bjh guideline

Investigation and management of a raised serum ferritin

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Summary

Serum ferritin level is one of the most commonly requested investigations in both primary and secondary care. Whilst low serum ferritin levels invariably indicate reduced iron stores, raised serum ferritin levels can be due to multiple different aetiologies, including iron overload, inflammation, liver or renal disease, malignancy, and the recently described metabolic syndrome. A key test in the further investigation of an unexpected raised serum ferritin is the serum transferrin saturation. This guideline reviews the investigation and management of a raised serum ferritin level. The investigation and management of genetic haemochromatosis is not dealt with however and is the subject of a separate guideline.

Keywords: hyperferritinaemia, ferritin, iron metabolism.

Scope

The objective of this guideline is to provide healthcare professionals with guidance on the management of patients with a raised serum ferritin. The guidance may not be appropriate to every patient and in all cases individual patient circumstances may dictate an alternative approach.

Methodology

This guideline was compiled according to the BSH process at: http://b-s-h.org.uk/guidelines/proposing-and-writing-a-new-bsh-guideline/. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

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Literature review details

The literature search entailed a systematic search of MEDLINE and PUBMED for publications that included an abstract and were published in English between 1980 and 2017 using the following key words: raised serum ferritin, hyperferritinaemia, as well as specific search terms relevant to each section.

Working group membership

The guideline group was selected to be representative of UK-based experts in the investigation and management of raised serum ferritin levels.

Review

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee General Haematology Task Force, the BSH Guidelines Committee and the sounding board of the BSH. It was also placed on the members section of the BSH website for comment.

Introduction

Since the development of a sensitive immunoradiometric assay in 1972 (Addison *et al*, 1972) measurement of serum ferritin (SF) as a surrogate measure of body iron stores has largely replaced laboratory assays of serum iron and transferrin or total iron binding capacity in clinical practice. Its great value to the clinician lies in the finding that, in health, the SF is directly proportional to the level of iron stores (Worwood, 1982). A study of quantitative phlebotomy in normal volunteers showed a correlation between storage iron and SF concentration with 1 μg/l of SF equivalent to approximately 8 mg of storage iron (Walters *et al*, 1973).

Reduced SF levels are only found in patients with reduced body iron stores. There is no other cause and guidelines for the management of patients with low SF and iron deficiency anaemia are well established in medical practice (Goddard *et al*, 2011). In some circumstances, for example in patients

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with co-existent inflammatory disorders, SF may be within the normal or elevated range even when iron stores are absent and anaemia is due to iron deficiency, and this is discussed further in the section of Inflammatory and Infective Disorders (below). However, the clinical and laboratory management of patients with raised SF values is not at all well recognised and is the subject of this guideline and the companion updated guideline on Genetic Haemochromatosis (GH) (Fitzsimons *et al*, 2018).

Structure and function of ferritin

Ferritin is a soluble 450 kDa protein. It is found in all cells of the body but is in high concentrations in marrow macrophages, the spleen and the liver. It provides intracellular storage of bio-available iron in a safe and readily accessible form. It protects cells from iron-mediated free radical formation and toxicity such as might result from the Fenton reaction between iron and hydrogen peroxide. Ferritin is comprised of 24 monomer subunits that consist of either Heavy (H) type (21 kDa) or Light (L) type (19 kDa) polypeptide chains encoded by 2 different ferritin genes. The 24 monomer subunits associate to form a hollow spherical particle that can store up to 4000 iron atoms as Fe^{3+} ions. The proportion of H and L type chains depends on the tissue of origin: liver and spleen ferritin are rich in L chains whereas ferritin in the heart or red blood cells is rich in H subunits. Haemosiderin, the "stainable iron" found in iron-laden macrophages, represents insoluble, denatured ferritin from which iron is less readily available. For a review of the structure and function of ferritin and haemosiderin, see Harrison and Arosio (1996).

Ferritin produced by the lens of the eye consists entirely of L chains. This L chain ferritin is capable of forming crystals under certain conditions, as seen in the hereditary hyperferritinaemia cataract syndrome (HHCS) (Cazzola *et al*, 1997).

