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A comprehensive review on methemoglobinemia

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ABSTRACT

Methemoglobinemia is a blood condition in which the production of methemoglobin (MetHb) is irregular and thus unable to adequately release oxygen to body tissues. This is largely because MetHb is the altered hemoglobin (Hb) state in which heme's ferrous iron has been oxidized to the ferric state. This review paper explores in depth the various forms of methemoglobinemia and the biochemical pathways and mechanisms of their causes. If they have cyanosis, patients with high MetHb in the blood can look blue, but the methylene blue solution will heal them. However, for strategic care, proper management should be identified. This analysis would be helpful in learning the basics of methemoglobinemia and its current treatment with recommendations for health care professionals, pharmacists, biochemists, and researchers. This study will allow readers to understand methemoglobinemia and will be a ready guide for it.

Keywords: Hemoglobin, Methemoglobinemia, Methylene blue, MetHb,

INTRODUCTION

Anemia is a disease in which the number of red blood cells or the concentration of hemoglobin (Hb) in the blood is low, thereby disrupting the concentration of oxygen in the body tissue due to low transport of oxygen. [1] Depending on its causes, it can have different signs and symptoms. Although there is hypotension or tachycardia in acute anemia, there is weakness, exhaustion, or light skin in chronic anemia. There are several forms of anemia, including sickle cell, aplastic, hemolytic, deficiency of iron, and lack of blood, each with different causes. There are some forms of anemia caused by more than one cause, however. For example, hemolytic anemia can be caused by enzyme deficiencies such as glucose 6 phosphate dehydrogenase (G_6PD) and pyruvate kinase or by the immune system that kills the erythrocytes.The disruption of the ability to effectively carry oxygen by the Hb is a functional anemia such as methemoglobinemia[2],[3]

Depending on the volume of the Hb and the availability of oxygen to the skin, the general color of the skin varies from pale to pinkish.Cyanosis, commonly referred to as blue skin, is the bluish or purple discoloration of the skin due to insufficient oxygen saturation. Methemoglobin (MetHb) results in a reduced concentration of oxygen in the blood, contributing to cyanosis; it is also referred to as blood blues. Furthermore, methylene blue is widely used to treat methemoglobinemia.

HISTORY

In the congenital (hereditary) form of the disorder, the hallmark background is the presence of diffuse, chronic, slate gray cyanosis, sometimes present from birth. No evidence of cardiopulmonary disease is available. In spite of the presence of cyanosis, patients with hereditary methemoglobinemia are asymptomatic. Methemoglobinemia is quite suggestive of the failure of 100 percent oxygen to correct cyanosis. Acute methemoglobinemia can be life-threatening and is

commonly acquired as a result of toxin or drug exposure. It is necessary, therefore, to obtain a comprehensive history of exposure to methemoglobinemia-inducing substances. Such a history may not always be forthcoming, but when long-term or repetitive exposure may occur, it should always be searched actively. It may be important to consult a toxicologist, especially when introduced to a new drug, since the list of medications known to cause methemoglobinemia is constantly evolving. A normal methemoglobin fraction is about 1% (range, 0-3%).At methemoglobin levels of 3-15%, a slight discoloration (eg, pale, gray, blue) of the skin may be present. Apart from moderate cyanosis, patients with a 15-20 percent methemoglobin level may be generally asymptomatic. Infants and children may experience methemoglobinemia, caused by chronic dehydration and diarrhea, at methemoglobin fractions greater than 70%, death usually occurs in combination with metabolic acidosis. The consumption of water from wells polluted with excess nitrates and exposure to local anesthetics in teething gels are the causes of unintended toxin exposure that must be addressed in infants and children. In a detailed history, these considerations may often be elicited.[4]

It is essential to explain any known family history of methemoglobinemia or glucose-6-phosphate dehydrogenase (G_6PD) deficiency. Even patients who are heterozygous for defects of the methemoglobin reductase enzyme are prone to low doses of methemoglobinemia-resulting oxidant medications. The existence of symptoms of the gastrointestinal (GI) system (e.g., nausea, vomiting, or diarrhea) may indicate the likelihood of a toxic material being ingested. In the case of anemia, the clinical symptoms of methemoglobinemia are compounded.

DEFINITION

A blood disease that occurs when too little oxygen is provided to the cells of the body is methemoglobinemia. There are two types of congenital and acquired methemoglobinemia.

