APPROACH TO ANEMIA IN CHILDHOOD

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Pediatric hematologist oncologist
Interpretation of CBC: what will you see in CBC?

- Hb, hematocrit, rbc count, wbc count, platelet count
- Rbc index: MCV, MCH, MCHC
- RDW (Red cell distribution width)
- Retic count
Interpretation of CBC

Normal range of Hb: mean (range)

- Cord blood: 16.8 (14-20)
- 3 mo: 12 (9.5-14.5)
- 6mo-6yr: 12 (10.5-14)
- 7-12yr: 13 (11-16)
- Female: 14 (12-16)
- Male: 16 (14-18)
Interpretation of CBC

Mean (range) of MCV: Femtolitre

Cord blood: 106(94-112)

2mo: 78(70-80)

2-8yr: 75(73-86)

8-12yr: 83(76-86)

Male: 85(78-90)

Female: 84(77-88)
Nadir of MCV in 2-8 years of age

- \( \{\text{age(year)} + 70\} \)
- So for a 5 years old child MCV < 75 needs workup, but for a 3 years old child MCV < 73 needs workup (has microcytosis)
Interpretation of CBC

RETIC COUNT:
It is useful in the DDx of hemolysis or chronic blood loss. It is increased in immune hemolytic anemia, spherocytosis, ovalocytosis, G6PD deficiency hemolysis, ....

But in the Thalassemia syndrome presence of NRBC is more prominent than reticulocyteosis.
Interpretation of CBC

RDW: (Red cell distribution width) May be increased in any condition Which sever anisocytis is present. (Iron deficiency, folate or B12 deficiency, thalassemia major or intermedia, sickle cell anemia, red cell fragmentation syndrome,...). It is very helpful in DDx of microcytic anemias.
Classification of anemia:

- Microcytic with normal RDW
- Microcytic with high RDW
- Normocytic with normal RDW
- Normocytic with high RDW
- Macrocytic with normal RDW
- Macrocytic with high RDW
MICROCYTIC ANEMIA:

- It is very common in all age groups.
- **Iron deficiency** is the most common acquired cause of anemia.
- **Thalassemia** is the most frequent gene mutation in human being. (6% of all human beings have one thalassemia gene mutation).
Value of MCV in neonatal screening

- In a neonate **MCV < 94** is highly in favor of alpha thalassemia and **Hb electrophoresis** for detection of **Hb Bart’s (γ 4)** is indicated.

- In the early neonatal period detection of α thalassemia is possible with simple **Hb electrophoresis**; **but after 2 weeks** many sophisticated genetic analysis (PCR, RFLP, DNA Sequencing) may be needed.
Figure 438-1 Organization of the globin genes. The bottom line reflects the scale in kilobases. Transcription of mRNA takes place from the 5' to the 3' end. The upper segment represents the beta-like globin genes on chromosome 11, and the lower segment the alpha-like genes on chromosome 16. Regions of the gene that code for primary globin proteins are shown as shaded segments, and regions that code for pseudogenes ("ψ", nonexpressed remnants) are shown as hatched segments. The composition of embryonic, fetal, and adult hemoglobins is listed. α = alpha; β = beta; γ = gamma; δ = delta; ε = epsilon; ζ = zeta.
MICROCYTIC ANEMIA WITH NORMAL RDW

- Minor thalassemia:
  - Alpha (Hb electrophoresis is Nl)
  - Beta (Hb A2 = 3.5-7%)
  - Delta-beta (Hb F = 2-15%) Deletion of delta & beta globin genes

- Anemia of chronic disease (in late stages specially in renal disease)

- Lead poisoning, copper deficiency

- Sideroblastic anemia
Minor thalassemia: size of RBC must be near to size of nucleous of a small lymphocyte: (microcytosis)
MICROCYTIC ANEMIA WITH HIGH RDW

- Iron deficiency anemia
- Beta thalassemia major & intermedia (high NRBC, high Hb F)
- Sickle thalassemia (high Hb S & F)
- Hb H disease (deletion of 3 alpha genes)
- Hb C and Hb E disease
- Red cell Fragmentation syndrome
IRON DEFICIENCY ANEMIA: severe anisocytosis, poikilocytosis, cigar shape RBC
KILONICHIA (SPOON NAIL )

Late finding in Iron deficiency
What is the cause of thrombocytosis in iron deficiency?

