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Review Article

METHEMOGLOBINEMIA (METHBA): ONE OF WORLD'S MOST ULTRA- RARE SILENT KILLER

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Abstract:
Known more commonly as **blue skin disorder**, this disease is characterized by an abnormal amount of methemoglobin, a type of hemoglobin that's transformed to carrying iron, in a person's blood. Most of us have less than 1% methemoglobin in our blood stream, whereas those who suffer from blue skin disorder possess between 10% and 20% methemoglobin. Because iron-carrying hemoglobin carries only a reduced amount of oxygen, patients diagnosed with methemoglobinemia are at higher risk of developing heart abnormalities, having a seizure, or even dying prematurely. The disease has been made most famous by a single family in Kentucky who appear to have passed the genetic trait onto its family members for some 200 years.
Keywords: Congenital Methemoglobinemia, Benzocaine

Introduction:

Methemoglobinemia is a blood disorder in which too little oxygen is delivered to your cells. Oxygen is carried through your bloodstream by hemoglobin, a protein that's attached to your red blood cells. Normally, hemoglobin then releases that oxygen to cells throughout your body. However, there's a specific type of hemoglobin known as methemoglobin that carries oxygen through your blood but doesn't release it to the cells. If your body produces too much methemoglobin, it can begin to replace your normal hemoglobin. This can lead to not enough oxygen getting to your cells. There are two types of methemoglobinemia: **Acquired and Congenital.**

Figure 1: Methemoglobinemia attackted patient and comparison between normal RBC and affected RBC

Congenital Methemoglobinemia: Methemoglobinemia can be congenital, which means you're born with the condition. Congenital methemoglobinemia is caused by a genetic defect that you inherit from your parents. This genetic defect leads to a deficiency of a certain enzyme, or protein. This protein is responsible for converting methemoglobin to hemoglobin. Congenital methemoglobinemia is much less common than the acquired form of the condition.

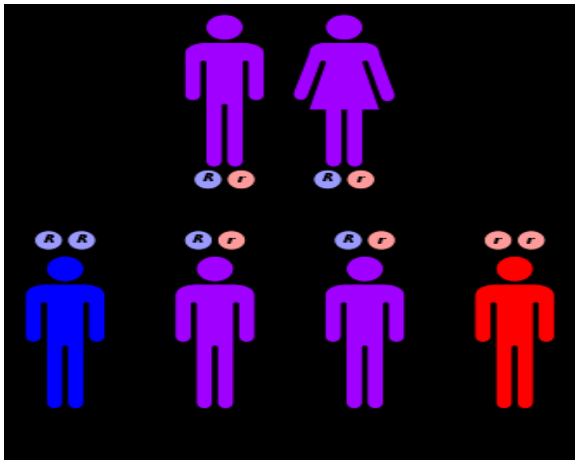

Figure 2: Genetic flow of Methemoglobinemia

Type 1: Type 1 is the most common type of congenital methemoglobinemia. It occurs when it's passed on by both parents, but they don't have the condition themselves. It affects only the red blood cells. Usually, its only symptom is cyanosis. People with type 1 can have bluish-tinted skin their whole lives without any other symptoms. They may get treated for cosmetic reasons. People with this type have a higher likelihood of developing acquired forms.

Type 2: Type 2 is also known as cytochrome b5 reductase deficiency. It's the rarest form of methemoglobinemia. Type 2 affects all cells. Only one of your parents needs to pass on the abnormal gene. It can cause severe developmental problems and failure to thrive. Babies born with type 2 usually die in their first year.

Accquired Methemoglobinemia: This is also known as acute methemoglobinemia. Acquired methemoglobinemia is the most common type of the condition. It's caused from exposure to certain medicines, chemicals, or foods. People who carry a genetic form of the condition have a higher chance of developing the acquired type. But most people who acquire this condition don't have a congenital problem. If acquired methemoglobinemia is not treated immediately, it can lead to death.

