in 50,000 adults. The mortality rate is reported to be 65-70%.

Malignant hyperpyrexia may develop during the first exposure to an anesthetic or it may not be apparent until the second, third, or even fourth exposure.

Theoretical considerations

The etiology of malignant hyperpyrexia has provided a wide field of study for anesthesiologists and pharmacologists. As a phenomenon, it remains incompletely understood. There have been three basic theories to explain this puzzling disease: (1) sepsis, (2) drug-induced hyperpyrexia, and (3) hereditary metabolic defect.

Sepsis, for the most part, presently has been discounted as a source of malignant hyperpyrexia, since careful examination of blood samples from patients who have died from this condition has failed to demonstrate any infectious cause.

Drug-induced hyperpyrexia as a theory was suggested after it was noted that early reports of the condition were associated with halothane and succinylcholine. This is understandable since these drugs were very popular and were the most frequently used. With more reports of malignant hyperpyrexia, a wider variety of drugs was implicated. The list includes any potent inhalation anesthetic agent, such as methoxyflurane, halothane, diethyl ether and cyclopropane, as well as any skeletal muscle relaxant, such as succinylcholine, decamethonium, gallamine and d-tubocurare.

The third and most well known theory suggests a hereditary metabolic defect. Such a defect is transferred as an autosomal dominant trait. Half the offspring of affected parents are easily susceptible to malignant hyperpyrexia. For three or more consecutive generations, the disease may be detected. Transmission may occur from an apparently normal parent to his offspring.

The biochemical features of this metabolic defect relate to the intracellular metabolism of the muscle which results in massive heat production.

The muscle cell is innervated by a nerve ending which releases acetylcholine and is enclosed by an outer basement membrane and an inner sarclemma. Cell membranes are of variable permeability, according to the action of the muscle cell. At rest, sodium is pumped out and potassium is pumped in. The extracellular fluid contains a high level of calcium as compared with muscle cytoplasm. Both the sarclemma and sarcoplasmic reticulum store calcium during relaxation. At rest, the calcium within the sarcoplasmic reticulum is 3,000 times greater than that in the cytoplasm. However, the cytoplasm is actively transporting calcium to the extracellular fluid.

At the time of contraction, an electrical impulse produces a release of acetylcholine. Calcium ions enhance this release; whereas, magnesium (important in depolarization) inhibits the release of acetylcholine. Calcium enters the cytoplasm from both the sarclemma and the extracellular fluid. As the level of calcium in the cytoplasm increases, the sarcoplasmic reticulum releases more calcium into the cytoplasm. When contraction ceases, the various storage sites re-accumulate calcium and the cell returns to its previous state of relaxation, provided that there is sufficient magnesium and adenosine triphosphate (ATP) present.

According to theory, malignant hyperpyrexia is produced by an unknown triggering substance or substances releasing calcium into both the extra-
cellular fluid and the intracellular myoplasm. Serum calcium is increased, but the source of the hypercalcemia is obscure and may not be the same for all persons. The defect may be either in the calcium-storing membrane, or secondary to a dysfunction of the innervating motor nerve.

Increased cytoplasmic calcium does produce a massive acceleration of cellular metabolism. With this, ATP production is lowered, but ATP utilization is accelerated. With low production, but high use, ATP is insufficient to supply the transport needs of the sarcolemma. The permeability of the muscle membrane increases rapidly. Ions and molecules leak across the sarcolemma in the direction of the concentration gradient. Enzymes, myoglobin, phosphate, and potassium leak outwardly, while calcium leaks inwardly, thereby inducing a neurogenic tetany and aggravating the intracellular metabolic derangement. Such metabolic derangements may be generalized to include the involvement of platelets, the brain, the liver, as well as skeletal and cardiac muscle.\[5,9\]

Recent research suggests that malignant hyperpyrexia may consist of at least two different varieties, that is, with or without rigidity. Little is known about the metabolic processes and sources of heat production in the hyperpyrexic patients in whom rigidity does not occur. Britt and Brown, in a July, 1974 article, suggest that lack of rigidity may be due to a weak triggering agent or to a mild defect. Muscle rigidity in malignant hyperpyrexia is a graver prognostic sign.\[10,11\]

Hyperpyrexia produces a number of changes in pathophysiology. Elevated body temperature results in an increase in the metabolic rate. An increased metabolic rate further enhances an even more elevated body temperature. Heat production may exceed the body's capacity for heat regulation. Peripheral vasodilatation occurs through a reduction of venous return and cardiac output. Capillary endothelial damage and extravasation of fluid may result from excessive heat production. These peripheral changes reduce the blood volume and oxygenation of tissues. Hypoxia and acidosis occur quickly from the increased demands of the tissues. Arrhythmias may occur from cardiac tetany. The abnormal bleeding, which is frequently noted, is similar to disseminated intravascular coagulation.\[12\]

**Diagnosis and course of malignant hyperpyrexia**

With the induction of general anesthesia, the first sign of malignant hyperpyrexia may be evident. Frequently, violent fasciculations with muscle rigidity similar to rigor mortis will develop following the administration of succinylcholine. This obviously makes intubation difficult, though not impossible with an experienced hand. The rigidity cannot be relieved by increased amounts of succinylcholine or other muscle relaxants. If succinylcholine has been omitted, muscle rigidity may be delayed and then have a gradual onset, or it may also not occur at all.

