Nutritional anaemia

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Classification of anaemia

Microcytic, hypochromic	**Normocytic, normochromic**	**Macrocytic**
MCV < 80fl MCH > 27pg	MCV 80 – 95fl MCH > 26pg	MCV > 95fl
Iron deficiency Anaemia of chronic disease Thalassaemia Lead poisoning Sideroblastic anaemia	Acute blood loss Haemolytic anaemias Anaemia of chronic disease Renal disease Mixed deficiencies Bone marrow failure	Megaloblastic: Vitamin B12 or folate deficiency Non-megaloblastic

Hepcidin

- Major regulator of iron homeostasis
- Acute phase protein
- Inhibits iron release from macrophages and intestinal epithelial cells by its interaction with the transmembrane iron exporter ferroportin
- Increased production of hepcidin is induced by inflammation via interleukin 6
- Hepcidin production is decreased in response to iron deficiency, hypoxia and ineffective erythropoiesis

Clinical features

- RES stores (haemosiderin and ferritin) become completely depleted before anaemia develops.

- Anaemia, painless glossitis, angular stomatitis, brittle, ridged or spoon nails (koilonychia), dysphagia as a result of pharyncheal webs (Paterson-Kelly or Plummer-Vinson syndrome) and unusual dietary cravings (pika).

- In children: irritability, poor cognitive function and decline in psychomotor development.

Laboratory features

- Peripheral blood morphology
  - Hypochromic, microcytic red cells, target cells and pencil-shaped poikilocytes
  - Reticulocytopenia
  - Combined deficiencies or recent iron therapy may result in a dimorphic blood film
  - A thrombocytosis is often present

- Bone marrow (not essential except complicated cases)
  - Erythroblasts are small and have ragged cytoplasm
  - Absent iron stores and sideroblasts.

Laboratory features

- Iron studies
  - S-iron falls and total iron-binding capacity (TIBC) rises
- S-transferrin receptor (s-TfR)
  - Increased in iron deficiency but not in ACD or thalassaemia trait
- S-ferritin
  - The concentration is related to tissue iron stores. Decreased in iron deficiency but raised in inflammation (acute phase response)
- Reticulocyte haemoglobin content (CHr)
  - Values below 28pg indicate iron deficient erythropoiesis. Unfortunately also in thalassaemia and haemoglobinopathies

Laboratory features

	Iron deficiency	Chronic inflammation or malignancy	Thalassaemia trait (α or β)	Sideroblastic anaemia
MCV/MCH	Reduced in relation to severity of anaemia	Normal or mild reduction	Reduced; very low for degree of anaemia	Usually low in congenital type but MCV often raised in acquired type
S-iron	Reduced	Reduced	Normal	Raised
TIBC	Raised	Reduced	Normal	Normal
S-Tfr R	Raised	Normal/low	Variable	Normal
S-ferritin	Reduced	Normal or raised	Normal	Raised
BM stores	Absent	Present	Present	Present
Sideroblasts	Absent	Absent	Present	Ring forms
Hb electro-phoresis	Normal	Normal	Hb A_2 raised in β form	Normal

Laboratory features

- Free Erythroid Protoporphyrin
  - Increased in iron deficiency. But also in lead poisoning and conditions of markedly increased erythropoiesis (e.g. SCD, severe haemolytic anaemias, thalassaemia major)
- Mentzer index = $MCV/RCC_{(1973)}$
  - < 13 thalassaemia more likely
  - >13 iron deficiency more likely

Investigation of the cause

- In premenopausal women menorrhagia and/or repeated pregnancies are the usual causes
- In men and postmenopausal women GIT blood loss should be excluded (history, physical and rectal exam, occult blood tests, upper and lower endoscopic exams or radiology)
- Endomysial and transglutaminase antibodies and duodenal biopsy for gluten-induced enteropathy
- Stool examination for hookworm ova
- Blood loss in the urine as haematuria or haemosiderinuria

Treatment

- Oral ferrous sulphate for long enough to replenish body iron stores (> 6 months).
- Parenteral iron only when high iron requirements (GIT bleeds, severe menorrhagia, chronic haemodialysis with erythropoietin therapy) or when oral iron is ineffective (malabsorption) or impractical (e.g. active Crohn's disease). The haematological response is not faster but stores are replenished quicker.