In babies: Babies are most susceptible to this condition. Babies can develop acquired methemoglobinemia from: **Contaminated well water:** Infants younger than 6 months may develop acquired methemoglobinemia from contaminated well water that has excess nitrates. Bacteria in a baby's digestive system mixes with the nitrates and leads to methemoglobinemia. Fully developed digestive systems keep children older than 6 months and adults from developing this nitrate poisoning.

In Adults: People have developed methemoglobinemia after having medical procedures that used certain topical anesthetics that are often sprayed on to the skin. These include benzocaine, lidocaine, and prilocaine. These may be used to: numb your throat before checking your lungs with bronchoscopy or checking your upper digestive system with endoscopy ease pain during procedures including circumcision, implantation of catheters for chemotherapy, and placement of pacemakers. Other medicines that have caused this condition are: **dapsone (Aczone)**, which can be used to treat conditions like acne, a type of dermatitis that causes blisters on your arms and buttocks, and a fungal lung infection in people with HIV/AIDS **antimalarial drugs**.

Causes: Benzocaine, Nitrates, Dapsone, Genetics

1. Benzocaine: The underlying mechanism of **benzocaine - induced methemoglobinemia** is not clear, but it appears to involve direct oxidation of the heme iron. Methemoglobinemia refers to the presence of an elevated, circulating fraction of methemoglobin within the erythrocytes.

2. Nitrates: Methemoglobin (MetHb) is formed when nitrite (for our purposes, formed from the endogenous bacterial conversion of nitrate from drinking water) oxidizes the ferrous iron in hemoglobin (Hb) to the ferric form.

3. Dapsone: Dapsone is metabolized in the liver via the cytochrome P450 pathway to potent oxidants that are responsible for its adverse hematologic effects—namely, hemolytic anemia and methemoglobinemia.

4. Genetics: Autosomal recessive congenital methemoglobinemia is caused by mutations in the CYB5R3 gene. This gene provides instruction for making an enzyme called cytochrome b5 reductase 3. This enzyme is involved in transferring negatively charged particles called electrons from one molecule to another.

Symptoms: Clinical symptoms of methemoglobinemia depend on the serum concentration of methemoglobin. Peripheral and central cyanosis are usually seen at a serum methemoglobin level of 15%. Methemoglobin levels of 30% to 45% result in headache, fatigue, tachycardia, weakness, and dizziness, while levels above 60% result in cardiac arrhythmia, dyspnea, seizures, and coma. Death typically occurs at methemoglobin levels greater than 70%.A baby born with the condition may have a bluish tinge to their skin, which is called cyanosis. This color might be apparent at birth or shortly afterward. They may show signs of: **blueness around the hands, blueness around the feet, difficulties in breathing, vomiting, and diarrhea.**

In severe cases, they may be: **extremely lethargic, salivate excessively, lose consciousness.** Symptoms vary according to the amount of methemoglobin in the blood, which is measured on a scale called the MetHb concentration. The normal level of MetHb concentration in a person's blood is between 0 and 3 percent. If MetHb reaches a concentration of 3 to 10 percent, a person's skin may take on a blue-grey appearance of cyanosis. MetHb levels of 15 to 30 percent lead to cyanosis, where blood starts to look chocolate brown. Concentrations of 30 to 50 percent start to cause more severe symptoms. These symptoms may include a headache, fatigue dizziness, anxiety, and confusion, as well as temporary loss of consciousness, rapid heartbeat, and weakness. When levels reach 50 to 70 percent, the person may experience seizures, kidney problems, or an abnormal heartbeat. MetHb concentrations of 70 percent and over can be fatal.

