Use of plasma ferritin concentration to diagnose iron deficiency in elderly patients

T L Holyoake, D J Stott, P J McKay, A Hendry, J B MacDonald, N P Lucie

Abstract

Aims—To determine a concentration of ferritin below which the possibility of iron deficiency should be considered in elderly patients.

Methods—Consecutive new referrals to a geriatric unit (n = 472) were studied prospectively. Full blood count, ferritin, serum vitamin B12 and red cell folate were measured for all patients. A blood film was assessed independently by three haematologists for features of iron deficiency. For those with ferritin of 12–45 ng/ml, bone marrow aspirates were performed and examined for the presence of stainable iron. When possible, a trial of oral iron was given to those with ferritin of ≤ 45 ng/ml and response was determined by remeasurement of full blood count and ferritin after a minimum of three weeks of treatment.

Results—Bone marrow examination was performed in 32 patients with ferritin of 12–45 ng/ml, of whom 27 (84%) had absent stainable iron, suggesting that most elderly patients with ferritin in this range have iron deficiency. Compared with those with ferritin of 100–299 ng/ml, in whom iron stores were presumed to be normal, patients with ferritin of 12–45 ng/ml had a significantly lower mean haemoglobin and mean red blood cell volume. Furthermore, patients with ferritin up to 75 ng/ml had a significantly higher mean red cell distribution width, and were more likely to have an iron deficient blood film.

Conclusion—Iron deficient erythropoiesis can occur in elderly patients with ferritin up to 75 ng/ml. This is much higher than the lower limit of the “normal” range usually quoted for younger subjects; this difference should be taken into account when ferritin concentrations are interpreted in elderly patients.

(J Clin Pathol 1993;46:857–860)

The diagnosis of iron deficiency from the full blood count is often difficult in elderly patients. Multiple pathology is common in old age, and iron deficiency and the anaemia of chronic disease may both be present. A hypochromic microcytic anaemia in association with characteristic blood film appearances is suggestive of iron deficiency. All of these features, however, can be caused by

malignancy, chronic sepsis, rheumatoid arthritis or renal failure.^{1,2} Furthermore, in early iron deficiency the only abnormality in the full blood count may be a non-specific mild normochromic normocytic anaemia.³ Finally, patients may have latent iron deficiency, with absent bone marrow iron stores, but erythropoiesis remains unaffected and the full blood count is normal.³ Therefore, in elderly patients, iron deficiency of any severity cannot be diagnosed reliably from the full blood count alone.

The “gold standard” for the diagnosis of iron deficiency is confirmation of absence of iron stores in a bone marrow aspirate sample. Bone marrow aspiration, however, is invasive, and time consuming for laboratory staff. Measurement of serum or plasma ferritin is the best single blood test for the diagnosis of iron deficiency, but its interpretation in elderly patients is complicated by a tendency for it to rise with both ageing⁴ and various chronic diseases. Studies of elderly anaemic patients have suggested that the diagnosis of iron deficiency is likely in those with ferritin of ≤ 45 ng/ml, compared with the lower concentration of ≤ 12 ng/ml for young adults.⁵

We have studied further the association between plasma ferritin, the full blood count, and the blood film with iron deficiency in a large cohort of elderly patients referred to a geriatric medical unit. In particular, we aimed to determine a level of plasma ferritin below which the possibility of iron deficiency and iron deficient erythropoiesis should be considered.

Methods

We studied prospectively 472 consecutive new referrals to a geriatric medical unit. They comprised 330 inpatients and 142 outpatients or day hospital attenders. There were 333 women (mean age 82, range 63–101 years) and 139 men (mean age 79, range 62–94 years).

A standard venous blood sample was taken from all patients for full blood count (Coulter S Plus IV), plasma ferritin (immunoradiometric assay, Ciba-Corning), serum vitamin B12, red cell folate (radiosorbent assays, Becton Dickinson) erythrocyte sedimentation rate (ESR, Westergren), serum urea and electrolytes, liver function tests, calcium and phosphate, blood sugar, thyroxine and thyroid stimulating hormone. Other investigations were performed depending on the clinical presentation and the results of the

University
Department of
Haematology,
Western Infirmary,
Glasgow
T L Holyoake
P J McKay
N P Lucie

University
Department of
Geriatric Medicine,
Southern General
Hospital, Glasgow
D J Stott

Department of
Geriatric Medicine,
Gartnavel General
Hospital, Glasgow
A Hendry
J B MacDonald

Correspondence to:
Dr T L Holyoake,
University Department of
Haematology, Western
Infirmary, Glasgow
G11 6NT.

