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Investigation of iron deficiency anaemia

Authors: Sonia Bouri[A] and John Martin[B]

ABSTRACT

Iron deficiency anaemia (IDA) is an important, common clinical condition and 8–15% of these patients will be diagnosed with a gastrointestinal cancer. IDA is defined as haemoglobin below the lower limit of normal, in the presence of characteristic iron studies. This article will discuss the causes and clinical diagnosis of iron deficiency, including interpretation of common laboratory tests that differentiate this from other causes of anaemia. We suggest an initial approach for investigating the cause of iron deficiency in these patients and also consider the subsequent treatment and indications for further investigation.

Introduction

Anaemia is a haemoglobin (Hb) below the lower limit of normal, as defined by the laboratory performing the test.[1] Iron deficiency anaemia (IDA) is anaemia in the presence of iron studies that show iron deficiency and occurs in 2–5% of men and postmenopausal women.[1] It is important to clarify the cause of anaemia, as patients with IDA deserve urgent investigation, since 8–15% of these patients will be diagnosed with a gastrointestinal cancer.[1,2] If there is no iron deficiency, investigative efforts can be directed elsewhere. This article outlines the assessment, investigation and treatment of IDA.

Confirming iron deficiency

Where there is a suspicion of IDA, this can be confirmed as follows.

Ferritin

Ferritin is the best indicator of iron deficiency and a low ferritin alone is diagnostic of IDA. Iron is stored intracellularly as ferritin and in the presence of infection, malignancy or chronic inflammation, the ferritin rises as it is an acute phase protein. Therefore, the diagnosis of IDA is challenging when there is coexisting inflammation, as the ferritin can be up to 100 µg/L (normal range 20–200 µg/L in our institution), even in the presence of iron deficiency. In this case, further tests can help clarify the diagnosis.

Iron studies

Iron studies include serum iron level, transferrin saturations and total iron-binding capacity (TIBC) or transferrin concentration, in addition to ferritin. In the bloodstream, serum iron is carried bound to transferrin. The TIBC (expressed in µg/dL or µmol/dL) is the maximum amount of iron that can be bound by transferrin if this were 100% saturated. The transferrin saturation is the amount of iron that is bound to transferrin, expressed as a percentage of the TIBC. In IDA, the ferritin, serum iron and transferrin saturations are low, but the TIBC increases. The serum transferrin concentration (expressed in mg/dL) increases in IDA, as the body tries to compensate for low iron levels and this correlates positively with the TIBC. In contrast, in anaemia of chronic disease (ACD) the ferritin is raised, owing to an increase in the iron regulator hepcidin. The role of the peptide, hepcidin, in ACD became evident after key studies in 2000 and onwards. Mice studies have shown that deletion of the hepcidin gene results in iron overload[3] and, conversely, overexpression of this gene resulted in anaemia.[4] Studies have shown that hepcidin expression is upregulated when there is infection or inflammation, via inflammatory cytokines such as IL-6.[5] Hepcidin binds to ferroportin (the iron exporter on cells) which results in internalisation and degradation of this transporter, which reduces iron release from cells.[6] This failure of release of iron from the ferritin stores results in a low iron, low transferrin saturation and low TIBC, with a high ferritin (Table 1).

Key points

Any haemoglobin, in the presence of a ferritin below the lower limit of normal, or below 100 µg/L in the presence of infection/inflammation, should be investigated as IDA

All patients with IDA should have a coeliac screen and a urinalysis, regardless of age or gender

Gastroscopy/colonoscopy should be performed within 2 weeks in those over 60 with a new IDA. Patients under 60 years of age can be offered a gastroscopy/colonoscopy

Premenopausal women should undergo a gastroscopy only if they have upper GI symptoms and a colonoscopy only if they have lower GI symptoms or a family history of colorectal cancer

After the relevant investigations, patients with IDA should receive iron replacement. Then their Hb and ferritin should be checked regularly and if the Hb is either not restored or maintained, further investigations should be considered

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Authors: [A]gastroenterology registrar, Imperial College London, London, UK; [B]consultant gastroenterologist, Imperial College London, London, UK

Table 1. Iron studies patterns in IDA, anaemia of chronic disease and inflammatory conditions