- Megakaryocytes have endomytosis (duplication of nucleus without division of cytoplasm), Iron has negative control on endomytosis, so in iron deficiency and inflammation (due to effect of lactoferrin); this control is absent and megakaryocytes will have 8-16 nuclei and produce abundant number of microplatelets.
Endomitotic synchronous nuclear replication → Cytoplasmic granulation → Platelets
Effect of Iron deficiency on IQ and school performance

- Metaanalysis of researches on this topic shows that when diagnosis of iron deficiency is made by screening of infants during referral for vaccination, there is no association with IQ and school performance.
- But when infants with clinical and laboratory diagnosis of iron deficiency were followed they will have low school performance.
Prevention from Iron deficiency anemia

- For breast fed infants from 4-6 mo: start 1mg/Kg iron (maximum 15 mg)
- For Low birth, blood loosed, low Hb infants since 3 months of age & for premature when doubling birth Wt: start 2-6 mg/Kg (maximum 20 mg)
- For formula fed infants if they drink at least 1 liter, no supplement is needed; otherwise they need 1 mg/kg iron supplementation.
DDx of minor thalassemia & iron def.

- Mentzer index: MCV / RBC
- **Note**: Only If MCV < 80 fl
- < 13: Minor thalassemia => check Hb electro.
- 13-15: Mixed Iron def. & minor thalassemia => trial of iron + folate for 1 mo. Then check CBC & Hb electrophoresis
- >15: Iron deficiency
- Sensitivity=85%, Specificity=70%
DDx of minor thalassemia & iron def.

- **Kerman index 1**: \( \frac{MCV \times MCH}{RBC} \)
  - <250: minor thalassemia => check Hb elect.
  - 251-320: mixed iron def. & minor thalassemia => trial of iron & folate then check CBC & Hb elect
  - 321-370: iron def. => trial of iron for 1 mo.
  - >371: normal

- Sensitivity = 99%, Specificity = 86%
DDx of minor thalassemia & iron def.

Kerman index 2: \(\frac{MCV \times MCH}{RBC \times MCHC}\)

<8 : Minor thalassemia
8-10.5: Mixed iron def & minor thal.
10.5-13: Iron deficiency
>13: Normal

Note: Sensitivity = 99%, Specificity = 93%
DDx of minor thalassemia & iron def.

- Case 1: 6 Y/O boy with pallor, Hb=10, MCV=60, Rbc=6, MCH=20, MCHC=30, RDW=14, WBC & Plt=NI
- What is your Dx?
- What will you do for him?
- Mentzer index: 10, KI1: 200, KI2: 6.6
Hb A2

- **Normal** = 2.5-3.4%
- **In favor of β thalassemia trait** = 3.5-7%
- **False positive**: Thyroid disease (hypo and hyperthyroid disease), megaloblastic anemia, Hemoglobinopathies (HbD or HbS)
- **False negative**: Sever iron deficiency, pregnancy, Oral contraceptive pills
DDx of minor thalassemia & iron def.

- Case 2: one Y/O infant with pallor, irritability, blue sclera & palpable spleen. Hb=10, MCV=66, RBC=3.5, MCH=18, MCHC=30, plt=600000, WBC = Nl, RDW=19

- What is your Dx?
- What will you do for him/her?
- Mentzer: 18.8, KI1: 340, KI2: 11.3
DDx of minor thalassemia & iron def.

