Iron deficiency anaemia – an analysis of positive diagnosis and usefulness as a "red flag" for GI cancers

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Abstract

This study shows that we continue to under-investigate patients with iron deficiency anaemia, and adherence to BSG guidelines is low. In particular, coeliac screening and upper GI and lower GI investigations are being under-utilised. Only a small number of patients, around 8% with iron deficiency anaemia turned out to have a GI cancer, although none in the <50 age group. There is a need to improve clinical practice in this field.

Introduction

Iron deficiency anaemia affects around 1% of the population in the UK every year.[1] Data from General Practice suggest that only 43% of patients are investigated within three months and reasons for not investigating include mild or previous anaemia, female gender, and age <65.[2] There is evidence to suggest that a higher rate of definite diagnosis, up to 71% in one study, can be achieved with full investigation.[3] The British Society of Gastroenterology (BSG) produced guidelines for the investigation of iron deficiency anaemia in 2005 and recommended regular audits to assess adherence.[4]

This study was designed to assess our current practice in investigating this condition to arrive at a positive diagnosis and confirm adherence to the BSG guidelines. We also assess the usefulness of iron deficiency anaemia as an alarm sign for gastrointestinal (GI) cancers.

Patients and Methods

All patients with microcytic anaemia on the haematology database in primary and secondary care in the south of Durham and Darlington over 6 months (October 2005 March 2006) were included in this study. The population of south Durham and Darlington is 250,000. Inclusion criteria were: Hb <13 gm/dL in males and <12gm/dL in females, MCV <76fl and having a documented encounter with secondary care services.

The Hb levels selected are according to WHO criteria as suggested in the BSG guidelines. The MCV level was selected as the lower limit of the normal range of the local laboratory.

Exclusion criteria were pregnancy, age <16, routine post-operative and post-natal status, patient who were deceased immediately after haematology result, cases with an obvious non-GI cause at presentation, patients who refused investigation and patients investigated at another hospital. Patients with an obvious non-GI cause were excluded as these patients had extensive investigations as part of their work-up and therefore would not accurately reflect clinical practice.

Patients included in the study were those referred to secondary care by GPs for investigation of anaemia and those admitted for GI bleeding or other complaints who were found to be anaemic. Referrals to all specialties were included as adequate investigation of anaemia should be carried out by everyone, not just gastroenterologists. Patients in primary care

who were not referred to secondary care for investigations of anaemia were not included as they would not have had all the recommended investigations and details of presentation and management were difficult to access.

Data Collection

All hospital case notes were reviewed against standards set by the BSG guidelines (Table 1).

Demographic data were recorded as were the haematological indices and iron studies. Dietary history, use of NSAIDs/aspirin, family history of iron deficiency anaemia, haematological disorders, blood donation, menstrual history and upper and lower GI symptoms were also recorded. The point of data collection was after hospital consultation and not on the basis of the GP referral. Investigations in secondary care were reviewed including anti-

Table 1 – *BSG guidelines used for case note review*

BSG Guideline	Reviewed in case notes
Definition of anaemia	- Gender
- Hb <13 (males), Hb < 12 (females)	- Hb level
- Microcytosis	- MCV
- Low ferritin	- Ferritin, TIBC, serum iron
- Absence of chronic disease or haemoglobinopathies	- Excluded from review
Full history	- Dietary history
	- NSAIDs/Aspirin
	- Family history of iron deficiency anaemia
	- Haematological disorders
	- Blood donation
	- Menstrual history
	- Upper GI symptoms
	- Lower GI symptoms
Clinical examination	- Examination findings
- Rectal examination	- Rectal examination
- Urine testing	- Urine testing
Investigations	
- Coeliac screen	- Anti-endomysial antibody, small bowel biopsy
- Upper and lower GI endoscopy (all males, females >50,/post-menopause/ family history of colorectal carcinoma	- OGD and result, CLO test and result - Colonoscopy and result
- Colonoscopy or barium enema is acceptable	- Barium enema and result
- FOB is of no benefit	- FOB and result
Diagnosis	- Definite diagnosis made

endomysial antibody test as a screening test for celiac disease, upper and lower GI endoscopy, faecal occult blood testing, barium enema and other investigations such as video capsule endoscopy and CT scanning. Results were described as percentages and frequency of GI cancer determined in relation to iron deficiency anaemia.