Serum ferritin

A tiny amount of ferritin is found in the serum. This SF plays no role in iron transport or cellular iron uptake. That is the role of transferrin. Serum ferritin is almost entirely made up of L chains, has a half-life of 30 h, is not iron-bearing and is some 50–80% glycosylated. As glycosylation occurs intracellularly, this would indicate that SF is a secretory plasma protein. The cell of origin and the mechanism by which this glycosylated ferritin passes into the serum is not well understood.

The proportion of glycosylated ferritin in serum may alter in certain disease types that allow intracellular (non-glycosylated) tissue ferritin to leak into the plasma with a half-life of about 9 min (Worwood, 1986). The percentage glycosylation is low in liver necrosis and in Still disease (Worwood, 2012) but is almost 100% in certain hereditary hyperferritinaemic states.

Measurement of serum ferritin

Serum ferritin can be measured using immunoassays e.g. enzyme-linked immunosorbent assay (ELISA), immunochemiluminescence (Abbott Architect assay, ADVIA Centaur assay, Roche ECLIA assay) or immunoturbidometric assay (Tinta-quant assay). Immunoradiometric assays are now rarely used owing to the health and safety risks to laboratory personnel associated with using radioactive-labelled substances. Most immunoassays use antibodies to either spleen or liver ferritin. Assays should be calibrated against the Third International Recombinant Standard for Ferritin (National Institute for Biological Standards and Control Code 94/572). For further information on analysis see Worwood *et al* (2017) and Association for Clinical Biochemistry (2012).

Raised serum ferritin

The recognition of a raised SF is dependent upon the upper limit of the normal range. Thereafter the appropriate action taken depends on the source of the sample, whether it is taken in primary or secondary care and knowledge of the patient's medical history. SF shows an acute phase response such that levels may be raised beyond that appropriate for reticuloendothelial system (RES) iron stores by inflammation or by tissue damage. Levels in serum will also be raised by any condition or treatment (e.g. blood transfusion or iron infusion) that lead to a genuine increase in RES iron stores.

Upper limit of the normal range for serum ferritin

Most UK laboratories simply report 300–400 μg/l as the upper limit of normal for SF in adult males and 150–200 μg/l as the upper limit of normal for adult females (Association for Clinical Biochemistry, 2012; Worwood *et al*, 2017). There is however considerable variation in SF values in response to age, ethnic origin and sex. Mean SF values in neonates are high (around 200 μg/l) and remain so for about 2 months. From 2 to 12 years mean values approximate 30 μg/l for both boys and girls (Worwood, 1982). Within this age group values >100 μg/l are only seen in the context of inflammatory disease, malignant disease or juvenile hereditary haemochromatosis.

Mean SF values at 18 years are significantly higher in males (60–80 μg/l) than in females (25–30 μg/l) (White *et al*, 1993; Wiedemann & Jonetz-Mentzel, 1993; Custer *et al*, 1995; Milman *et al*, 2003). Thereafter, in males, SF values rise to plateau with median values of approximately 120 μg/l from the age of 30 years. Irrespective of age, approximately 20% of Caucasian male adults in primary care will have SF values >300 μg/l (Ogilvie *et al*, 2010; Adams *et al*, 2013). As a result of iron loss from menstruation and pregnancies, SF values in adult females only start to rise after 50 years of age, to plateau with median values of about 100 μg/l after 60 years. Values >200 μg/l in adult females show a significant

Table I. Causes of raised serum ferritin.

Increased ferritin synthesis due to iron accumulation	Increase in ferritin synthesis not associated with significant iron accumulation	Increased ferritin as a result of cellular damage
Hereditary (genetic) haemochromatosis	Malignancies	Liver diseases including: liver necrosis, chronic viral hepatitis, alcoholic and non-alcoholic steatohepatitis*
Hereditary acaeruloplasminaemia	Malignant or reactive histiocytosis	
Secondary iron overload from blood transfusion or excessive iron intake/administration	Hereditary hyperferritinaemia with and without cataracts	Chronic excess alcohol consumption
Ineffective erythropoiesis: sideroblastic anaemia, some myelodysplastic syndromes (e.g. refractory anaemia with ring sideroblasts)	Gaucher disease	
	Acute and chronic infections	
	Chronic inflammatory disorders	
	Autoimmune disorders	
Thalassaemias		
Atransferrinaemia		
Ferroportin disease		

*May also have iron overloading.

age effect and are seen in 3%, 10% and 17% respectively of women aged 30–50 years, 50–70 years and >70 years (Ogilvie *et al*, 2010; Adams *et al*, 2013).

