This lecture was done by 432 Physiology Team

1/11

Normal types of haemoglobin & Thalassaemia

432 ***Hematology*** *Team*

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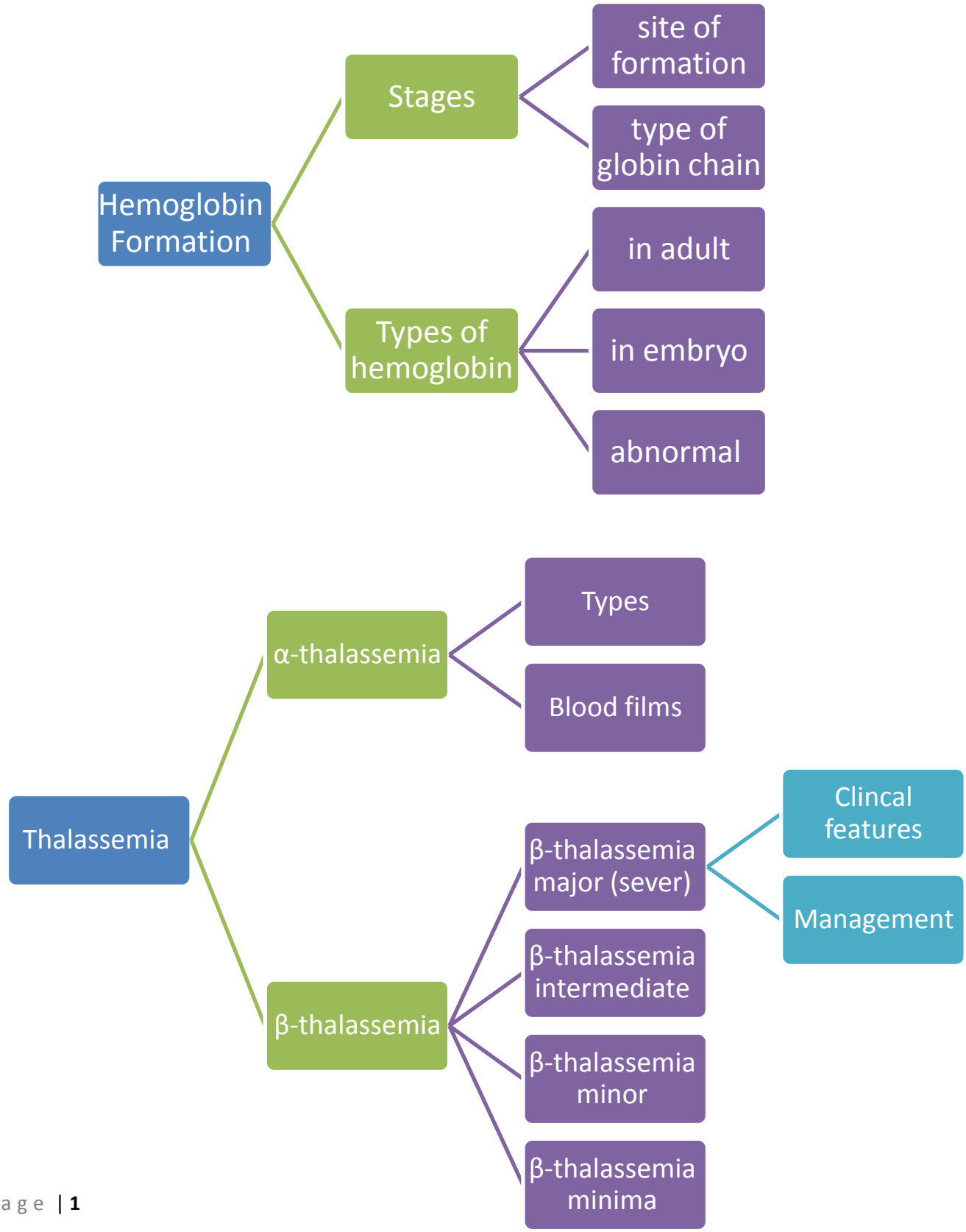
Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

Normal types of Haemoglobin and Thalassaemia

Mind Map:



Normal Hemoglobin

Introduction

- Blood composed of plasma and several kinds of cells. These blood cells consist of RBCs, WBCs, platelets & hemoglobin.
- A Hemoglobin molecule has 4 globin chains; each one is attached to heme.
- Hemoglobin is one member of functionally and structurally related family of proteins. Each of oxygen-carrying proteins is a tetramer, Composed of two α–globin polypeptides and two β–globin polypeptides. (α–globin & β–globin chains are very important 2 chains which make normal adult hemoglobin).
- Any abnormalities in the amount of α–globin & β–globin chains or\and in the structures can cause many diseases; the most common one is thalassemia.

