

RAPID COMMUNICATION

## The epidemiology of hyperferritinaemia

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### Abstract

**AIM:** To discover the causes of markedly raised ferritin levels in patients seen at a teaching hospital in Newcastle Upon Tyne, United Kingdom.

**METHODS:** Demographic and medical data were collected for all patients over 18 years who had a serum ferritin levels recorded as  $\geq 1500 \mu\text{g/L}$  during the period January to September 2002. The cause or causes for their hyperferritinaemia were identified from their medical notes. Patients from a defined local population were identified.

**RESULTS:** A total of 19 583 measurements were provided of which 406 from 199 patients were  $\geq 1500 \mu\text{g/L}$ . An annual incidence for the local population was determined to be 0.44/1000. 150/199 medical notes were scrutinised and 81 patients were identified as having a single cause for their raised ferritin level. The most common single cause was alcoholic liver disease in the local population and renal failure was the most common single cause in the overall population. Confirmed hereditary haemochromatosis was the 10<sup>th</sup> most common cause. Liver disease contributed to hyperferritinaemia in 44% of the patients. Weight loss may have contributed to hyperferritinaemia in up to 11%.

**CONCLUSION:** Alcohol related liver disease, haematological disease, renal failure and neoplasia are much more common causes of marked hyperferritinaemia than haemochromatosis. The role of weight loss in hyperferritinaemia may warrant further investigation.

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**Key words:** Ferritin; Epidemiology; Haemochromatosis

### INTRODUCTION

Ferritin is a protein with a molecular mass of 450 kilo Daltons (kD) and is composed of 24 subunits<sup>[1]</sup>. These subunits form a hollow sphere, which can contain up to 4000 atoms of iron stored as ferric oxyhydroxide phosphate; haemosiderin is a condensate of ferritin. Ferritin acts as an intracellular store of iron whilst the protein coat protects the cell from potentially toxic ionised iron. In normal and iron overload states, serum ferritin levels correlate with mobilisable, stored iron. Iron overload may result from disease; e.g. haemochromatosis, administered iron or iatrogenically from recurrent blood.

Raised ferritin levels that are not due to iron overload are seen in many other conditions. Parenchymal liver damage, infection, inflammation (e.g. rheumatoid arthritis) and malignant disease may all be associated with raised serum ferritin. It has also been postulated that weight loss per se may be associated with elevated levels of ferritin<sup>[2]</sup>.

Clinicians may request a serum ferritin test to exclude iron deficiency in an anaemic patient or when considering a condition that is associated with elevated levels of ferritin. However, clinicians may not be aware of all the reasons for markedly elevated levels of ferritin and the relative frequencies of these different causes, and therefore may miss a potentially important diagnosis.

We conducted a study to look at the frequency of various diseases in a patient group with markedly raised ferritin levels who lived within a defined area. The patient group was made up of those seen at a teaching hospital that had various specialist units. We also looked at weight loss as a contributing factor in hyperferritinaemia.

### MATERIALS AND METHODS

#### Patients

The Newcastle Hospital's NHS Trust serves a local population of around 270 000 and is a tertiary referral centre for up to 4 million people. Among other services it provides the regional renal transplant, liver and haematology service.

All patients aged over 18 years who had serum ferritin

Table 1 Conditions associated with raised ferritin and diagnostic criteria used

Condition	Requirements for diagnosis
Hereditary haemochromatosis	Genotyped and / or biopsy proven
Renal failure	Dialysis dependent
Alcoholic liver disease (ALD)	Liver biopsy or Liver Function Test (LFT) abnormality compatible with ALD in patients with history of alcohol excess (> 30 u/wk) in whom other causes have been excluded
Inflammatory disease	Raised C-Reactive Protein (CRP) and/or Erythrocyte Sedimentation Rate (ESR) on more than one consecutive test and recognised active inflammatory disease
Repeated blood transfusion	More than 4 unit packed cell transfusion in preceding 6 mo
Autoimmune disease	Recognised autoimmune disease with positive auto-antibody test
Other liver disease	All other recognised causes of parenchymal liver damage with abnormal LFTs, excluding ALD and HHC
Haematological disease	Bone marrow or blood film proven primary haematological disorder
Neoplasia	Histologically proven neoplastic disease
Weight loss	More than 10% body mass (kg) lost in preceding six months
Human immuno-deficiency virus (HIV)	Positive HIV test

