COMMENTARY

Iron deficiency anaemia in older people: investigation, management and treatment

Introduction

Anaemia is the commonest haematological abnormality in the older population. It should never be considered as a normal physiological response to ageing [1]. The overall prevalence of anaemia in older people in the UK is 20.1% in elderly men and 13.7% in elderly women [2]. The causes of anaemia are diverse: the anaemia of chronic disease is probably the commonest in old age [3]. However, iron deficiency anaemia is also common and merits investigation and treatment [1]. In one study, almost a quarter of patients admitted to an acute elderly care ward were found to be anaemic with anaemia of chronic disease (35%) and iron deficiency anaemia (15%) being the commonest causes [4].

The World Health Organisation (WHO) criteria for diagnosing anaemia are a haemoglobin (Hb) level of less than 13 g/dl in men and 12 g/dl in women [5]. There is considerable variation regarding this lower cut-off value between studies (Hb < 10–11.5 g/dl for women and Hb < 12.5–13.8 g/dl for men); perhaps the lower limit of the reference range of haemoglobin for the laboratory performing the test should be used to define anaemia [6]. With advancing age there is a progressive and apparently physiological decrement of marrow haematopoiesis [7]. However, in older patients with haemoglobin levels of less than 12 g/dl or a haematocrit below 36% there can be an underlying cause for the anaemia [8]. In one study, anaemia—as defined by the WHO criteria—was associated with an increased mortality in people aged 85 years and older [9].

In the United States, iron deficiency anaemia occurs in up to 4% of elderly patients [10]. Similarly in the UK 3.5–5.3% of older people admitted in the hospital have iron deficiency anaemia [11]. Iron deficiency typically presents with a microcytic anaemia. Microcytosis is not specific for iron deficiency but may be found in chronic inflammation, sideroblastic anaemia and thalassaemia, and may not be present in combined deficiency with vitamin B12 or folate.

Laboratory investigations

The serum ferritin is the best non-invasive test for the diagnosis of iron deficiency in patients of all ages [12]. However, in the older population it should be interpreted judiciously. Serum ferritin level tends to rise with ageing [13]. In one study of healthy 85-year-old individuals, men had a mean serum ferritin level of 130 µg/l, women a value of 98 µg/l and there was no significant difference between the two sexes [14]. Whereas a low serum ferritin level always indicates iron deficiency, a normal or even raised level can be found in patients with iron deficiency and concurrent chronic inflammation, malignancy or liver disease [6]. In adults, a serum ferritin concentration of <12 µg/l is diagnostic of iron deficiency [15, 16]. However, in anaemic patients over 65, the diagnosis of iron deficiency anaemia is highly likely in those with ferritin levels of up to 45 µg/l [17]. One study of elderly patients (men: mean age 79, women: mean age 82) revealed 84% of patients with a serum ferritin of 12–45 µg/l had absent stainable bone marrow iron store. The authors suggested that iron deficient erythropoiesis can occur in elderly patients with a ferritin level of up to 75 µg/l [18]. Iron deficiency is highly unlikely if the serum ferritin concentration is >100 µg/l [6, 12].

Occasionally, other tests may be helpful in more complicated patients. A low serum iron (<10 µmol/l) with increased serum total iron binding capacity (TIBC) (>70 µmol/l) and a low percent saturation of transferrin (<15%) also suggest iron deficiency [1] but may be unreliable as iron and transferrin levels are often decreased in elderly people. Furthermore, serum iron levels often show a diurnal fluctuation [19, 20]. Similarly, estimations of red cell distribution width are not a sensitive or a specific test in screening patients with suspected iron deficiency [21]. Serum transferrin receptor (sTfR) assay is useful for distinguishing iron deficiency anaemia from the anaemia of chronic disease: sTfR concentration is usually elevated in patients with iron deficiency anaemia but remains normal in patients with anaemia of chronic disease [22]. It is expensive and is not yet of proven utility in older people. In one study it was claimed to be beneficial as all elderly patients with iron deficiency anaemia had raised sTfR levels (mean 65.2 ± 17.7 nmol/l) [23]. However this study was of very small scale and did not use an appropriate interpretation of serum ferritin. Bone marrow aspiration and staining for iron (Prussian blue stain) provides a definite diagnosis of iron deficiency anaemia or sideroblastic change. It is considered to be the standard for assessing...
D. Mukhopadhyay, K. Mohanaruban

iron status, but is seldom necessary because of the availability of serum ferritin assay and other non-invasive tests [17].