Hemoglobin formation

Stage	Site of formation	Globin chain present
Embryonic Stage (lasts until about 8weeks after fertilization) = first 2 months of pregnancy	**Yolk sac**	**α ζ ε γ**
Fetal Stage 2nd to 7th month of pregnancy	**Liver, spleen**	**α γ** "β&δ in small amount"
Before Birth (about week 30 "7th month" until birth)	**Bone marrow**	
After Birth + adulthood	**Bone marrow**	**α β** mainly **γ** & **δ** in small amount

- **ζ** = zeta, **ε** = epsilon, **γ** = gamma, δ = delta.

REMEMBER:

- Normally liver & spleen will shut down at the time of birth. (Unless if there is any problem or disease affects the bone marrow, the liver & spleen then can produce hemoglobin).

NOTE:

The genes that control synthesis of globin chain carried on 2 chromosomes:

- **Chromosome 16 >> (α + ζ)**
- **Chromosome 11 >> (ε γ β δ)**

Alpha (α) chains are made of 141 amino acids.
Beta (β) chains are made of 146 amino acids.

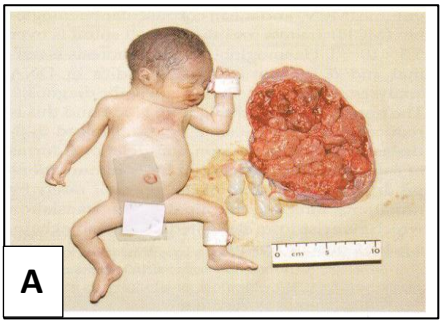
Hemoglobin						
	Name	Chains		Percentage		
				Fetal	At birth	Adults
Adult Hb	Haemoglobin A	α2	β2	15-40%	15-40%	95-97%
	Haemoglobin A2	α2	δ2	-	<0.3%	2.5-3.5%
	Haemoglobin F*	α2	γ2	60-85%	60-85%	0.5-1.5%
Embryonic Hb	Haemoglobin Gower I	ζ 2	Ɛ2	-		
	Haemoglobin Gower II	α2	Ɛ2			
	Haemoglobin Portland	ζ 2	γ2			
Abnormal Hb	Haemoglobin H	-	β4	-		
	Haemoglobin Bart's	-	γ4		<0.5%**	
	Haemoglobin Lepore	α2	(δβ)2	-		

- *Heamoglobin F is a fetal and adult hemoglobin.
- ** It is normal to present at birth in minimal amount (less than 0.5%) ,but it has to disappear after that or it will be abnormal (α thalassaemia).
- Haemoglobin H: Seen after one year and result in α thalassaemia.
- Haemoglobin A2 if > 3.5 will result in β thalassaemia, but if < 1.5 will result in α thalassaemia.