A reliably early sign (occurring with or without muscle rigidity) is tachycardia. Ventricular arrhythmias or arrhythmias characteristic of hyperkalemia may also occur.

Other signs include rapid and deep respirations, excessive heat of the soda lime canister, hot skin, decreased chest wall compliance, and peripheral cyanosis. All these signs can readily be noted if one is observing carefully. Keeping a hand on the patient is very important. Signs of malignant hyperpyrexia may appear within 45 minutes of induction or may present more insidiously, as late as 90 minutes into the case.

The most important diagnostic finding is an increased temperature of continued duration. A core body temperature of more than 107°F for a prolonged period is a grave prognostic sign. Temperatures as high as 112°F have been recorded. The increase in temperature may be as much as 1°F every 15 minutes and as rapidly as 8°F per hour.\[18\]
With the progression of hyperpyrexia, laboratory data would show arterial oxygen desaturation, as well as respiratory and metabolic acidosis. Hyperkalemia and hypercalcemia occur initially, followed by hypokalemia and hypocalcemia. The potassium from the cells is rapidly excreted by the kidneys, resulting in the hypokalemia. Calcium moves back into the intracellular space because of the lower concentration gradient; the result is an extracellular hypercalcemia and an elevated total muscle calcium.

There is a marked elevation of serum enzymes, particularly creatine phosphokinase (CPK). Excess myoglobin release and the subsequent myoglobinuria may lead to anuria.

Later clinical signs which would indicate an irreversible condition include hemolysis, coagulopathy, acute left heart failure, and decerebrate movements. Fixed and dilated pupils, loss of deep tendon reflexes, convulsions, coma, and loss of central temperature regulation indicate severe cerebral dysfunction.

Favorable prognostic signs would be an improvement of the conscious state and hyperactivity of the deep tendon reflexes. Those who survive complain of tenderness, stiffness, weakness and swelling of skeletal muscles, particularly in the legs. More severe complications seen in survivors include brain damage due to fever or cardiac arrest, and renal insufficiency resulting from acute tubular necrosis. With an abnormal anesthetic induction, one author suggests stopping the procedure and obtaining a consultation. Certainly, the availability of additional knowledgeable personnel would be a guide in this decision. Difficulty in achieving paralysis or any indication of masseter muscle spasm should make one suspicious of the possibility of malignant hyperpyrexia. This should warrant either curtailing the procedure, if it should permit, or most definitely, monitoring the patient very carefully. All the equipment necessary for the treatment of malignant hyperpyrexia should be available.

It has been noted that survival has occurred in all patients in whom malignant hyperpyrexia was recognized and where treatment was instituted within 10 minutes of the anesthetic induction. Therefore, survival depends ultimately on prompt recognition of the problem.

Once the diagnosis of malignant hyperpyrexia has been made, all anesthetic agents must be discontinued. The patient should be provided ventilatory support using 100% oxygen via an endotracheal tube without rebreathing apparatus. It is important to control respirations and use high minute volumes to counteract the excessively high arterial carbon dioxide tension that occurs with the increased metabolic state. Ventilation must be continued until the patient can maintain a normal pO2 and pCO2.

Cooling of the patient should be instituted as quickly as possible. External cooling may be achieved with a cooling blanket or application of ice packs. The body may also be immersed into an ice bath. Internal cooling may be accomplished by iced stomach lavage, cold intravenous fluids, or irrigation of an open body cavity with iced fluids. A more drastic measure would be cooling by extracorporeal circulation. Cooling is more difficult in adults than in the pediatric patient, due to the greater total body mass relative to the surface area. Frequently, after cooling has been instituted, the temperature may drop to very low levels, such that rewarming may be necessary to establish normothermia.

Arterial blood gases should be measured. Sodium bicarbonate or tromethamine (THAM) should be administered to correct the metabolic acidosis. It is important not to alkalinize the patient's pH for two reasons. First, metabolic acidosis is of assistance in driving the potassium into the cell. Second, the oxygen demands are so great that it is beneficial to have the oxyhemoglobin dissociation curve shifted to the right.
to facilitate the delivery of oxygen to
the tissues.\(^6\)\(^{14}\)

If the calcium theory is correct, drugs which lower myoplasmic calcium should be of therapeutic benefit. Procaine hydrochloride and procainamide have produced a dramatic decrease in temperature within a few minutes. Procaine in an ionized state decreases myoplasmic calcium by accelerating active uptake in the sarcoplasmic reticulum. Lowering of myoplasmic calcium reverses the rapid increase of muscle metabolism.

