Methemoglobinemia Clinical Presentation

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History

The history is important for distinguishing methemoglobinemia between cyanosis that is due to cardiopulmonary abnormalities and that from other causes of discoloration of the skin and mucous membranes. Acute methemoglobinemia can be life threatening and usually is due to toxic exposure or drugs. Therefore, obtaining a history of exposure to substances that can induce methemoglobinemia is important. In contrast, patients with hereditary methemoglobinemia are often asymptomatic despite the presence of cyanosis. The failure of 100% oxygen to correct cyanosis is suggestive of methemoglobinemia.

- Symptoms are proportional to the level of methemoglobin.
  - Less than 10% methemoglobin – No symptoms
  - 10-20% methemoglobin – Skin discoloration only (most notably on mucus membranes)
  - 20-30% methemoglobin – Anxiety, headache, dyspnea on exertion
  - 30-50% methemoglobin – Fatigue, confusion, dizziness, tachypnea, palpitations
  - 50-70% methemoglobin – Coma, seizures, arrhythmias, acidosis
  - Greater than 70% methemoglobin – Death

- Infants and children can develop methemoglobinemia in association with metabolic acidosis that is caused by prolonged dehydration and diarrhea. Sources of accidental toxin exposure that need to be considered in infants and children include the ingestion of water from wells contaminated with excess nitrates and exposure to local anesthetics in teething gels.[21] These factors can sometimes be elicited in a thorough history.
- Any known family history of methemoglobinemia or G6PD deficiency is important to clarify. Even patients who are heterozygous for methemoglobin reductase enzyme deficiencies are susceptible to low doses of oxidant drugs with resultant methemoglobinemia.
- The presence of gastrointestinal (GI) symptoms (nausea, vomiting, diarrhea) may suggest the possibility of ingestion of a toxic substance.
- The clinical effects of methemoglobinemia are exacerbated in the presence of anemia.

Physical

The physical examination of patients suspected of methemoglobinemia should include careful examination of the skin and mucous membranes for discoloration or cyanosis.

- Vital signs should be documented, along with an assessment of the patient's mental status.
- Careful attention should be paid to the cardiac, respiratory, and circulatory examinations to assess for evidence of an underlying disease (either congenital or acquired).
- Pallor of the skin or conjunctiva may suggest anemia (and possible hemolysis).
- Significant anemia may mask the cyanosis of methemoglobinemia.
- Skeletal abnormalities and mental retardation are associated with certain types of methemoglobin reductase enzyme deficiencies.

Causes
The pathophysiology of methemoglobinemia has been previously discussed (see Pathophysiology). In general, methemoglobinemia can be acquired or congenital. Acquired methemoglobinemia is usually due to the ingestion of drugs or toxic substances. Congenital causes of methemoglobinemia include methemoglobin reductase enzyme deficiencies or abnormal hemoglobins (Hb M) that are more prone to form methemoglobin.

- Organic and inorganic nitrites/nitrates are common causes of methemoglobinemia. Many of these substances can also be absorbed through the skin, and many prescription cardiac medications contain these compounds. Dietary intake may occur in infants or adults who ingest well water that has been contaminated with nitrites caused by water runoff from fertilized fields.[21]
- Chlorates are another group of oxidizing agents that can cause methemoglobinemia. These substances are found in matches, explosives, and fungicides.
- Topical and injected local anesthetics have also caused methemoglobinemia. Predisposing factors for the development of this toxicity include the presence of a mucosal injury with resultant increased absorption or a previously undiagnosed methemoglobin reductase enzyme deficiency. This toxicity can also be idiosyncratic.
- Dapsone is another medication that can cause methemoglobinemia. It is used to prevent and treat Pneumocystis carinii pneumonia (PCP) and to treat leprosy and other skin diseases. This drug should be used with great caution in patients with known G6PD deficiency, methemoglobin reductase deficiency, or hemoglobin M.
- Patients with low catalase activity (inherited or acquired) may be at risk for the development of methemoglobinemia secondary to the formation of hydrogen peroxide after being treated with rasburicase for tumor lysis syndrome.[22] Some authors have suggested that catalase activity be measured before initiating therapy with rasburicase in this setting.
- Red blood cells in patients with liver cirrhosis undergo severe oxidative stress, especially in the setting of bleeding complications.[23] The level of methemoglobin is significantly higher in the red blood cells of these patients as compared with nonbleeding patients.
- Idiopathic methemoglobinemia can occur in association with systemic acidosis. This typically occurs in infants younger than 6 months and is usually caused by dehydration and diarrhea. Idiopathic methemoglobinemia is exacerbated by the lower levels of methemoglobin reductase enzyme found in infants (50% of adult levels).