Response

- Hb should rise by ~2g/dl every 3 weeks
- Failure may be caused by:
  - Continuing haemorrhage
  - Non-compliance
  - Wrong diagnosis
  - Mixed deficiency
  - Another cause for the anaemia
  - Malabsorption
  - Slow-release preparations

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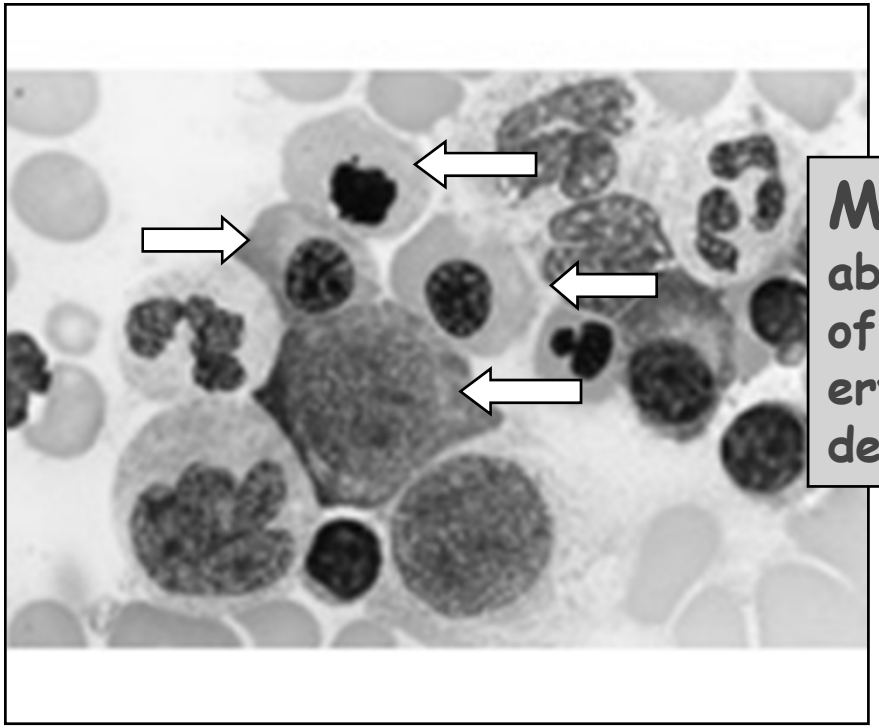
Other causes of macrocytosis

- Pregnancy
- Neonatal
- Reticulocytosis
- Alcohol
- Smoking
- Liver disease
- Myxoedema
- Aplastic anaemia
- Myelodysplastic syndrome
- Myeloma
- Cytotoxic drugs

Vitamin B12 and folate

- Vitamin B12 and folate are essential for the synthesis of DNA



Megaloblasts:
abnormal appearance of bone marrow erythoblasts → nuclear development is delayed

Vitamin B12 (Cobalamin)

- Present in foods of animal origin e.g. meat, fish, eggs, milk etc.
- Daily requirement is 1µg.
- Stored in the liver; sufficient to last for 2-4 years
- After B12 is released from food, it combines with intrinsic factor secreted by parietal cells. The IF-B12 complex attaches to ileal receptors where it is absorbed
- Once absorbed, B12 is transported by transcobalamin

Causes of vitamin B12 deficiencies

- **Nutritional**
  - Vegans
- **Malabsorption**
  - Gastric causes e.g. pernicious anaemia, gastrectomy, congenital IF deficiency (rare)
  - Intestinal causes e.g. bacterial colonisation, stagnant loop syndromes, defects of the ileum