Results

A total of 144 patients with microcytic anaemia were identified over the six month period. There were 52 males and 92 females, giving a sex distribution of M: F of 1: 1.77. 113 (78%) were aged over 50 years. 74% of females were documented as being post-menopausal state.

Haematology and Iron Studies

3% of patients had Hb <5gm/dL, 17% between 5-7gm/dL, 41% between 7-10gm/dL and 38% had Hb >10gm/dL. 56% of patients had serum ferritin measured, 59% of which were less than 15. Serum iron and TIBC were measured in only 3% of cases. (Fig 1 and 2).

Figure 1

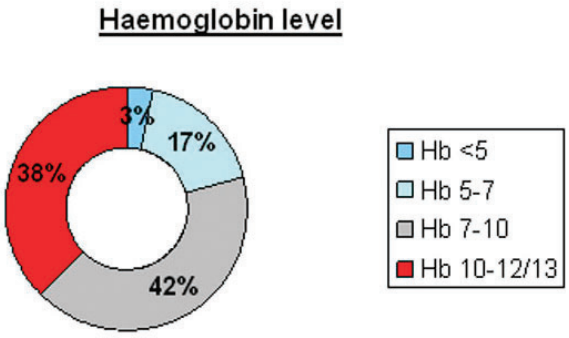
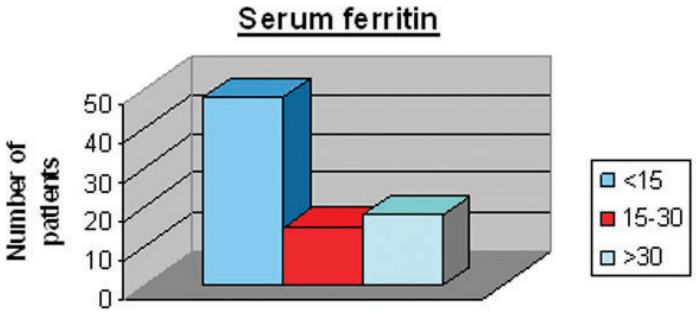


Figure 2



Clinical evaluation

Menstrual history was documented in 89% of female patients, and 12% reported menorrhagia. 24% patients had a history of using NSAIDs or aspirin. Dietary history was documented in only 7% of cases and blood donation not at all. Upper GI symptoms were present in 22% of patients, the most common being melaena (10%), then dyspepsia (6%). Lower GI symptoms were present in 14%, most common being rectal bleeding (9%). Rectal examination was performed in only 20% of patients and urine testing in 7%. On examination, 3 patients had obvious haemorrhoids and 11% had valvular heart disease of varying severity.(Fig 3 and 4).

Investigations in secondary care

Table 2 shows the results of investigations in these patients. Only 33% of patients had upper GI endoscopy, the majority of which were normal (50%), followed by peptic ulcer disease in 19%. Only 22% patients had colonoscopy, the majority of which were again normal (28%), followed by carcinoma and diverticular disease in 25%. 8% patients had a barium enema, the majority being normal (45%), followed by diverticular disease (18%). Only 26 patients (18.1%) had both upper and lower GI endoscopy. 17% of patients had alternative investigations, most commonly CT scan (13% of patients). Three patients had small bowel radiology and 2 patients underwent video capsule endoscopy.

