All India Institute of Medical Sciences Rishikesh (AIIMSR)
Department of Paediatrics

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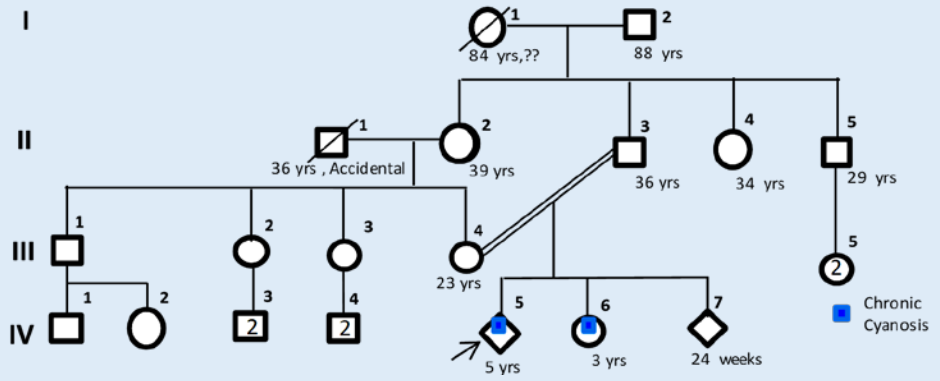
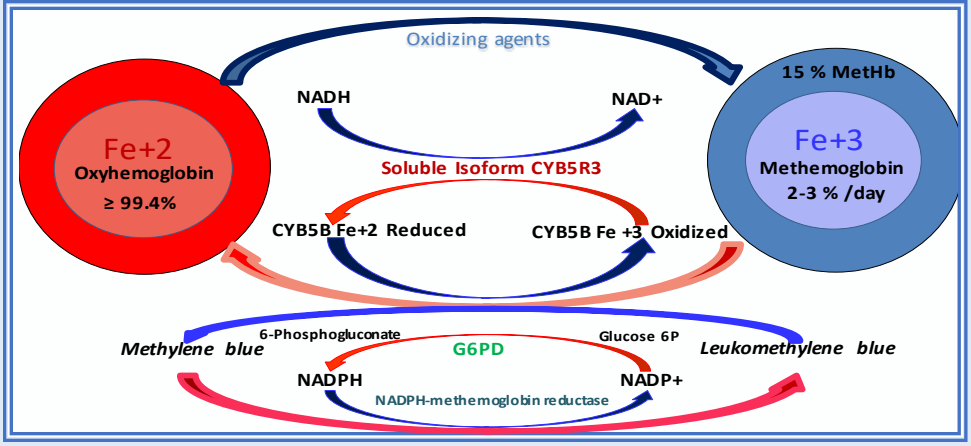
From the desk of Editor

The Department of Paediatrics is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and a deliberate attempt to enhance awareness for genetic disorders with recent updates.

Hereditary disorders of RBCs -**VI**: **Hereditary Methemoglobinemia (MetHb)**



Genes related to MetHb.



Insight:

1. How would you diagnose a case of MetHb?
2. What are the conditions reported with polymorphism of the CYB5R3 gene?
3. What is the mechanism for disorders of sex differentiation (DSD) with CYB5A mutations?
4. What is the first human enzyme deficiency found in literature?
5. How would you counsel the family with the **case IV (5)**?
6. Is it possible to have Heinz body anemia in a case of MetHb?

Plausible tenets:

Inherited MetHb:

AR: Type I to IV

- **Type I (common type):** MetHb 10-35%, cyanosis with stable hemodynamically, normal life span and may have headache, easy fatiguability & exertional dyspnea.
- **Type II(rare variant):** Severe developmental and neurological manifestation (opisthotonos, microcephaly, strabismus, seizure, quadriparesis, failure to thrive, etc.). Short life expectancy.
- **Type III:** omitted (found out later as a type I methemoglobinemia)
- **Type IV:** mild to moderate cyanosis with infertility and hypergonadotropic hypogonadism due to isolated 17,20-lyase deficiency (elevated ratio of 17-alpha-hydroxyprogesterone over androgen metabolites). Normal glucocorticoid & mineralocorticoid levels

AD : Hemoglobin-M – Chronic cyanosis. The onset at birth (**HBA1- alfa type**) or during infancy (**HBB -beta type**).