	Iron deficiency	Anaemia of chronic disease	Iron deficiency and inflammation
Ferritin	Low	Normal or high	Normal (up to 100 µg/L)
TIBC/ transferrin	High	Low	Low or normal
Transferrin saturation	Low	Low	Low
Iron	Low	Low	Low

IDA = iron deficiency anaemia; TIBC = total iron-binding capacity

If IDA and ACD coexist, a ferritin of greater than 100 µg/L can reliably rule out iron deficiency.[2]

Mean cell volume and mean cell haemoglobin

The mean cell volume (MCV) and mean cell haemoglobin (MCH) are quite sensitive for IDA in the absence of B12 deficiency or folate deficiency. However, they may also be reduced in ACD, haemoglobinopathies and sideroblastic anaemia. The MCH may be more reliable than the MCV as it is less influenced by storage and the counting machine.[1] In patients of certain ethnic origins, or with an MCV disproportionately low for the Hb, Hb electrophoresis should be performed to exclude a haemoglobinopathy. If iron deficiency coexists with B12 or folate deficiency, the MCV can be high, normal or low.

Red cell distribution width

The red cell distribution width (RDW) is a measure of the variation in the diameter of the red cells. The normal diameter of a red cell is 6–8 µm. A high RDW occurs in conditions such as IDA, B12 deficiency and folate deficiency. The RDW would be expected to be normal in ACD and haemoglobinopathies.

Measurement of soluble transferrin receptor

Measurement of soluble transferrin receptor is more reliable at identifying IDA than TIBC and iron, but it is not widely available.

Causes of iron deficiency anaemia

IDA can be caused by blood loss (gastrointestinal [GI] or other), or reduced absorption of iron. The commonest cause of IDA in menstruating women is menstrual blood loss. The commonest cause in men and non-menstruating women is GI blood loss. In a study of 100 patients with IDA, no cause could be found in 14 patients and inadequate dietary intake was felt to be the cause in five patients.[7] Other causes of IDA include malabsorption, and non-GI causes such as haematuria and epistaxis.[1]

Assessment/investigations of iron deficiency anaemia

History

In patients with IDA, particular note should be taken in the history to:

- previous or recent blood donation
- previous history of IDA
- adequate dietary intake
- overt blood loss
- family history of iron deficiency anaemia
- family history of haemoglobinopathies.

In addition, a meticulous drug history should be checked for non-steroidal anti-inflammatory drug (NSAIDs) or aspirin use that have ulcerogenic actions on the GI tract and also for anticoagulant use, which can provoke lesions, for example, ulcers or angiodyplasia lesions, to bleed.

Examination

The examination in cases of IDA is often unhelpful, but particular care should be taken to exclude:

- abdominal masses
- cutaneous signs of Peutz Jeghers
- cutaneous signs of hereditary haemorrhagic telangiectasia.

Investigations

Any level of Hb in the presence of iron deficiency should be investigated.[1] Every patient with IDA patient should have a coeliac screen (prevalence is 0.5–1%) and urinalysis to exclude haematuria, as 1% of IDA is due to a renal tract malignancy. One-third of patients with renal cell carcinoma have IDA.[8] A positive coeliac screen should be confirmed with duodenal biopsies. If coeliac disease is confirmed and the patient is under 50 years old, colonoscopic examination can be deferred.[1]

Table 2 summarises the recommendations for endoscopic investigations for IDA in patients. All men and postmenopausal women should undergo bidirectional endoscopies. If they are over 60 years old, this should be via a two-week wait (2WW) pathway,[10] as 8–15% of patients will be diagnosed with a GI tract cancer.[2] In men and postmenopausal women under the age of 60, the urgency of investigation can be determined after consideration of patient's age and duration and degree of anaemia.[1]

The prevalence of IDA in menstruating women due to menstrual blood loss is high; therefore, a gastroscopy is only indicated in this group if symptoms of upper GI disease are present. A colonoscopy

Table 2. Recommended further investigations in patients with IDA

Category	Investigation	Urgency
Men and postmenopausal women	OGD and colonoscopy	2WW if over 60 years old[b] Urgency determined by symptoms if less than 60 years old
Premenopausal women	Colonoscopy[a] if lower GI symptoms or family history OGD if upper GI symptoms	Urgency depends on symptoms – refer to NICE guidelines (NG12)[b]

[a]BSG guidelines: Goddard *et al*, 2011[1]
[b]National Institute of Health and Care Excellence, clinical guidance NG12[10]
BSG = British Society of Gastroenterology; GI = gastrointestinal; OGD = oesophagogastroduodenoscopy; NICE = National Institute for Health and Care Excellence; 2WW = two-week wait

is indicated in this group only if there are symptoms of lower GI disease or a strong family history of colon cancer.[1] The presence of associated red-flag symptoms, such as dysphagia or rectal bleeding at any age, should trigger endoscopies via a 2WW pathway.

