Cases in primary care laboratory medicine

Investigating iron status in microcytic anaemia

Michael J Galloway, W Stuart A Smellie

Microcytic anaemia is often assumed to indicate iron deficiency, but up to 20-30% of patients will have another diagnosis, particularly anaemia of chronic inflammation or myelodysplasia. Measurement of serum ferritin offers the best means of confirming iron deficiency, although in some cases a trial of iron may be required.

The investigation of possible iron deficiency has changed in recent years. Traditionally, measurements of iron and iron binding capacity were performed by laboratories, but serum ferritin has now become established as a more reliable test for iron deficiency, although results in both situations can be influenced by the presence of acute or chronic inflammation.

In populations in which the prevalence of haemoglobinopathy genes is low, the finding of a microcytic anaemia is considered by some to be sufficient to indicate iron deficiency anaemia. However, this can lead to an erroneous diagnosis, as shown in the cases below.

Case 1

A 69 year old man was referred for investigation of iron deficiency anaemia. History revealed that he had been feeling generally tired for two months and had lost 6 kg in weight. His haemoglobin concentration had not increased despite taking ferrous sulphate 200 mg thrice daily for eight weeks. Full blood count taken in primary care had shown haemoglobin 95 g/l, mean cell volume 73 fl, white cell count 7.5×10^9/l, and platelets 480×10^9/l. Subsequent investigations in secondary care also showed an erythrocyte sedimentation rate of 80 mm in first hour and a ferritin concentration of 577 µg/l, and these high values indicated that the diagnosis was anaemia of chronic inflammation (chronic disease). Subsequent computed tomography revealed the presence of a renal carcinoma in the left kidney, and the patient was therefore referred for surgical removal of the tumour.

Case 2

A 75 year old woman had been investigated for what was thought to be iron deficiency due to chronic gastrointestinal blood loss. Her blood count had shown haemoglobin 85 g/l, white cell count 6.5×10^9/l, platelets 597×10^9/l, and mean cell volume 70 fl. Further investigations, including gastroscopy and colonoscopy, did not indicate any source of blood loss, and the patient was referred for haematological assessment after failing to respond to ferrous sulphate for six weeks.

Summary points

- Microcytic anaemia alone is not sufficient to diagnose iron deficiency, especially in elderly patients (≥ 20% of elderly patients with a mean cell volume < 75 fl will not be iron deficient)
- Measurement of serum ferritin is superior to measurement of serum iron and iron binding capacity (in practice serum ferritin < 15 µg/l effectively confirms iron deficiency and > 100 µg/l excludes it)
- A trial of iron therapy should be considered in patients with serum ferritin ≤ 40 µg/l (or ≤ 70 µg/l in the presence of chronic inflammation)
- The source of the iron deficiency requires investigation

Subsequent examination of the blood film indicated that the diagnosis was probably a myelodysplastic syndrome. Bone marrow examination confirmed the diagnosis of sideroblastic anaemia. A subsequent measurement of her ferritin concentration showed this to be 1900 µg/l.

Discussion

Both of these cases show the limitation of using only a full blood count as the basis for diagnosing iron deficiency. Studies have shown that 36% of patients older than 65 years who are anaemic are iron deficient.[1] The differential diagnosis in these patients consists of several disorders, including anaemia of chronic inflammation, myelodysplastic syndrome, and other underlying bone marrow malignancies that are not usually seen in younger patients. Elderly patients therefore require a ferritin assay in order to establish with sufficient certainty whether iron deficiency is present. Mean cell volume may help to further discriminate

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City Hospitals Sunderland NHS Foundation Trust, Sunderland Royal Hospital, Sunderland SR4 7TP
Michael J Galloway *haematologist*
Clinical Laboratory, General Hospital, Bishop Auckland DL14 6AD
W Stuart A Smellie *chemical pathologist*
Correspondence to: M J Galloway mike.galloway@chs.northy.nhs.uk

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patients with iron deficiency from those with other disorders, particularly anaemia of chronic inflammation. However, only 56% of elderly patients with a mean cell volume <85 fl will have iron deficiency (rising to about 70-80% with a mean cell volume <75 fl).[1 2] Most of the remaining patients (that is, those with a low mean cell volume who are not iron deficient) will probably have anaemia of chronic inflammation.[3]

For other groups of patients the pretest probability of iron deficiency may be sufficiently high that a ferritin assay is not required—for example, the pretest probability of iron deficiency is 80% in women with heavy menses and a microcytic anaemia.[4]

