Chapter 77

Methemoglobinemia: A Reappraisal with an Indian Perspective

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SYNONYMS
Hemoglobin M disease; Erythrocyte reductase deficiency; Generalized reductase deficiency, Gibson’s syndrome.

INTRODUCTION
Methemoglobin is the oxidized form of hemoglobin, which does not bind oxygen and increases the affinity of oxygen for the partially oxidized portion of hemoglobin. Increased levels of methemoglobin in the blood are secondary to congenital changes or exposure to several drugs, chemical agents, or food items resulting in a disorder with cyanosis. It can lead to death if not treated. The objective of this attempt is to review the subject, emphasizing relevant information for the clinical diagnosis of patients with methemoglobinemia, and to create awareness among the concerned.

INTERNATIONAL
Methemoglobinemia occurs rarely throughout the world. Cytochrome b5 reductase deficiency (type Ib5R) is also endemic in the Yakutsk people of Siberia.

RACE
The congenital form of methemoglobinemia due to cytochrome b5 reductase deficiency (type Ib5R) is endemic in certain ethnic groups. These groups include the Navajo, Athabascan Alaskans, and the Yakutsk people in Siberia.

SEX
No difference exists in disease occurrence of acquired methemoglobinemia between males and females.

AGE
Infants (especially premature infants) are more susceptible to the development of methemoglobinemia after drug or toxin exposure. This is because infants have significantly lower levels of cytochrome b5 reductase.

INDIAN PERSPECTIVE
• In India, methemoglobinemia is not very common, which may be due to lack of awareness or lack of epidemiological studies on the disease.
• Groundwater is a major source of drinking water in rural Karnataka. Most districts, where drinking water is supplied through bore wells, have a high concentration of nitrates and fluorides. The main cause for these high concentrations is open sewage disposal and use of nitrogen fertilizers (D Majumdar–2003, the blue baby syndrome—Indian Academy of Sciences/Resonance, October 2003. pp. 20-30).
• The sanitation coverage in some districts like Gulbarga, Bijapur, Raichur and Tumkur is below 20%.
• Fertilizer consumption in India is concentrated in about one-third of the cultivated area.
• In India, the chemical industry is growing rapidly in the western part, mainly in Gujarat and Maharashtra. Ahmedabad, is surrounded by a large number of industrial units manufacturing dyes and dye intermediates. Workers in these units are at high-risk of developing acute methemoglobinemia.
• An analysis of nitrates in the groundwater in Punjab by Greenpeace revealed nitrate pollution in drinking water. The most significant

HISTORICAL ASPECTS
• Cyanosis resulting from drug administration has been recognized since 1890.
• Quentin Howieson Gibson discovered methemoglobinemia after studying properties of hemoglobin. He discovered that in certain people, the hemoglobin molecules could not carry oxygen. This condition was eventually known as Gibson’s syndrome, or methemoglobinemia (Ref. The Journal of Biological Chemistry: Ligand Binding in Hemoglobin: the Work of Quentin H Gibson)
• In 1912, Sloss A and Wybauw R reported a case of a patient with methemoglobinemia.
• In 1948, Horlein and Weber described a family in which eight members over four generations manifested cyanosis.
• Clinical infant methemoglobinemia was first recognized in 1945.
• Methemoglobinemia has not been reported where water contains less than 10 mg/l of NO_3.

EPIDEMIOLOGY

UNITED STATES
Hereditary methemoglobinemia is a rare condition. This enzymatic deficiency is endemic in certain Native American tribes (Navajo and Athabascan Alaskans).

SYNONYMS
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KEYWORDS: Cyanosis, Methemoglobinemia

MET’HE MO’GLO’BI’NE’MI’A (mĕťhē-mĕ-głō’bĕ-nĕ’mĕ-a)
potential health effects of drinking water contaminated with nitrate are the blue-baby syndrome, methemoglobinemia and cancer.

- A study from three districts of West Bengal, highlights occupational morbidity among agricultural child labor. Apart from deaths due to explosions and fire, coughing, sore throat, dizziness, methemoglobinemia, and anemia are common effects of ingestion or inhalation of chlorate dust.5
- Congenital methemoglobinemia due to NADH-methemoglobin reductase deficiency in three Indian families recognized in a Mumbai-based study6.