TYPES OF METHEMOGLOBINIMEA

Methemoglobinemia can result from either congenital or acquired processes.

CONGENTIAL

Congenital/hereditary forms of methemoglobinemia are either caused by enzyme deficiency (autosomal recessive defects of the cytochrome b5 reductase enzyme) or by autosomal dominant mutations, called hemoglobin M, in the genes that code for globin proteins. It is characterized by a decrease in methemoglobin's enzymatic reduction back to functional hemoglobin. Hemoglobin M disease patients are normally asymptomatic and should be consulted as to the benign aspects of their condition. There is no suitable alternative available if care is needed for this disorder.Patients with congenital methemoglobinemia can have 20-40% methemoglobin levels.They are generally cyanotic from birth, but with normal growth, they are asymptomatic. Siberian Yakuts, Athabaskans, Eskimos, and Navajo have been found to have an elevated prevalence of the disease. [5-7]

ACQUIRED

Acquired methemoglobinemia is more prevalent and results from direct oxidizing agent exposure. It can be fatal and generally results from the ingestion of specific medications or agents that cause methemoglobinin production to increase. Nitroglycerine, dapsone, sulfonamides, phenytoin, phenacetin, and local anesthetics are typical medicines with oxidizing impact. Many agrochemical compounds contain a solvent that can result in serious, even fatal, methemoglobinemia. Most of these compounds do not have compositional specifics and can lead to extreme methemoglobinemia. Neonates and infants are at a higher risk of methemoglobin accumulation when exposed to such medications due to underdeveloped methemoglobin reduction mechanisms.[8-10]

COMPLICATIONS

Methemoglobinemia can be chronic or acute. The physiological level in the blood of methemoglobin is 0 to 2 percent.2 Methemoglobin concentrations of 10 to 20 percent are well tolerated, although symptoms are frequently associated with levels above this. Levels above 70% can trigger death. The rapidity of its formation often depends on symptoms. Many patients with lifelong methemoglobinemia are asymptomatic, although there may be serious symptoms in patients exposed to medications and toxins that abruptly experience the same levels of methemoglobinemia.

There is cyanosis in small infants with methemoglobinemia that fails to respond to supplemental oxygen. Cyanosis commonly occurs shortly after birth in those with congenital methemoglobinemia. At methemoglobin levels of 30 percent or more, dyspnea, nausea, and tachycardia occur. As methemoglobin levels reach 55 percent, lethargy, stupor, and declining consciousness occur. Higher levels of cardiac arrhythmias and circulatory failure may lead to Drug-induced methemoglobinemia, especially with exposure to dapsone, sulfasalazine, or phenacetin, may be accompanied by hemolytic anemia. Heinz bodies (precipitated hemoglobin or globin subunits due to hemoglobin denaturation in erythrocytes) and scattered red blood cells characterize anemia. Acute intravascular hemolysis can sometimes lead to renal failure. Jaundice hemolytic anemia can also be a characteristic of hemoglobin MSaskatoon and hemoglobin MHyde Park, rare forms of hemoglobin associated with hereditary methemoglobinemia and identified by where they were detected. [11]

DIFFERENTIAL DIAGNOSIS

Cyanotic congenital heart disease is included in the differential diagnosis of methemoglobinemia in small infants, especially when right to left shunting is present. Children with cyanotic congenital heart disease receiving supplemental oxygen have low partial oxygen pressure and low measured oxygen saturation, however, despite cyanosis

and normal calculated oxygen saturation, children with methemoglobinemia have high partial oxygen pressure. Methemoglobinemia should be separated from sulfhemoglobinemia in older children. The insertion of a sulfur molecule into the heme moiety leads to sulfhemoglobinemia. Sulfhemoglobinemia can also be caused by most drugs, especially sulfonamides and phenacetin, that produce methemoglobinemia, although this condition is less common than methemoglobinemia.[12]

The symptoms appear to be milder than in methemoglobinemia patients. The diagnosis is confirmed by either spectrophotometry or gas chromatography-mass spectrometry of elevated levels of sulfhemoglobin, Sulfhemoglobinemia does not respond and is tolerant of methylene blue therapy.Exchange transfusion can be useful in extreme cases.[13]

