Why Is My Patient Blue?

Undiagnosed Congenital Methemoglobinemia

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Agenda and Objectives

1. Case presentations
2. What is Methemoglobinemia?
    a. Acquired
    b. Congenital
3. Presentation: Symptoms and Exam
4. Treatment
5. Genetics
6. Wrap up

- Recognize clinical presentations of congenital methemoglobinemia
- Understand pathophysiology and genetics of congenital methemoglobinemia
- Identify history, exam, and diagnostic clues of congenital methemoglobinemia
- Review evidence-based treatment strategies
- Discuss relevance in patients of Native American ancestry

Case #1

- 7-month old infant presents to the emergency department during winter surge for respiratory distress
  - No medical or surgical history, no daily medications
  - On exam: respiratory distress with tachypnea and hypoxemia (84%), non focal lung exam

Case #1

- Admitted to the general pediatric service on low flow nasal cannula
  - Tested positive for Influenza and RSV
- HFNC escalated without success
- Patient was transferred to the PICU and intubated

Case #1

- After intubation in the PICU additional testing showed a methemoglobinemia percentage of 10.1%, with repeat testing showing 13.1%
- Patient was treated with methylene blue. Methemoglobinemia percentage dropped to 0.7% by the following morning and they were extubated the next day
- Detailed history could not elicit any external causes

Case #2

- 12 year old presents to an outside emergency department for chest pain/discomfort. You receive a call with the following information:
  - No medical or surgical history, no daily medications
  - On exam (outside facility): Comfortable appearing but hypoxemic (low 80's), non focal lung exam
  - Diagnostics (outside facility): CBC/d, Chem, Trop, and BNP normal. EKG normal. Chest x-ray normal. CT for pulmonary embolism normal.
  - Treatment (outside facility): attempts at nasal cannula, high flow nasal cannula, and non-rebreather did not improve oxygen saturations above 90%, did not tolerate bi-pap. Transferred for further management.

Case #2

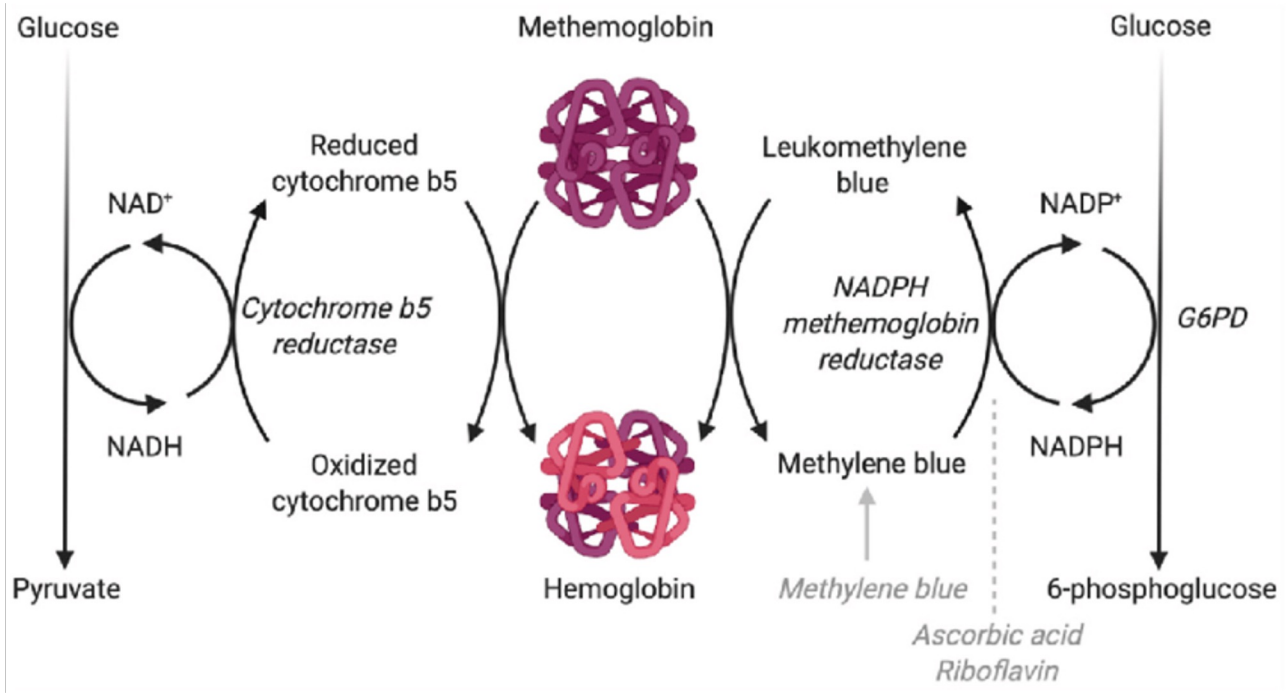
- On presentation, being supported by a non-rebreather over a high flow cannula, no increased work of breathing and speaking comfortably but with perioral and peripheral cyanosis
  - Blood draw for repeat labs noted to be very dark in color.
  - Point of care testing showed methemoglobinemia percentage of 24%.
  - Treatment started with methylene blue and admitted