Mean SF values are higher at all ages in adult black males than in adult white males. In black females, higher SF values are only seen after the menopause. In multi-ethnic population studies in the USA it was found that elevated SF values are found more frequently in Afro-Caribbean and Asian subjects than in whites or Hispanics. Indeed, very high SF levels >1000 μg/l are 2–3 times more common in black and Asian volunteers despite an almost total absence of iron loading genotypes in these 2 populations (Adams *et al*, 2005).

Recommendation

- **The normal ranges for serum ferritin in an individual patient should take into account the variation due to age, gender and possibly ethnic origin (Grade 2A).**

Raised serum ferritin levels (hyperferritinaemia)

Raised serum ferritin values for primary care

Serum ferritin is the most frequently requested haematinic assay in the UK and some 50% of SF requests are made from primary care. The primary care population is predominantly a well patient population, thereby reducing (although not eliminating) the effect of secondary care disorders on SF values. Major studies of raised SF values in primary care have been reported, particularly in relation to population screening for GH and iron overload [see (Fitzsimons *et al*, 2018)]. It is, however, an acute phase protein and only a minority of subjects with elevated SF levels in the population-based Hemochromatosis and Iron Overload Screening study were found to be homozygotes for C282Y in the *HFE* gene, demonstrating that hyperferritinaemia is usually due to causes other than GH (Adams *et al*, 2005).

The commonest causes of hyperferritinaemia without iron overload relate to inflammatory disorders, malignancy, chronic alcohol consumption, liver disease or metabolic abnormalities. A study of patient samples from primary and secondary care in Newcastle with SF levels ≥1500 μg/l showed that liver disease, alcohol, inflammatory disorders, malignancy, renal failure and haematological disorders were all commoner causes of raised SF than GH (Hearnshaw *et al*, 2006).

Raised serum ferritin values in secondary care

In 627 patients seen in a tertiary academic medical centre with SF ≥ 1000 μg/l, the commonest causes were malignancy, followed by iron overload (Moore *et al*, 2013). Other causes included adult onset Still disease, systemic juvenile idiopathic arthritis and haemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome: seven patients appeared to have anaemia of chronic disease, and in five the cause of the elevated SF was not defined. In 83 patients identified with SF levels >3000 μg/l at a teaching hospital in Vancouver, 21 cases (25%) were due to transfusional iron overload, 16 (19%) due to liver disease and 15 (18%) due to mixed factors. HLH was diagnosed in 6 patients (7%) (Wormsbecker *et al*, 2015). Finally, a study of markedly elevated SF levels ≥10 000 μg/l in patient samples analysed over a 12-month period in a district general hospital biochemistry laboratory revealed 23 cases, with an incidence of 0·08% of SF requests: malignancy accounted for 6/23 cases, liver disease 5, transfusion or thalassaemia 5 and infections 4 (Crook & Walker, 2013).

Overview of causes of raised serum ferritin

Table I gives a brief outline of the causes of a raised SF. Further investigations can be tailored to narrow down the possible aetiologies. Conditions associated with primary iron

overload, such as GH, are outside the scope of this guideline, and readers are directed to the recently updated management guideline for this condition (Fitzsimons *et al*, 2018).

Common causes of hyperferritinaemia

For the majority of persons with a raised SF, chronic inflammatory or infective causes as well as liver disease, alcohol and malignancies will be the more likely conditions seen in practice, and if clinically apparent, further investigations of the causes of hyperferritinaemia may not be necessary.