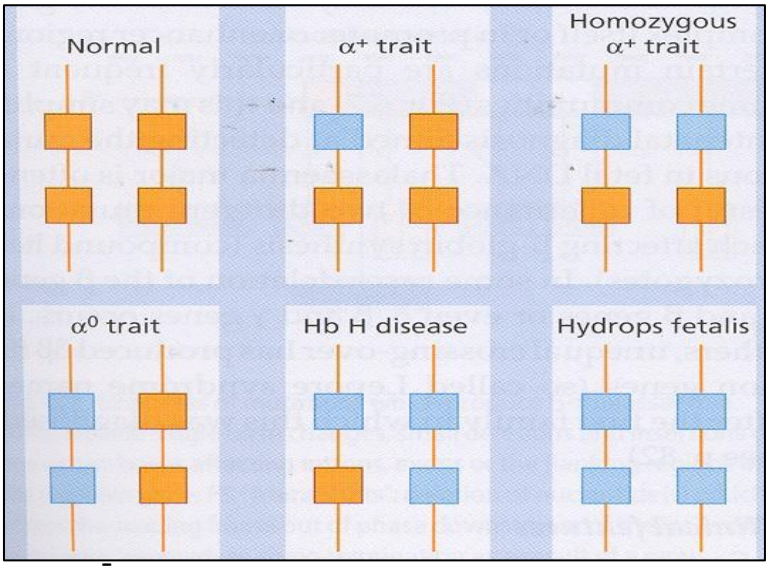
THALASSAEMIA – α or β

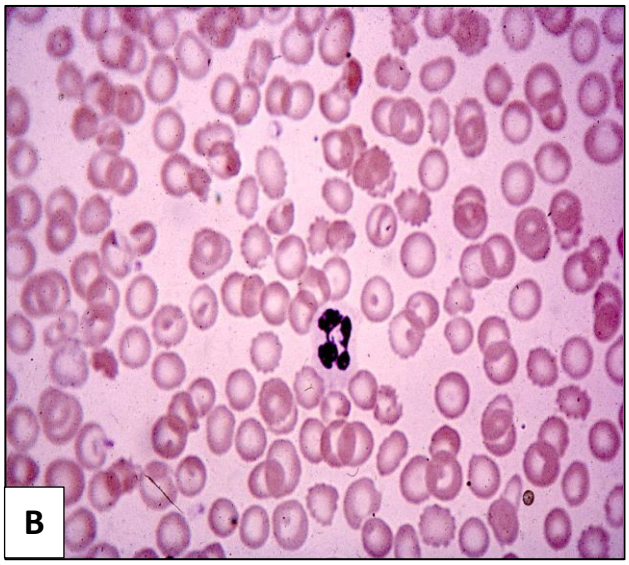
- Could be heterozygous or homozygous.
- Normal person has two α and two β.
- **If α present and β absent: β thalassemia**
- **If α absent and β present: α thalassemia**

α -THALASSAEMIA

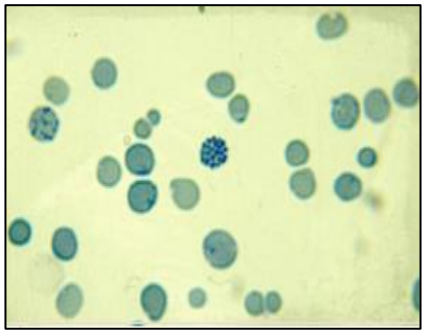

A

- **Normal** person has 4 copies of α-globin gene**.**
- **Silent carrier** has 3 copies of α-globin gene.
- Person with **thalassemia Trait** has 2 copies from α-globin gene are **absent**, either in the same side or in the opposite side.
- Person with **Hemoglobin H** has 3 copies of α-globin gene are **absent**.
- **Hydrops fetalis:** absence of all 4 copies of α-globin gene. (die after delivery; pic A)

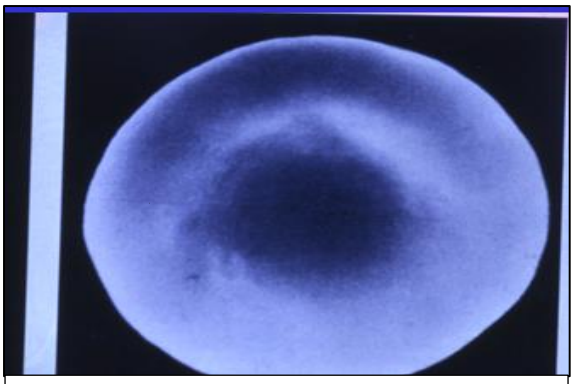



B

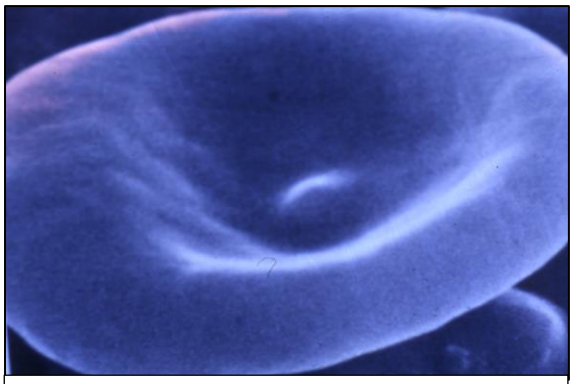
- **Picture B: blood film of patient with α thalassemia.**
- Abnormal, fragile, small size RBCs (intravascular hemolysis) lead to anemia.
- Presence of target cells (abnormal concentration of HB in RBCs).
- Type of anemia: **hypochromic microcytic anemia**.



