MEGALOBLASTIC ANEMIA

Marrow Failure

- Metabolically highly active, 2nd to rapid cell turnover
  - White cell life span 12-24 hours
  - Platelet life span 7 days
  - Red blood cell lifespan 120 days
- Any slowing of DNA production → marrow failure
MEGALOBLASTIC ANEMIA

• Hemoglobin production probably normal
• Defect in nuclear replication & division
• Affects all marrow elements

MEGALOBLASTIC ANEMIA

• Trademark cell: Oval macrocyte, (MCV > 100 fl)
• Hypersegmented neutrophils - 98%
• Pancytopenia, esp if anemia severe
• Reticulocytopenia
• LDH elevated (90%)
• Serum Fe normal or elevated
• Serum B₁₂ or folate low
• Marrow ➔ classic megaloblastic changes
FOLIC ACID

One Carbon Fragment Forms

N[^5,10] methylene THF
Thymidylate biosynthesis

N[^5] methyl THF
Transport

Purine biosynthesis

FOLATE ABSORPTION

dATP → dGTP → dCTP → dTTP → dTTP

THF polyglutamate

5, 10-methylene THF polyglutamate

Methyl THF

Methionine
Homocysteine

Cell membrane
Plasma

Methyl THF

Small intestine
Dietary folates
FOLATE DEFICIENCY

Causes

• Folate-poor diet
  - Alcoholism
  - Severe poverty
• Increased folate requirement
  - Pregnancy
  - Severe hemolytic anemia
  - Severe Psoriasis
• Drug therapy
• Malabsorption
  - Tropical sprue

FOLATE DEFICIENCY

Manifestations

• Megaloblastic anemia
• Glossitis/stomatitis
• GI malabsorption 2º to impaired GI epithelium (rare)
COBALAMIN (Vitamin B<sub>12</sub>)

*Functions*

- Folate metabolism - Required for demethylation of methyl-THF
- Methylation of myelin
- Conversion of methylmalonyl CoA to succinyl CoA

*COBALAMIN*

*Structure*

Beta-groups:
- ON - Cyano; inactive
- OH - Hydroxyl; inactive
- Methyl - Folate metabolism
- Adenosyl - Mutase activity
**COBALAMIN REACTIONS**

Homocysteine → Methionine → Methylmalonyl CoA → Succinyl CoA

- THF
- Adenosyl Cobalamin

**GI ABSORPTION OF COBALAMIN**

- Stomach
- Duodenum
- Terminal Ileum

- Cbl
- IF
- IF-Cbl
- TCII-Cbl
- TCII
- TCI-Cbl
COBALAMIN DEFICIENCY

Causes

- Gastric Failure
  - Pernicious Anemia
  - Total gastrectomy
- Ileal Failure
  - Regional enteritis (Crohn's disease)
  - Ileal resection
  - Tropical sprue
- Competing organisms
  - Bacterial overgrowth (Blind loop)
  - Diphyllobothrium latum

PERNICIOUS ANEMIA

- Autoimmune destruction of parietal cells
- Antibodies vs. parietal cells, intrinsic factor
- Achlorhydria is universal
- Increased incidence of gastric cancer
- Increased incidence American blacks, northern Europeans
- Often associated with other immune diseases (eg Hashimoto's thyroiditis)
**COBALAMIN DEFICIENCY**

*Peripheral Folate Depletion*

- N⁵-methyl-THF
- THF
- N⁵-methyl-THF
- Cbl
- THF
- Methionine
- Homocysteine
- Conjugated folates

**COBALAMIN DEFICIENCY**

*Peripheral Manifestations*

- Megaloblastic anemia - Indistinguishable from folate deficiency & due to intracellular folate deficiency
- Stomatitis/glossitis
- GI Mucosa alterations
- Can correct all of the above with high dose folate;

**DON'T DO THIS!!!!!**
COBALAMIN DEFICIENCY

Manifestations-Central

- Both brain and spinal cord
- Brain:
  - Dementia
  - Psychological disturbances
- Spinal cord:
  - Demyelinating disease
  - Loss of posterior & lateral columns—hence name "Combined system disease"
- Neurologic disease stabilized with treatment, but usually not reversed
- Treatment with folate does nothing for neurologic disease

SUBACUTE COMBINED DEGENERATION

Fig. 4.9 Cross-section of the spinal cord in a patient who died with subacute combined degeneration of the cord (Weigert–Pal stain). There is demyelination of the dorsal and dorsolateral columns.
COBALAMIN DEFICIENCY
Usual Sequence of Events

- Serum homocysteine & methylmalonic acid rise
- Serum cobalamin falls
- MCV rises; neutrophil hypersegmentation
- MCV rises above normal
- Anemia
- Symptoms

FOLATE/COBALAMIN Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Folic Acid</th>
<th>Cobalamin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Food Source</strong></td>
<td>Almost all foods</td>
<td>Animal protein only</td>
</tr>
<tr>
<td><strong>Water soluble</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Site of absorption</strong></td>
<td>Duodenum/Jejunum</td>
<td>Ileum</td>
</tr>
<tr>
<td><strong>Mech of absorption</strong></td>
<td>Deconjugation of poly-Glu</td>
<td>Uptake of IF-Cbl complex</td>
</tr>
<tr>
<td><strong>Metabolic Function</strong></td>
<td>One Carbon transfers</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Body stores</strong></td>
<td>4-5 months</td>
<td>2-12 years</td>
</tr>
<tr>
<td><strong>Dietary deficiency</strong></td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Deficiency states</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Megaloblastic anemia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
MEGALOBLASTIC ANEMIA

Diagnosis / Therapy

• Draw levels at first suspicion of problem, BEFORE ANY THERAPY
• Once levels drawn, begin treatment with both $B_{12}$ and folate
• Once levels are back, can stop the normal vitamin
• Transfusions to be avoided unless hemodynamic compromise is present, or patient having angina
MEGALOBLASTIC ANEMIA

Response to Therapy

SCHILLING TEST

<table>
<thead>
<tr>
<th>Cause of Cobalamin Deficiency</th>
<th>Part I Without IF</th>
<th>Part II With IF</th>
<th>Part III After Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pernicious Anemia</td>
<td>Low</td>
<td>Normal</td>
<td>Not needed</td>
</tr>
<tr>
<td>Bacterial Overgrowth</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Ileal dysfunction</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Megaloblastic Anemia

MEGALOBLASTIC ANEMIAS

Summary

- Deficiency in folate or B₁₂
- Macrocytic anemia; ± other cytopenias
- Slowly developing anemia, usually well compensated
- Response to therapy rapid and dramatic
- Treatment essential to avoid other complications
- Anemia is secondary to an underlying disease process