Dr. Beverley Britt, a well known researcher in the field of malignant hyperpyrexia, advocates procaine be given prior to the correction of fever and acidosis, since a high fever and a low pH will insure maximum drug ionization. Large doses are necessary to penetrate the sarcoplasmic reticulum. Up to 1 gm may be given over several minutes, with constant monitoring of the electrocardiograph. When a sinus rhythm is noted, sufficient procaine has been administered, suggesting that the cardiac rigor has been controlled and the threat of arrhythmia reduced.

Xylocaine\(^\circ\) hydrochloride is contraindicated during an acute hyperpyrexic crisis, since it has the opposite effect of procaine hydrochloride and procainamide. It accelerates calcium release from the sarcoplasmic reticulum. Xylocaine\(^\circ\), however, may be used as a local anesthetic in patients with malignant hyperpyrexia of the rigid variety when the acute episode has passed. Recent literature advocates only procaine hydrochloride or procainamide administration in the rigid type malignant hyperpyrexia. It is contraindicated in the nonrigid variety.\(^2\)

Steroids in high doses should be administered to minimize cerebral edema. Administration of a 50% glucose solution will help supply adequate energy sources for increased brain and other organ metabolism during hyperpyrexia. Insulin may also be administered to help the intracellular uptake of glucose and, thereby, also promote intracellular uptake of potassium as well.

Thorazine\(^\circ\), or a similar drug, may be used as a peripheral vasodilator to encourage cooling if hyperpyrexia has not begun to respond within 15 minutes to the external cooling measures.

Routine measures are taken to monitor cardiac output and rhythm. If congestive heart failure becomes evident, digitalis and diuretics may be necessary.

Fluid replacement is necessary to correct dehydration and maintain adequate diuresis so as to prevent renal damage from myoglobinuria. If massive intravenous fluids are necessary, monitoring of fluid administration should be done with a central venous pressure catheter and renal output with a foley catheter. Late treatment may require hemodialysis.

It is also suggested by several authors that, after the initial therapy is underway, consideration should be given to the coagulation problems similar to the disseminated intravascular coagulation which has been described in several patients. Blood for coagulation studies should be drawn and, if coagulopathy is present, heparization may be advised.

Without our present knowledge of malignant hyperpyrexia, the most important factors of treatment are a high index of suspicion and a preplanned regimen.\(^5\)\(^{14}\)

**Prevention of malignant hyperpyrexia**

Of course, as with any disease, prevention is the best cure. A careful history taken during the preoperative visit is essential. If there is any suspicion, surgery should be delayed until further investigation can be completed.

A history of malignant hyperpyrexia during a previous anesthetic almost always indicates that all future general anesthetics will be associated with a similar phenomenon. Almost one third of the affected patients have had relatives who developed malignant hyperpyrexia during an anesthetic. However, absence of positive family history
does not guarantee freedom from the disease. In some affected families, no members have ever experienced general anesthesia.

Coexisting muscle disease is valuable in helping to recognize potential candidates for malignant hyperpyrexia. Correlation between muscle disease and malignant hyperpyrexia in individuals within an affected family is not well established at this time. Elevated preoperative CPK levels in a patient with a positive family history of malignant hyperpyrexia or with coexisting muscle disease or abnormality, may be of some diagnostic value, but this is not yet conclusive.

Careful preoperative investigation of previous anesthetic history, family history, and notation of muscle abnormalities or myopathy may help to detect many but certainly not all potential cases of malignant hyperpyrexia.

What about the patient who is obviously a suspicious candidate or known to be affected? He must have surgery. Many methods have been tried, including a cervical epidural.

Regional anesthesia is usually the technique of choice, that is, spinal, epidural, or regional block. Caution and careful monitoring must be employed when local anesthetics are used on this high risk group.

For general anesthesia, the most promising and successful technique currently is a combination of nitrous oxide and oxygen in conjunction with a narcotic, barbiturate, or neuroleptanalgesic.

The strong clinical suspicion that the patient is a potential candidate for malignant hyperpyrexia must be clearly pointed out to the surgical team members, so they are aware of the contraindications of muscle relaxants and the complications of malignant hyperpyrexia.

One must keep in mind the moral obligation to the patient. It is our responsibility to inform those suspected patients and their families of the possible development of malignant hyperpyrexia and make them fully aware of the complications.