Table 2 Causes of ferritin  $\geq 1500$   $\mu\text{g/L}$  in local and general population

Condition	All patients, $n = 150$ (% total)	Local patients, $n = 71$ (% total)	Number with condition as single cause for raised ferritin (%)
HHC	13 (8.6)	8 (11.3)	5/13 (38.5)
Alcoholic liver disease	33 (22)	22 (31.0)	24/33 (72.7)
Other liver disease	20 (13.3)	10 (14.1)	8/20 (40.0)
Inflammatory Disease	28 (18.6)	9 (12.6)	7/28 (25.0)
Neoplasia	29 (19.3)	11 (15.4)	6/29 (20.7)
Repeated blood transfusion	26 (17.3)	9 (12.6)	1/26 (3.8)
Autoimmune disease	21 (14.0)	8 (11.3)	2/21 (9.5)
Haematological disease	38 (25.3)	11 (15.4)	6/38 (15.7)
Renal failure	42 (28.0)	15 (21.1)	20/42 (47.6)
Weight loss	17 (11.3)	6 (8.4)	2/17 (11.7)
HIV	1 (0.7)	1 (1.4)	0/1 (0)
Unexplained	3 (2.0)	3 (4.2)	3/3 (100)

assayed between January 2002 and September 2002 were identified. All those with a ferritin level of  $\geq 1500$  micrograms/litre ( $\mu\text{g/L}$ ) (normal range 12-200  $\mu\text{g/L}$ ) were included in the study. Demographic data, medical histories (including blood transfusion history and documented weight loss), biochemical markers and histopathological data were collected for each patient. The medical notes of patients with specific diagnoses, such as Hereditary Haemochromatosis (HHC), were scrutinised to ensure diagnostic criteria had been met before the patients were classified<sup>[3]</sup> (Table 1).

## RESULTS

19 583 ferritin level results were obtained for a nine month period (equivalent to 80 tests per day). 199 patients had serum ferritin results of  $\geq 1500$   $\mu\text{g/L}$  (from 406 samples among them). Hyperferritinaemia was thereby identified with an annual incidence of 0.44/1000 in the local population.

150/199 (75%) case notes were retrieved for 97 male

Table 3 The most common causes of hyperferritinaemia

All patients (%)	Local Patients (%)
Renal failure (28.0)	Alcoholic liver disease (31.0)
Haematological disease (25.3)	Renal failure (21.1)
Alcoholic liver disease (22)	Neoplasia (15.4)
Neoplasia (19.3)	Haematological disease (15.4)
Inflammatory disease (18.6)	Other liver disease (14.1)
Repeated blood transfusion (17.3)	Repeated blood transfusion (12.6)
Autoimmune disease (14.0)	Inflammatory disease (12.6)
Other liver disease (13.3)	HHC (11.4)
Weight loss (11.3)	Autoimmune disease (11.4)
HHC (8.6)	Weight loss (8.4)
Unexplained (2.0)	Unexplained (4.2)
HIV (0.7)	HIV (1.4)

patients and 53 female patients (ratio 1.8:1). The median age (taken at 1/1/02) was 54 years. 71 (47.3%) were "local" from Newcastle upon Tyne (postcode NE1 - NE12) (Table 2). Of the notes we were unable to obtain, 27/49 were local patients (55%) and 30/49 were male (ratio 1.6:1). The median age of this group was 54 years.