○ Case 3: 15 month girl with pallor, Hb=9, MCV=66, RBC=5, MCH=24, MCHC=31, RDW=17, WBC & plt = Nl
○ What is your Dx ?
○ What will you do for her ?
○ Mentzer: 13.2, KI1: 316, KI2: 10.2
DISTRIBUTION OF ABNORMAL Hb GENES in ancient world
Usual feature of thalassemic patient who is not transfused adequately
SKULL X-RAY OF THALASSEMIC PATIENTS, DUE TO B.M. EXPANSION and narrowing of outer table of the skull
CASE 4

- 8 M/O boy with pallor, hepatosplenomegaly, irritability, FTT.
- Lab data: Hb = 8, WBC = 40000, MCV = 70, RBC = 3.5, MCH = 22, MCHC = 33, RDW = 18, PLT = 600000
- What is your impression?
- What will you request for him?
Case 4 😞 (continued)

- Hb electrophoresis:
  - Hb A1 = 0%, Hb F = 98.2%, Hb A2 = 1.8%
- When you will transfuse him?
- When you will request serum Ferritin level for Desferal therapy?
**Hemoglobin Electrophoresis**

<table>
<thead>
<tr>
<th>Fraction</th>
<th>%</th>
<th>G/dl</th>
<th>Ref. Range [%]</th>
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<tbody>
<tr>
<td>HBA</td>
<td>0.0</td>
<td>0.0</td>
<td>95.0 - 98.0</td>
</tr>
<tr>
<td>HBF</td>
<td>98.2</td>
<td>7.4</td>
<td>0.1 - 2.0</td>
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<tr>
<td>HBA2</td>
<td>1.8</td>
<td>0.1</td>
<td>1.5 - 3.5</td>
</tr>
</tbody>
</table>

Total: 100  7.5

**Reference Patterns**

- **Normal**
- **Present F**
- **Increased A2**
- **Present S/D/G**

**CBC Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>3.3 [M/ul]</td>
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<tr>
<td>HGB</td>
<td>7.5 [g/dl]</td>
</tr>
<tr>
<td>HCT</td>
<td>24.5 [%]</td>
</tr>
<tr>
<td>MCV</td>
<td>75.2 [fl]</td>
</tr>
<tr>
<td>MCH</td>
<td>23.0 [pg]</td>
</tr>
</tbody>
</table>

**Comments:**

- Hb A2 was checked by column chromatography: 1.8
- Hb F was checked by chemical method: 98.2
- Sickling test was negative

**Signature:** DR.S.R.SAGHANEZHAHAD
β-thalassemia major
Alpha thalassemia syndrome

- Everybody has 2 copies of α globin gene on every chromosome 16.
  - α α/ α α (healthy)
  - α α/ α _ (silent carrier)
  - α _/ α _ (α thalassemia trait)
  - α α/_ _ (α thalassemia trait)
  - α _/ _ _ (Hb H Disease)
  - _ _/ _ _ (Hydrops fetalis)
Case presentation: 7 Y/O boy with pallor, jaundice, splenomegaly

- Lab data: Hb=9.3, MCV=73.5, RBC=4.6, RDW=15, T.BILI=5, D.BILI=0.45, SGOT=95, SGPT=25, Both parents have microcytosis + normal Hb Electrophoresis
What tests do you request for Dx?

- Retic count,
- vital stain for Hb H,
- Hb electrophoresis
Dx: Hemoglobin H disease
(13.5% fast running Hb)
Golf-ball pattern
(Hb H inclusions)
HYDROPS FETALIS : ALPHA THALASSEMIA
NORMOCYTIC ANEMIA WITH NORMAL RDW

- Anemia of chronic disease
- Non-anemic hemoglobinopathy (Hb S, C, D trait)
- Post chemotherapy
- Spherocytosis, Ovalocytosis
- CLL (WBC < 150000)
Case history:

- 12 Y/O boy with pallor, some facial bone changes, splenomegaly, mild jaundice, Height=120 cm, Wt=21 Kg, Hb=9, MCV=80, MCH=28, MCHC=37, RDW=15, Retic =27%

- Which data is abnormal?
- What is your impression?
- What will you request for him?
Spherocytes
NORMOCYTIC ANEMIA WITH HIGH RDW

- Mixed deficiency (Folate & Iron)
- Early iron or folate deficiency
- Anemic hemoglobinopathy (Hb SS, Hb SC, Hb SD, Hb SG, ...)
- Myelofibrosis
- Sideroblastic anemia
SICKLE DACTILITIS: HAND FOOT SYNDROME

