Iron Metabolism and Anemia

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Hemoglobin structure

HB is made by 4 subunits of globin (protein), each subunit is bound with a heme (non protein)

Heme is composed of:
Iron and 4 protoporphyrin ring.

Hemoglobin has 4 polypeptide chains: A1,A2,B1,B2

Normally, In adults:
HbA = 95% of total hemoglobin
HbA2 = 1.5-3% of total hemoglobin
HbF (fetal hemoglobin) = 1% of total hemoglobin

Types of anemia

1 - Iron deficiency anemia: is the most common type of anemia in Uk, USA, Jordan.

Iron is the major component of hemoglobin as it binds with 4 protoporphyrin ring to make the heme, so any deficiency in iron will decrease the amount of HB.

2- a defect in Red blood cell production:

A-Plastic anemia

B-Vitamin B12 and folic acid (nutritional anemia as vt.b12 and folate are in RBC DNA structure)

C-Chronic inflammation anemia

3- Excessive Red blood cell destruction

A-extravascular, B- intravascular hemolysis

Types of Anemia (continue….)

Revision:

- A-extravascular hemolysis: from reticuloendothelial system (sequestration from spleen)(lymph node)

- B-Intravascular hemolysis: occur inside the blood cells due to defects in:

1-loss of flexibility of RBC = hereditary spherocytosis

2-deficiency on G6PD that makes NADPH and ATP to destroy free radicals

3-deficiency on pyruvate kinase that generate pyruvate and destroy free radicals, and thus increase 2,3-BPG

4-defect in HB DNA due to some mutation causing sickle cell anemia

5-autoimmune disease or failure on blood donation as it stimulate immune system to destroy RBC

Iron deficiency anemia (IDA)(Bleeding)

It occurs in male as a result from bacteria in GIT that causes GIT loss as it cause inflammation and hemorrhage

It occurs in female as a result from Heavy menstruation that reduce the amount of blood

Iron is absorbed in the mucosa of duodenum as a ferrous (Fe+2), then it is bound with Apo ferritin protein (inactivated ferritin that is present in liver and spleen) to make ferritin and be stored in tissue. When iron go to blood it must be converted to ferric (Fe+3) and bind with transferrin protein.

*** Iron and Hemoglobin can't be free as they are toxic and generate free radicals (H_2O_2)**

Transferrin receptor protein (TRP) on erythroid precursor and in case of iron deficiency there will be more TRP that break off and detected by TRP test

Anemia of inflammation (chronic inflammation) (ICA)

It is caused by a bacteria in GIT that causes hemorrhage and inflammation.

As inflammation occurs, cytokines are activated so there will be a lysis in erythrocyte through autolysis and apoptosis. Bone marrow is insensitive and do not respond to erthropotein (EPO) and cause a suppression of RBC production

In ICA, our body make strategies to prevent bacteria from growth:

1-Iron is stored into ferritin in tissue (spleen and liver) so ferritin is increased, however it decreases transferrin (decreasing of transferrin and increasing ferritin is managed through IL-6).

2-It increases the amount of Hepcidin which decrease the absorption of iron in blood so it decrease the amount of iron binding with protoporhyrin, and thus there will be a huge amount of free protoporphyrin (FEP).

3-there will be a reduction in EPO amount to prevent bacterial growth (through IL-6)

In Lab test: ferritin level is increased, transferrin saturation is decreased, FEP (free erythrocyte protoporhyrin)is increased

Iron deficiency anemia (IDA) vs Chronic inflammatory anemia (ICA)

- **IDA and ICA result from a bacteria in GIT that cause an inflammation and destruction of RBC, and both decrease in iron amount in blood (have iron deficiency. So We can differentiate between them through these tests:**

1-Serum total iron binding capacity (TIBC): measure the amount of Iron (Fe+3) that bind with transferrin

2-Iron saturation percentage (transferrin saturation): measure the saturation of transferrin with Iron

3-Soluble Transferrin Receptor (STFR): measure the amount of transferrin receptor (when there is deficiency in iron the number of receptors increase)

***these methods are too expensive and mostly not used, usually if a patient has an anemia he gets iron as a drug, if he improves then he has IDA, if he's not then he has ICA, but the problem is that if the patient has an ICA and does not have a deficiency in iron, getting drug will stimulate bacterial growth and worsen the case.**

***ICA has lower amount of Iron in the blood, however, the Iron amount in body tissue is normal or slightly increased**

Continue….

