

Update on Microcytic Anaemias

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Microcytic hypochromic anaemia can result from a defect in globin genes (ie, haemoglobinopathies or thalassaemias), a defect in heme synthesis, a defect in iron availability, or in iron acquisition by the erythroid precursors. Although diagnosing a microcytic anaemia is relatively straightforward, identifying the aetiology may be problematic. It is helpful to categorize microcytic anaemias as either inherited or acquired.

Inherited Microcytic Anaemia

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Inherited microcytic anaemias can be sideroblastic or not, a trait that reflects the implications of different gene abnormalities. Sideroblastic anaemias are characterized by the presence of bone marrow sideroblasts, but this condition is genetically heterogenous, and four different genes related to heme synthesis could cause this condition. Several clinical and laboratory parameters are useful for differentiating between inherited forms due to defects in heme synthesis and defects in iron metabolism. Here, we will review the new available information on regulation of the iron acquisition pathway by developing erythrocytes, and consider only new forms of inherited microcytosis due to iron metabolism defects. (Microcytic anaemias due to defects in heme synthesis and globin synthesis are the topic of other courses within the *Iron Curriculum*.)

Two new forms of these anaemias are recently described. The first is deficiency of divalent metal transporter 1 (DMT1). DMT1 deficiency is characterized by the presence of high serum iron and transferrin saturation levels in association with hypochromic microcytic anaemia, a noncongruence suggestive of an iron metabolism defect. Iron overload is present and hepcidin levels are low. Furthermore, this form is partially responsive to erythropoietin treatment.

Very similar to this type of inherited microcytic anaemia is iron-refractory iron-deficient anaemia, or IRIDA. It was first described soon after DMT1 deficiency, first in a mouse model

and soon after in several human patients, and is a more frequent form in comparison. To date, 19 patients (in six papers) are described in literature. The associated anaemia is not as severe compared with DMT1 deficiency. Therefore, the clinical appearance—followed by diagnosis—may develop during infancy, in childhood, or later. Mean corpuscular volume (MCV) is less in IRIDA compared with DMT1 deficiency, although compared with thalassaemia, MCV in IRIDA may be greater. Transferrin saturation is typically reduced. Almost all patients with IRIDA are nonresponsive to oral iron supplementation. In contrast, intravenous iron results in an increase in serum ferritin levels and an almost complete correction of anaemia. The response is usually sustained for several months.

Acquired Microcytic Anaemia

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Iron deficiency anaemia (IDA) is the most common form of microcytic anaemia. In the great majority of cases, IDA is secondary to blood loss, limited iron supply by nutrition, and increased iron requirements. Recently, IDA secondary to iron malabsorption has been described. Here we will focus on acquired IDA in patients with negative gastrointestinal workup. These cases are also known as acquired unexplained IDA.

Hershko et al prospectively studied 300 patients referred for nongastrointestinal bleeding IDA. Excluding gynaecologic (menorrhagia) and gastrointestinal lesions, three main categories were identified: autoimmune atrophic gastritis, *Helicobacter pylori* infection, and celiac disease. Of the 300 patients, 26% were identified with autoimmune atrophic gastritis, 19% with *H. pylori* (as the only diagnosis), and 6% with celiac disease. Furthermore, *H. pylori* infection was a coexisting finding in 51% of patients with autoimmune atrophic gastritis and in 69/300 patients with menorrhagia, gastrointestinal lesions, and celiac disease. Mechanisms of IDA genesis in *H. pylori* infection are multiple, and include occult GI bleeding, alterations in intragastric pH and ascorbic acid concentration, induction of interleukin-1 β and tumor necrosis factor- α (inhibitors of parietal cell function), and induction of parietal cell apoptosis. The possible role of *H. pylori* in the pathogenesis of autoimmune gastritis is suggested by the demonstration of *H. pylori* antibodies directed against gastric parietal cells.

Many of these patients do not respond to oral iron treatment, and this is the main clinical argument for the diagnostic workup of these conditions: anti-tissue transglutaminase (tTG)

antibodies and anti-endomysial (EM) antibodies for celiac disease; IgG antibody screening and urease breath test for *H. pylori* infection; and serum gastrin and parietal cell antibodies for autoimmune atrophic gastritis. In many cases, *H. pylori* eradication will cure the anaemia even without the addition of iron therapy. Intravenous iron therapy is indicated in autoimmune atrophic gastritis.

Suggested Readings

Inherited Microcytic Anaemia

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Acquired Microcytic Anaemia

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