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

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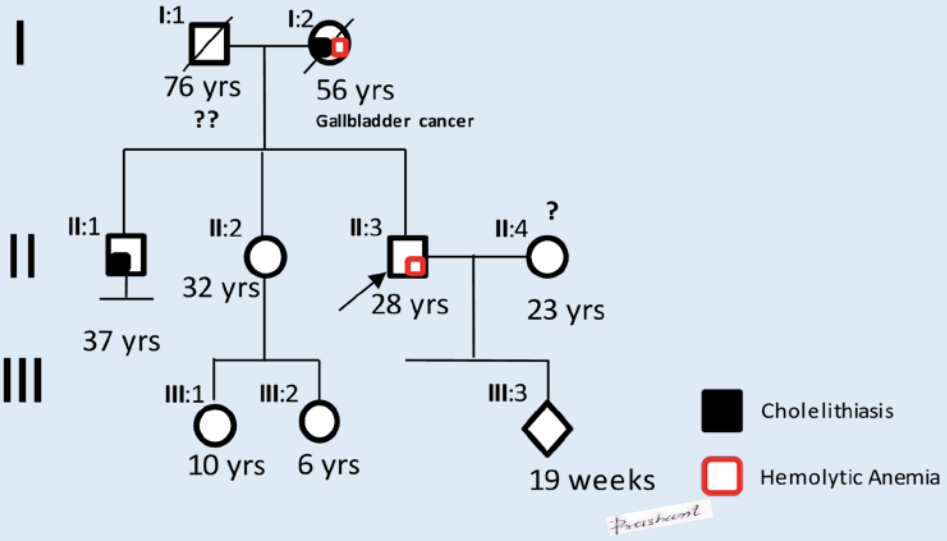
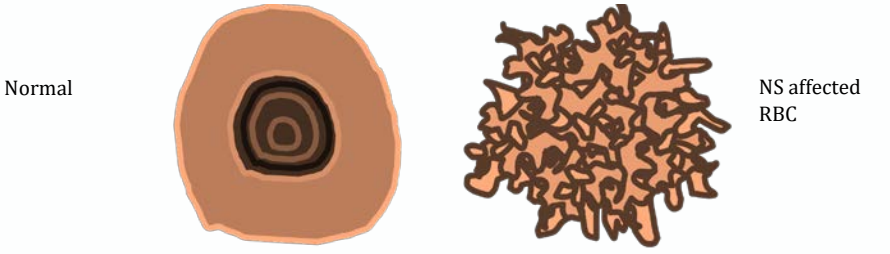
From the desk of Editor

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 – **V: Non-membranopathic Hemolytic Anemia (NMHA)/ nonspherocytic hemolytic anemia (NSHA)**



RBCs Scanning electron microscopy image



Insight:

1. Is there any role of splenectomy in the management of NSHA?
2. How to investigate a NSHA in low & high resource centers?
3. How to do antenatal counselling for NSHA family if genetic loci could not be identified in a proband?
4. Which glycogen storage disease also has characteristic NSHA phenotype?
5. Which of the NSHA disorder has resemblance of chronic granulomatous disease?

Plausible tenets:

- **Inherited form for NMHA (36%):** Intrinsic defects in RBCs as enzymopathy **(40 %) &** hemoglobinopathy**(60%).** Although**,** The **most common** type of Inherited hemolytic anemias (**IHAs**) is due to membranopathy- **64%**
- **Clinical features:** weakness/tiredness, pallor, jaundice, cholelithiasis, hepatosplenomegaly; few have Psychomotor impairment(**Plus**)
- **Stepwise specific investigation process:** Peripheral smear **(PS for RBC morphology)**→HPLC→**(**RBC enzyme levels→Membrane protein analysis or **MPA) OR/ (NGS panel for IHAs)**
- **Management-** Symptomatic ; avoid precipitating factors,;splenectomy results in significant improvement in the majority of cases

XL: NHSA

S. No.	Disease	Gene	Function	Key features	Onset
1.	Phosphoglycerate kinase 1 deficiency (XLR)	PGK1	Generate one molecule of ATP	CNS involvement (50%), hemolytic anemia (60%)	infancy to adult
2.	G6PD (XLD)	G6PD	Synthesis of Ribose 5-Po4 and NADPH	Induced by drugs or Fava beans, resemble CGD	