Summary

Malignant hyperpyrexia is a pharmacogenetic disease that is being reported with increasing frequency. The phenomenon is recognized as a complex complication of anesthesia that could be fatal. Potent inhalation anesthetics and muscle relaxants appear to trigger this complication, which is thought to be some form of a metabolic defect associated with the calcium-storing membrane or is secondary to a dysfunction of the innervating motor nerve. Fever to 107°F or higher is the characteristic symptom.

Once the diagnosis is made, treatment must be instituted rapidly and efficiently in order to maximize chances of survival for the patient. Mortality of malignant hyperpyrexia has not decreased significantly even since the earlier case reports. Further work is required to develop still better methods of preoperative diagnosis and intraoperative management. However, at present, careful preoperative screening with interviews, correlation of muscle disease and CPK levels can be valuable in recognizing potential candidates for malignant hyperpyrexia.

**Treatment of malignant hyperpyrexia**

The most important factors of treatment of malignant hyperpyrexia are a high index of suspicion and a preplanned regimen. Once the diagnosis of malignant hyperpyrexia has been made, the speed with which the therapy is instituted is of extreme importance for the survival of the patient. With this in mind, the following is a regimen suggested as a guideline for the treatment of malignant hyperpyrexia. It is divided into three parts: problems and complications; treatment; and a brief explanation of various aspects of the treatment.
**Treatment of malignant hyperpyrexia**

**Problems and complications**

- Hyperthermia
- Metabolic and respiratory acidosis
- Hyperventilation
- Arrhythmias
- Rigidity
- Electrolyte imbalance, particularly hyperkalemia
- Hypermetabolism
- Dehydration
- Myoglobinuria and possible renal failure
- Cerebral edema
- Coagulation problems

**Treatment**

- Cool patient. Vasodilation chemically.
- Measure arterial blood gases and treat accordingly.
- High oxygen flows with a non-rebreathing apparatus. Control respirations.
- Maintain electrolyte balance. Chemical control. Xylocaine® is contraindicated.
- Procaine up to 1 gm.
- Draw electrolytes. Attempt to balance chemically. Administer insulin.
- Massive fluid replacement. Central venous pressure catheter and foley catheter.
- Administer steroids.
- Adequate urinary output. Diuretics.
- Monitor cardiac output and rhythm. Chemical control such as diuretics and digitalis may be necessary.
- Fluid replacement is necessary and should be monitored through a central venous pressure catheter. Dehydration should be corrected. Diuresis should be established to prevent possible renal damage from myoglobin.
- Urinary output must be monitored. It may result in an early diagnosis of renal failure caused by myoglobinurie. Late treatment may include hemodialysis.
- After initial therapy is underway, consideration must be given to possible coagulopathy problems such as DIC. Blood for coagulation studies should be drawn. Heparization may be necessary.

**A brief explanation of various aspects of the treatment**

1. Discontinue all anesthetic agents. Maintain the patient on high oxygen flows to counteract excessively high carbon dioxide tension. Finish the surgery as rapidly as possible.
2. Cool the patient with maximum efforts internally and externally. If shivering should occur, Thorazine® or a narcotic may be administered. Cooling should be stopped as core temperature approaches normal.
   Use cooling blanket, cold intravenous fluids, ice packs to body, ice lavage, and irrigation of any open body cavities with ice fluids.
   If available, use an inflatable rubber boat to immerse the patient’s body in ice.
   A more drastic measure for cooling is extracorporeal circulation.
3. Procaine may be administered prior to correction of fever and acidosis since a high fever and a low pH will insure maximum drug ionization. Up to 1 gm of procaine may be given over several minutes, with a constant monitoring of the electrocardiograph. When a sinus rhythm is noted, sufficient procaine has been given.
4. Xylocaine® is contraindicated. It has the opposite effect of procaine which is to lower myoplasmic calcium.
5. Steroids may be administered in an attempt to prevent cerebral edema.
6. Glucose 50% is given to supply adequate energy sources for increased metabolism.
7. Insulin may also be administered. There are two advantages: one, it assists with intracellular uptake of glucose, and two, it decreases the extracellular potassium by causing an intracellular shift.
8. Thorazine®, or a similar drug, may be used as a peripheral vasodilator to encourage cooling, if the hyperthermia has not begun to respond within 15 minutes of therapy.
9. Routine measures are taken to monitor cardiac output and rhythm. Chemical control such as diuretics and digitalis may be necessary.
10. Fluid replacement is necessary and should be monitored through a central venous pressure catheter. Dehydration should be corrected. Diuresis should be established to prevent possible renal damage from myoglobin.
11. Urinary output must be monitored. It may result in an early diagnosis of renal failure caused by myoglobinurie. Late treatment may include hemodialysis.
12. After initial therapy is underway, consideration must be given to possible coagulopathy problems such as DIC. Blood for coagulation studies should be drawn. Heparization may be necessary.
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