Diagnosis: Arterial blood gas analysis showed chocolate color blood with a pH of 7.43, oxygen saturation of 68%, partial pressure of oxygen 416 mm of Hg, partial pressure of carbon dioxide of 30 mm of Hg, and elevated methemoglobin levels of 32.1%. Immediate injection of methylene blue 1 mg/kg intravenously was initiated. Repeat arterial blood gas analysis 1 hour later showed improving methemoglobin levels of 9.1% with oxygen saturation of 90%. She was more alert and awake. An additional dose of methylene blue 1 mg/kg was administered intravenously. Two hours later, venous blood gas analysis showed a methemoglobin level of 0.4% with complete resolution of cyanosis. When the concentration of methemoglobin in the blood is above 1.5%, the patient develops cyanosis, the main characteristic of this disorder. The color of the arterial blood changes to dark brown with normal PaO2.

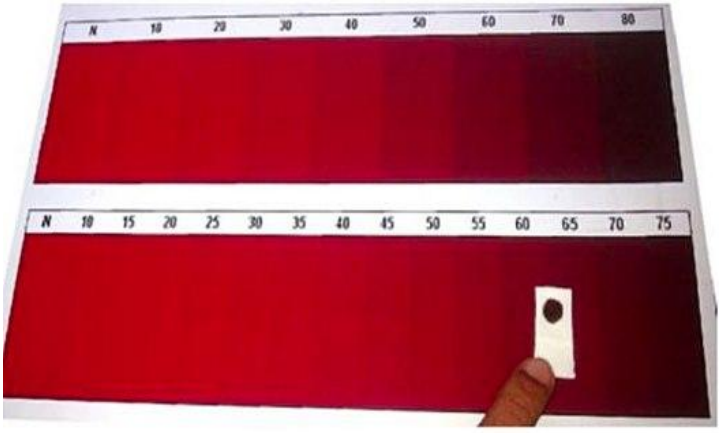

Figure 3: Color chart for the detection of the amount of methemoglobin in the blood

One should suspect the diagnosis in patients with cyanosis and low saturation (SpO2) without significant cardiopulmonary dysfunction. Co-oximetry is the gold standard and defines the diagnosis. Treatment should be based on whether the syndrome is acute or chronic (etiology) and on the severity of symptoms. Blood levels of methemoglobin are important, especially in acute cases. Basic treatment includes removal of the agent responsible for the disorder, administration of oxygen, and observation. Severe cases should be treated with the specific antidote, methylene blue, which is not effective in some situations.

Treatment: Treatment of patients with MetHba should be guided, primarily, by the severity of the disorder. Blood levels of MetHb represent a secondary parameter in the definition of the treatment. Usually, the symptoms are mild. In those cases, treatment consists of removing the inducing agent, administration of high-flow O2, observation, and evolutive co-oximetric assessment. After discontinuation of the causative agent, fMetHb returns to baseline levels within 36 hours. The use of supplementary

O2 increases plasma levels of dissolved O2, contributing, discretely, to the improvement of DO2 and oxygen consumption (VO2) during tissue hypoxia. Hyperoxic pulmonary ventilation (inspired fraction of O2 of 1.0) can accelerate the degradation of MetHb and prolong the survival of pigs submitted to lethal acute MetHba.

In situations of significant clinical manifestations (e.g., dizziness, headache, anxiety, dyspnea, symptoms of low cardiac output, somnolence, and seizures), besides the basic conduct mentioned, methylene blue should be used as a specific antidote. Several authors suggest that methylene blue should be used with MetHb above 30%, regardless of the presence or absence of symptoms. This is especially recommended when the patient is unconscious (e.g., head trauma, deep sedation, or general anesthesia). Evidence of tissue hypoxia obtained by the usual monitoring - metabolic acidosis, hyperlactatemia, tachycardia, changes in ST segment, cardiovascular shock - can be a late development and might result in severe damages and irreversible sequela.