Hepatic disorders

Elevated SF is seen in almost any cause of liver injury, including alcoholic and non-alcoholic steatohepatitis (NASH), and viral hepatitis (Wong & Adams, 2006). SF increases in response to alcohol intake, is affected more by beer than wine or spirit consumption, and is especially increased in subjects with a history of alcohol dependence (Whitfield *et al*, 2001). Thus, it is important to document alcohol intake, measure liver function tests (LFTs) and consider abdominal ultrasonography in subjects with unexplained raised SF. The finding of fatty infiltration in the liver on ultrasound may suggest the presence of alcohol-related or non-alcoholic fatty liver disease, while chronic or excessive alcohol consumption will usually cause elevation of liver enzymes, especially the γ-glutamyltransferase (GGT). Hepatitis B and C infection often cause elevated SF with normal transferrin saturation (Tsat), so hepatitis virus serology should be considered as part of the work-up if LFTs are abnormal.

Renal disorders

SF is not a useful marker of iron stores in patients with chronic kidney disease (CKD), and is elevated in almost half of all patients on maintenance haemodialysis (Kalantar-Zadeh *et al*, 2006) but the raised SF does not represent iron that is available for erythropoiesis. Current National Institute for Health and Care Excellence (NICE) guidelines (NICE 2015) advise against the use of SF and Tsat alone (unless thalassaemia or thalassaemia trait is present) to assess need for iron replacement in CKD patients. Novel markers for functional iron deficiency, such as percentage hypochromic red cells (%HYPO) or reticulocyte haemoglobin concentration (CHr) (as reported by Bayer Advia 120 haematology analyser, Siemens Healthcare Diagnostics, Deerfield, IL, USA), have improved clinical utility (NICE, 2015) and should be used, if available, in UK laboratories. For CKD patients on treatment with erythropoietic stimulating agents (ESA), iron supplementation should routinely be offered to patients to keep their %HYPO <6% or CHr >29 pg or Tsat >20% unless their SF is >800 μg/l, with markers checked every 1–3 months in patients on haemodialysis, or every 3 months in patients who are pre-dialysis or on peritoneal dialysis. Current guidelines from The Renal Association (2017) recommend that SF should not exceed 800 μg/l in patients treated with iron, and to achieve this, iron management should be reviewed when SF is >500 μg/l.

Malignancy

SF is frequently elevated in the setting of malignancy, and cancer has been the most frequent association in some studies of the causes of hyperferritinaemia (Moore *et al*, 2013): ferritin is variably overexpressed by various tumours (Alkhateeb & Connor, 2013), including hepatocellular carcinoma, haematological malignancies (Matzner *et al*, 1980) and breast and pancreatic tumours.

Inflammatory and infective disorders

SF may be elevated in a variety of inflammatory and infective conditions. SF levels may correlate with disease activity in systemic lupus erythematosus (SLE) and rheumatoid arthritis (Yildirim *et al*, 2004; Zandman-Goddard & Shoenfeld, 2007; Tripathy *et al*, 2015). The pathogenesis of hyperferritinaemia is thought to be cytokine-mediated, with interleukin (IL)1α, IL1β, IL6, IL18, tumour necrosis factor-α, γ-interferon and macrophage-colony stimulating factor all implicated. Other inflammatory conditions and acute or chronic infections will also produce elevations in SF, usually with elevated levels of C-reactive protein, but normal Tsat.

Mention should be made of anaemia of chronic disease (ACD), also termed anaemia of inflammation, the pathogenesis of which includes IL6-mediated increased levels of hepcidin, which produces a state of functional iron deficiency, in which iron absorption from the intestine and release from macrophages is inhibited, making it unavailable for haemopoiesis (reviewed in Cullis, 2011). Identifying accompanying iron deficiency in patients with ACD can be difficult as SF levels will frequently be normal or raised due to circulating inflammatory cytokines. Typically, Tsat is low: algorithms using the ratio of the serum transferrin receptor to log SF concentration may help distinguish ACD from ACD with accompanying iron deficiency (Skikne, 2008), but guidelines now support the use of novel red cell parameters, such as CHr and %HYPO (Thomas *et al*, 2013). Measurement of serum transferrin receptor (sTfR) levels have been advocated in distinguishing iron deficiency anaemia from ACD, levels being elevated in the former but normal in ACD (Ferguson *et al*, 1992; Cazzola *et al*, 1996; Berlin *et al*, 2011), but other studies have suggested no advantage over conventional indicators of iron stores (Mast *et al*, 1998; Wians *et al*, 2001; Lee *et al*, 2002) and the test has not been widely adopted.