Figure 3

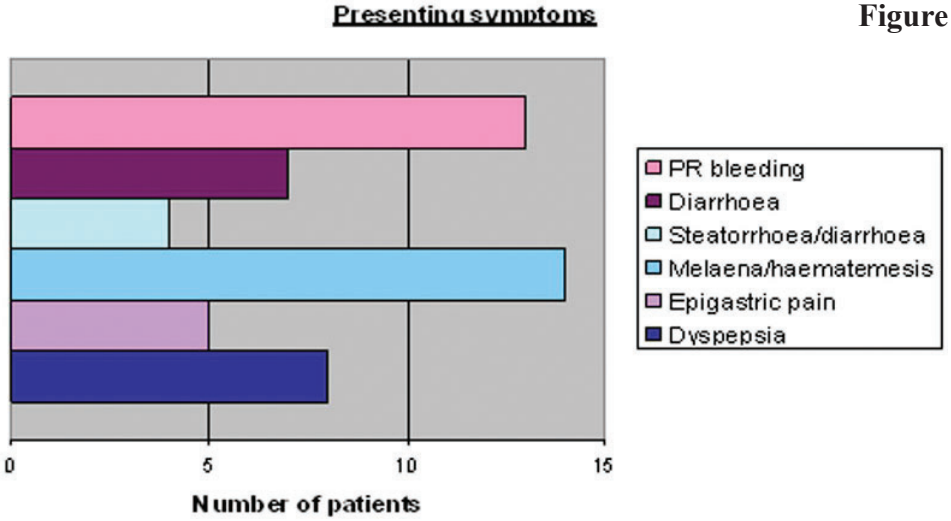


Figure 4

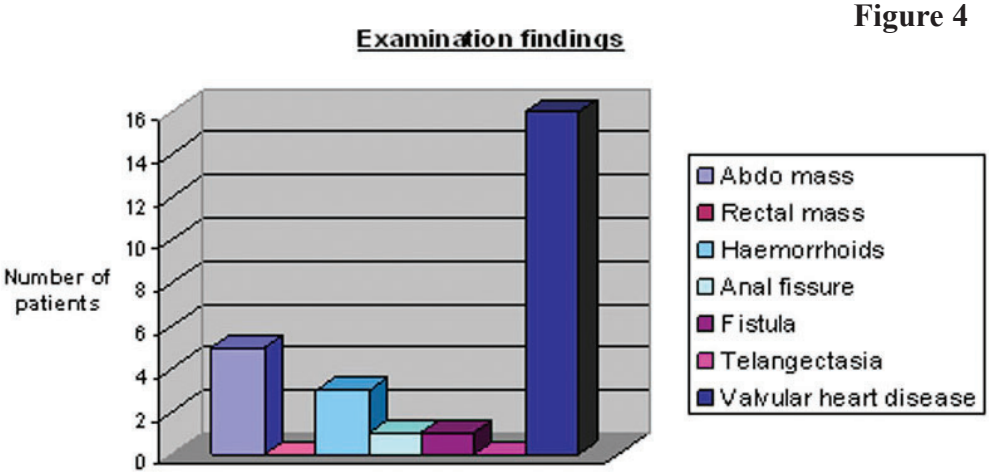


Table 2 – *Results of investigations*

Investigation	**Proportion of patients**
EMA	12%(1 positive, 16 negative)
Small bowel biopsy	2%,(all negative)
OGD	33%(2 gastric Ca, 9 peptic ulcer, 1 small bowel tumour, 4 oesophagitis, 24 normal, 6 Barrett's oesophagus, 4 gastric erosions, 3 gastric polyps, 1 varices, 2 uncertain)
CLO test	15%(1 positive, 21 negative)
FOB	8%(4 negative, 8 positive)
Colonoscopy	22%(9 normal, 8 diverticular disease, 7 carcinoma, 6 polyps, 2 haemorrhoids)
Barium enema	8%(5 normal, 2 diverticular disease, 1 polyps, 3 carcinoma)
Other	17%

Diagnosis

A definite diagnosis of iron deficiency was obtained in only 32% patients. 18 cases of tumour were diagnosed, 7 benign and 11 malignant. All but one patient with cancer was >50years age. Table 3 shows the histology of malignant tumours.

Table 3 – *Histology of malignant tumours*

Malignant tumour	Number of patients
Colon adenocarcinoma	14
Caecal adenocarcinoma	1
Duodenal adenocarcinoma	1
Gastric adenocarcinoma	2

Discussion

This study shows that despite clinical practice guidelines, iron deficiency anaemia continues to be under investigated in south Durham. Since a definite diagnosis of iron deficiency anaemia was reached in only a third of our patients, it is reasonable to assume that the remaining patients were likely to be treated with empirical iron replacement therapy. This may be appropriate in the elderly and frail patients and those with significant co-morbidities but would certainly result in persistent anaemia in the others once iron replacement was stopped. The reasons for under-investigation may be a low referral rate to secondary care for investigations. This has also been reported by others prior to the BSG guidelines with the number of patients being appropriately managed in primary care being as low as 47% in one study.[5] A previous audit carried out at another District General Hospital, also before the introduction of the BSG guidelines, found a positive diagnosis rate of 38%, suggesting practice has not changed even in secondary care in recent years.[6] It had been expected that the implementation of the BSG guidelines would improve this situation, but clearly this has not happened. The most likely reason would be the lack of dissemination of specialist society advice to primary care physicians.

It has been suggested that decision to refer depends on level of Hb, gender and history of previous anaemia.[2] A low rate of investigation in this audit may be partly attributed to the fact that 38% of patients had a haemoglobin level above 10gm/dL and 8% had borderline haemoglobin for diagnosis of anaemia. It has been suggested by NICE to investigate Hb <11 in males and <10 in females, and we suspect that the rates for referral might increase if the NICE guidance were to be followed.[7] The majority of female patients being referred were post-menopausal but for the others, a full menstrual history was not available and that is recommended.