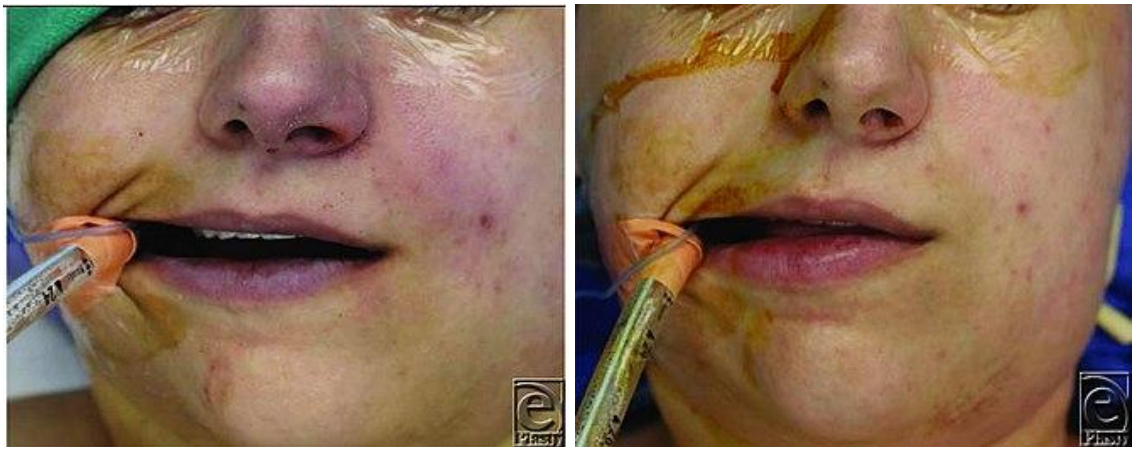

Figure 4: Cyanosis from methemoglobinemia & Resolved after methylene blue

As mentioned before, cases of congenital MetHba evolve with elevated levels of fMetHb (up to 35% to 40%) without symptoms of hypoxia. However, several conditions leading to imbalances in the global supply/demand ratio of O_2 in those individuals (SIRS, cardiopulmonary disorders, anemia, etc.) can cause clinical decompensation. Similarly, exposure to oxidizing drugs can increase the levels of MetHb, leading to the development of acute symptoms. Therefore, the decision to treat or not should be individualized and oriented according to the clinical presentation.

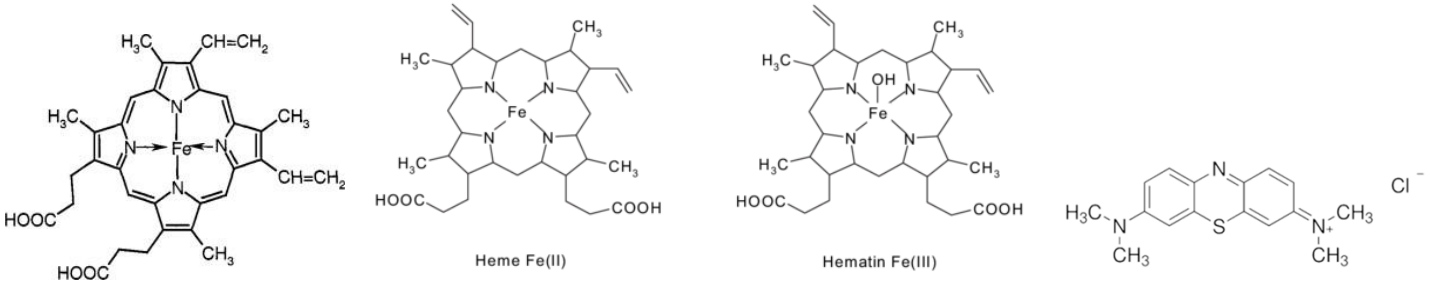

Figure 5: Hemoglobin, Methemoglobin, Methylene Blue

Methylene blue is a thiazine dye with dose-dependent antiseptic and oxidizing properties. During its use, the alternative enzymatic system (NADPH methemoglobin reductase) becomes fundamental in the reduction of MetHb. Methylene blue activates NADPH methemoglobin reductase, which reduces methylene blue to methylene leucoblue, which transforms MetHb in HHb by a non-enzymatic mechanism. In reality, methylene blue is an oxidizer; it is its metabolic by-product - methylene leucoblue - that reduces MetHb.