- In IDA:

TIBC is very low

STFR is very high (the more the iron is reduced the more it increase the number of Transferrin receptor protein (TPR))

Iron percentage saturation is very low

Ferritin level is decreased

In ICA:

TIBC is not decreased

STFR is normal

Iron percentage saturation is not decreased

Ferritin level is increased

Transferrin saturation is decreased

FEP is increased

Nutritional anemia: (megalocytic / macrocytic anemia)

1-Vitamin B12 pernicious anemia:

Vit.b12 normally is absorbed through Intrinsic factor from parietal cells in the gut

Vit b12 work as a Co-enzyme in the production of DNA and a Co- enzyme of myelin

2-Folate deficiency: is caused by

1-Malnutrition

2-Alcohol abuse

*Folate and Vit.B12 are required for RBC's DNA

* Both (folate and vit.b12 deficiency) cause macrocytic anemia. But once I see someone with macrocytic anemia, I immediately suspect folate deficiency as the latter is more common than vit.b12 deficiency (because folate needs more time to be stored than vit.b12)

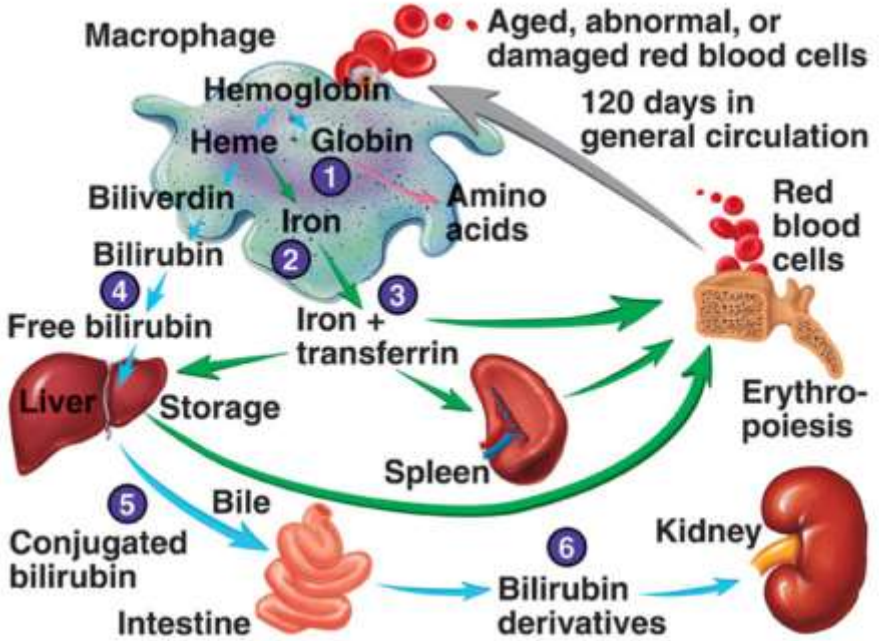
Extravascular vs Intravascular hemolysis

**In hemolysis, Heme is broken to Iron and protoporhyrin,
then protoprophyrin is converted to biliverdin then to free bilirubin,
free bilirubin go to the liver and then Converted to
be conjugated bilirubin, the latter will bind with Ca+2 in intestine**

extravascular or intravascular hemolysis marks:

1- decrease the amount of haptoglobin (that is bound to hemoglobin)
2-increase the amount of bilirubin (free and conjugated)
3-increase LDH
4- increase the amount of reticulocytes
5-abnormal RBC morphology

* Those marks occurs in both (intravascular and extravascular)



extravascular or intravascular Hemolysis (continue…)

Intra vascular hemolysis marks:

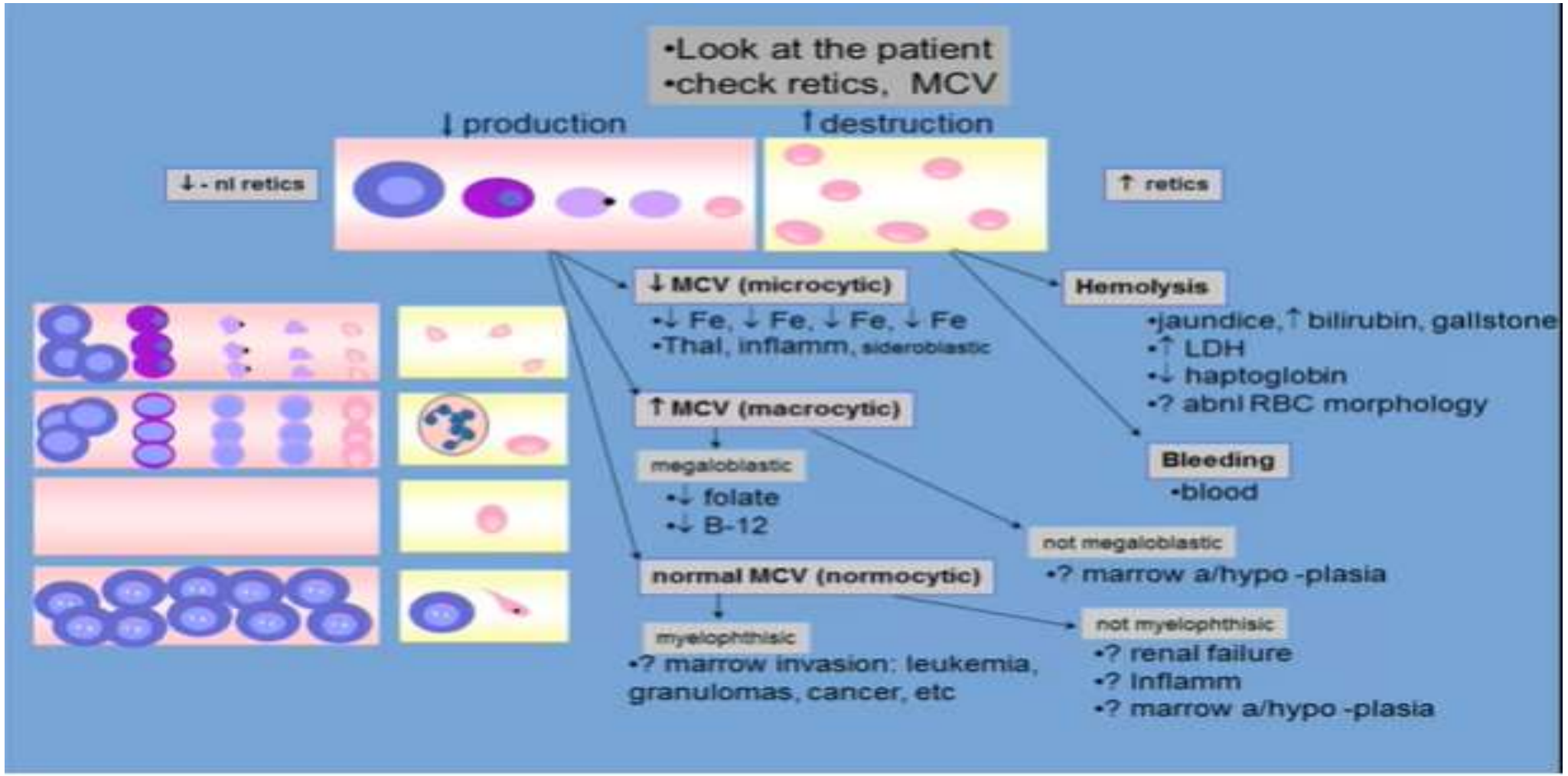
1-Free hemoglobin in plasma (in high amount)
2-Hemoglobinuria (as Hb is found in high amount)
3-Hemosiderinuria (due to high presence of Ferrous (Fe+2))

- If Intravascular hemolysis continue to occur and become chronic then Fe deficiency occurs as Iron will be excreted in high amount through urine (by Hemosiderinuria)

- If Hemolysis (either extravascular or intravascular) continue to occur then:

1-gall stones may occur (as more bilirubin bind with more salts(Ca+2))
2-Bone marrow erythroid hyperplasia (as BM is stimulated to make more reticulocytes)
3-Increase folate requirement

How to approach Differential diagnosis of anemia



شرح الصورة:

If we want to diagnose Anemia, first we use new school Medicine method by measuring the response of BM (to make sure it has good response and produce enough reticulocyte or not) so we check on reticulocyte count then we use Old school medicine method (diagnose anemia based on MCV), if reticulocyte was in high amount then there is an increase in RBC destruction, otherwise there will be a problem in RBC production.

