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

Rishi Vansh

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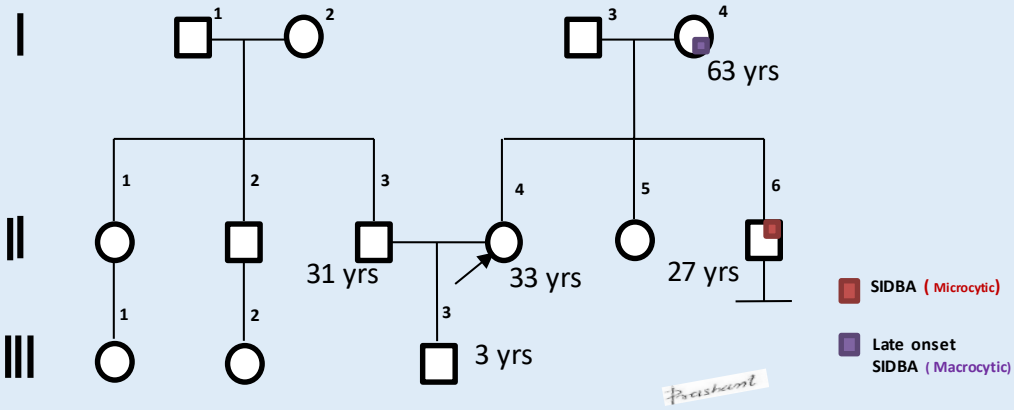
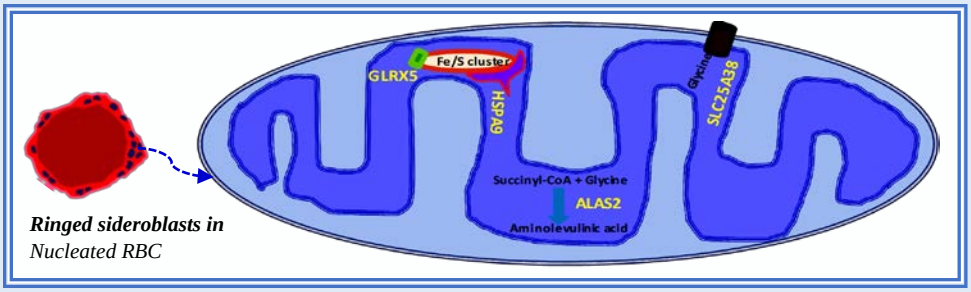
From the desk of Editor

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 -V: **Hereditary Sideroblastic Anemias (HSIDBA)**



Genes related to classical HSIDBA



Insight:

1. What is the most characteristic lab finding for HSIDBA?
2. Is there any use of Vitamin B1 and B6 for HSIDBA?
3. Why is the HSPA9 inheritance pattern called pseudodominant?
4. What are the hereditary syndromes associated with SIDBA?
5. Are there chances of carrier females becoming symptomatic in the later stage of life **[case I (4)]**?
6. How will genetic counseling tread for consultand **case II (4)?**

Plausible tenets:

- **Heme synthesis disorders** due to defects of **iron metabolism within mitochondria.**
- **Acquired SIDBA** are **more common** and develop **later in the life** (causes drugs, alcohol, myeloproliferative disorders, or idiopathic) **while inherited SIDBA** are **rare** and present in an **early age.**
- X-linked SIDBA-I, Pearson syndrome and Thiamine-responsive megaloblastic anemia are **the most common types.**
- In SIDBA-I: 5-aminolevulinic acid synthetase (**ALAS2**), the **rate-limiting enzyme** in heme synthesis, has a cofactor pyridoxal phosphate binding site which is a hot spot for several mutations. It is reported in elderly women (**acquired skewing with age**)
- **Clinical features:** pallor, organomegaly, icterus and growth failure
- **Therapy:** no absolute treatment, RBC transfusions depends upon the severity, selected patients respond to pyridoxine, BMT for selected cases. Iron chelating therapy to all including asymptomatic cases especially if co-inheritance of hereditary hemochromatosis.
- Few sideroblastic anemia with mitochondrial disorder spectrum cases are reported to have spontaneously recovered in infancy (**Revertant mosaicism**)