From the secondary care point of view too, there are lessons to be learnt. The audit showed that assessment of patients in hospital clinics is particularly deficient in areas such as dietary history, history of blood donation, menstrual history, rectal examination and urinalysis. These have been well documented as causes for iron deficiency anaemia that may be missed without a thorough assessment. Studies of iron deficiency anaemia in populations with low dietary iron have found increased incidence of anaemia attributable to this cause.[8] Blood donation has been reported as an important cause of iron deficiency anaemia. One blood donation in females and regular donation in males has been suggested to increase the incidence of iron deficiency.[9] Use of NSAIDs is a well documented cause of iron deficiency anaemia, increasing the risk by 6-9 times.[10] In pre-menopausal women, menorrhagia is an important cause, increasing the risk by 3-6 times.[10]

Interestingly, the audit showed that faecal occult blood testing is still being used despite the

lack of evidence for efficacy and its use being discouraged by the BSG guidelines. A celiac screen was only carried out in 12% of patients even though this has been recommended for all patients. This could lead to an under-detection of an easily treatable cause of iron deficiency anaemia. We have previously shown that atypical presentations of celiac disease are now more common than the classical GI presentation and iron deficiency anaemia is an important form of presentation in undetected celiacs (reference Varma V, Bloxham C, Dhar A. Gut 2006, abstract). There was a low rate of investigating GI blood loss by upper and lower GI endoscopy as recommended by the guidelines and there was little documentation in the case notes of the rationale behind the choice of investigation when both were not carried out or lack thereof. The most common alternative investigation was CT scan, which was usually for suspicion of a tumour or when endoscopy was not considered appropriate.

The lack of appropriate investigation is probably not unique to the United Kingdom, and a study from Singapore looking at use of BSG guidelines found that 30% of patients there did not undergo adequate lower GI investigations.[11]

We found that a substantial number of patients with iron deficiency anaemia had tumours of the GI tract, mostly aged >50 years. However, we did not find any tumours in patients under the age of 50, which leads us to believe that the predictive value of iron deficiency anaemia as an alarm symptom for patients under the age of 50 years is low. The exact cut off age for iron deficiency anaemia as a "red flag sign" for GI cancer needs to be established from large scale studies. The fact that most cases were in people over 50 supports the guidelines which recommend investigating all males >50 and post-menopausal females.

Conclusion

This audit clearly shows that the 90% investigation target set by the BSG is not being met in our region. It also highlights that a thorough history and examination in patients with iron deficiency anaemia and complete laboratory investigations including full iron studies are particularly deficient. All male patients >50 and post-menopausal females need to be investigated with a coeliac screen and both upper and lower GI endoscopy. A larger audit of the predictive value of iron deficiency anaemia in the diagnosis of GI cancers needs to be carried out to define whether this is a useful alarm sign in all patients or in those over 50 years. We believe that the key to improving practice is the dissemination of specialist society guidance to primary care together with good clinical governance and re-audit.

There are obvious limitations to the interpretation of the results of this audit. Being retrospective it relies heavily on previous documentation and is therefore unable to ascertain the rationale for not completing various investigations. Inclusion criteria of Hb and MCV were necessary to obtain sufficient numbers of patients with microcytic anaemia but cases of iron deficiency with a lesser degree of microcytosis would have been missed and patients with microcystosis but not iron deficiency will have been included. The only data available to this study was from secondary care case notes, providing a somewhat biased analysis by referral and further work is needed to assess adherence to the guidelines in primary care. Details of how different specialties investigated anaemia was not ascertained, however, all specialties should be aware of the guidelines. This could be focused on during re-audit to assess which specialties need more direction in relation to the guidelines. And finally, it is difficult to assess cancer rates accurately when patients are not being fully investigated.

Contribution: AD conceptualised the audit and contributed to the writing of the paper. HC carried out the data collection, analysis and contributed to the writing of the paper. HC is the guarantor for the data.

This work has also been presented at the United European Gastroenterology Week meeting in Paris, 2007.

Conflicts of interest: HC has no conflicts of interest. AD has received unconditional financial support for clinical research and to attend meetings from a number of pharmaceutical companies. He has also received honoraria for advisory work outside of NHS contractual time.

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