MACROCYTIC ANEMIA

(MCV >100 in child older than 2 years)

- Non-Megaloblastic
- Megaloblastic
Red cells are usually approximately the size of a small lymphocyte nucleus (arrow). In this case the red cells are slightly larger than the lymphocyte nucleus on average. Macrocytic anemia is most often a result of folate or vitamin B12 deficiency.
FOLIC ACID DEFICIENCY

• Etiology
  - Nutritional
    • Sources: leaves, vegetable, fruits, animal organs e.g. liver and kidneys
    • Body stores for folic acid is limited 2-3 months on folate free diet
  - Inadequate intake - during pregnancy, growth in children, and hemolytic anemia
  - Goat milk consumption
    • Decreased folic acid absorption - removal of ileum or IBD
    • Anticonvulsant medication e.g. phenytoin, primidone
    • Congenital dihydrofolate reductase deficiency
    • Drug induced abnormal metabolism - Methotrexate
FOLIC ACID DEFICIENCY

• Clinical presentation
  – Megaloblastic anemia
  – Glossitis
  – Irritability
  – Inadequate weight gain
  – Chronic diarrhea
  – Hemorrhage from thrombocytopenia in severe cases
FOLIC ACID DEFICIENCY

- Laboratory
  - Macrocytic anemia (MCV >100)
  - Megaloblastic changes including hypersegmented neutrophils (>5 lobes)
  - Elevated LDH
  - Low serum folate
  - High serum homocysteine
  - Hypercellular bone marrow

Peripheral smear for a patient with megaloblastic anemia
FOLIC ACID DEFICIENCY

- Treatment
  - Rule out B12 deficiency before starting folic acid therapy
  - Folic acid 0.5-1mg/day IV or oral
  - Hematologic response can occur within 72 hr (diagnostic test as well)
  - Treatment continued for only 3-4 weeks
  - Maintenance dose is 0.2mg daily

Warning:
- Treating Vit B12 deficiency with folic acid will correct the macrocytosis
  But
- The neurological symptoms will keep getting worse
VITAMIN B12 DEFICIENCY

• Know that
  – Vitamin B12 stores last for 3-5 years
  – Sources – animal products

• Etiology
  – Inadequate B12 intake (strict vegan)
  – Exclusively breast fed and maternal vegan diet
  – Removal of terminal ileum
  – Inflammatory bowel disease
  – Fish tapeworm (Diphyllobothrium latum)
  – Absence of Vitamin B12 transport protein and stomach intrinsic factor (IF)
VITAMIN B12 DEFICIENCY

Clinical Presentation
- Weakness
- Fatigue
- Failure to thrive
- Irritability
- Pallor
- Glossitis
- Vomiting
- Diarrhea
- Icterus

Neurologic symptoms
- Subacute combined degeneration of spinal cord
- Impaired vibration sense
- Ataxia
- Paresthesias
- Developmental regression
- Neuropsychiatric changes

Methylmalonic Acid → B12 → Succinyl-CoA
VITAMIN B12 DEFICIENCY

- **Laboratory**
  - Macrocytic anemia (MCV > 100)
  - Megaloblastic changes including hypersegmented neutrophils (>5 lobes)
  - Elevated LDH
  - Normal iron and folic acid levels
  - Increased methylmalonic acid in urine
  - Increased homocysteine
  - Low reticulocyte count for degree of anemia
  - Anti-parietal cell antibody positive in pernicious anemia
  - Less than 10% of cases present under age 40

Classic Schilling test no longer is regarded as the diagnostic test.
VITAMIN B12 DEFICIENCY

- **Treatment**
  - Parenteral administration of Vitamin B12 1mg daily
    - With neurologic involvement continue for minimum of 2 weeks
  - Maintenance of monthly IM Vitamin B12 for life
  - Diagnosis and treatment of tapeworm infestation, celiac disease, Crohn diseases
Macrocytic anemia (MCV > 100)

Megaloblastic anemia

- Test folate and vitamin B12 levels

  - Low Vit B12
    - Vit. B12: Treat and retest; consider treating for pernicious anemia or ileal disease
    - Folate: treat and retest; provide dietary counseling
  
  - Low Folate
  
  - Both levels are low

Non-megaloblastic anemia

- Reticulocyte count

  - Low
    - Refer to pediatric hematologist

  - High
    - Hemolysis or hemorrhage

Hypothyroidism

- Hepatic disease

- Tx of the cause
DIAMOND-BLACKFAN ANEMIA
(Congenital Hypoplastic Anemia)

- **Cause**
  - Primary defect in the erythroid progenitors

- **Clinical Presentation**
  - Profound anemia manifested by 2-6mo of age
  - More than 50% have congenital anomalies
    - Short stature
    - Craniofacial dysmorphism (snub nose, wide-set eyes, thick upper lip)
    - *Triphalangeal thumbs*
    - Bifid, sublaxed, absent, or supernumerary thumbs
DIAMOND-BLACKFAN ANEMIA
(Congenital Hypoplastic Anemia)

