Hemoglobinopathies

At least 250,000 people each year with disorders of hemoglobin (Hb), called Hemoglobinopathies.

Hb is the protein present in red blood cells that is responsible for oxygen transport.

Hb being made up of a tetramer consisting of two pairs of different polypeptides referred to as the α and β globin chains.
Disorders of Hemoglobin

1) Structural globin chain variants such as sickle cell disease

2) Disorders of synthesis of the globin chains such as the thalassemias

Structural Variants/Disorders

- More than 300 Hb electrophoretic variants have been described due to a variety of types of mutation
- The majority are rare and not associated with clinical disease
- A few are associated with disease and relatively prevalent in certain populations.
Sickle Cell Disease Mutation

The amino acid glutamic acid, at the sixth position of the β-globin chain, is substituted by valine.

Disorders of Hemoglobin Synthesis

The thalassemias are the commonest single group of inherited disorders in humans.

Persons from the Mediterranean region, Middle East, Indian subcontinent, and Southeast Asia.

The same pathophysiology. An imbalance of globin-chain production results in the accumulation of free globin chains in the red blood cell.

α and β Thalassemia

α Thalassemia

Results from underproduction of the α-globin chains and occurs most commonly in Southeast Asia.

Two main types of α-thalassemia.

The severe form
- No α chains are produced, fetal death
- Hydrops fetalis
- Tetramer of γ chains, called Hb Barts

The milder form
- Some α chains but still a relative excess of β chains
- β-globin tetramer Hb H-known as Hb H disease
Normal and Deleted α-globin Structural Genes

β Thalassemia

Caused by underproduction of the β-globin chain of Hb.

Two main types of β-thalassemia:

The major form:
- Homozygotes for β chains defect, Cooley's anemia
- Severe transfusion-dependent anemia
- An unusually shaped face and skull
- Affected individuals used to die in their teens or early adulthood

The minor form:
- Heterozygotes for β chains defect
- Usually have no symptoms or signs
- Mild hypochromic, microcytic anemia, may be confused with iron deficiency anemia.

β Thalassemia Major Bone Changes

J. Jamshidi
Fasa University of Medical Sciences, November 2017
Biochemical Disorders

- Amino acid metabolism
- Urea cycle
- Carbohydrate metabolism
- Steroid metabolism
- Lipid metabolism
- Lysosomal storage disorders
- Disorders of purine/pyrimidine metabolism
- Porphyrin metabolism
- Copper metabolism
- Peroxisomal disorders

Disorders of Amino Acid Metabolism

Phenylketonuria

- Deficiency of the enzyme required for the conversion of phenylalanine to tyrosine: phenylalanine hydroxylase (PAH)
- Children with phenylketonuria (PKU), if untreated
  - Severely intellectually impaired
  - Often develop seizures
  - Often have blond hair and blue eyes
- Treatment by controlling phenylalanine diet intake
- Maternal PKU
Oculocutaneous Albinism (OCA)

Deficiency of the enzyme tyrosinase, which is necessary for the formation of melanin from tyrosine

- Lack of pigment in the skin, hair, iris, and ocular fundus
- Poor visual acuity and uncontrolled pendular eye movements - nystagmus

OCA is genetically and biochemically heterogeneous.

- OCA1 located on 11q
- OCA2, mutation in the P gene locates on 15q
- There are some other loci
Disorders of Monosaccharide Metabolism

- Galactosemia

- Hereditary Fructose Intolerance

Galactosemia

- Deficiency of the enzyme galactose 1-phosphate uridylyltransferase, necessary for the metabolism of galactose.
- Newborns present with vomiting, lethargy, failure to thrive, and jaundice in the second week of life.
- If untreated, they develop complications that include mental retardation, cataracts, and liver cirrhosis.
- Can be prevented by early diagnosis and feeding infants with milk substitutes that do not contain galactose or lactose.

Hereditary Fructose Intolerance

- Autosomal recessive, resulting from a deficiency of the enzyme fructose 1-phosphate aldolase.
- Affected, present at different ages, depending on when fructose is introduced into the diet.
- Symptoms include failure to thrive, vomiting, jaundice, and seizures.
Glycogen Storage Diseases (GSDs)

- Glycogen in muscle and liver, acting as a reserve energy source.
- In GSDs glycogen accumulates in excessive amounts because of a variety of inborn errors of the enzymes.

Glycogen Storage Diseases (GSDs)

- Primarily Affect Liver
  - Von Gierke Disease (GSD-I)
  - Cori Disease (GSD-II)
  - Anderson Disease (GSD-IV)
  - Hepatic Phosphorylase Deficiency (GSD-VI)

- Primarily Affect Muscle
  - Pompe Disease (GSD-II)
  - McArdle Disease (GSD-V)

Familial Hypercholesterolemia

- The most common autosomal dominant single-gene disorder in Western society
- Raised cholesterol levels with a significant risk of developing early coronary artery disease
- Dietary restriction of cholesterol intake and drug treatment with 'statins' that reduce the endogenous synthesis of cholesterol
- High cholesterol levels are due to deficient or defective function of the LDL receptors leading to increased levels of endogenous cholesterol synthesis.
Lysosomal Storage Disorders

A deficiency of a lysosomal enzyme involved in the degradation of complex macromolecules leads to their accumulation.

Children are usually normal initially but with the passage of time commence a downhill course.

Mucopolysaccharidoses

- Hurler Syndrome (MPS-I)
- Hunter Syndrome (MPS-II)
- Sanfilippo Syndrome (MPS-III)
- Morquio Syndrome (MPS-IV)
- Maroteaux-Lamy Syndrome (MPS-VI)
- Sly Syndrome (MPS-VII)

Hurler and Hunter Syndromes
Disorders Affecting Mitochondrial Function

- Myoclonic Epilepsy and Ragged Red Fiber Disease (MERRF)
- Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS)
- Neurodegeneration, Ataxia, and Retinitis Pigmentosa (NARP)
- Leigh Disease
- Leber Hereditary Optic Neuropathy
- Barth Syndrome