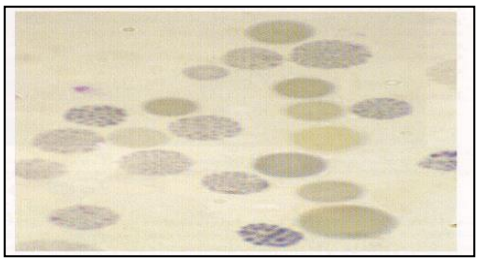
- **Blood film stained by supravital stain shows:**
- target cell & Golf Ball cell Appearance
- Indicates HbH α-thalassemia disease



Normal RBC with normal center



Abnormal RBC with hemoglobin concentrated in the center



β-THALASSAEMIA

The mutations associated with β-thalassemia fall into 2 categories:

1. β^0 , in which no β-globin chains are produced.
2. β+ , in which there is reduced β-globin synthesis.

Molecular Defects in the β-Thalassemia Syndrome

	β-Globin synthesis	β-mRNA	β-Globin Gene	δ-Globin Synthesis	γ-Globin Synthesis
1. β^+-Thalassemia 2. β^0-Thalassemia	Decreased Absent	Decreased Absent	Present Present	Present Present	Present Present

Types of β-Thalassemia:

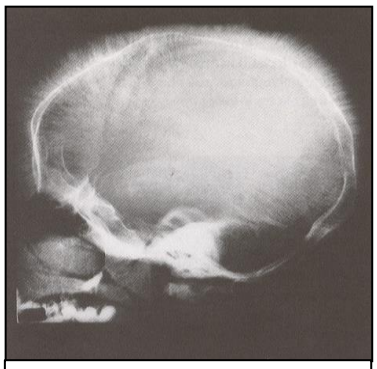
1. β-thalassemia major: (very severe)
2. β-thalassemia intermediate: inherited two β+ alleles (moderate to severe)
3. β-thalassemia minor: inhered one abnormal allele (trait, asymptomatic or mildly symptomatic)
4. β-thalassemia minima (Silent like α thalassemia trait, not causing problem unless the carrier married to the same inherited abnormality)

Hemoglobin Fractions in the Genotypic Variants of the β-Thalassemia Syndromes

Genotype	HbA	HbA_2	HbF (%)	Other Hemoglobins
Normal β/β	97	2.5-3.2	<1	**None**
Thalassemia Major β^0/β^0 or β^+/β^0	0	1.0-5.9	>94	**Free α chains**
Thalassemia intermediate β^+/β^+	Present	5.4-10	30-73	**None**
Thalassemia minor β^+/β	>90	3.5-8	1-2	**None**
Thalassemia minima β^{silent}/β	97	<3.2	<1	**None**

Clinical Manifestations in Thalassaemias (start from 6 months and usually with sever types of thalassemia (Hb H, thalassemia major):

- Pallor
- Jaundice (due to abnormal hemolysis)
- Apathy and Anorexia
- Failure to Thrive
- Hepato-splenomegaly, splenomegaly (increase ineffective hematopoiesis, will cause the liver and spleen to produce more RBCs with the bone marrow, leading to enlarge spleen and liver)
- Skeletal Deformity
- Iron Overload manifestations



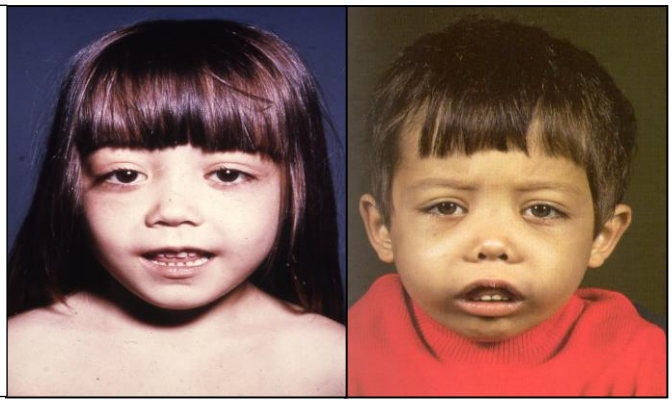
Hair-on-ends appearance in x-ray

Thalassemic face in β-thalassemia major

They have the same facial characteristics:

1- Forehead bossing (protrusion)
2- Prominent maxilla
3- Widen space between eyes