- Laboratory
  - Macrocytic RBCs with no hypersegmentation of neutrophils
  - Normal B12 and folate
  - Increased adenosine deaminase activity in most patients
  - Decreased RBCs precursor in bone marrow
  - Elevated serum iron
  - Normal bone marrow chromosomal studies
  - Normal to low reticulocytic count
  - Negative PCR for Parvovirus B19
DIAMOND-BLACKFAN ANEMIA
(Congenital Hypoplastic Anemia)

• **Treatment**
  - Steroids
  - Iron chelating agents (if transfusion dependent)
  - Stem cell transfusion for who do not respond to corticosteroids, after several years of RBC transfusions

• **Prognosis**
  - Median survival >40 years
NORMOCYTIC ANEMIA
(MCV > 70 + age and < 100 in child older than 2)
TRANSENT ERYTHROBLASTOPENIA OF CHILDHOOD

• **Background**
  - Most common acquired red cell aplasia in childhood
  - More common than Diamond-Blackfan Anemia
    (congenital hypoplastic anemia)

• **Etiology**
  - Transient suppression of RBC production
  - Often noted after a viral infection
  - No evidence of Parvovirus B19
TRANSIENT ERYTHROBLASTOPENIA OF CHILDHOOD

• Age - 3 months to 3 years of age, most >12 months

• More common in males

  – Most common presentation (despite the severity)
    • No symptoms
    • Gradual increasing pallor

  – Uncommon presentation
    • Increased fatigue or decreased energy
    • Breath-holding spells
TRANSIENT ERYTHROBLASTOPENIA OF CHILDHOOD

• Laboratory
  - MCV normal for age
  - Hemoglobin can be as low as 2.2 g/dL
  - Reticulocytes decreased
  - Bone marrow biopsy rarely needed but erythroid suppression seen
  - Normal adenosine deaminase (ADA)

• Treatment
  - Reassurance
  - Recover within 2-3 months
  - Occasionally transfusion is necessary
Reticulocyte Count

- Normal retic count full-term infants (3-7)
- Normal retic count in pre-term infants (5-10)
- In infants and children > 6 months (0.5-1)
- CRC = % Retic x patient HCT/Normal HCT
- CRC > 1.5 → suggest hemolysis or blood loss

Anemia

False high Retic count %

Retic count 4%
HCT=25%
\[
CRC = 4 \times \frac{25}{45} = 2.2\%
\]
Hemolytic Anemia

- **Intravascular hemolysis** → hemolysis within the blood vessels → (hemoglobin + haptoglobin) → decrease haptoglobin → hemoglobinemia → hemoglobinurea

- **Extravascular hemolysis** → hemolysis by macrophages in spleen, liver and lymph nodes → splenomegaly
HEREDITARY SPHEROCYTOSIS

Autosomal dominant inheritance

Biconcave RBCs

Spectrin deficiency
Spectrin and ankyrin deficiency
Band 3 deficiency
Protein 4.2 defects

Spherical RBCs

Splenomegaly
HEREDITARY SPHEROCYTOSIS

- Clinical Presentation
  - May be asymptomatic into adulthood
  - Anemia
  - Pallor
  - Jaundice
  - Pigment gallstones may form as early as 4-5 years of age
  - Fatigue
  - Exercise intolerance
  - Splenomegaly

Parvovirus B19 infections → Aplastic crisis:
  - Profound anemia
  - HCT<10%
  - High cardiac output failure
  - Hypoxia
  - Cardiovascular collapse and death
HEREDITARY SPHEROCYTOSIS

- Laboratory
  - Reticulocytosis
  - Indirect hyperbilirubinemia
  - High LDH
  - Low haptoglobin
  - Normal MCV
  - Elevated MCHC
  - High percentage of spherocytes on smear
  - Can be confirmed with osmotic fragility test
Red cells should be similar in size to the small lymphocyte nucleus (center). In **hereditary spherocytosis** the red cells are small and hyperchromatic, lacking central pallor (40x). Red arrows point out a few of the examples in this field.
HEREDITARY SPHEROCYTOSIS

- Treatment
  - Folic acid 1 mg PO daily to prevent deficiency and the resultant decrease in erythropoiesis
  - Splenectomy indications:
    - Hgb <10g/dl
    - Reticulocytosis
    - Aplastic crisis
    - Poor growth
    - Cardiomegaly
  - Some do not recommend splenectomy in patients with hemoglobin >10g/dl and reticulocytes <10%
HEREDITARY SPHEROCYTOSIS

• **Treatment**
  
  – Vaccination for encapsulated organism hemophilus influenza, meningococcus, pneumococcus should be given before splenectomy, then prophylactic penicillin V 125mg BID <5 years and 250mg BID for >5 years
  
  – Partial splenectomy is useful in children <5 years