Anaemia of Chronic Disease

The World Health Organization's criterion for anaemia in adult men is haemoglobin (Hb) values less than 130 g/L, non-pregnant women less than 120 g/L and pregnant women less than 110 g/L. Children aged 6 months to 6 years are considered anaemic at Hb levels less than 110 g/L, and children aged 6-11 years are considered anaemic when Hb levels are less than 115 g/L. Anaemia of chronic disease (ACD) may be secondary to:

- Chronic infection.
- Inflammation - including connective tissue disorders.
- Neoplasia.

Anaemia is also commonly associated with chronic kidney disease.

Pathogenesis

ACD is still not fully understood. Different causes contribute to anaemia in chronic diseases, including diversion of iron, reduced erythropoiesis and reduced response to erythropoietin.

- Interleukin-6 appears to be the central mediator of ACD in a range of inflammatory diseases, including end-stage kidney disease and rheumatoid arthritis. Interleukin-6 is associated with hyposideraemia (low serum iron) and altered iron transport. Cytokines are implicated by reducing erythropoiesis and increasing iron sequestration in the reticuloendothelial system. Interleukin-6 induces the expression of hepcidin, which suppresses the expression of the iron transporter, ferroportin-1, so inhibiting the absorption of iron from the duodenum and the release of iron from the reticuloendothelial system.
- Hepcidin is a peptide hormone produced by the liver and is a key regulator of iron homeostasis.
- Hepcidin binds to the iron export protein, ferroportin, causing ferroportin to be phosphorylated and degraded in lysosomes. Hepcidin inhibits iron release from the reticuloendothelial system. Increased expression of hepcidin also leads to decreased iron absorption and iron-deficient anaemia. The regulation of iron absorption across the epithelium of the proximal small intestine is essential for maintaining body iron concentrations.

The anaemia of chronic kidney disease is thought to be slightly different. See also separate Anaemia in Chronic Kidney Disease article.

Presentation

The presentation may be quite subtle in a patient who already has chronic disease. The presentation may include the new onset or increased tiredness, pallor, breathlessness and tachycardia.

Investigations

ACD typically occurs despite adequate reticuloendothelial iron stores.

- Reduced serum iron, transferrin and total iron-binding capacity.
- Exclusion of a mixed cause for anaemia - B12 and folate levels.
- Measuring serum ferritin is essential in investigating unexplained anaemia:
  - Serum ferritin concentration is directly related to reticuloendothelial iron stores, and normally 1 μg/L serum ferritin roughly corresponds to about 8 mg of storage iron.
  - Normal or raised ferritin is typical in ACD. This is because of the increased storage and retention of iron within the reticuloendothelial system. There are also increased ferritin levels due to immune activation accompanying the chronic disease.
  - In the presence of inflammation, ferritin concentrations may remain normal even when reticuloendothelial iron stores are absent.

- High erythrocyte sedimentation rate (ESR).
- Red cells are often normochromic, normocytic but may be hypochromic, microcytic (as frequently seen in rheumatoid arthritis and Crohn's disease).
- Bone marrow examination for iron is the definitive test for deficiency - very uncomfortable and expensive.
Estimation of soluble transferrin receptor (if available):
- Measurement of soluble transferrin receptor provides a marker of bone marrow iron stores and improves the diagnosis of iron-deficiency anaemia, therefore helping to differentiate between iron-deficiency anaemia and ACD.[6]
- The test is much more expensive than ferritin measurement.

Bone marrow examination for the sole purpose of assessing iron stores is rarely justifiable.[7]

Differential diagnosis
- Other causes of anaemia, particularly iron-deficiency anaemia.
- Any other cause of general deterioration in a patient with chronic disease.

Management
Treatment of the underlying condition should cause the Hb level to rise.

Pharmacological treatment
- The degree of anaemia is often mild and does not require treatment.
- Iron supplements should only be used for patients with established iron deficiency.
- Transfusion of packed red blood cells should be reserved for patients who have severe, symptomatic anaemia. This is a palliative measure only and its use should be weighed against the associated risks with transfusion - eg, volume overload, iron overload and transfusion reaction.
- Novel erythropoiesis-stimulating protein (NESP) - darbepoetin alfa - stimulates erythropoiesis by the same mechanism as recombinant human erythropoietin (rHuEPO) but it is biochemically distinct:
  - It has a threefold greater serum half-life and can maintain Hb levels as effectively as rHuEPO in anaemic patients with chronic kidney disease, with less frequent dosing[8].
- Also, consider erythropoiesis-stimulating agents in rheumatoid arthritis, heart failure and cancer[9, 10].

Prognosis
Usually this will depend on the underlying cause of the anaemia. However, the severity of the anaemia and the speed with which it developed can play a significant role. Similarly, the age of the patient and the existence of other comorbid conditions influence outcome.

Further reading & references
1. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity; World Health Organization, 2011
2. Raj DS; Role of Interleukin-6 in the Anemia of Chronic Disease. Semin Arthritis Rheum. 2008 Mar 11.;
7. Guideline for the laboratory diagnosis of functional iron deficiency; British Committee for Standards in Haematology (May 2013)

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