Emerging disorders

A more recently described cause of raised SF is the metabolic syndrome, sometimes referred to as dysmetabolic hyperferritinaemia, first described in France (Moirand *et al*, 1997; Mendler *et al*, 1999), and increasingly recognised in western society: cardinal features include hyperglycaemia, dyslipidaemia, obesity and hypertension (Ford *et al*, 2002; Alberti *et al*, 2009): patients typically demonstrate elevated SF levels with normal Tsat (Chen *et al*, 2011). In some, but not all studies, hepatic iron stores are increased (Chen *et al*, 2011; Castiella *et al*, 2016). The increase in SF levels correlates with increased hepcidin production, as well as levels of other inflammatory cytokines in these patients (Andrews *et al*, 2015).

Haematological causes

A variety of red cell disorders, characterised by ineffective erythropoiesis or haemolysis, are associated with increased iron absorption from the gastrointestinal tract and the resultant increased SF, even in the absence of red cell transfusion therapy (Porter *et al*, 2017); these include thalassaemic disorders, such as thalassaemia intermedia, pyruvate kinase deficiency, hereditary spherocytosis (Bolton-Maggs *et al*, 2012), and inherited or acquired sideroblastic anaemias. Prolonged or chronic transfusion therapy, for example in patients with major haemoglobinopathies, myelodysplastic syndromes, or during treatment for haematological malignancies, will also cause transfusional iron overload.

There is a well-recognised correlation between SF and hepatic iron concentration in transfused patients with beta thalassaemia major and sickle cell disease (Brittenham *et al*, 1993; Pakbaz *et al*, 2007) but the relationship between SF and hepatic iron concentration is different for patients with non-transfusion dependent, but iron loading anaemias, such as thalassaemia intermedia and haemoglobin H disease, in which SF levels may be lower despite comparable degrees of hepatic iron overload (Taher *et al*, 2008, 2015; Ang *et al*, 2017). This is important to recognise in parts of the world where methods of assessing hepatic iron concentration, such as magnetic resonance imaging (MRI), are unavailable and SF is therefore the only available means of assessing iron stores: lower SF thresholds may need to employed in decisions about iron chelation in these non-transfusion dependent thalassaemic disorders (Taher *et al*, 2015).

Recommendation

- **Reactive causes of raised serum ferritin levels, including malignancy, inflammatory disorders, renal failure, liver disease and metabolic syndrome, should always be considered as they are all considerably more common than true iron overload (Grade 1B).**

Causes of a significantly elevated serum ferritin

Markedly elevated SF levels (>10 000 μg/l) may be seen in adult onset Still disease, a rare, immune-mediated, multisystem inflammatory disorder characterized by fever, rash and arthritis, typically affecting young individuals (75% cases are between 16 and 35 years of age) and frequently presenting as pyrexia of unknown origin. In a recent series, 89% of cases demonstrated elevated SF levels, with over half having levels five times the upper limit of normal (Uppal *et al*, 2007): levels may reach 50 000 μg/l.

Haemophagocytic lymphohistiocytosis is another condition associated with markedly elevated SF levels. This heterogeneous group of disorders share clinical features of pancytopenia, hypertriglyceridaemia, hyperferritinaemia and multiorgan failure, and often have a fatal outcome. The condition may be familial but can also develop in the setting of Still disease or other autoimmune conditions, including SLE, as well as in lymphoproliferative disorders and following viral infections, particularly Epstein–Barr virus and cytomegalovirus. It should be considered in the differential diagnosis of any critically ill patient with evidence of systemic inflammation or multiple organ involvement with multiple cytopenias. Ferritin levels are frequently >10 000 μg/l, and associated rises in other markers of the disease, such as serum IL2 receptor-α, may support the diagnosis (Filipovich, 2009).