The recommended dose of methylene blue ranges from 1 to 2 $mg.kg^{-1}$, administered intravenously as a 1% solution over 5 minute. It can also be administered by the oral or intra-osseous routes in selected cases. The subcutaneous administration of this drug is associated with abscess formation at the injection site. The levels of fMetHb fall significantly 30 to 60 minutes after the first dose. Additional doses can be administered every hour if necessary, up to a maximum total dose of 7 $mg.kg^{-1}$. Fast intravenous administration or the use of doses above the

recommended dose can cause thoracic pain, dyspnea, hypertension, diaphoresis, and paradoxal increase of fMetHb. Doses above 15 $mg.kg^{-1}$ cause direct damage of red blood cells and hemolysis with Heinz bodies. This drug should be administered carefully in patients with renal failure, since both methylene blue and leucoblue are slowly excreted by the kidneys. During treatment, the urine has a bluish tint. The same occurs, in varying degrees, to the skin and mucous membranes, hindering the interpretation of cyanosis after the treatment. Gastrointestinal symptoms may also be seen and, rarely, anaphylactic reaction. The bispectral index (BIS) may show marked reduction after treatment with ethylene blue.

In cases of congenital MetHba, only patients with deficiency of CB5R reductase show consistent results to methylene blue. In HbM disease, patients do not show adequate response to exogenous electron donors because the enzymatic machinery responsible for the reductive activity of red blood cells is normal and iron oxidation is stabilized by the globin chain. In general, methylene blue is not indicated in cases of HbM. Other causes of unresponsiveness to methylene blue include: NADPH methemoglobin reductase deficiency, glucose-6-fosfate dehydrogenase (G6PD) deficiency, and the presence of SHb erroneously identified as MetHb by the co-oximeter. In G6PD deficiency, red blood cells do not produce enough NADPH to reduce methylene blue to methylene leucoblue; N-acetyl-cysteine (another electron donor) has been used on those cases. Other treatments for MetHba include ascorbic acid, exsanguination-transfusion, and hyperbaric oxygen therapy. Selected cases of non-severe NADH-MR deficiency can be treated with the intravenous administration 300 to 1,000 mg of ascorbic acid daily. On the other hand, acquired (acute) MetHba does not respond to ascorbic acid because its capacity to reduce MetHb is much inferior to that of endogenous enzymatic systems. Hyperbaric oxygen therapy increases the level of O_2 dissolved in the plasma and brings CO_2 close to the minimum necessary to maintain the metabolism, even in the of severe anemia. With hyperbaric treatment it is possible to maintain the DO_2 temporarily, until the oxygen carrying capacity is restored with exsanguination-transfusion. Therefore, both hyperbaric oxygen therapy and exsanguination-transfusion are reserved for severe cases that do not respond to methylene blue. Those patients also benefit from ventilatory and cardiovascular support, and are better followed in the intensive care unit.

Conclusion: MetHba is a syndrome with multiple etiologies, including different congenital changes and toxic reactions to several chemical agents, but its prevalence is unknown. Since it presents frequently in the perioperative period, the diagnosis should be considered in cases of severe cyanosis non-responsive to oxygen administration, after ruling out cardiopulmonary dysfunction. Artifacts and uncertainties related with pulse oximetry and conventional arterial blood gas determination can both suggest the diagnosis and hinder institution and follow-up of the treatment. Only with the knowledge of those particularities it is possible to institute adequate conducts. Congenital type 2 MetHb can be serious and often leads to death in the first few years of life. As such, people with a family history of the condition are advised to speak to a healthcare professional before having children. People with type 1 MetHb and hemoglobin disease tend to do well. Acquired MetHb can be fatal, but once the cause of the problem has been identified and removed, outcomes are good. Most cases will not even require treatment.

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