Severe Methemoglobinemia and Syncope in a Patient with Glucose-6-Phosphate Dehydrogenase Deficiency

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Methemoglobin is hemoglobin with iron oxidized to the ferric (Fe³⁺) state from the reduced ferrous (Fe²⁺) state. MetHb is incapable of binding oxygen and shifts the oxygen-hemoglobin dissociation curve to the left, resulting in decreased oxygen delivery to the tissues. We report the case of a 37 year old woman with glucose-6-phosphate dehydrogenase deficiency who presented with methemoglobinemia induced by inhalation and dermal exposure to potassium nitrate. The patient developed severe hemolytic anemia and muscle damage with myoglobinuria. She received oxygen and blood transfusion and made a complete recovery. The MetHb concentration decreased from 45.8% to 0% after 4 days.

Patient Description
A 37 year old Yemenite patient was admitted because of an episode of syncope. She complained of dizziness, shortness of breath, marked cyanosis and muscle weakness. The patient worked in the diamond industry, and except for G6PD deficiency she was healthy. On physical examination, confusion and mild dyspnea were noted. Blood pressure was 120/80 mmHg, pulse 120 beats/min, 26 breaths/min. The skin and mucous membranes were a deep slate-gray color. The nail beds were deeply cyanotic without clubbing. Arterial blood gas analysis on 100% oxygen by mask showed pH of 7.36, PO₂ of 158 mmHg, bicarbonate 23 and standard base excess of 0. However, the saturation on oxygen meter was 85%. Hemoglobin was 13 g/dl and white blood cell count 12,600/mm³ with a normal differential count. Blood urea nitrogen, serum electrolytes and creatinine were within normal limits. The initial MetHb level was 45.8% of the total hemoglobin. The chest X-ray was normal, and the electrocardiogram revealed sinus tachycardia. A diagnosis of methemoglobinemia was made.

Because of the patient’s G6PD deficiency she was not treated with methylene blue but with blood transfusions. A gradual decrease in the MetHb level (45.8% to 0% in 4 days) was combined with a decrease in hemoglobin (13 to 10 g/dl following transfusion of six blood units). The bilirubin (predominantly indirect) level rose to 3.8 mg/dl. Pronounced reticulocytosis with Heinz bodies was observed. The haptoglobin level decreased (285 to 83 ng/dl), while lactate dehydrogenase level increased (161 to 1660 U/L). Myoglobin was detected in the urine. Electromyography showed myopathic changes. The patient was discharged on the fifth day and was followed for several months.

Comment
Methemoglobinemia may be congenital or acquired. Acquired methemoglobinemia, the common form, has been associated with many agents, including analgesic, anesthetic, antimalarial and antibacterial, as well as nitrite and nitrate salts [1]. Treatment consists of supportive measures, oxygen supplementation and prevention of further absorption. In asymptomatic patients with MetHb concentrations up to 30%, close observation is sufficient. Specific treatments comprise intravenous administration of methylene blue 1–2 ng/kg over 5 minutes and exchange transfusion in more severe cases or in cases where methylene blue should be avoided, such as patients with G6PD deficiency. Hyperbaric oxygen therapy can bypass the poor oxygen-carrying capacity of the hemoglobin by dissolving sufficient oxygen in the blood; this method is usually reserved for life-threatening situations [1].

In the patient presented here, the severe methemoglobinemia was acquired by inhalation of, and dermal exposure to potassium nitrate, an agent used by the patient at work during the diamond polishing process. Nitrates are metabolized in the liver to glycerol dinitrate, glycerol mononitrate and inorganic nitrite, which oxidizes hemoglobin to MetHb.

On admission the PO₂ was 158 mmHg while the oxygen saturation and MetHb concentration were 85% and 45.8%, respectively. Usually, patients with methemoglobinemia have a normal PO₂ and a low but higher than expected oxygen saturation measurement. This phenomenon is due to the method used to measure oxygen saturation with pulse oximeter. Blood oxygen saturation is measured by comparing the relative light absorption of two wavelengths (660 and 940 nm). Reduced hemoglobin has a peak absorption at 660 nm, whereas oxyhemoglobin absorption peaks at 940 nm. Because methemoglobin is absorbed at both wavelengths, the ratio remains constant, such that the pulse oximeter yields false near-normal oxygen saturation results. The SO₂ measured by
It has been shown that sodium nitrate is sensitive to the oxidizing effects of nitrite. Hemoglobin protein may also be oxidized by nitrite, causing denaturation and erythrocyte hemolysis. These effects combined with the intrinsic methemoglobin capacity for inducing hemolysis may explain the severe hemolytic anemia in our patient.

Our patient presented with syncope, dizziness, shortness of breath with tachypnea, weakness and marked cyanosis. There is a correlation between the MetHb percentage and the symptoms. Less than 3% is normal, 5-15% usually cause no symptoms. MetHb > 15% produces asymptomatic cyanosis. Dyspnea, headache, fatigue, dizziness and syncope appear with MetHb of 30-50%, which correlated with SO2 of 85%. Symptoms worsen as the MetHb increases, with death occurring at MetHb over 70% [5]. Syncope is a rare manifestation of methemoglobinemia, and we found only two case reports in the literature [2,5]. The mechanism of syncope in methemoglobinemia is not clear but it correlates with MetHb of 30-50%. It might be that the exposure to potassium nitrate that finally oxidizes hemoglobin to MetHb combined with its vassodilatory effect induces the syncope.

In conclusion, we present a patient with combined G6PD deficiency and exposure to potassium nitrate, which induces severe methemoglobinemia. A prompt diagnosis and therapy is mandatory. Near normal SO2 and PO2 may be misleading and should be carefully interpreted.

References

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Capsule

Antibody diversity

Antibody diversity in B cells is achieved through the somatic rearrangement of variable-(diversity)-joining (V(D)J) genetic segments. Allelic exclusion ensures that only one recombined allele is expressed in a given cell, in part through the selective acquisition of epigenetic marking by demethylation of the allele that is to undergo rearrangement. Fraenkel and co-workers show that a second major mechanism, which further enhances antibody diversity and is known as somatic hypermutation (SHM), is under the same allele-restricted control. They generated mice in which developing B cells were engineered to carry a pre-rearranged antibody kappa light chain at both alleles. In these cells, both alleles, rather than only one, were expressed, yet demethylation and extensive hypermutation were confined to just one of the two. Thus, although differences in methylation did not influence the level of transcription after recombination (explaining how both rearranged alleles could be expressed in this system), these differences did correspond to SHM levels. The findings suggest that the same epigenetic marking system that mandates monoallelic expression of productively recombined alleles also targets the rearranged antibody genes for further mutation, and that this discrimination occurs independently of transcription in mature B cells.

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