Causes

In the absence of any history of haemorrhage, iron deficiency anaemia in older people is sometimes related to diet, but is usually a result of occult gastrointestinal bleeding. Common causes include NSAID use, colonic cancer or polyp, gastric cancer, angiodysplasia and inflammatory bowel disease. Rare causes include coeliac disease, previous gastrectomy, intestinal telangiectasia, lymphoma, leiomyoma and other small bowel tumour. Oesophagitis and peptic ulceration may be responsible for chronic gastrointestinal blood loss but they usually cause acute bleeding [6]. In a study of 100 patients with iron deficiency anaemia who had gastrointestinal investigation, 37% had an upper gastrointestinal lesion and 26% had a colonic source for blood loss. Half (51%) of the upper gastrointestinal causes were related to peptic ulcer and 41% of the colonic causes were due to colon cancer [24].

Gastrointestinal investigations

Gastrointestinal evaluation should be contemplated in all patients with iron deficiency anaemia unless there is a history of clinically important non-gastrointestinal blood loss. Usually, an upper gastrointestinal endoscopy is carried out first but in elderly patients colonoscopy is likely to be more helpful in determining a cause [6]. Small bowel biopsies should be taken during upper gastrointestinal endoscopy, even in elderly subjects, to exclude coeliac disease [25]. In a series of 656 patients who had colonoscopy for various reasons, colonoscopy was safe in older patients (mean age 77 years). Older subjects were more likely to have an adenocarcinoma (6% vs 2%) and were more likely to have diverticular disease (31% vs 18%) than their younger counterparts. Benign adenomatous polyps were found in 24% of the elderly patients (and 25% of the younger age group) [26]. Where facilities for colonoscopy are limited, double contrast barium enema is an alternative. Sigmoidoscopy should also be performed in such cases in the event of unreliable history or if there are symptoms of rectal disease [27]. One study of elderly hospital inpatients (mean age 71 years) with iron deficiency anaemia found a high incidence (16%) of dual pathology when both the upper and lower gastrointestinal tracts were examined [28].

A key issue is what level of haemoglobin justifies these investigations. Gastrointestinal lesions can be demonstrated in more than 80% of elderly patients with iron deficiency anaemia and a haemoglobin of <10 g/dl and two-thirds of such patients may have a treatable cause [29]. A recent study has suggested that elderly patients with iron deficiency (serum ferritin level <50 μg/l at two separate occasions) should undergo gastrointestinal investigation, irrespective of the haemoglobin level. In this study, an upper gastrointestinal lesion was found in 49% of the 96 patients who had a serum ferritin level <50 μg/l and a haemoglobin level <13 g/dl (men) or <12 g/dl (women). A colonic lesion was detected in 32% of the patients in this group. In comparison, 56% of the 55 patients who were not anaemic—but who were iron deficient—had an upper gastrointestinal lesion and 16% had colonic pathology. There was no significant difference in the detection rate of colon cancer between the two groups [30]. It is justified to conclude that there is clear evidence to investigate older people with iron deficiency anaemia who have a haemoglobin level <13 g/dl (men) or <12 g/dl (women). Further research is necessary to ascertain risk stratification of important disease according to haemoglobin level and the necessity to investigate patients who have iron deficiency without anaemia [6].

Treatment

Treatment of an underlying cause should prevent further iron loss. However, all patients with iron deficiency anaemia should have iron supplementation both to correct anaemia and replenish body stores [31, 32]. This is a simple and effective treatment and can be achieved by giving oral ferrous iron. Ferrous sulphate 200 mg three times daily is the cheapest option although ferrous gluconate and ferrous fumarate are effective alternatives [33]. Non-compliance with treatment is common and can be easily detected by noting if the stools are black. Prolonged treatment with a once-daily regimen of oral ferrous iron can avoid therapeutic failure resulting from non-compliance [34]. There is a trend for prescribing slow release and compound iron preparations as a first line treatment for iron deficiency anaemia [35]: this should be discouraged [32]. Enteric coated or slow release preparations may fail to produce the desired therapeutic benefit because of their reduced availability at the iron absorption sites in the duodenum and upper jejunum [1, 36].

The reticulocyte count increases 3 to 4 days after the initiation of iron replacement therapy and reaches a peak of 5 to 10% at about 10 days [37]. As recovery from the iron deficiency anaemia continues a normocytic cell population gradually replaces the microcytic erythrocytes. This could be observed from serial red cell size distribution histograms [38]. As a consequence the red cell volume distribution width, which is usually raised (>15%) in iron deficiency anaemia [39], may show a further rise, reflecting active erythropoiesis [40]. The haemoglobin concentration should rise by 2 g/dl after 3–4 weeks [32]. A lack of these responses implies non-compliance, continued blood loss, misdiagnosis or malabsorption [6]. To replenish body iron stores, iron
supplementation should be continued for at least three months after correction of anaemia [32, 33].