The ferritin assay provides a simple method of discriminating between iron deficiency and anaemia of chronic inflammation in most cases. A pragmatic approach to interpreting ferritin concentrations is that serum ferritin of <15 µg/l in adults (12 µg/l in children) confirms the diagnosis of iron deficiency anaemia,[5] whereas levels >100 µg/l rule it out. Patients with a low mean cell volume are most likely to have either anaemia of chronic inflammation or a myelodysplastic syndrome. However, the probability of iron deficiency remains high until the serum ferritin concentration is >40 µg/l for the general population or >70 µg/l for those with chronic inflammation or liver disease.[1] Therefore iron therapy should be offered to patients with anaemia when their ferritin concentration is <15 µg/l and should be considered for those with a concentration of 15-40 µg/l. Iron therapy should also be considered for patients with a coexisting chronic inflammatory process if their ferritin concentration is <70 µg/l. Response to iron therapy should be assessed by checking haemoglobin level after two to four weeks, with a further check at two to four months to ensure that haemoglobin concentration has returned to normal.[5 6] A 10-20 g/l rise in haemoglobin after two to four weeks confirms iron deficiency.[5]

In the two cases discussed a ferritin assay would have prevented unnecessary delay in the diagnosis in the first case and also unnecessary investigations in the second case. However, for those patients in whom the diagnosis is still in doubt despite a ferritin assay a response to iron replacement therapy is a definite confirmation of deficiency.

Once diagnosed, the cause of the deficiency requires investigation.[7]

Guidance for investigating iron deficiency

In which patients with anaemia should iron deficiency be assessed and what tests should be used?

- In anaemic patients the probability of iron deficiency increases with decreasing mean cell volume, but no specific cut-off value can be used
- Even in patients with a mean cell volume <75 fl, up to 20-30% will not have iron deficiency
- In patients with anaemia and a mean cell volume >95 fl, there is a low probability of iron deficiency being present. Other causes should be investigated initially
- Measurement of serum ferritin concentration is superior to measuring iron and iron binding capacity or transferrin saturation

Guidance for monitoring iron deficient patients receiving replacement iron

How should iron deficiency be monitored in patients who have received replacement treatment?

- Remeasurement of ferritin concentration is not necessary
- Assess recovery from iron deficiency anaemia by measuring haemoglobin concentrations:
  - After 3 weeks, to confirm response
  - After 9 weeks to confirm recovery once the source of iron deficiency has been identified and corrected

Questions and answers: learning points

The questions and answers shown in the boxes summarise the guidance for assessing iron deficiency and monitoring patients receiving iron replacement that may be found in the third review of best practice in primary care pathology published in the *Journal of Clinical Pathology*.[6]

What are the sources of evidence?

This guidance has been drawn from consensus guidelines, a systematic review, and observational studies. The observational studies show that a substantial number of elderly patients with microcytic anaemia do not have iron deficiency, and the guidance not to rely on microcytosis alone as an indicator of iron deficiency seems sound, at least in older patients.

One recent trial of enhanced feedback in primary care used a recommendation that confirmation of ferritin concentration was unnecessary if microcytic anaemia was present, although the evidence for the guidance was not shown.[8] Pretest probability of iron deficiency will vary between patient groups, and in older patients the increased probability of coexistent disease being present would argue in favour of confirming ferritin status. Further observational studies may clarify in which patient groups confirmation of iron status is unnecessary, but the guidance to check ferritin would seem justified in elderly patients and in populations with a high prevalence of haemoglobinopathy, particularly thalassaemia genes.

The systematic review by Guyatt et al in 1992 confirmed that serum ferritin is a superior measure of iron

Useful websites

- Lab Tests Online (UK) (www.labtestsonline.org)—a comprehensive guide to laboratory tests and their use for patients
- Cochrane Library (www.nelh.nhs.uk/cochrane.asp)—information and systematic reviews on evidence based medicine. The Cochrane Collaboration is beginning reviews on laboratory diagnostic testing
- *Journal of Clinical Pathology* (www.jclinpath.com)—subscription website containing electronic access to the *Journal of Clinical Pathology*, with full content of the questions and answers examined in this article
- *Clinical Evidence* (www.clinicalevidence.com)—summaries of current evidence based management guidelines
- PRODIGY (www.prodigy.nhs.uk)—clinical decision making guidelines principally for general practitioners