NORMAL BIOCHEMISTRY

Adult human blood usually contains four species of hemoglobin:
1. Oxyhemoglobin (O₂Hb)
2. Reduced hemoglobin (Hb)
3. Methemoglobin (MetHb)
4. Carboxy hemoglobin (CO Hb).

METHEMOGLOBIN

If the ferrous ion loses an electron to another drug or chemical and is oxidized to the ferric (Fe³⁺) state, (Figure 1) methemoglobin (MeHb) is formed. It can no longer bind oxygen. So methemoglobin reduces oxygen carrying capacity and reduces oxygen release to tissues.

In normal conditions, only ~1-2% of the body’s hemoglobin exists as MeHb.7,8 Naturally it becomes oxidized during oxygen transport, and the reduction of methemoglobin is accomplished by the enzyme NADH—methemoglobin reductase, NADPH methemoglobin reductase and to a lesser extent the ascorbic acid and glutathione enzyme systems. Disruption of anyone or a combination of these enzyme systems lead to methemoglobinemia.9

CHEMISTRY AND GENETICS

- The cyanotic families carry an ineffective allele of the gene for NADH diaphorase. NADH diaphorase is an enzyme that repairs hemoglobin when it has been damaged by oxidation, leaving the iron atom in the +3 state.
- However, if the enzyme is inactive due to DNA sequence variation, the damaged hemoglobin cannot be repaired, and accumulates producing blue skin color. Then physician used methylene blue to repair the damaged hemoglobin. And after therapy, urine was found to be blue. Wide infra
  - Methylene blue (blue in color)—when administered, Met Hb++++ is converted to hemoglobin Hb++ and urine contains the blue pigment hence blue colored urine (Figure 2).
  - Whereas ascorbic acid (colorless) when administered, Met Hb++++ is converted to hemoglobin Hb++ and urine is colorless.

CLASSIFICATION OF METHEMOGLOBINEMIA (TABLE 1)

**Congenital**

Type I: Cytochrome b5 reductase deficiency, demonstrable only in the erythrocytes, presents as uncomplicated, benign methemoglobinemia.

Type II: Generalized cytochrome b5 reductase deficiency, demonstrable in all tissues, is accompanied by severe, lethal and progressive neurological disability, in addition to methemoglobinemia.

Type III: Deficiency is limited to hematopoietic cells and resembles Type I clinically.

Type IV: Clinically like Type I, is associated with deficiency of the cofactor.

**Acquired**

1. Occupational causes: Due to absorption of nitro and amino aromatic derivatives (nitrobenzene), nitrates, aniline (usually absorbed through lungs).
2. Related to ICU hemodialysis.15
3. Household causes include furniture and shoe polish containing marking ink, shoe dyes containing aniline, perfume and flavoring essence.
4. Drug causes:
   - Acetaminophen10
   - Dapsone7
   - Hydrogen peroxide14,15
   - Lidocaine11
   - Phenazopyridine18,19
   - Nitrates and nitrates (amyl nitrite, silver nitrate, nitroglycerin, nitric oxide)10,21

**Clinical Features**

Type 1: Methemoglobinemia12 (Cytochrome b5 reductase deficiency):
- Bluish coloring of the skin (cyanosis)

Type 2: Methemoglobinemia (generalized cytochrome b5 reductase deficiency):
Figure 2: Metabolic process depicting Hb++ converting to—Met Hb++

- Developmental delay, failure to thrive, mental retardation, seizures

Hemoglobin M disease:
- Bluish coloring of the skin (cyanosis)

Acquired methemoglobinemia includes:
- In chronic occupational cases: bluish coloring of skin, symptoms of anoxia including headache, dizziness, tachycardia, shortness of breath, muscular cramps, and weakness
- In cases of acute poisoning, vomiting, lethargy, loss of consciousness, circulatory failure and death can occur.