Marked hyperferritinaemia has often been uniquely ascribed to such rare rheumatological and inflammatory disorders (Rosário *et al*, 2013), and may be very specific for them. A retrospective study at Texas Children's Hospital (Allen *et al*, 2008) reported that levels of >10 000 μg/l had 90% sensitivity and 98% specificity for HLH, but another study (Schram *et al*, 2015) in adults in three large US hospitals identified over 800 patients with SF > 10 000 μg/l, of whom 113 had levels >50 000 μg/l: the most frequently observed conditions in this adult population with marked hyperferritinaemia included renal failure (65%), hepatocellular injury (54%), infection (46%) and haematological malignancy (32%). Rheumatological conditions and HLH accounted for 18% and 17% respectively, suggesting that marked hyperferritinaemia in adults is associated with a variety of disorders and is not uniquely predictive of HLH.

Recommendation

- **Markedly elevated serum ferritin levels (>10 000 μg/l) should prompt consideration of rare conditions, such as adult onset Still disease or haemophagocytic lymphohistiocytosis, but may also be seen in commoner conditions, such as renal or liver disease, infections and malignancies (Grade 2B).**

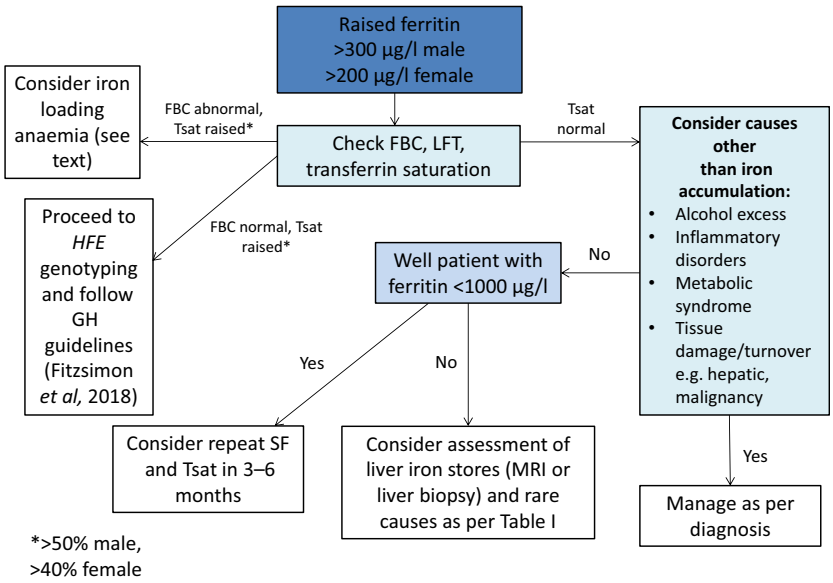

Fig 1. Suggested algorithm for investigation of isolated elevated serum ferritin levels in patients without known secondary iron overload. FBC, full blood count; GH, genetic haemochromatosis; LFT, liver function tests; MRI, magnetic resonance imaging; SF, serum ferritin; Tsat, transferrin saturation.

Rare disorders associated with raised SF

Porphyria cutanea tarda is the commonest human porphyria, and is characterised by photosensitive dermatosis with blistering skin lesions. It is caused by reduced levels of uroporphyrinogen decarboxylase, and exists in both familial and non-familial forms, the latter frequently associated with inheritance of GH mutations, alcoholic liver disease, hepatitis C infection or oestrogen usage (Roberts *et al*, 1997; Elder, 1998). SF and Tsat are frequently both increased (Bulaj *et al*, 2000). The condition should be considered in patients with increased SF in the presence of a photosensitive rash.

Hereditary hyperferritinaemia cataract syndrome (HHCS) is a rare autosomal dominant condition due to various mutations in the iron responsive element of the gene encoding L-ferritin (Bonneau *et al*, 1995). SF levels are increased, but Tsat is not raised. L-ferritin deposition in the ocular lens results in bilateral cataract formation at an early age.

Another rare genetic disorder associated with elevated SF levels but normal Tsat is Gaucher disease (Stein *et al*, 2010; Mekinian *et al*, 2012). Inherited in autosomal recessive fashion and caused by deficiency in glucocerebrosidase, Gaucher disease presents with hepatosplenomegaly, painful bone lesions, anaemia and thrombocytopenia, and some correlation is seen between SF levels and disease severity, particularly anaemia (Stein *et al*, 2010).