deficiency than serum iron and iron binding capacity, which show considerable overlap between healthy and iron deficient populations.[2] The review included 55 studies in which laboratory results and histological bone marrow findings were available for at least 50% of identifiable patient groups. Serum ferritin was by far the most powerful diagnostic test (area under receiver operating characteristic (ROC) curve, 0.95); however, as can be predicted from the physiology and biochemistry of the acute phase response in inflammation (which influences serum iron, transferrin, and ferritin concentrations), the test properties were different in patients with inflammatory, liver, or neoplastic disease compared with other patients. This accounts for the different diagnostic thresholds incorporated in the guidance for patients with these diseases, and the role of a therapeutic trial of iron in borderline situations (deficiency being confirmed by a rise in serum haemoglobin in response to iron). The British Columbia guidelines include adding assays of serum iron and iron binding capacity if serum ferritin is not diagnostic in a patient with chronic inflammation.[5] It is not clear from published work whether this addition is superior to the pragmatic policy of a therapeutic iron challenge. An alternative approach is to undertake a bone marrow biopsy to assess iron stores. However, this is rarely necessary providing a blood film has been examined to exclude a myelodysplastic syndrome.

Finally, there seems to be no reason to question the guidance on establishing the cause of the iron deficiency, and, in view of the possibility of malignancy as the underlying cause, it would not be appropriate to subject this to a trial in patients. Extensive investigation could reasonably be considered unnecessary in patients at low risk of malignancy when the doctor is confident of the clinical diagnosis—such as hypermenorrhea in a young woman with heavy menses.

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Anaesthesia, Elvis, and lawnmowers

I was interested to see my specialty in the daily "listed" feature in the *Guardian* newspaper, which, on 13 September 2006, nominated the following "specialist museums": Anaesthetic Museum, Barts and The London NHS Trust; Business Card Museum, Pennsylvania, USA; Decoy Duck Museum, Maryland, USA; Dog Collar Museum, Leeds Castle; "Elvis is alive" Museum, Missouri, USA; Hair Museum, Missouri, USA; British Lawnmower Museum, Southport; Museum of Questionable Medical Devices, Minnesota, USA; Mushroom Museum, Saumur, France; Pencil Museum, Cumbria; Potato Museum, Brussels; Quilt Museum, Massachusetts, USA; Sock Museum, Sakata, Japan; Typewriter Museum, West Virginia, USA.

Although I certainly cannot argue with an anaesthetic museum being specialist, I thought it was an interesting association to be listed with the Museum of Questionable Medical Devices (www.mtn.org/quack), which includes a foot operated breast enlarger that sold four million in the 1970s and a chair that shakes violently and is uncomfortable to sit in (from the same sanatorium that invented *Kellogg's Corn Flakes*). The museum at Barts and the London is not, in fact, a museum of anaesthesia but of the history of Barts itself, although I was told that one of the consultants has a private collection. There is, however, a well kept anaesthetic museum at the Association of Anaesthetists of Great Britain and Ireland, 21 Portland Road, London, which is open to the public.

At the risk of belittling the importance of socks and potatoes, I couldn't help getting the impression that the *Guardian*'s list was of things that might be expected to be too trivial to warrant a museum. Should it be unexpected that anaesthesia is grouped together with exhibitions of dog collars and lawnmowers? My university educated father was surprised to find that there is even one monthly journal devoted solely to the practice of anaesthesia. When I stated my commitment to my specialty my grandfather hoped that I was also keeping up my interest in medicine. When my former girlfriend, who had a PhD in biological science, received an anaesthetic she presumed that the induction dose was also the maintenance of anaesthesia, that the anaesthetist had to estimate the amount to cover the whole duration of surgery, and that the anaesthetist's job was pretty much over after that.

I think that, for many people, anaesthesia is as complicated as a cloth soaked in chloroform used to facilitate abduction of the pretty blonde victim in the *A-Team*, who, of course, is never seriously harmed in the process. It is an event that provokes much fear and anticipation beforehand. When it happens, only the instant of losing consciousness is remembered, and afterwards it is as though nothing has happened—so long as the antiemetics and analgesia have worked. It is perhaps counter intuitive to many that this practice should require a medical degree and then years of postgraduate training.

In Zambia when you leave medical school it is impossible to train as an anaesthetist without leaving your country. You can become an obstetrician, but only non-physician medical officers can train to anaesthetise for caesarean sections. Anaesthetic pay is poor—even in the private sector it is just 10% of the modest fee, whereas the surgeon gets 55%. No medical student wants to become an anaesthetist, with the consequence that anaesthesia (and intensive care and pain management) is undervalued. Patients suffer as a consequence, and it is difficult to see an end to this vicious circle.

I'm fortunate that I don't have to worry about appreciation by my colleagues in the same way that the few physician anaesthetists in Zambia do. Consequently, when people ask me what I do at dinner parties, I run the risk of them underestimating the full extent of my education but I never had to think twice about choosing this challenging, enjoyable, and useful specialty.

M Dylan Bould *specialist registrar, Great Ormond Street Hospital, London (dylanbould@yahoo.co.uk)*