AR: NHSA

S. No.	Disease	Gene	Function	Key features	Onset
1.	HK deficiency	HK1	Catalyzes glucose to glucose-6-phosphat (G-6-P)	Early infantile onset, Increased Hb F level	At Birth
2.	Glucose phosphatase Isomerase deficiency	GPI	Catalyzes the interconversion of G-6-PO4 & F-6- PO4	Psychomotor impairment, Spontaneous hemolytic crises	in utero or at birth
3.	Due to defect in porphyrin metabolism	??	??	increased amount of porphobilinogen & delta-aminolaevulinic acid in Urine, chronic jaundice	Infancy
4.	Adenylate Kinase Deficiency	AK1	energy metabolism and homeostasis	Onset since birth, rapidly progressive hemolysis, intellectual disabilities in some	3 to 8 years
5.	Glycogen storage disease XII	ALDOA	Catalyzes the reversible conversion of F-1,6-bisPO4 to glyceraldehyde 3- PO4 & di-OH-acetone PO4	Dysmorphic features, delayed puberty, myopathy, Mental retardation	Infantile
6.	Glycogen storage disease VII	PFKM	Do irreversible change from F-6- PO4 to F-1,6- bisPO4	Gout, variable severity, Myoglobinuria,	Early childhood
7.	Gamma-glutamylcysteine synthetase deficiency	GCLC	Rate-limiting enzyme in glutathione biosynthesis.	Myopathy, Late-onset spinocerebellar degeneration, Peripheral neuropathy	Early childhood
8.	Glutathione synthetase deficiency	GSS	Detoxification, antioxidant & membrane transport	Severe form allied with neurological features	Early childhood
9.	Triosephosphate isomerase deficiency	TPI1	Catalyzes the interconversion of DHAP & glyceraldehyde-3-phosphate	Variable neurodegenerative disease, mixed motor neuron involvement, Increased susceptibility to infections	Infantile
10.	Uridine 5-Prime Monophosphate Hydrolase Deficiency	NT5C3A	Catalyze- dephosphorylation of nucleoside 5'-monoPO4	Hemoglobinuria & excess loss of iron in urine	Early childhood
11.	Erythrocytosis, Familial, 8; ECYT8	BPGM	Regulating hemoglobin oxygen affinity through 2,3-BPG	Increased oxygen affinity of Hb, both observed polycythemia & hemolytic anemia	Late onset

AD: NHSA

S. No.	Disease	Gene	Function	Key features	Onset
1.	Heinz body anemias	HBA1, HBA2, HBB	Instructions for making alpha-globin protein of Hb	Heinz bodies in erythrocytes after splenectomy, Heat-labile Hb	Late onset
2	Red cell phospholipid defect with hemolysis	??	??	Hemolysis on exposure to drugs and possibly viruses	??
3.	Adenosine triphosphatase deficiency	??	??	Infrequent hemolytic episodes, ATP-ase deficiency	??

Next generation sequencing (NGS): High throughput DNA sequencing methodology, **Sequencing techniques beyond the first generation** (Sanger sequencing based**).** **2nd generation-** sequencing by hybridization or synthesis (SBS), Ion Torrent, pyrosequencing; **3rd generation** – long SMRT (Single Molecule Real Time); **4th generation**-apply nanopore systems

Genetic Counseling for II:3 case with inconclusive NGS test reports of II:1 & II:3

- 50 % chance for HA in the case **II:3**
- Redefine the clinical phenotype, reevaluate the lab reports subclassify the RBCs defects
- **Explain:** IHAs are not the recommended genetic disease that need antenatal testing **EXCEPT very severe forms or involvements of other systems (Plus)**
- Plan functional study of RBCs (PS, HPLC, Enz and MPA) in **II:1 & II :3** if irrefutable finding
- **Cordocentesis** (after taking consent) and find out the same finding (Look for **maternal contamination**)
- In case of negative functional study:
  - **Linkage study** could be tried but has its own limitations (Need to discuss first)

Heinz bodies (Scanning electron microscopy image) (Heinz-Erlich bodies): denatured precipitated non function intracellular inclusions of Hb.

Dr. Robert Heinz: 1890 discovered Heinz body

Dr. Carson et al: discovered G6PD enzyme in 1956- the commonest enzymopathy

Valentine et al.: discovered Pyruvate kinase (PK) deficiency in 1961- the commonest enzyme-related glycolytic defect

Thought Riveting:

- ***What could be the precipitating factor for neonatal death with selected cases of GPI mutations?***
- ***How does Hb F increase with hexokinase deficiency?***
- ***What is the possible phenotypic modifier for mutations in the RBCs pyruvate kinase?***
- ***What are the technical issues & standard guidelines of selecting a birth defect with hereditary enzyme deficiency for enzyme replacement therapy?***
- ***At what stage of embryonic development, HK1 gene facilitates neural tissue growth & development?***

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