Accepted for publication
5 May 1993

Table 1 Association between plasma ferritin and full blood count indices and blood film in elderly patients

Plasma ferritin (ng/ml)	0-11	12-45	46-74	75-99	100-299	≥ 300
No of patients	26	79	38	35	180	105
Male:female ratio	3:23	21:58	8:30	3:32	56:124	45:60
Known inflammatory disease	3 (12%)	9 (18%)	6 (16%)	2 (6%)	23 (13%)	23 (22%)
Hb (g/l)	91 (24)***	120 (22)***	126 (19)	124 (18)	130 (20)	126 (21)
MCV (g/l)	79 (8.1)***	87.2 (8.2)***	90.3 (7.5)	92.5 (7.1)	92.4 (6.3)	92.2 (6.2)
RDW	16.2 (2.7)***	15.6 (2.6)***	15.9 (3.6)**	14.7 (1.6)	14.2 (1.4)	14.5 (2.0)
Proportion (%) with "iron deficient" blood films	23/26 (88%)***	32/39 (41%)***	10/36 (28%)**	4/35 (11%)	25/178 (14%)	16/105 (15%)
ESR mm/h	44 (28)	41 (27)	38 (30)	51 (43)	44 (34)	57 (39)
ESR ≥ 100 mm/h	2/24 (8%)	3/62 (5%)	2/32 (6%)	5/29 (17%)	12/152 (8%)	13/85 (15%)

***p ≤ 0.001, **p ≤ 0.01 compared with group with ferritin 100-299 ng/ml.

Hb = haemoglobin.

MCV = mean cell volume.

RDW = red cell distribution width.

above blood tests. Patients found to have malignancy (n = 39), inflammatory joint disease (n = 12), other connective tissue diseases (n = 4), or chronic sepsis (n = 14) were coded as having chronic inflammatory disease (n = 67, two patients each had two conditions coded).

A blood film was assessed (without knowing the results of the full blood count and plasma ferritin) independently by three haematologists, and graded as features suggestive of iron deficiency, or no evidence of iron deficiency; in cases of disagreement the film was reviewed by all three and a consensus view obtained for final statistical analysis.

Patients with plasma ferritin of 12-45 ng/ml were considered to have possible iron deficiency, and consent for bone marrow aspiration was requested. Bone marrow aspirate was stained by Perls's Prussian blue method and iron stores were then graded as present or absent.

Where possible, the response to iron was assessed in patients with plasma ferritin of ≤45 ng/ml; iron was given for a minimum of three weeks and full blood count and serum ferritin were then remeasured. A rise in haemoglobin of ≥10 g/l on this single further reading was accepted as a positive response to iron, and those in whom it rose by <10 g/l were designated as non-responders. Patients who received blood transfusion and those who received intramuscular vitamin B12 or oral folic acid were excluded from this analysis.

Statistical analyses were by the Wilcoxon rank sum test, Student's unpaired *t* test (2-tailed), and the χ^2 test. Differences were accepted as significant at the 5% level of probability. Results are expressed as mean (1 standard deviation) except where otherwise stated.

Results

Plasma ferritin and haemoglobin concentrations were significantly higher in men than in women (men: median ferritin 199 ng/ml, mean haemoglobin 132 (24) g/l; women:

median ferritin 117 ng/ml, mean haemoglobin 122 (21) g/l); Wilcoxon rank sum test $p < 0.004$ and $p < 0.001$, respectively).

Bone marrow examination was performed in 32 of 78 patients with ferritin of 12-45 ng/ml; 27 of 32 (84%) had absent stainable iron. Patients with plasma ferritin of ≤45 ng/ml had a significantly lower haemoglobin concentration and mean red blood cell volume (MCV) compared with those with ferritin of 100-299 ng/ml in whom iron stores were presumed to be normal (table 1). Furthermore, patients with plasma ferritin up to 75 ng/ml had a significantly higher red cell distribution width (RDW, an index of red blood cell size heterogeneity), and an increased proportion of individuals with blood films suggestive of iron deficiency (table 1). Exclusion of the 67 patients identified as having chronic inflammatory disease did not affect these results.