Aceruloplasminaemia is caused by a mutation in the *CP* gene that encodes ceruloplasmin, and results in raised SF with normal Tsat (Nittis & Gitlin, 2002). Iron overload is present and clinical manifestations include retinal problems and neurological abnormalities. Microcytic anaemia may be present.

Loss-of-function mutations in the *SLC40A1* (also termed *FPN1*) gene, encoding ferroportin, an iron transport protein that acts as a receptor for hepcidin, result in a rare iron overload disorder known as ferroportin disease, characterised by raised SF, normal Tsat and hepatic iron overload. This is discussed further in the GH guideline (Fitzsimons *et al*, 2018).

Atransferrinaemia, caused by congenital deficiency due to autosomal recessive mutations in the *TF* gene, is also extremely rare, and usually presents at birth with severe hypochromic, microcytic anaemia requiring red cell transfusion, but paradoxical iron overload in tissues. SF is very high, but iron and transferrin levels will be very low. Infusion of fresh frozen plasma combined with phlebotomy or iron chelation may be indicated (Beutler *et al*, 2000).

A recently described condition is benign hyperferritinaemia (Kannengiesser *et al*, 2009) in which a novel mutation has been found in the coding sequence of the *FTL* gene encoding L ferritin: subjects carrying this mutation had SF levels ranging from 400 to 6000 µg/l but did not have raised Tsat levels nor increased liver iron.

How to investigate raised serum ferritin

When SF is raised, the most crucial questions to ask are (i) is it secondary to a known clinical condition, and (ii) is it associated with iron overload? A suggested algorithm for the investigation of a patient with a finding of raised SF is shown in Fig 1. The understanding that many chronic inflammatory and hepatic disorders can raise SF as outlined in the previous section means that the potential cause of hyperferritinaemia may be clear from the outset, while measurement of Tsat will

identify whether iron stores are increased and is therefore a key investigation.

A clinical history and examination, together with a few simple investigations, will often reveal the probable underlying cause. In particular, patients should be questioned about alcohol intake and other risk factors for liver disease, transfusion history or oral iron supplementation, family history of iron overload and the presence or absence of diabetes mellitus, obesity and hypertension, history of early cataracts, as well as for symptoms and signs that may point to an underlying inflammatory or malignant disorder. Initial investigations should include a full blood count, repeat SF, Tsat, renal function tests and LFTs (with viral hepatitis serology if LFTs are abnormal) and inflammatory markers, such as C-reactive protein, erythrocyte sedimentation rate or plasma viscosity. Marked fluctuations in SF values and elevated aspartate aminotransferase rather than alanine aminotransferase, with increased GGT, are more typical of alcohol-induced liver damage than GH (Adams & Barton, 2011). Glycosylated haemoglobin levels may indicate impaired glucose tolerance, and raised serum lipids, body mass index and hypertension may point to underlying metabolic syndrome. Abdominal ultrasonography may demonstrate an echogenic liver suggesting alcohol- or non-alcohol-related fatty liver disease. In such cases non-invasive fibrosis assessment is indicated using transient elastography (Fibroscan®). Iron overload is more likely to be present if the SF has risen progressively or the SF is >1000 μg/l: in an otherwise well patient with SF > 1000 μg/l or abnormal LFTs proceeding directly to screen for GH is therefore indicated (Adams & Barton, 2011; Beaton & Adams, 2012), whereas secondary causes are more likely with more modest increases in SF.

Commonly advocated to be performed on a fasting sample, a raised Tsat indicates increased trafficking of iron through the body. Given the issues of patient compliance, potential negative impact of abnormal results upon the patient and the lack of evidence to the contrary, Tsat need not necessarily be measured on a fasting sample provided borderline results are either repeated or checked on fasting if desired (Adams & Barton, 2011). It is worth noting that acute infections, menstrual bleeding and recent blood donation can temporarily reduce Tsat to within the normal range in patients with iron overload (Barton *et al*, 1991), indicating that normal Tsat does not completely exclude iron overload. In the setting of persistent borderline results, genotyping for GH should be performed.

