Food Preservative Induced Methemoglobinemia: A Case Report

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ABSTRACT
Diseases caused by food preservatives is an underrated area of study. Acquired methemoglobinemia is one such rare disease caused by nitrates. We here present one such case which presented after eating Chinese food. As the presentation mimicked many other diseases, a thorough history and knowledge of methemoglobinemia helped us in reaching a diagnosis. Slightest delay in diagnosis and management could be fatal for the patient. Growing demand for Chinese food is promoting unchecked use of food preservatives by many food vendors.

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. Methemoglobinemia is an altered state of hemoglobin in which the ferrous (2+) form of heme is oxidized to the ferric form (3+) thus making the heme moiety unable to bind oxygen. 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.

Case Report
A 16 year old girl presented to our emergency Shalby Hospital Jabalpur Madhya pradesh with complaints of chest pain, low grade fever, dyspnea, fatigue, weakness and cyanosis. There was a history of ingestion of Chinese food one day back. On examination there was mixed cyanosis, pulse rate 140/min, respiratory rate of 30/min, Spo2- 65% not responding to high flow oxygen or Bipap support. Rest all other systems were normal.

Investigation revealed Hb- 13.6%, TLC- 12210/cu mm, total serum bilirubin- 3.1mg/dl, direct 0.5 and indirect 2.6mg/dl, blood for ABG drawn which was dark chocolate brown in colour which showed pH – 7.4, PaCO2- 33mmHg, high PaO2 – 205mmHg, HCO3- 22.7 and oxygen saturation of 100%. G6PD, Echocardiography and X ray chest was within normal limit. Patient was treated with I/V Methylene blue 2mg/kg bolus infusion over 15 -20 min followed by infusion of 1mg/kg infusion over 24hrs, along with I/V Vitamin C 200mg twice daily by infusion and Tab Riboflavin
100mg. Immediately after infusion of methylene blue patient’s clinical condition started improving, cyanosis decreased, tachycardia settled and oxygen saturation improved. After three days of methylene blue therapy patient’s oxygen saturation became normal and patient feels better.

Discussion
Pathophysiology
Acquired methemoglobinemia is a rare but fatal condition. In literature, many substances are known to cause it, the most common being dapsone, topical anesthetics like benzocaine, and antimalarial agents like quinine.1 We are reporting an uncommon case of methemoglobinemia induced by ingestion of Chinese food. Chinese food ingredients like Chinese spinach, Shanghai cabbage, petiole Chinese cabbage, broccoli, cauliflower are known to contain high concentration of nitrates and nitrites.2 Also the preservatives used in food items contain nitrates and nitrites.3

Methemoglobin consists of ferric ion which makes it incapable of oxygen transport. Normally, methemoglobin levels remain below 1% which is maintained through 2 important mechanisms. The first is the hexose-monophosphate shunt pathway within the erythrocyte. The second and more important mechanism involves two enzyme systems- diaphorase I (which requires Cytochrome b5 reductase and nicotinamide adenine dinucleotide (NADH) and diaphorase II (which requires glutathione production and glucose-6-phosphate dehydrogenase (G6PD) and nicotinamide adenine dinucleotide phosphate (NADPH), to reduce methemoglobin to its original ferrous state. The NADPH-dependent methemoglobin reduction pathway can be accelerated by exogenous cofactors such as methylene blue to as much as five times its normal level of activity.4

Classification Of Methemoglobinemia5
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.
3. Household causes include furniture and shoe polish containing marking ink, shoe dyes containing aniline, perfume and flavoring essence.
4. Drug – Acetaminophen, Benzocaine, Dapsone, Disulfiram, Hydrogen peroxide, Ibuprofen, Lidoceaine, Metoclopramide, Phenazopyridine, Prilocaine, Nitrites and nitrates, Pyridium

Clinical Features (Table 1)

| TABLE 1 Signs and symptoms correlate with Met Hb level |
|------------------------------------------------------|
| Met Hb concentration (%) | Signs and symptoms                                      |
|--------------------------|--------------------------------------------------------|
| 0–3% (normal)            | None                                                   |
| 3–10%                    | Blue-gray skin appearance (cyanosis), may be asymptomatic |
| 10–20%                   | Cyanosis, chocolate brown color of blood                |
| 20–50%                   | Mental changes (headache, fatigue, anxiety, confusion, dizziness), syncope, tachycardia, dyspnea and tachypnea, weakness, exercise tolerance |
| 50–70%                   | Metabolic acidosis, seizures, coma, dysrhythmias        |
| > 70%                    | Potentially lethal                                      |
Diagnosis (table 2)\textsuperscript{5}

The hallmark of methemoglobinemia is cyanosis that is unresponsive to high oxygen concentrations in the absence of cardiac or pulmonary disorders.\textsuperscript{4}

**TABLE 2 - Features suggestive of methemoglobinemia\textsuperscript{5}**

| Feature                        | Description                                                                 |
|-------------------------------|-----------------------------------------------------------------------------|
| Appearance                    | When an arterial blood gas is drawn, the blood is commonly referred to as having a brown or chocolate color |
| Exposure to air               | 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 |
| Response of cyanosis          | The cyanosis induced by increasing serum methemoglobin is not responsive to increasing FiO2 concentrations of inspired oxygen |
| PaO2                          | PaO2 is normal or even increased |
| Metabolic acidosis            | A metabolic acidosis may be present secondary to decreased delivery of oxygen to tissues |
| Oxygen saturation             | The oxygenation saturation determined by pulse oximetry and that determined by the arterial blood gas (calculated) differ by more than 5%. |

**Differential Diagnosis**

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. Methemoglobinemia in older children should be distinguished from sulfhemoglobinemia, which does not respond to methylene blue, and the treatment is supportive.\textsuperscript{5}

**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. 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. Methylene blue may not work in some patients with severe G6PD deficiency and can cause hemolysis. 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. 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.\textsuperscript{5}

**Conclusion**

The growing demand for Chinese food puts our population at risk of exposure to substances that can lead to methemoglobinemia. Although a treatable condition, lack of knowledge and improper history can create diagnostic confusions. Every physician must be aware of this potential complication of Chinese food. Also the food and health department of the country should keep vigilance on the maximum permitted levels of nitrates in various food ingredients.

**References**

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