A total of 38 of 472 patients had an MCV of <80 fl; in 33 of these the ferritin was ≤75 ng/ml, and in the remaining five the ferritin was ≥100 ng/ml. There was a history of chronic inflammatory disease or an unexplained increase in ESR (≥100 mm/h) in four of five of these patients with an MCV of <80 fl and ferritin of ≥100 ng/ml.

Of 41 patients with serum ferritin of ≥100 ng/ml who had features of iron deficiency on blood film examination, only 15 had known chronic inflammatory disease, and one further patient had an increased ESR of ≥100 mm in the first hour that was unexplained.

In 66 (14%) of patients all three haematologists agreed that the blood film appearances were consistent with iron deficiency, and in 311 (66%) all agreed the film was normal. This left 91 (19%) patients in whom there was disagreement about the presence or absence of iron deficiency on blood film examination.

The haematological response to iron (oral administration n = 48, intramuscular administration n = 2) was assessed in 50 patients with plasma ferritin of ≤45 ng/ml. A median total dose of 5.0 (range 3.8-11.3) g of elemental iron was given over a median time of

Table 2 Baseline haematology in 50 elderly patients with plasma ferritin ≤ 45 ng/ml

	"Responders"	"Non-responders"
No of patients	23	27
Hb (g/l)	102 (19)***	127 (19)
MCV (fl)	80.7 (8.5)***	88.4 (5.7)
RDW	17.0 (2.1)**	14.8 (2.6)
Ferritin (ng/ml)	19.7 (12.7)*	28.1 (11.8)
Number (%) with "iron deficient" blood films	19 (83%)***	7 (26%)

* $p < 0.05$ ** $p < 0.01$ *** $p \leq 0.001$.

Hb = haemoglobin.

MCV = mean cell volume.

RDW = red cell distribution width.

Comparing "responders" (those in whom Hb rose by ≥ 10 g/l after a minimum of 3 weeks of iron treatment) with "non-responders" (those in whom haemoglobin rose by ≥ 10 g/l).

four (range three to nine) weeks. With iron treatment there was a rise in haemoglobin of 11.8 (18.9) g/l from a baseline of 115.8 (22.5) g/l, an increase in MCV of 2.1(5.9) fl (baseline 84.8 (8.1) fl) and plasma ferritin rose by 49 (69) ng/ml (baseline 24 (13) ng/ml). Patients who responded to oral iron with an increase in haemoglobin of ≥ 10 g/l had significantly lower baseline mean MCV and ferritin, higher mean RDW, and were more likely to have a blood film suggestive of iron deficiency, when compared with patients who did not respond (those with an increase in haemoglobin of <10 g/l) (table 2). There was a large overlap between responders and non-responders in most of these variables, but a response to iron was seen in 19 of 26 (73%) of patients with changes suggestive of iron deficiency on their blood films, compared with only four of 24 (17%) of those with normal films.

Discussion

There was good evidence to suggest that a plasma ferritin of ≤ 45 ng/ml usually indicated iron deficiency and was often associated with iron deficient erythropoiesis; 84% of patients with ferritin of 12–45 ng/ml who had a bone marrow examination performed had absent stainable marrow iron stores; a plasma ferritin of ≤ 45 ng/ml was associated with reductions of haemoglobin and MCV, a raised RDW, and an increased prevalence of iron deficient blood films. About half the patients with ferritin of ≤ 45 ng/ml who were treated with iron responded with a rise in haemoglobin of ≥ 10 g/l. The non-responders are likely to be patients with latent iron deficiency or to be only very mildly affected by erythropoiesis, although a few may have failed to respond due to poor absorption of iron or continuing gastrointestinal blood loss.

Although we have further established the validity of a plasma ferritin of ≤ 45 ng/ml as indicating likely iron deficiency, this may not be the most appropriate cutoff point to exclude this diagnosis. Indeed, we found that a plasma ferritin of up to 75 ng/ml was associated with a raised mean RDW and an increased prevalence of iron deficient blood films. A raised RDW is thought to be a more

sensitive measure for early iron deficiency than MCV or mean cell haemoglobin concentration.⁶ Therefore, our results suggest that iron deficiency should be considered in elderly patients with plasma ferritin up to 75 ng/ml. Similar results have been reported from a study of anaemic elderly patients, in which absent bone marrow iron stores were found in 64% and 21% of those with ferritins of 18–45 ng/ml and 46–100 ng/ml, respectively.⁵

An initial MCV of <80 fl was highly likely to be associated with iron deficiency, particularly when those patients with known chronic inflammatory disease or a grossly raised ESR were excluded; in these circumstances measurement of serum ferritin may be unnecessary. Pronounced microcytosis, however, was present in only a minority of those with iron deficiency, limiting the utility of the MCV as a diagnostic aid.