Recommendation

- **Patients found to have raised serum ferritin should be questioned about alcohol intake and other risk factors for liver disease, transfusion history, family history of iron overload and the presence or absence of type 2 diabetes mellitus, obesity and hypertension, as well as for symptoms and signs that may point to an underlying inflammatory or malignant disorder (Grade 1C).**

Recommendation

- **In patients with a finding of elevated serum ferritin levels, first line investigations should include full blood count and film, repeat serum ferritin, transferrin saturation, inflammatory markers (C-reactive protein, erythrocyte sedimentation rate or plasma viscosity) to detect occult inflammatory disorders, serum creatinine and electrolytes for renal function, liver function tests with consideration of viral hepatitis screening and abdominal ultrasonography (if abnormal liver function), and blood glucose and lipid studies (Grade 1C).**

Males with SF > 300 μg/l and Tsat >50% and females with SF > 200 μg/l and Tsat > 40% will usually have iron overload and have a 19% and 16% likelihood, respectively, of being C282Y homozygotes (Ogilvie *et al*, 2015), and genotyping for GH is indicated: this is not dealt with further in this guideline (see Fitzsimons *et al*, 2018). In unresolved cases, quantitation of liver iron, using either liver biopsy or newer MRI techniques, along with more detailed genetic testing, may be useful in distinguishing some of the rarer causes of hyperferritinaemia (Fig 1), but further discussion of these techniques is outside the scope of this guideline and should be discussed with a hepatologist.

How to manage raised serum ferritin without elevated transferrin saturation

In otherwise well patients with unexplained elevated SF and Tsat <40% (female) or <50% (male), a period of observation may be informative: stable, moderately increased levels may not require further investigation, whereas fluctuating levels are typically seen in hepatic steatosis or alcohol excess. Persistent unexplained hyperferritinaemia, especially at levels >1000 μg/l, merits consideration of onward referral to a specialist, usually a hepatologist.

Recommendation

- **In otherwise well patients with unexplained and moderately elevated serum ferritin levels (<1000 μg/l) and normal transferrin saturation, a period of observation, with lifestyle adjustment if appropriate, may be reasonable with repeat assessment after 3–6 months (Grade 2C).**

Recommendation

- **Patients with unexplained persistent hyperferritinaemia (especially >1000 μg/l) require referral to a hepatologist (Grade 2C).**

In most cases of hyperferritinaemia secondary to inflammatory or other conditions, management of the underlying

condition will lead to reduction in SF levels. For example, alcohol abstinence will usually lead to improvement in SF within weeks to months; and weight loss and improved control of diabetes and blood pressure will usually lead to lowering of levels in patients with metabolic syndrome.

The role of phlebotomy in patients with increased SF associated with liver disease other than GH is most likely of little benefit. Although the practice of phlebotomy in patients with non-alcoholic fatty liver disease (NAFLD), with the aim of reducing liver iron stores, is quite common on the basis that elevated SF levels in NAFLD are an independent predictor of the presence of non-alcoholic steatohepatitis (NASH) and hepatic fibrosis (Kowdley *et al*, 2012), randomised trials of venesection in NAFLD patients did not show improvement in prognostic markers with venesection (Adams *et al*, 2015).

Recommendation

- **There is no evidence to support venesection therapy to reduce serum ferritin levels in patients with non-alcoholic fatty liver disease (Grade 1B).**

Conclusions

The finding of a raised serum ferritin is a common conundrum in modern day clinical practice, both in primary and secondary care. Iron overload is a relatively uncommon cause of this picture and can be excluded by the finding of a normal transferrin saturation, so consideration of the many reactive (hepatic, malignant, renal, haematological and metabolic) causes is important: many cases will not require further investigation if a few simple investigations are performed. Our understanding of rarer causes of hyperferritinaemia is expanding but will require specialist molecular genetics for diagnosis.

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Author contributions

All authors were involved in formulation, writing and approval of the guidelines. All authors approved the final version of the manuscript. The authors would like to thank the BSH General Haematology Task Force, the BSH sounding board and the BSH executive committee for their support in preparing these guidelines.

Declaration of interests

All authors have made a full declaration of interests to the BSH and Task Force Chairs, which may be reviewed on request.

Review process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines).

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