Pernicious anaemia

- Autoimmune gastritis → gastric atrophy → reduced acid and IF.
- ♀ > ♂
- Peak @ 60 years. ± Associated autoimmune diseases.
- N European, blue eyes, early greying, familial, blood group A
- 2 – 3X incidence of gastric carcinoma
- 90% parietal cell Ab → not specific (16 % women > 60)
- IF Ab are specific for pernicious anaemia but only present in 50%

Folate

- Found in most foods, especially liver and green leafy vegetables.
- Daily requirements 100 µg.
- Body stores are sufficient for ~4 months.
- Absorbed through the upper small intestine.

Causes of folate deficiency

- **Nutritional** – poor dietary intake e.g. old age, famine, poverty
- **Malabsorption** e.g. gluten induced enteropathy, tropical sprue
- **Excess utilisation**
  - Physiological: pregnancy, lactation, prematurity
  - Pathological: haemolytic anaemia, malignant disease and inflammatory diseases
- **Excess urinary folate loss** e.g. congestive heart failure, chronic dialysis
- **Drugs** e.g. anti-convulsants
- **Mixed** e.g. liver disease and alcoholism

Pathogenesis

- Impaired DNA synthesis
- Ineffective erythropoiesis (intramedullary destruction). Ineffective granulopoiesis and thrombopoiesis. Exaggerated apoptosis of late precursors.
- Haemolysis reduces red cell life span by 30-50%

Clinical features

- Gradual onset with features of anaemia
- Mild jaundice
- Glossitis (beefy red, sore tongue)
- Angular stomatitis
- Purpura (thrombocytopenia)
- Reversible melanin pigmentation
- Progressive neuropathy due to Vit B12 deficiency (not caused by folate deficiency)
- Risk for neural tube defects and cardiovascular disease (↑ homocysteine)

Laboratory findings

- Oval macrocytes
- Low reticulocyte count
- Leucocyte count and platelets may be reduced
- Hypersegmented neutrophils
- Bone marrow: hypercellular (erythroid hyperplasia), megaloblasts, giant metamyelocytes and bands
- Raised unconjugated bilirubin
- Raised LDH
- Raised homocysteine

Laboratory findings

- S-vit B12
  - Radioisotope dilution, ELISA
  - Concentrations of haptocorrin and transcobalamin influence the test
- S-folate
  - Radioassay or ELISA
  - Sensitive. Low in folate deficient patients, affected by recent diet, rises with B12 deficiency (↓conversion of Methyl THF)
  - High levels with acute renal failure, acute liver damage, folic acid therapy, haemolysis

Laboratory findings

- Red cell folate
  - Valuable test of body folate stores
  - Less affected by diet and haemolysis
  - Subnormal levels with both folate and B12 deficiency (2/3)
  - False normal: recent blood transfusion, reticulocytosis

- S-methylmalonate (B12) and homocysteine levels (B12 and folate) not specific, difficult to establish reference ranges and not widely available

Tests for the cause

- Diet history
- IF, parietal cell Ab
- Gastroscopy
- Gastric function (acid, IF)
- Anti-gliadin and endomysial Ab
- Duodenal biopsy

Treatment

- Don't give folic acid alone unless B12 deficiency excluded → aggravate neuropathy
- Treat with appropriate vitamin
- Avoid blood transfusion if possible → circulatory overload
- Correct heart failure with diuretics and oral potassium

Response

- Symptoms improve after 24-48h → retik response on 2-3rd day → Hb rise by 2-3 g/dl each fortnight → WCC and platelets normal by 10 days.
- Marrow normoblastic in 48h. Giant metamyelocytes persist for up to 12 days
- Peripheral neuropathy may improve, spinal cord damage is irreversible.

References

- Mehta A, Hoffbrand V. Haematology at a glance. Third edition. Blackwell Science. 2009

- Hoffbrand V, Pettit J, Moss P. Essential haematology. 6th Edition. Blackwell Science. 2011