### Causes of raised ferritin in general and local populations

Of the 150 patients evaluated in detail, 81 had one single identifiable cause for their hyperferritinaemia, with only 3 patients having none of the listed potential causes (Table 1) recorded in their medical records as well as no significant weight loss. Table 2 gives details of the frequency of conditions associated with a markedly elevated serum ferritin level. Table 3 lists the 10 most common causes for hyperferritinaemia in all patients studied as well as for patients who lived locally.

Renal failure was the most common cause for hyperferritinaemia in the overall patient population of the hospital trust that provides significant tertiary care, however, alcoholic liver disease was the most common cause of a raised ferritin level in the local population. 51% of patients in our study had only one cause identified for their hyperferritinaemia, with alcoholic liver disease being the most common single cause for a raised ferritin

level. Hereditary haemochromatosis accounted for only 9% of cases, ranking as the 10<sup>th</sup> commonest cause of hyperferritinaemia. Liver disease (alone) accounted for 25% of cases, but contributed to raised ferritin levels in 44%.

### Degree of hyperferritinaemia

The median ferritin level was 2613 µg/L. Those with liver diseases had the highest ferritin levels (Table 4). Patients with haematological disease (or repeated blood transfusion) as the single cause of a ferritin level  $\geq$  1500 µg/L also had very high median ferritin level results. Patients with renal failure had relatively lower median ferritin level results.

## DISCUSSION

Tests to determine serum ferritin levels are frequently requested, and causes of a markedly raised ferritin level are multiple. This study concentrated on the conditions found in patients known to have hyperferritinaemia, and did not look at the initial indication for checking the serum ferritin level. Clinicians may not routinely check serum ferritin in all patients with, for example, normal liver function tests or normal haemoglobin, and thus our list of associated conditions may not accurately reflect all the causes of hyperferritinaemia.

We chose 1500 µg/L (more than seven times the upper limit of normal) as our cut-off for defining hyperferritinaemia. This gave us a large enough study cohort to provide meaningful data, whilst producing a manageable number from which to accurately retrieve patient information.

### Hereditary Haemochromatosis

Dying red blood cells in macrophages are broken down to release iron to serum transferrin, which is then taken up by transferrin receptors on parenchymal tissues and in the bone marrow. In HHC, it is thought the binding of transferrin receptor 1 is inhibited in crypt and reticuloendothelial cells via the protein hepcidin<sup>[4]</sup>. This leads to raised ferritin, high transferrin saturation and high liver iron concentration.

HHC is a relatively rare cause of markedly raised ferritin ranking as the 8<sup>th</sup> most common cause in the local population. Local guidelines for the diagnosis of HHC suggest that unless the transferrin saturation is  $>$  45% genotyping is not indicated<sup>[3]</sup>. A serum ferritin greater than 300 µg/L (for men and post-menopausal women) is regarded as requiring further investigation for HHC. Our cut-off of 1500 µg/L is likely to have missed a large proportion of patients with HHC, which would include both those with a mild degree of iron overload and patients with HHC undergoing successful venesection treatment. HHC has a prevalence of 1/300 (which should be 900 patients locally). Clearly, if stable patients are having their ferritin levels checked twice yearly as recommended, our study would have missed a large proportion of these patients, suggesting that local venesection therapy is working.

It is well-known now that patients who are ho-

Table 4 Median ferritin levels in each condition

Condition (n)	Median ferritin µg/L	Number with condition as single identifiable cause for ferritin $\geq$ 1500 µg/L	Median ferritin in those with = cause for ferritin $\geq$ 1500 µg/L
HHC (13)	5031	5	7432
Other liver disease (19)	2889	8	3055
Unexplained (3)	2606	n/a	n/a
Weight loss (16)	2508	2	2160
ALD (31)	2484	24	2121
Autoimmune disease (21)	2203	2	2017
Haematological disease (31)	2075	5	3974
Inflammatory disease (24)	1995	3	2877
Repeated blood transfusion (29)	1977	1	6315
Renal failure (40)	1975	20	1954
Neoplasia (26)	1767	3	2409
HIV (1)	1711	0	n/a

mozygous for HHC and who drink more than 60 g alcohol per day are approximately 9 times more likely to develop cirrhosis than those who drink less. This is associated with a massive rise in iron concentrations on biopsy<sup>[5]</sup>. All eight patients with HHC who had more than one identifiable risk factor for hyperferritinaemia were heavy drinkers.

