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AMPATHCHAT

Dr Ingrid Aronson, BSc(Hons), MBChB, MMed(Path)(Haem)

Anaemia of chronic disease/ inflammation

Anaemia of chronic disease (ACD)/inflammation is the leading cause of anaemia in hospitalised patients and the second-most common cause of anaemia after iron deficiency. The main aetiologies are infection, autoimmune disorders and malignancies.

The pathophysiology is multifactorial and complex, involving disordered iron metabolism and distribution secondary to increased hepcidin, which is a peptide hormone produced in the liver and which is the central regulator of iron metabolism. Other factors contributing to anaemia include inappropriate erythropoietin levels or hyporesponsiveness to erythropoietin, suppression of erythropoiesis in the bone marrow and reduced red cell survival.

Iron metabolism

Iron is an essential micronutrient, which is required for haemoglobin synthesis. The total iron content in the body is tightly regulated as excess iron is toxic to the tissues. The body requires >20 grams of iron per day, with the majority being provided through recycling by the degradation of senescent red cells within macrophages of the reticulo-endothelial system. The main storage sites of iron are hepatocytes and macrophages.

Iron is not excreted from the body, and absorption and release from storage sites is strictly regulated by hepcidin.

Disordered iron metabolism is the hallmark of ACD as a consequence of increased hepcidin levels, which are stimulated by cytokines. This leads to a block in release of iron from storage sites into the plasma and thus hypoferremia, resulting in functional iron deficiency and iron-restricted erythropoiesis.

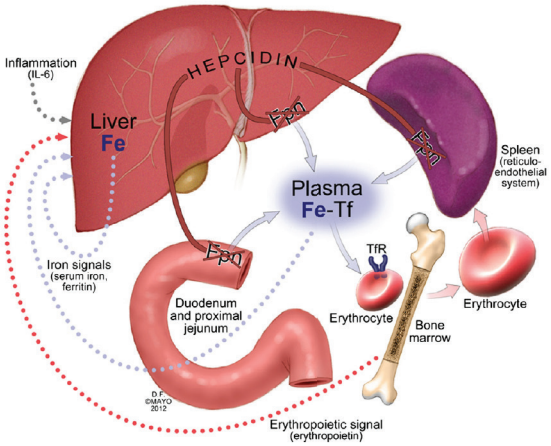

Figure 1: *Regulation of iron metabolism by hepcidin. Abbreviations: Fpn: Ferroportin; Tf: Transferrin; Tfr: Transferrin receptor*

Hepcidin production by the liver is regulated by inflammation via cytokines, iron stores and erythropoiesis. Hepcidin binds to its receptor ferroportin (iron export protein) present on hepatocytes, macrophages and duodenal enterocytes, resulting in the internalisation and degradation of ferroportin. This results in iron not being released into the plasma and being trapped within hepatocytes and macrophages. Thus, there is an increase in iron stores, which is reflected in raised levels of serum ferritin.

ACD is thus characterised by a low serum iron and a raised ferritin. Transferrin is low due to down-regulation of its synthesis as a result of the increased ferritin.

ACD is a mild to moderate anaemia, most often normochromic normocytic and in <25% of cases it is hypochromic and microcytic. The severity of the anaemia correlates with the activity and severity of the underlying chronic disease.

It is often challenging to distinguish between ACD and iron deficiency, especially when the two conditions co-exist; in these cases, measurement of soluble transferrin receptor (sTfr) may be useful – in iron deficiency the sTfr levels are high since iron availability is low, and the levels are normal in ACD.

Hepcidin levels are decreased in iron deficiency, but standardised assays of hepcidin are not yet available.

Laboratory

- Mild to moderate normochromic normocytic anaemia, < 25% hypochromic microcytic
- Iron studies ACD vs Fe deficiency:

	s Fe	Transferrin	% Saturation	Ferritin	STfr*
ACD	low	low	low	high	normal
Fe deficiency	low	high	low	low	high

* STfr = soluble transferrin receptor

Treatment of ACD

Treat the underlying disease where possible.
Red cell transfusions (Hb < 8g/dL).
Iron supplementation (intravenous preferable) in select cases.
Erythropoiesis-stimulating agents (keep Hb <13g/dL).
Novel agents – hepcidin antagonists – in development.

References

Gangat N, Wolanskyj, AP. 2013. Anaemia of chronic disease. *Seminars in Haematology* 50 (3): 232–238

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