If there is a problem in RBC production we detect RBC size:

1-if it was Microcytic: the cause is by Iron deficiency anemia(mostly), thalassemia, chronic inflammatory anemia, or sideroblastic

2-if it was Macrocytic: the cause is Nutritional anemia (Vit.B12 or folate deficiency) that makes megaloblastic anemia, or aplastic and hypoplastic marrow that cause non-megaloblastic anemia.

3-if it was Normocytic: which is classified to myelophthisic as there is a problem in BM itself (leukemia, Cancer, granuloma, marrow invasion), and non-myelophthisic as there is renal failure, ICA or aplastic or hypoplastic marrow

If there is an excessive RBC destruction: we suspect there is a bleeding, or hemolysis by detecting any mark of hemolysis : (increase LDH and reticulocyte and bilirubin, decrease heptoglobin, Hemoglobinuria, Hemosiderinuria, abnormal RBC morphology (spherocytosis))

65 yr old woman with fatigue, wt loss, and night sweats.

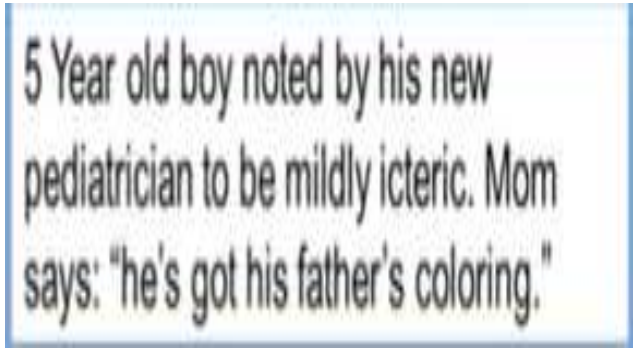
Test ordered	Result	Units	Ref range
Hemoglobin	6.8L	g/dL	13-18
Hematocrit	22L	%	37-55
Reticulocytes	0.3L	%	0.4-1.5
MCV	93	fL	78-93
Bilirubin, total	1.2	mg/dL	0.2-1.2
Bilirubin, dir.	0.1	mg/dL	0.1-0.3
LDH	230	U/L	100-230
Haptoglobin	200	mg/dL	30-200

*HB, HCT, reticulocyte are in lower amount

*MCV, bilirubin, LDH and Haptoglobin are in normal amount

*As reticulocyte is in low amount we suspect there Is a problem in production of RBC

There is no nutritional anemia or IDA
as MCV is normal, and thus we suspect there is A problem in Bone marrow itself (tumor, leukemia, Granuloma)



Test ordered	Result	Units	Ref range
Hemoglobin	11.5L	g/dL	13-18
Hematocrit	35L	%	37-55
Reticulocytes	5H	%	0.4-1.5
MCV	89	fL	78-93
Bilirubin, total	1.6H	mg/dL	0.2-1.2
Bilirubin, dir.	0.3	mg/dL	0.1-0.3
LDH	380H	U/L	100-230
Haptoglobin	10L	mg/dL	30-200

*HB, HCT are in lower amount

*reticulocyte, bilirubin, LDH and Haptoglobin are in high amount

*MCV is normal

As reticulocyte is in high amount, we suspect there is an excessive destruction of RBC which mean there is a hemolysis

*in lab test: RBC are found spherical in shape, so we suspect that the boy has hereditary spherocytosis

*المثال نفسه الي موجود بالانترنت محطوط فيه صورة خلايا الدم الحمراء والي من خلالها عرفوا تشخيص المرض, بس الدكتورة مو حاطيتها بالسلايد ^_^