Case #2

- After admission, methemoglobinemia percentage dropped to 1.3% by the afternoon
- There was rapid clinical resolution of symptoms
- Detailed history could not elicit any external causes

What is Methemoglobinemia?

- Impaired oxygen delivery due to the oxidation of hemoglobin iron
  - Ferrous (Fe2+) to Ferric (Fe3+)
  - Ferric state cannot bind and transport oxygen
- Acquired vs. congenital
  - Acquired
    - Oxidative stress or oxidizing agents
  - Congenital
    - Limited to erythrocytes - Type 1
    - Systemic - Type 2



Acquired Methemoglobinemia

- More common than congenital
- Numerous causes - take a good history!
  - Medications
    - Topical anesthetics - think teething infant
    - Antimalarial drugs
    - Dapsone
    - Sulfonamides
  - Environmental
    - Nitrates and nitrites
      - including foods contaminated by fertilizers or preservatives
    - Well water
    - Root vegetables / leafy greens

(Discontinued/Descontinuado)

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Congenital Methemoglobinemia

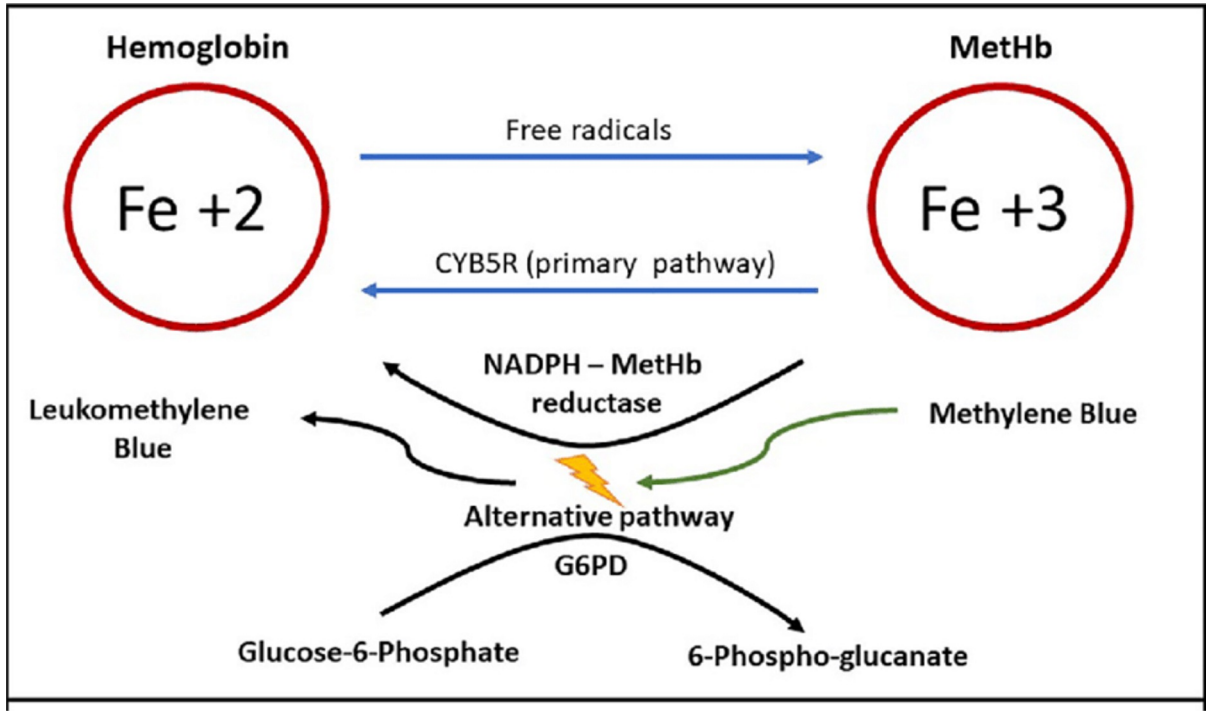
- Type 1
  - Erythrocyte specific
  - Variable presentation
  - May not be diagnosed until an exacerbation
- Type 2
  - Systemic with more severe presentations