A Case Report Congenital Methemoglobinemia (Figure 3)
- A 55-year-old male patient, an agricultural laborer, admitted with chief complaints of weakness, syncope, headache and bluish discoloration of tongue and other parts of the body since 20 years off and on.
- Prior to hospitalization, the patient was seen as an out-patient for fatigue, syncope and lethargy at many hospitals.
- Headache occurred bilaterally at temporal region inter-mittently, no history of dyspnea or seizures.
- A known case of HTN, on regular treatment with telmi-sartan 40 mg once daily, no history of diabetes, or seizures.
- He is a smoker since 25 years and smokes three cigars per day, and occasional alcoholic. No history suggestive of offending drug intake like dapsone or use of anesthetics like prilocaine or benzocaine, paracetamol.
- No family history of glucose-6-phosphate dehydrogenase (G6PD) deficiency, or any other hemoglobinopathies by report. He has two brothers and three sisters who are healthy.
- No history of usage of nitrogen fertilizers or pesticide products at farm or at home.

On Examination
- Central cyanosis and clubbing present
- No pallor, no icterus, no significant lymphadenopathy, height-164 cm, weight-76 kg, BMI-28.2
- Pulse rate: 80/min, regular, BP: 150/100 mm Hg, respiratory rate: 18/min
- Oxygen saturation was 85% at ambient air with no improvement with 100% oxygen administration.
- Examination of cardiovascular system, respiratory system, abdomen and central nervous system (CNS) revealed nothing specific.

Investigations
- Hb: 15.3 g%, PCV: 47.3%, TRBC count : 5.3 mil/cmm, MCV: 89.4 fl, MCH: 28.8 pg, MCHC: 32.2%, T WBC count: 8100/cmm, differential count: P-69, L-24, E-04, M-03, ESR-25 mm at the end of 1 hour, Platelet count: 2.18 lakhs/cumm
- RBS: 89 mg/dL, Blood urea: 34.1 mg/dL, Serum creatinine: 1.3 mg/dL, Na: 145 mmol/l, K: 4.0 mmol/l, Cl:107 mmol/l.
- Liver function tests: Total bilirubin: 0.7 mg/dL, SGOT: 24.2 IU/l, Alkaline phosphatase: 113.9 IU/l, SGPT: 20.1 IU/l
- Negative for HIV antibodies, Hbs Ag or HCV Ab
- ABG analysis: Chocolate brown blood, pH: 7.412, PCO2: 42.4 mm Hg, PO2:80.7 mm Hg, Na140, K:3.89, HCO3(-act), 26.4, HCO3(B):25.8, BE (ecf):1.8, BE(B):1.5, O2 SAT:96.0.
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Section 10

Methemoglobin Estimation in Blood: 30.8% (N: 0.00 - 2.00%) Initially

- G6PD test decolorization time: 30 minutes (N: 30–60 min). G6PD deficient subjects 140 min-24 hours G6PD carriers 30–90 mins, hence negative.
- Hemoglobin electrophoresis: Normal Hb A-95.7%, A2-2.5%, F-0.3%, S-0%, D-0%, C-0%, unknown unidentified peak-1.5% Hb variant analysis-normal, hence no hemoglobin-opathies
- NADH-cytochrome b5 reductase activity was 16.10 IU/g Hb (normal 35.0 +/- 5.00 IU/g Hb).

Note:
- Reduced NADH-cytochrome b5 reductase (diaphorase l) activity, long symptom free survival, having only giddiness and fatigue, and absence of other lethal neurological diseases, confirms that it is a case of congenital type – I methemoglobinemia.
- He was treated with vitamin C 500 mg twice daily and riboflavin 10 mg once daily for 2 months.
- A repeat methemoglobin level showed a drop to 16.3%.

Note:
- Reduction of methemoglobin is accomplished by the enzyme NADH–methemoglobin reductase, NADPH–methemoglobin reductase and to a lesser extent the ascorbic acid and glutathione enzyme systems. Disruption of any one or a combination of these enzyme systems lead to the condition.