FIG 49-8.
Multiple lesions of the “hand-foot syndrome” in the tubular bones of the hands and swellings of the fingers in a girl 12 months of age who had sickle cell anemia and probably shigellosis. A, diffuse swelling of the soft tissues. B, destructive and productive osteitis of the phalanges and metacarpals. (Redrawn from Ivey RE, Howard FH; J. Pediatr 1953; 43:312–315.)
COMPLICATION OF DACTILITIS
Avascular necrosis of the head of Femur
CASE HISTORY:

- 15 Y/O boy with secondary enuresis
  Hb=10, MCV=81, MCH=29, MCHC=33, WBC& PLT=NORMAL, FBS=87, BUN=17, CREATININ=1, U/A:S.G=1.002, SUGAR–VE

- What is your impression?
- What you will request for him?
MACROCYTIC ANEMIA WITH NORMAL RDW

- Aplastic anemia (Fanconi) (untransfused)
- Preleukemia (Myelodysplastic Syndrome)
- Bleeding in perinatal period
16 Y/O GIRL (FANCONI) & HER 12 Y/O DONOR SISTER IN BM TRANSPLANTATION WARD

Note:
- microcephaly
- micrognathia
- microphthalmia
- absence of thumbs
- severe short stature
Fanconi anaemia—the phenotype

Growth retardation and abnormal development

Stem cell failure

1000 fold risk of cancer
MACROCYTIC ANEMIA WITH HIGH RDW

- Folate deficiency
- B12 deficiency
- Aplastic anemia (Fanconi) (transfused)
- Immune hemolytic anemia (Rosette)
- Cold agglutinins (Roleux formation)
- C.L.L (WBC > 150000)
IMMUNE HEMOLYTIC ANEMIA

- WARM Ab:
  - Idiopathic, secondary
    (Lymphoproliferative disorders, CVD like SLE, Ovarian tumors & ulcerative colitis)

- COLD Ab:
  - Idiopathic, secondary
    (Lymphoproliferative disorders, infections like Mycoplasma & EBV, Paroxysmal cold hemoglobinuria due to viral, syphlis or primary)
CASE PRESENTATION:

- Thirteen M/O baby with pallor and involuntary movements (mimicking partial seizure) for 2 weeks, has no organomegaly, normal head circumference.
- Lab data: Hb = 9, MCV = 106, RBC = 2.5 WBC & PLATELET = Normal, FBS, Ca, Ph,... = Normal
- What is your impression?
PERNITIOUS ANEMIA: LEMON YELLOW FACE
Folate dependency

- 6 months old boy with abnormal movements of lips, and fingers for more than 2 weeks.
- Serum level of folate & B12 = normal
- Treatment: Lifelong folic acid (5 mg/day)
Macrocytosis + hypersegmented neutrophil
Howell-Jolly bodies in macrocytic Pernicious anemia
Megaloblastic change
Case Presentation:

- Six M/O baby with severe irritability, mild pallor, moderate hepatosplenomegaly
- Hb=10.5, MCV=102, RBC=2.3, TORCH W/U -Ve
- Serum folate & B12 level = Normal
TRANSCOBALAMIN II DEFICIENCY
Case presentation:

- Twelve Y/o previously healthy boy, 3 weeks after a common cold; developed pallor, jaundice, fever, splenomegaly.
- Lab data: Hb=8, MCV=125, RBC=2, WBC=15000, Platelet=400,000, RETIC=35%, T.Bili=6, D.Bili=0.9, SGOT=200, SGPT=34, LDH=600
What is your impression?

- Warm antibody (isoimmunisation)
- Treated with prednisolone and had good response
ROSETTE FORMATION: IMMUNE HEMOLYTIC ANEMIA
Cold agglutinins

- Each IgM Molecule activates a C1 molecule and complement activation leads to intravascular hemolysis + hepatic and splenic removal of RBC.
- Steroid and splenectomy is not useful, self limited in most cases, plasmaphersis and immunosuppressive therapy may be indicated in few patients.
Cold antibody or cold hemagglutinins

- 14 years old boy with dry hacking cough, sever ear ache, redness of fingers in cold exposure then paleness and pain
Rouleaux formation)
RAYNAUD’S PHENOMENA : COLD AGGLUTININ