Methemoglobin and sulfhemoglobin can be separated by the potassium cyanide examination. Methemoglobin becomes bright red after the addition of a few drops of potassium cyanide, but sulfhemoglobin stays dark brown. This is due to the attachment of cyanide to methemoglobin, creating cyanomethemoglobin, which has a bright red hue. Sulfhemoglobin, on the other hand, is inert and does not bind cyanide.Because of NADH cytochrome b5 reductase deficiency from hemoglobin M disorder, family history is typically helpful in separating methemoglobinemia. The existence of hemoglobin M is indicated by cyanosis in successive generations; normal parents but potentially affected siblings mean the presence of deficiency of NADH cytochrome b5 reductase.[14]

DIAGNOSIS

Blood containing elevated methemoglobin levels tends to be chocolate brown. Despite life-threatening methemoglobinemia, subjects with methemoglobinemia may have normal partial oxygen pressure levels. Saturation levels of oxygen, measured by a pulse oximeter, are wrongly elevated. An elevated level of methemoglobin is observed in methemoglobinemia due to drug exposure, but the activity of NADH cytochrome b5 reductase is normal. The function of the enzyme is less than 20 percent average in inherited type II methemoglobinemia. Hemoglobin M may be distinguished by its absorption spectrum in the range of 450 to 750 nm from the methemoglobin formed from hemoglobin A. For the separation of hemoglobin Melectrophoresis at pH 7.1 is most useful.[15]

SYMPTOMS

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. The symptoms based on the concentration of Methemoglobinemia is given in the Table: 1

Table: 1 Symptoms of Methemoglobinemia

	Conc. of Methemoglobin	Symptom
1	0-3%	No symptoms
2	10-20%	Cyanosis, Chocolate brown blood
3	20-50%	Dyspnea, ↓Exercise Tolerance, Fatigue, Dizziness, Tachycardia
4	>50%	CNS hypoxia, Seizure, Coma, Dysrhythmias, Ischemia, Tachypnea, Metabolic acidosis
5	>70%	Severe hypoxia, death

They may also show signs of blueness around the mouth, blueness around the hands, blueness around the feet, difficulties in breathing, vomiting, and diarrhea. In severe cases, they may be extremely lethargic, salivate excessively, and 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 concentration of MetHb in a person's blood is between 0 and 3%. If MetHb reaches a concentration of 3 to 10%, a person's skin may have a blue-grey appearance of cyanosis. MetHb levels of 15 to 30 percent lead to cyanosis, where the blood begins to look chocolate brown. Concentrations of 30 to 50 percent begin to cause more serious symptoms.

These symptoms may include headache, tiredness, anxiety, and confusion, as well as temporary loss of consciousness, rapid heartbeat, and weakness. When levels are between 50% and 70%, a person may experience seizures, kidney problems, or abnormal heartbeat. MetHb concentrations of 70% and above may be fatal.[16]

CLINICAL FEATURES

Methemoglobinemia can be chronic or acute. The physiological amount in the blood of methemoglobin is 0 percent-2 percentNormal healthy patients will tolerate 10 percent to 20 percent methemoglobin levels, but at levels above this, symptoms grow. Levels of methemoglobin above 70 percent .While survival with a methemoglobinemia (MetHb) level of 81 percent-91 percent may be fatal, symptoms also depend on the rapidity of methemoglobin formation. Most patients with congenital/hereditary methemoglobinemia remain asymptomatic, but highly symptomatic may be patients who are exposed to medications and toxins resulting in acquired methemoglobinemia.[17-19]

TREATMENT

Methylene blue solution followed by supplemental oxygen is the treatment widely used to treat methemoglobinemia. Methylene bluetrihydrate (3,7-bis

(dimethylamino) phenazantionium chloride trihydrate) is the active ingredient. It is a pro-drug that the flavin reductase in the erythrocytes converts to leucomethylene blue (colorless) for it to serve as an electron donor. As an electron acceptor, the formation of leucomethylene blue requires NADPH. When converting back to methylene blue, Leucomethylene blue reduces MetHb to Hb, rendering it recyclable for the next conversion to MetHb. It is suitable to treat acute methemoglobinemia due to its rapid action of oxidizing MetHb. However, due to its oxidizing nature, methemoglobinemia is further induced at a high methylene blue concentration.[20]

Methylene blue does not treat a person with G_6PD deficiency who acquires methemoglobinemia because it causes methemoglobinemia and encourages hemolysis. As G6PD is responsible for generating NADPH in the pentose phosphate pathway, this is because of the inadequate amount of NADPH to form leucomethylene blue. The correlation between G_6PD deficiency and MetHb is seen. Due to the inadequate amount of reductasto transform it to leucomethylene blue for its therapeutic effect, a flavinreductase deficient person who acquires methemoglobinemia has no response to tomethylene blue. For inherited methemoglobinemia, the dosage of methylene blue for a lifetime is 50-250 mg per/day orally.