Because of increasing the demand on bone marrow, facial bones become expanded



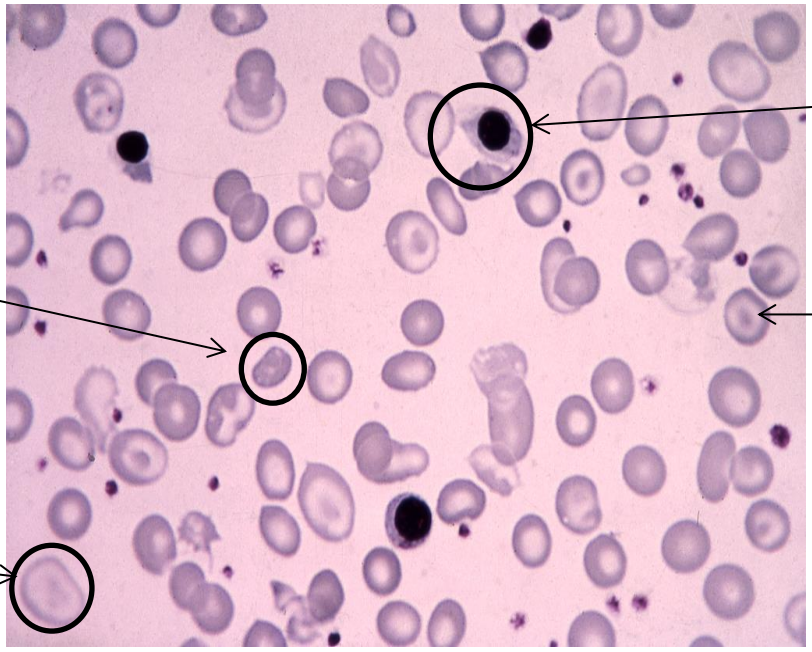
Clinical and Hematologic Features of the β-Thalassemia Syndrome:

	Major	Intermedia	Minor	Minima
Severity of mainfestations	++++	++	+, ±	±, 0
Genetics	Homozygotes, double heterozygotes	Homozygotes, double heterozygotes, rarely heterozygotes	Heterozygotes	Heterozygotes
Splenomegaly	++++	++,+++	+,0	0
Jaundice	+++	++,+	0	0
Skeletal changes	++++,++	+,0	+,0	0
Anemia (Hb, g/dl)	<7	7 – 10	>10	Normal
Hypochromia	++++	+++	++	+
Microcytosis	+++	++	+	0
Target cells	10 – 35%	++	+	±
Basophilic stippling	++	+	+	0, +
Reticulocytes (%)	5 – 15	3 – 10	2 – 5	1 – 2
Nucleated red cells	+++	+, 0	0	0
±, little or no abnormality; +, mild abnormality; ++++, prominent abnormality				

Basophilic stippling it is an abnormal collection of nucleic acid in dots throughout the cell

Hypochromia: Low pigment of RBCs

Targets cells: Abnormal hemoglobin concentration in the center



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HEMATOLOGY UNIT

Pat.No
Name:
Hospital:KING KHALID UNIVERSITY HOSPITA DOB:
Location: (PCF01) PCC (Female)
Doctor:UNKNOWN *

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DTA Whole Blood

	Full Blood Count				
[*]	WBC	5.60		4 - 11	x10.e9/L
[ ]>	RBC	5.67	H	4.2 - 5.5	x10.e12/L
<[ ]	HGB	98	L	120 - 160	g/L
<[ ]	HCT	31.0	L	37 - 47	%
<[ ]	MCV	54.6	L	80 - 94	fl
<[ ]	MCH	17.3	L	27 - 32	pg
<[ ]	MCHC	315	L	320 - 360	g/L
[ ]>	RDW	15.6	H	11.5 - 14.5	%
[*]	PLT	426		140 - 450	x10.e9/L
[*]	MPV	7.9		7.2 - 11.1	fl
<[ ]	PDW	15.6	L	20 - 70	%
[ ]>	PCT	0.339	H	0.150 - 0.32	%
	Differential				
[*]	%NEUT	74		40 - 75	%
<[ ]	%LYMP	19	L	20 - 45	%
<[ ]	%MONO	2	L	3 - 9	%
[*]	%EOS	5		0 - 6	%
[*]	#NEUT	4.14		2 - 7.5	x10.e9/L
[*]	#LYMP	1.06		1 - 5	x10.e9/L
<[ ]	#MONO	0.11	L	0.2 - 0.8	x10.e9/L
[*]	#EOS	0.28		0.0 - 0.8	x10.e9/L
	Morophology				
	Flag Comments	3+ ,3+			
	Flag Comment 1				
	ANISO				
	MICRO	MK			
	MACRO				
	POIKILO				
	HYPO	MK			
	Polychromasia				
	LSHIFT				
	TARGET CELLS	SL			
	Ovalocytes	SL			
[*]	Retic Count	1.4			
[ ]>	ESR	35			

If the hemoglobin level is low and high RBCs (increase production but abnormal structure) it means the patient have thalassemia

But if the RBCs level is low also that means another disease

Management:

Extra Info

- For further investigation (DNA analysis)
  If DNA analysis done to pregnant woman for prenatal diagnosis there is risk of abortion.