### Other Liver Diseases

The liver diseases (particularly HHC) produce the most markedly raised ferritin levels, especially in those with no other contributing factors (Table 4). There is evidence now of an association between iron excess on liver biopsy with other metabolic disorders<sup>[6]</sup>. A study in 2001 confirmed that an increased ferritin level with normal transferrin saturation is frequently found in patients with hepatic steatosis<sup>[7]</sup> but reflects iron overload only in those in whom it persists despite an appropriate diet. We did not include non-alcoholic steatohepatitis or fatty liver disease as separate diagnoses, nor did we look at associated metabolic disease, other than HHC, but it seems likely given the above evidence, that some of the patients in the “other liver disease” category had these conditions.

Investigating patients who were referred with abnormal liver function tests who were found to have a raised serum ferritin level is potentially time-consuming and costly. Time and resources could be reduced if cut-off levels for serum ferritin, above which specific diagnoses could be included or excluded from the differential diagnosis, were available. To do this most effectively, we would need to look at median ferritin levels at diagnosis for all patients with each of the liver diseases (e.g., ALD, HHC, fatty liver, autoimmune hepatitis) and not just at those patients identified with marked hyperferritinaemia. This may then enable greater targeting in subsequent investigations. From our limited study, it seems likely that patients with massively raised ferritin levels (e.g.  $>$  5000 µg/L) are more likely to have HHC than any of the other chronic liver diseases or conditions commonly associated with hyperferritinaemia.

### Weight Loss

More patients had weight loss as an identifiable potential cause of their hyperferritinaemia than had haemochromatosis. The weight loss in the majority of these patients was associated with neoplasia or chronic inflammatory disease. It is not possible to determine whether this was a significant factor in the development of hyperferritinaemia. Only two patients seemed to have weight loss alone as a cause for their hyperferritinaemia.

Patients with anorexia nervosa may be found to have increased ferritin and abnormal liver biopsies with high iron content. A study looking at malnourished children demonstrated abundant iron stores in the liver despite evidence of iron deficiency [personal communication, Professor Alan Jackson, University of Southampton]. The causes for this are unclear but it is postulated that the demand for oxygen carriage is reduced in the face of a diminished lean body mass, and hence red cell mass is lower due to the release of iron to be stored. It is also thought that bone marrow activity may be directly or indirectly suppressed due to ongoing stress or infection-related challenge, thus reducing demand on stored iron. Limited nutrient availability may also suppress marrow activity<sup>[8]</sup>. These possible explanations are not mutually exclusive.

### Renal Failure

Usual tests to diagnose iron deficient anaemia and measure iron stores are suspect in those with chronic renal failure, who are plagued by poor nutrition, multiple medications and acute and chronic inflammatory processes<sup>[9]</sup>. Iron replacement therapy in chronic renal failure is common and these patients frequently undergo ferritin checks as a measure of their iron stores. There may be therefore a disproportionately high number of patients with chronic renal failure included in our study. The median ferritin level in patients with renal failure was 1959 µg/L (1954 µg/L in those with RF as a single cause). 52% (22/42) of patients

with renal failure had a ferritin level < 2000 µg/L making up 38% of all those with ferritin levels < 2000 µg/L in this study.

## CONCLUSIONS

Serum ferritin level tests are frequently requested by clinicians. Clinicians should remember that alcohol related liver disease, haematological disease, renal failure and neoplasia are much more common causes of marked hyperferritinaemia than haemochromatosis. Further investigations into the role of weight loss as a contributing factor to raised ferritin levels are needed.

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