For acquired acute methemoglobinemia, 1-2 mg/kg of 1% methylene blue solution is administered intravenously for >20 minutes, and repetition is needed if an appropriate response after 1 h is not present.To avoid the continuation of MetHb formation and suspected drug-drug interaction such as aniline and dapsone, acquired methemoglobinemia can stop the administration of drug-inducing methemoglobinemia until treatment with methylene blue. Many asymptomatic patients are treated with supplemental oxygen and not with methylene blue, similar to those treated with methemoglobinemia in patients with G_6PD deficiency.The apparent half-life of methylene blue in the human body is approximately 10 h, whereas bioavailability for 200 mg of methylene blue is approximately 73 percent. In addition, the plasma-time curve indicates that it is well absorbed in the gastrointestinal tract and achieves peak plasma concentration after an oral dose of approximately 1-2 hours.

Intravenous administration is favored for acute methemoglobinemia because of its rapid‐onset effect. The half-life of methylene blue administered intravenously is calculated to be about 5-6.5 h.Methylene blue is quickly transformed into leucomethylene blue in the tissue of the body. As a result, it is mainly excreted in the urine as leucomethylene blue and finally becomes green or blue on standing.It can be excreted through the blue stool arising from the bile. Around 75% of it is excreted in the urine for the oral dose, mainly as leucomethylene blue and few through the bile.Methylene blue is not intended to be given to a pregnant or lactating woman because there have been no clinical trials and possible alleged harmful effects have been identified. Methylene blue has some adverse effects if administered orally, mostly in the gastrointestinal region.Nausea, vomiting, diarrhea, stomach pain, oral dysesthesia, blue saliva, and blue stools may be felt by the patient. Headaches, mental confusion, and dyspnea are other typical symptoms. Due to the administration of methylene blue, patients may experience excessive transpiration and blue urine.

It is recorded that the patient may develop extreme burning pain, necrosis, abscess, ulceration, and thrombophlebitis at the site of intravenous infusion injection. Excessive methylene blue may dose causes blue skin discoloration that may be mistaken for cyanosis or methemoglobinemia. Signs were cognitive dysfunction, hyper pyrexia, hyperreflexia, clonus. Thus, the administration of either one or both medications should be avoided. Another drug, aniline, especially its intermediates, can block the entry into the erythrocytes of methylene blue, rendering it unable to reduce MetHb, which in its presence contributes to a reduction in the efficacy of methylene blue.Methylene blue should not be treated in patients who have methemoglobinemia during the treatment of cyanide poisoning and in patients who have acute methemoglobinemia, as it may cause adverse results.Other treatments such as exchange transfusion and hyperbaric oxygen can be considered if the patient is unresponsive or unsuitable for methylene blue therapy. For patients with G_6PD deficiency or HbM variant, these therapies are sufficient. Other alternative medicines for methemoglobinemia therapy, particular, ascorbic acid with a dosage of 200-500 mg/day, which may induce stone formation after long-term ingestion, or riboflavin with a dosage of 20 mg/day, is used in the chronic kind.[21]

CONCLUSION

It is not considered that methemoglobinemia is anemia. It is one of the hematological conditions in which Hb is unable to operate properly. There may be congenital or acquired methemoglobinemia. There is no pharmacological cure for chronic congenital methemoglobinemia, while acquired methemoglobinemia requires methylene blue emergency treatment. However, with methylene blue therapy, people with HbM and G_6PD deficiency are ineffective, but the reverse effect can be induced.Any other risks that could contraindicate methylene blue therapy should also be tested in patients with methemoglobinemia. Patients prone to methemoglobinemia should be advised to contact their physician before taking any new drugs and, if the medications are unavoidable, strictly follow the prescription provided.

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