- **MetHb levels & Phenotype: Acute state** >20→Hypoxia features, **chronic state** < 50% →Minimal symptoms **but** coma & death if > **70 %**
- **Diagnosis:** refractory hypoxia is a clue. Hypoxia ± chocolate-colored blood. Confirmation by venous/arterial blood gas with co-oximetry.
- **MetHB Treatment- if symptomatic**: methylene blue (MB), vitamin C . **Pret-herapy testing:** G6PD & Education for Acquired causes

Genes related to MetHb.

Gene	Function	MOI	Phenotype
CYB5R3*	Transfer electrons	AR	Methemoglobinemia, type I (Unstable Enz) and II (Inactive Enz)
CYB5A	Enzyme binding, electron carrier & Oxygenase	AR	Methemoglobinemia and ambiguous genitalia, Isolated 17,20 Lyase deficiency, Pure
HBB	beta-globin of Hb	AD	Methemoglobinemia (M hemoglobin), beta type
HBA1	alpha-globin of Hb	AD	M hemoglobin
?	? Reduce methemoglobin to hemoglobin	AR	NADPH-methemoglobin reductase deficiency
?	? deethylation	AR	Acetophenetidin sensitivity

***CYB5R3 (31 kb, 9 exons, two promoters), 22q13.2:**
- Membrane-bound isoform in somatic cell(300 AA): desaturation and elongation of fatty acids, in cholesterol biosynthesis, and in drug metabolism
- Soluble isoform in RBCs(275AA): Reduce ferric cytochrome b5, so indirectly reduce methemoglobinemia

Acquired methemoglobinemia: selected drugs, chemicals, or foods.
Online resources for drugs reported or may lead to MetHb: http://www.uptodate.com/crlsql/interact/frameset.jsp, https://www.longdom.org/open-access/drugs-may-be-induced-methemoglobinemia-2329-8790-1000270.pdf, https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling,

DNA Polymorphism: Two or more variant of wild DNA sequence with the following characteristics:

1. No significant effects on genomic function
2. present in **≥ 1 %** in the reference population
3. It may be SNP (pronounced snip) or a copy number variant (Small or large repetitive DNA sequence numbers).

Genetic Counselling for consultand case IV (5)

- Define Chronic cyanosis and autosomal recessive MOI in view of consanguinity and two siblings affected.
- Clinically diagnosed as a congenital MetHb type IV because having disorder of sexual differentiation
- Plan Karyotyping, CYB5A mutation study by *Target gene sequencing* & confirm the metabolic cause for DSD by biochemical testing.
- 25 % chance for recurrence risk in each sibling in next pregnancy and transmitting the disease in offspring depends upon spouse genetic status.
- Timely Antenatal testing & *discuss the limitation*
- Follow up: Pubertal abnormality in both cases IV (5,6) -Endocrinal Rx

Conditions reported with polymorphism of CYB5R3 gene:

1. 9015G>A - reduced risk of methemoglobin toxicity in newborn with Nitric oxide.
2. I1M+6C>T (rs8190370) - 90-fold risk of developing of breast cancer in African Americans women who smoke cigarettes. CYB5R3 enzymes metabolize the carcinogenic chemicals into nontoxic substances. The polymorphic alteration decreases the enzyme activity.

Other causes for cyanosis:

- **Deoxygenated hemoglobin (> 5 g/dl)**
- **Sulfhemoglobin (> 0.5 g/dl)**
- **Methemoglobin (> 1.5 g/dL)**

Idiopathic MetHb was the *first human enzyme deficiency* identified by Gibson (1948)

But the first true *Garrodian inborn error of metabolism*, is Glucose-6-phosphatase (1952).

***Sir Archibald Edward Garrod (1857--1936)* Established the concept of 'Chemical individuality.' & IEM**

Thought Riveting:

- ***Can CYB5R3 gene be used as a new target for adjuvant therapy for cancer and aging?***
- ***What is the exact genetic mechanism for cyanosis in G6PD deficiency cases with oxidative stress?***
- ***What is the role of riboflavin (vitamin B2) in the treatment of congenital methemoglobinemia?***
- ***What is the molecular association between polymorphism and epimutation with respect to MetHb phenotypes?***
- ***Which is the more effective treatment option (Ascorbic acid or Methylene blue) for congenital MetHb?***
- ***17,20-lyase deficiency is a disease or a biochemical phenotype?***

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