Parenteral iron replacement should only be considered when there is intolerance to at least two oral preparations or non-compliance or severe iron mal-absorption [1, 6]. It is available as iron sucrose (iron dextran), which can be given by slow intramuscular injection or by intravenous infusion. Another preparation is iron sorbitol, which is given by deep intramuscular injection and is not suitable for intravenous use [32]. Anaphylactic shock is a potentially serious side effect of parenteral iron and a pre-treatment test dose should be given after consulting the product literature [1, 32].

This form of treatment is expensive and the rise in haemoglobin level is no faster than with oral iron [6]. The total dose of iron sucrose (iron dextran) can be given as a single intravenous infusion. In 40% of patients treated with total dose infusion (TDI) an arthralgia-myalgia syndrome develops as a delayed reaction. Routine intravenous administration of 125 mg of methylprednisolone before and after the TDI reduces its frequency and severity [41].

Treating latent or mild iron deficiency in older people (low serum ferritin with normal haemoglobin level) could potentially be harmful and at present there is no clear evidence for benefit of iron replacement in such patients. Iron is a double-edged sword as iron excess is associated with increased free radical production and the theoretical risks that accompany this. Free radical damage is produced primarily by the hydroxyi radical, most of which is generated in vivo from iron-dependent reduction of H2O2 (Fenton reaction). High body iron stores are associated with an increased cancer risk [42]. Redox-active iron accumulation in plaques and neurofibrillary tangles has been demonstrated in Alzheimer's disease, which could contribute toward the oxidative neuronal damage [43].

Iron is a potential oxidant of low-density lipoprotein (LDL) cholesterol and oxidative modification may increase the atherogenic effects of LDL [44]. One study in middle-aged men concluded that a high stored-iron level (serum ferritin 200 μg/l or above) was a risk factor for myocardial infarction, especially in those with LDL cholesterol levels of 5 mmol/l or above [45]. Another study found an association between raised serum iron and fatal acute myocardial infarction but could not demonstrate any association between the risk of fatal acute myocardial infarction and either dietary iron or iron supplement use [46]. Genetic haemochromatosis is not uncommon in Caucasians and to prevent organ damage these subjects should be protected against actions aimed at increasing the iron intake and bioavailability in the general population [47].

**Appropriateness for red cell transfusion**

The role of erythrocyte transfusion in the management of iron deficiency anaemia in older people is contentious. It is the most expensive and potentially hazardous way to correct iron deficiency [19]. Arguably, the erythrocyte transfusion can be justified in elderly patients if the anaemia is symptomatic and unlikely to respond promptly to treatment of the underlying cause [1]. Iron deficiency produces a chronic anaemia that usually does not require immediate correction by transfusion. Many patients with chronic anaemia are asymptomatic with a haemoglobin concentration > 8 g/dl [48]. The British Society of Gastroenterology guidelines for the management of iron deficiency anaemia have not mentioned erythrocyte transfusion as a treatment option [6]. However, transfusion of red cells is frequently asked for and can be overused in patients with iron deficiency. In a study of 263 hospitalised patients with iron deficiency, 19% were transfused with one or more units of red cells. Transfusion therapy could not be justified in almost a quarter of those patients [31]. Transfusion in patients with iron deficiency having an Hb level greater than 10 g/dl was found to be not a rare event in another study [49].

In chronic anaemias transfusions should only be used when they are unresponsive to oral agents and should be based on the patient’s symptoms [50]. In such cases, criteria for appropriate erythrocyte transfusion may include symptomatic cardiovascular deterioration associated with anaemia (angina pectoris, myocardial infarction, congestive cardiac failure), symptomatic deterioration of functional capacity to NYHA class III/IV attributable specifically to anaemia, a haematocrit of less than 26% or Hb < 9 g/dl associated with a history of cardiovascular disorder, a haematocrit of less than 26% or Hb < 9 g/dl preoperatively, Hb < 9 g/dl before chemotherapy or Hb < 8 g/dl with end stage renal disease [31, 51]. It is more important to establish the cause of the anaemia and treat that accordingly. The British Society for Haematology guidelines for the clinical use of red cell transfusion recommend erythrocyte transfusion in chronic anaemias (such as iron deficiency anaemia) only if the anaemia is life-threatening [48].

If patients with iron deficiency anaemia who are compliant to iron treatment and are without the above-mentioned comorbidity require frequent red cell transfusions, further investigations such as small bowel radiology, small bowel enteroscopy, mesenteric angiography and even laparotomy with whole gut endoscopy and external inspection of the transilluminated gut should be considered [27]. The practice of transfusing patients with chronic anaemias should be regularly audited [52].

**Diptarup Mukhopadhyay, Kanthaya Mohanaruban**

Department of Integrated Medicine, Withybush General Hospital, Fishguard Road, Haverfordwest SA61 2PZ, UK

Fax: (+44) 1437 773328

Email: diptarup@aol.com
References


