Rishi Vansh

All India Institute of Medical Sciences, Rishikesh

Department of Paediatrics

Volume 1, Issue 5 **November 2020**

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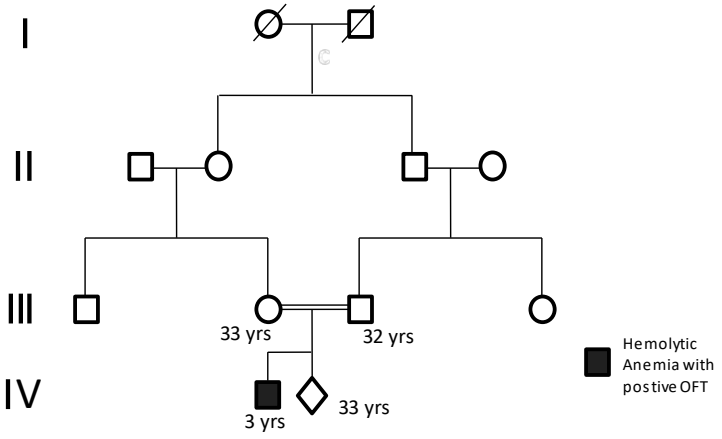
From the desk of Editor

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

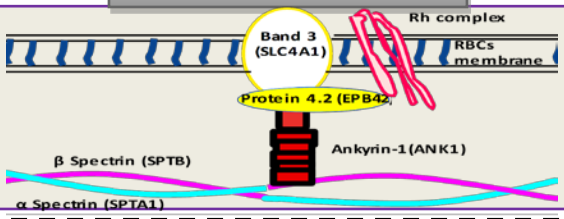
Genetic Facts related to RBCs- I

HEREDITARY SPHEROCYTOSIS(HS)



OFT -osmotic fragility test

HS- Linked Genes' liaison



Insight:

1. What is Ektacytometry?
2. What are the other genetic disorders apart from HS linked to the HS gene spectrum?
3. Which RBCs indices are used as screening tests for HS?
4. How ethical is an antenatal diagnosis of HS?
5. What are the possible biological effects of long-term high dose (5 mg) folic acid?

Plausible tenets

HS Genes: *Predominantly five genes*; regulate shape, stability & flexibility of the membrane

Gene		HS (Frequency)	Inheritance	Non-HS Phenotypes
ANK1(8p11)	Ankyrin 1	**Type 1 (55 %)**	AD**, AR**	-
SPTB (14q23)	Spectrin Beta, Erythrocytic	Type 2 (15-30 %)	AD	Neonatal hemolytic anemia(fatal, or near-fatal), Elliptocytosis-3
SPTA1(1q21)	Spectrin Alpha, Erythrocytic 1	Type 3 (5%)	**AR**	Elliptocytosis-2(AD), Pyropoikilocytosis (AR)
SLC4A1(17q21)	Erythroid Protein Band 3	Type 4 (15 -33%)	AD	[Various Blood groups], [resistance to Malaria], Cryohydrocytosis (AD), Distal RTA 1 (AD)& **Distal RTA 4 with hemolytic anemia (AR),** South Asian Ovalocytosis (AD)
EPB42(15q15)	Erythrocyte Membrane Protein Band 4.2	Type 5 (?)	**AR**	-
Homozygous - Severe phenotype, heterozygous - Mild -moderate phenotype				

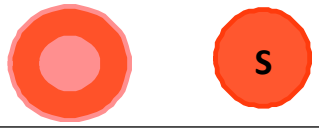
Hereditary Spherocytosis:

- Heterogeneous disorder clinically ranging from **asymptomatic to hemolytic anemia**, jaundice and splenomegaly.
- Classified into three groups: **mild, moderate and severe** based on hemolysis. -

Common complications are cholelithiasis, hemolytic episodes and aplastic crises. -

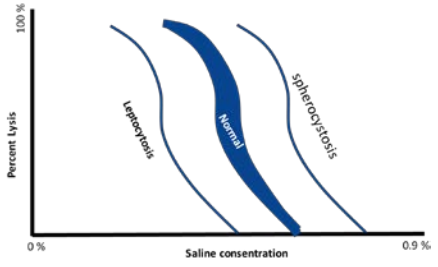
The mean age at diagnosis is **5.2 years.**

- **First** described in **1871.** Prevalence ranges from **1:2000 to 1:5000**
- **First line tests** are the peripheral blood smear and osmotic fragility.



Spherocytes: sphere-shaped RBCs in place of normal bi-concave disk shape resulting from defective membrane

- Osmotic fragility test (**OFT**) measure RBCs hemolytic endurance to varying levels of dilution of a saline solution.
- **Normal OF**: approx. 5-45% hemolysis at concentration of 4.5 g NaCl/l as per **Dacie (1954).**
- Positive OFT in HS-related gene mutations is approx. **86.8%**.
- OF decreases in thalassemia, sickle cell disease, chronic liver disease, hyponatremia, polycythemia vera, iron deficiency anemia and **increases in** spherocytosis, autoimmune hemolytic anemia, and hypernatremia, spherocytic elliptocytosis.
- Separate **neonatal osmotic fragility curve** for newborns.
- Also used for **screening of thalassemia trait** as a recent new parameter "**Hemolysis area."** (*novel hemolysis parameter generated by portable spectrophotometer in kinetic based OFT technique that eliminates interobserver variations*)
- **Ektacytometry** evaluate the deformability of RBCs by laser diffraction viscometry at a constant value of applied shear stress against increasing shear stress or an osmotic gradient.
- Ektacytometry is used as a Second-line test in non-immune hemolytic anemia with normal HPLC.



Role of RBCs indices in HS:

- No single index for screening
- Increased MCHC, decreased MRV (mean reticulocyte volume), [**MSCV (mean sphered corpuscular volume) — MCV ≤ 0**], and increased Ret. (absolute reticulocyte count) without increased IRF (immature reticulocyte fraction) are characteristic blood cell parameters in HS.
- MSCV (mean sphered corpuscular volume) **—** MCV **≤** 0.6 fl has a sensitivity of **95.5%** and specificity of **94.9%,** seen in one study.

Important considerations in genetic counselling and molecular testing in HS:

- Presence of a genetic mutation does not determine the severity of the disease or its course.
- Testing is useful in distinguishing between a polymorphism and a gene mutation.
- **HS** has the most severe presentation in the neonatal period and treatment is to tackle complications (hyperbilirubinemia, kernicterus) as most of the patients become asymptomatic by 12 months.
- No hotspot mutations (*Nucleotide positions with an exceptionally high mutation frequency)* in HS, mostly sporadic mutations which are specific to individual patients or their families.

- Daily 5 mg folic acid in HS leads to high serum folic acid and unmetabolized folic acid (UMFA) concentration and higher DHFR mRNA expression.
- Although the long-term systemic side-effects are unknown; Folic acid dose can be titrated based on serum levels of substrate and metabolite.

Thought Riveting:

- *What is the scope of Nonenzymatic **Gene Editing Therapy** for HS?*
- *Is the use of **Trehalose** promising for RBC membrane stabilization in HS?*
- *How is **spectrin deficiency** associated with the clinical response to splenectomy?*
- *What can be the further possible uses of **OFT** beside HS in future research?*

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