Presentation

- Presentation can be non specific and multifactorial requiring an index of suspicion
- **Symptoms**
  - Chest discomfort
  - Shortness of breath
  - Fatigue / Weakness
  - Headache
  - Severe presentations can include CNS dysfunction, seizures, coma, death
- **Exam**
  - Cyanosis / pallor
  - “Chocolate blood”
  - Not responding to supplemental oxygen

Treatment

- When should you treat?
- Stop exposure
- Optimize oxygen delivery (although saturations may not improve until methemoglobinemia +/- exposures are corrected)
- Methylene blue
  - Avoid in neonates and pregnancy
  - Caution in G6PD (debated)
  - Avoid if at risk for serotonin syndrome (concurrent mediation or ingestion)
- Ascorbic acid
  - acute and chronic management
- Hyperbaric oxygen
- Exchange transfusion



Genetics

- Description of hereditary methemoglobinemia affecting an enzyme in red blood cells in Navajo patients described by Balsamo Et Al. in 1964
  - Family members of the first patient were tested showing a recessive inheritance pattern and identified an additional family member with clinical symptoms
- Further discussion of congenital methemoglobinemia in people of Athabaskan heritage was revisited by Erickson in 2021 looked at CYB5R3 as the causative in gene, but questioned if this variant was still found in present day southwestern Athabaskans
- We have seen a series of patients with Navajo ancestry that were found to have the same CYB5R3 mutation

Are We Missing Cases?

- The estimated frequency for congenital methemoglobinemia is 1 in 100,00
  - A 1958 study by Scott and Hoskins looking at ‘Alaskan Eskimos and Indians’ estimated a frequency of 75 in 100,00
- Previous pediatric screening guidelines for Congenital Heart Disease have used a minimum cutoff of 90% when testing with pulse oximetry, this has since been revised to 95%
  - Ward Et Al. Reported a patient that was diagnosed after further investigation prompted by screening values of 92% and 94% with repeat indication 93% and 97%
- How does high altitude affect methemoglobinemia?
  - Are there lower pulse oximetry readings due to altitude that may have a pathological cause
  - Some studies have found reversible methemoglobinemia believed to be induced by being at high altitude
  - Some studies discuss the possibility of methemoglobinemia being protective by shifting the oxygen dissociation to the left

Key Takeaways

- Congenital methemoglobinemia, while rare, is likely underdiagnosed and should be considered in unexplained or refractory cyanosis and hypoxemia
  - Look for patients whose cyanosis does not clinically match their pulse oximetry
  - Look for “chocolate blood”
- Acquired is more common and may require a very thorough history
- Congenital may be undiagnosed for years and masked by a confounding/contributory diagnosis
- Early recognition can be care changing and potentially life saving
  - Treatment can cause very rapid improvement if methemoglobinemia is identified
- Genetic forms may be more common than previously realized in people of athabaskan descent

Citations

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