We found that a high percentage (22%) of patients had a serum ferritin of ≥ 300 ng/ml. This is likely to be due to a combination of the effects of ageing and the burden of acute and chronic illness within this population. Ferritin is an acute phase reactant and increases dramatically in acute as well as chronic illness.⁷ Ageing has a separate and additional effect, however, causing a rise in serum or plasma ferritin.⁴

The classic blood film appearances of red blood cell anisocytosis, poikilocytosis (including elongated cells), and hypochromia had poor specificity for iron deficiency when the blood film was interpreted in the absence of other haematological data. About 15% of patients with serum ferritin of ≥ 100 ng/ml had blood film features suggestive of iron deficiency; these findings could be attributed to chronic inflammatory disease in less than half of these patients. Other investigators have reported variability in the reporting of anisocytosis⁸ and red blood cell fragments⁹ on blood films. Furthermore, some features suggestive of iron deficiency can be due to artefacts produced in the preparation and staining of films.¹⁰ It is clear that patients with mild anaemia and blood film features of iron deficiency cannot be assumed to have iron deficiency; measurement of serum ferritin to clarify iron status is indicated in such individuals. The blood film was of some value, however, in determining whether patients with low serum ferritin (≤ 45 ng/ml) would have a haematological response to iron. Patients with a normal blood film were unlikely to respond, while a haematological response to iron occurred in most patients with blood film appearances consistent with iron deficiency.

Accurate diagnosis of iron deficiency anaemia is important as it can be readily treated with iron, and, even more importantly, as it is often caused by chronic gastrointestinal blood loss.¹¹ The pickup rate of treatable gastrointestinal pathology on endoscopy or barium studies is as high as 66% in elderly patients with iron deficiency anaemia and a haemoglobin of <100 g/l.¹²

The value of investigating the gastrointestinal tracts of elderly patients with mild iron deficiency anaemia or latent iron deficiency is unclear.

In conclusion, this study provides evidence that iron deficient erythropoiesis can occur in elderly patients with plasma ferritin up to 75 ng/ml. This is much higher than the lower limit of the "normal" or reference range usually quoted for young subjects; this difference should be taken into account when plasma ferritin concentrations are interpreted in elderly patients.

- 1 Lipschitz DA. The anemia of chronic disease. *J Am Geriatr Soc* 1990;38:1258-64.
- 2 Cash JM, Sears DA. The anemia of chronic disease: spectrum of associated diseases in a series of unselected hospitalized patients. *Am J Med* 1989;87:638-44.

- 3 Schultz BM, Freedman ML. Iron deficiency in the elderly. *Baillieres Clin Haematol* 1987;1:291-313.
- 4 Casale G, Bonora C, Migliavacca A, Zurita IE, de Nicola P. Serum ferritin and ageing. *Age Ageing* 1981;10:119-22.
- 5 Guyatt GH, Patterson C, Ali M, *et al.* Diagnosis of iron-deficiency anemia in the elderly. *Am J Med* 1990;88:205-9.
- 6 McClure S, Custer E, Bessman JD. Improved detection of early iron deficiency in nonanemic subjects. *JAMA* 1985;253:1021-3.
- 7 Witte DL. Can serum ferritin be effectively interpreted in the presence of the acute-phase response? *Clin Chem* 1991;37:484-5.
- 8 Simel DL, DeLong ER, Feussner JR, Weinberg JB, Crawford J. Erythrocyte anisocytosis. Visual inspection of blood films vs automated analysis of red blood cell distribution width. *Arch Intern Med* 1988;148:822-4.
- 9 Bessman JD. Red blood cell fragmentation. Improved detection and identification of causes. *Am J Clin Pathol* 1988;90:268-73.
- 10 Lewis SM. Blood film evaluations as a quality control activity. *Clin Lab Haematol* 1990;12(Suppl 1):119-27.
- 11 Cook JJ, Pavli P, Riley JW, Goulston KJ, Dent OF. Gastrointestinal investigation of iron deficiency anaemia. *Br Med J* 1986;292:1380-2.
- 12 Croker JR, Beynon G. Gastro-intestinal bleeding—a major cause of iron deficiency in the elderly. *Age Ageing* 1981;10:40-3.