The use of faecal occult blood testing (FOBt) in the investigation of IDA is recommended by the National Institute for Health and Care Excellence (NICE) as an alternative to endoscopic investigation in patients less than 60 years of age. However, in the view of the authors this approach is inappropriate because the low sensitivity of FOBt makes it inadequate for this purpose and significant pathology will be missed. A meta-analysis of 13 studies looking at the sensitivity of the FOBt in the detection of colorectal cancer (CRC), compared to colonoscopy showed that the sensitivity was 71.2% in the proximal colon and 80.1% in the distal colon.[11] Faecal immunochemical testing (FIT), an alternative stool test that detects the presence of human globin, has a significantly higher sensitivity and specificity for the detection of colonic neoplasia[12] and may be appropriate as an alternative to FOBt. Currently, however, there is insufficient evidence to recommend its use in symptomatic patients and it should be confined to the screening population.

Dual pathology can be found in 1–10% of patients,[1] so it is important that both investigations are performed, even if the first examination finds a cause for the iron deficiency.

Endoscopic investigations should only be performed if the benefit of the procedure outweighs the risk. If a patient has significant comorbidities, endoscopic procedures may be too risky and may not alter patient management, and so these examinations should not be performed.

Positive findings on a colonoscopy, which can account for IDA include: malignancy, polyps, angiodysplasia or inflammatory bowel disease (IBD).[2] Colonoscopy is preferable to a computed tomography virtual colonoscopy (CTVC) to investigate IDA as it can detect superficial lesions such as angiodysplasia. In some patients in whom a colonoscopy is contraindicated, however, a CTVC is a reasonable alternative, as the sensitivity for identifying lesions larger than 10 mm is over 90%.[9]

Positive findings on a gastroscopy, which can account for IDA include: ulcers, angiodysplasia and cancer macroscopically, and coeliac disease or atrophic gastritis microscopically.[2]

Small bowel investigation with a CT enterography, small bowel magnetic resonance imaging (MRI) or capsule endoscopy should be considered after negative bidirectional endoscopies if there are symptoms suggestive small bowel disease (eg Crohn's disease), such as abdominal pain, weight loss, or raised inflammatory markers.

Treatment of iron deficiency anaemia

Once investigations have been performed, underlying causes should be treated. If no cause is identified then an iron replacement strategy is appropriate.[1] Iron replacement (eg ferrous sulphate or ferrous fumarate once or a twice a day) is continued until the Hb normalises, which may takes up to 6–12 weeks depending on the degree of anaemia.[2] Subsequently a further 3 months of oral iron should be taken to replenish the stores. The Hb should then be checked every 3 months for a year, then after a further year. If the Hb is not restored or if it falls within 1 year of replenishing the stores, persistent obscure bleeding is present and should be investigated. This strategy has been shown to be safe, provided that dietary deficiency is replaced, NSAIDs have been stopped and the Hb is being reliably monitored[13] because small bowel tumours are rare, comprising only 3.5% of small bowel pathology in this setting. If oral iron is not tolerated, or not absorbed due to intestinal inflammation, then intravenous iron should be given.

Investigations for persistent obscure bleeding

If there is persistent obscure bleeding as evidenced by a failure to restore or maintain the Hb with iron supplement treatment, as described above, a small bowel capsule endoscopy should be considered to identify small bowel pathology such as Crohn's disease, angiodysplasia or neoplasia.[14,15] If this is normal, or the Hb continues to fall without an explanation, non-GI cancer should also be sought. ■

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Address for correspondence: Dr John P Martin, Imperial College London, London SW7 2AZ, UK.
Email: johnp.martin@imperial.nhs.uk