Genes related to HSIDBA

Characteristic	SIDBA-I	SIDBA -II, B6-refractory	SIDBA -III, B6-refractory	SIDBA -IV
Cytogenic location	Xp11.21	3p22.1	14q32.13	5q31.2
MOI	XLR	AR	AR	AD
Gene	ALAS2	SLC25A38	GLRX5	HSPA9
Gene function	First step of porphyrin biosynthesis	SLC25A38 Mitochondrial glycine transporter	Mitochondrial iron-sulfur (Fe/S) cluster transfer	Chaperone protein & biogenesis of mitochondrial iron-sulfur cluster (ISC)
Other phenotypes by gene	Erythropoietic protoporphyria		Spasticity, childhood-onset, with hyperglycinemia	Even-plus syndrome
Lab findings	McHc anemia	McHc anemia	McHc anemia	Dimorphic
Onset	Variable age	Infancy	Mid-adulthood	Late adulthood

Revertant mosaicism: Pathological variation that reverses to normal genotype & phenotype in a subset of cells during DNA replicationz

Additional Syndromic form of Sideroblastic anemia

- **Pearson marrow-pancreas syndrome, a contiguous gene deletion/duplication syndrome involving several mtDNA genes:** normocytic or macrocytic anemia, 3-methylglutaconic aciduria, pancytopenia, presence of vacuolization of RBC, pancreatic fibrosis, commonly death in infancy, survivors develop Kearns-Sayer syndrome later
- **Thiamine-responsive megaloblastic anemia syndrome (TRMA), also known as thiamine metabolism dysfunction syndrome-1 (THMD1), SLC19A2, AR:** Onset in early childhood (infancy to 6 years), megaloblastic anemia, diabetes, and deafness; diabetes and anemia respond to high doses of thiamine supplementation; additional variable features include optic atrophy, congenital heart defects, short stature, and stroke
- **Myopathy, lactic acidosis, and sideroblastic anemia; type 1(PUS1/AR), type 2(YARS2/AR) and type 3(MTATP6/ Mitochondrial):** childhood onset exercise intolerance, myopathy, lactic acidosis, mental retardation, microcephaly& ringed sideroblasts
- **Anemia sideroblastic with spinocerebellar ataxia (ASAT), ABCB7, XLR:** onset in early childhood, ataxia, incoordination with long motor tract signs
- **Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay, TRNT1, AR:** onset in the neonatal period or early infancy, immunodeficiency which is progressive, death in the first decade
- **Hydrops, lactic acidosis, and sideroblastic anemia (HLASA), LARS2 (also do Perrault syndrome 4), AR:** onset of hydrops in utero with variable severity, may include hepatosplenomegaly or cholestasis, hypoglycemia, pancreatic insufficiency, and micropenis or hypospadias, onset at birth and death in early infancy

Sideroblastic Anemia, Acquired Idiopathic (AISA), Complex IV, Cytochrome C Oxidase Subunit I; MTCO1: heteroplasmic point mutations of mitochondrial DNA.

Genetic Counseling for consultand case II (4):

- **50 % chance to be carrier for HSIDBA**
- **50 % chance for transmitting mutant gene in each pregnancy.**
- **Severity and disease course depends upon the phenotype of case II (6) (if an affected family member has the same variant in the genome)**

Characteristic finding: perinuclear distribution of iron aggregating mitochondria in the nucleated red cells in the bone marrow aspirate that differ from non-pathological sideroblasts having diffuse cytoplasmic ferritin granules.

Thought Riveting:

- ***Why may sideroblasts not be used as lab marker in all suspected cases of mitochondrial disorders especially with inconclusive WES report?***
- ***What are the nuclear functions of "Mitochondrial Fe/S cluster (ISC) assembly machinery"?***
- ***What are the key environmental factors for acquired skewing of the lyonization in ageing females?***
- ***Is it ethical for sex selection in sex linked disorders without recognition of mutation?***
- ***Are there any predetermined preconditions for using B1 and B6 for mild undiagnosed dimorphic anemia cases?***

Author: Dr. Prashant Kumar Verma
Reviewer: Dr. Raksha Ranjan, Dr Vinod Kumar