- Blood Transfusion (risk for infection)
- Iron chelation therapy (Deferiprone)
- Splenectomy
- Hormone replacement
- Bone marrow transplantation
- Gene therapy

Summary

- There are 3 stages of Hemoglobin formation: embryonic stage (from yolk sac), fetal stage (from spleen & liver) & at birth – adulthood (from bone marrow)
- The genes control synthesis of globin chain carried on chromosome 11 & chromosome 16.
- Hemoglobin occurs in the embryo: Hemoglobin Gower I, Hemoglobin Gower II & Hemoglobin Portland.
- Hemoglobin occurs in Adults: Hemoglobin A, Hemoglobin A2 & Hemoglobin F.
- Abnormal Hemoglobin: Hemoglobin H, Hemoglobin Bart's & Hemoglobin Lepore.
- β- thalassemia is a disorder by which the synthesis of β- globin chains is decreased or absent due to mutation of one allele or two.
- β- thalassemia major is the sever type caused by mutation of both alleles and Hb A is totally absent. Usually the patient comes pale, jaundiced with Hepatosplenomegaly and skeletal deformity
- Thalassemic face is characteristic for β- thalassemia major
- We do DNA analysis for further investigation but we do electrophoresis to confirm the diagnosis.

Questions

1/ A 10-month-old boy is brought to the physician by his parents who complain that their child is failing to thrive. Physical examination reveals splenomegaly and jaundice. A CBC shows a microcytic, hypochromic anemia (hemoglobin = 7.4 g/dL). Fetal hemoglobin accounts for most of the hemoglobin. Which of the following is the appropriate diagnosis?
(A) G6PD deficiency
(B) Hereditary spherocytosis
(C) Iron deficiency anemia
(D) β-Thalassemia

2/ Which of the following best describes the pathogenesis of splenomegaly seen in the patient described in Question 1?
(A) Amyloidosis
(B) Chronicmalaria
(C) Extramedullary hematopoiesis
(D) Splenic vein thrombosis

3/ A 22-year-old woman is screened for a familial blood disorder. The results of laboratory studies include a hemoglobin of 9.5 g/dL and a smear displaying mild microcytosis, hypochromia, and a few target cells. Hemoglobin electrophoresis shows a mild increase in hemoglobin A2 (7.5%). What is the appropriate diagnosis?
(A) G6PD deficiency
(B) Heterozygous β-thalassemia
(C) Homozygous β-thalassemia
(D) Silent carrier α-thalassemia

4/ Hemoglobin is formed in the liver & spleen:
(A) From the 7th month of pregnancy till the birth
(B) First 2 months of pregnancy
(C) From the 2th to the 7th month of pregnancy
(D) None

5 /The alpha genes (4 genes) are located on which one of the following chromosome ?
(A) Chromosome 11
(B) Chromosome 12
(C) Chromosome 16
(D) Chromosome 20

6/ All of these hemoglobin are present in adults except:
(A) HB A_2
(B) HB A
(C) HB F
(D) HB Portland

7. The structure of Hemoglobin A is composed of?
(A) 2 alpha globin chains and 2 delta globin chains
(B) 2 alpha globin chains and 2 beta globin chains
(C) 2 alpha globin chains and one beta globin chains
(D) 2 alpha globin chains and 2 gamma globin chains

8. Alpha thalassaemia silent, found mostly in which region of kingdom:
(A) Jaizan
(B) Al-Hofuf
(C) Al-Ula
(D) Khaiber

9. Which one is correct regarding beta thalassaemia major?
(A) Mild anemia
(B) Both genes are affected
(C) One gene is affected
(D) Silent

Answers:

- 1- D
- 2- C
- 3- B
- 4- C
- 5- c
- 6- D
- 7-B
- 8-A
- 9-B

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com