Diagnosis
- Blood containing high concentrations of methemoglobin appears chocolate brown (Figure 7).
- Subjects with methemoglobinemia may have normal partial pressures of oxygen, despite life-threatening methemoglobinemia.
- In methemoglobinemia due to drug exposure, an elevated level of methemoglobin is found, but the activity of NADH cytochrome b5 reductase, is normal.
- In hereditary type II methemoglobinemia, the enzyme’s activity is less than 20% of normal.
- Electrophoresis at pH 7.1 is most useful for the separation of hemoglobin M.
- In chronic methemoglobinemia compensated poly-cythemia is seen with cyanosis and clubbing (Figures 4 and 5).

Differential Diagnosis
- Children with cyanotic congenital heart disease who receive supplemental oxygen have a low partial pressure of oxygen and a low calculated oxygen saturation, but children with methemoglobinemia have (Table 2) a high partial pressure of oxygen despite cyanosis and normal calculated oxygen saturation.
- Methemoglobinemia in older children should be distinguished from sulfhemoglobinemia,22,23 which does not respond to methylene blue, and the treatment is supportive.24 In severe cases, exchange transfusion may be useful.
- Cyanosis may be present in adults with severe ILD, COPD and rarely cyanotic congenital heart diseases.
- Cyanosis in successive generations suggests the presence of hemoglobin M. Normal parents but possibly affected siblings imply the presence of NADH cytochrome b5 reductase deficiency.

Treatment
- The mainstay of treatment is discontinuation of the offending agent.
- If a patient is symptomatic or has a Met Hb level greater than 10%, supportive measures like supplemental oxygen, exchange transfusion are required.

Table 2 | Features suggestive of methemoglobinemia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>When an arterial blood gas is drawn, the blood is commonly referred to as having a brown or chocolate color (Figure 6)</td>
</tr>
<tr>
<td>Exposure to air</td>
<td>Upon exposure to air, the color of the blood does not change. If methemoglobin levels are greater than 35%, the observation of a lack of color change when exposed to air may be sufficient to make a diagnosis</td>
</tr>
<tr>
<td>Response of cyanosis</td>
<td>The cyanosis induced by increasing serum methemoglobin is not responsive to increasing FiO2 concentrations of inspired oxygen</td>
</tr>
<tr>
<td>PaO2</td>
<td>PaO2 is normal or even increased</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>A metabolic acidosis may be present secondary to decreased delivery of oxygen to tissues</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>The oxygenation saturation determined by pulse oximetry and that determined by the arterial blood gas (calculated) differ by more than 5%</td>
</tr>
</tbody>
</table>

Figure 4: Central cyanosis

Figure 5: Clubbling
Intravenous methylene blue at 1–2 mg/kg usually results in rapid reduction in Met Hb levels and improvement in symptoms. Repeated doses may be required in some cases. Along with this intravenous dextrose to be given because the major source of NADH in the red blood cells is the catabolism of the sugar through glycolysis (Figure 2)

Milder cases and follow-up severe cases can be treated orally with methylene blue 60 mg three to four times a day. Ascorbic acid 300–600 mg/day may be added for several days to replenish ascorbic acid pathway.

Note: Methylene blue may not work in some patients with severe G6PD deficiency and can cause hemolysis.11

Complications
• Shock
• Syncope
• Seizures
• Death.

Prognosis
• People with type 1 methemoglobinemia and hemoglobin M disease usually do well.

• Type 2 methemoglobinemia is much more serious, and usually causes death within the first few years of life.
• People with acquired methemoglobinemia usually do very well once the drug, food, or chemical that caused the problem is identified and avoided.

Prevention
• Genetic counseling is recommended for couples with a family history of methemoglobinemia who are considering having children.
• Avoidance of offending drugs, toxic and occupational agents, and contaminated water.
• Suitable protective methods in industries in Gujarat and other states are recommended.

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EPILOGUE
• Severe methemoglobinemia is a medical emergency
• A good history and high index of clinical suspicion are required for early diagnosis
• Exposure to medication or a toxin is the most common cause of methemoglobinemia.
• Methylene blue is the traditional treatment of choice when history is that of exposure to drug or toxin in addition to supportive measures in emergency unit and ascorbic acid 300–600 mg bid for several days.

REFERENCES


