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CASE STUDY

How to Follow Up on Unexplained Hyperferritinemia in Primary Care

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Abstract

50-years-old Bahraini male had an increased level of serum ferritin. The patient showed mildly high alanine aminotransferase and γ-glutamyltransferase and positive chronic hepatitis B.

Introduction

Seventy-five percent of Iron is present in hemoglobin, while 10-20% is stored in the protein ferritin. The remainder 5-15% is found in the iron transport protein transferrin, as well as in myoglobin, cytochromes and as unbound serum iron [1]. Elevated Serum Ferritin (SF) is commonly encountered in primary care. Hyperferritinemia is considered high when the level of ferritin is > 200 mcq/l in a premenopausal women, and the level of > 300 mcq/l in men & postmenopausal women [2]. Worldwide, 90% of detected Hyperferritinemia cases are found related to non-iron overload conditions (e.g. Alcohol related liver disease, hematological disease, renal failure, neoplastic, infection or inflammation and metabolic syndrome), whereas only 10% of cases. Hyperferritinemia cases are due to iron overload (Hemochromatosis (HH)) [3-5].

Serum iron presents diurnal variation, so the best sample for iron studies is a fasting morning sample [6,7]. Mild elevations of SF < 1000 µg/L are tolerable levels in the absence of HH; the risk of hepatic iron overload is exceedingly low, whereas high elevation of SF > 1000 µg/L requires specialist review to rule out HH with an increased risk of hepatic iron overload, which leads to hepatic fibrosis and cirrhosis [8]. There are many types of hyperferritinemia presented in primary care.

"Metabolic Hyperferritinemia" must be considered when evaluating patients with elevated SF and associated with hypertriglyceridemia, hypertension and insulin resistance which are more prevalent in the Gulf countries states, reaching up Arab 29% to 33% in males, and 38% to 41% in females respectively [9,10].

"Hepatic Hyperferritinemia" is another source of elevated SF, since any injured hepatocytes such as injured will seep ferritin into the serum, so SF deemed be reflected as another type of Liver Function Test (LFT) in liver disease (hepatitis B, hepatitis C, alcoholic liver disease, HH). Consequently, any elevated SF with abnormal LFTs will usually require further investigation in order to rule out hepatic Hyperferritinemia [11].

"Alcohol Hyperferritinemia" is also highly associated with alcohol consumption level. Elevated SF, with two or more standard beer drinks cause increases in ferritin secretion by the liver [12,13].

"Iatrogenic Hyperferritinemia" is common in patients receiving many blood transfusions; especially those with thalassemia major, sickle cell diseases & myelodysplastic syndrome. Moreover, patients on oral iron pills or iron intravenous injection for a long time can develop high serum Hyperferritinemia [14].

"Malignant, Infective and Inflammatory Hyperferritinemia" requires a screening test for SF, C-reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and Antinuclear Antibody (ANA) which can help exclude serious disease [15].

Objective

To use up to date evidence- based investigation for interpretation of high serum ferritin in primary care.

Case Study

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50-years-old Bahraini male came to the local health center to follow up in a chronic disease clinic for his medical issues. He is a known case of good controlled DM type 2 {FBS 6.4 (3.6-5.6 mmol/l)}, HBA1c 48 FBS mmol/L (20-39 mmol/mol) on oral hypoglycemic treatment [Glucophage 500 mg twice daily], and dyslipidemia mainly elevated triglyceridemia {Total cholesterol 4.9 mmol/L; mean HDL cholesterol 1 mmol/L (0.83-1.86 mmol/l); mean LDL cholesterol 2.85 mmol/L (1.68-3.367 mmol/l); mean Triglycerides 2.3 mmol/L (0.2-1.8 mmol/l)} on fibrates [Bezalip 400 mg daily]. Incidentally, the patient was found to have high serum ferritin level. His mean serum ferritin was 561 mcq/l {S. ferritin range from 502 to 600 mcq/l. (normal range in male 12-300 mcq/l)}. The patient's investigation showed abnormal liver function test {alanine aminotransferase 53 IU/L (normal range is 10-40 IU/L) and γ-glutamyltransferase 66 IU/L (normal range 0-37 IU/L). Patient's CBC, ESR and renal function tests were normal. He was otherwise obese, his weight was 104 kg, and height 175 cm (BMI = 33.9), and waist circumferences was 110 cm in diameter, blood pressure was 160/100 mmHg.

Patient's family's history was negative for the familial liver disease or iron overload. It was also showed, negative personal history of iron overload, ineffective erythropoiesis, hereditary hemochromatosis, and porphoria cutanea tarda. The patient denied any alcohol intake, liver disease; renal disease, previous infection or inflammation and malignancies.

While patient's examination showed that his abdomen was soft and lax, with no tenderness; the liver was palpable 2 cm; below the costal margin (notch was not palpable). Other examination (chest and cardiovascular examination) were unremarkable. Eye examination showed no eye redness, abnormal pigmentation or cataract.

The next investigation was iron studies with results being all normal. The concomitant Hepatitis B virus was shown (Core IgG positive; HBSAG negative; Anti-HBS negative; positive PCR), while the hepatitis C virus was negative. Hemoglobin Pattern by HPLC showed normal pattern (no hemoglobinopathy), Anti-nuclear antibody was negative, whereas plasma fibrinogen was normal 377 mg/dL (fibrinogen: 150-400 mg/dL).

Liver ultrasound shows mild hepatomegaly with moderate to severe fatty changes, and mild splenomegaly.

Case Discussion

Generally, the patient had high serum ferritin with metabolic syndrome without iron overload (obesity, type 2 diabetes mellitus, hypertriglyceridemia and hypertension) [1,16,17].

The patient also had moderate to severe Nonalcoholic Steatohepatitis (NASH), with liver parenchymal inflammation due to "fatty liver" combined with positive hepatitis B [18,19].

The chronic viral hepatitis combined with metabolic NASH was believed to be the cause of the hyperferritinaemia. There was no evidence of iron overload. Lifestyle modifications and Hepatology referral were recommended.

There are two main causes for increased serum ferritin:

1. Raised serum ferritin without iron overload (90% of cases) (Table 1) [18-20].
2. Raised serum ferritin with iron overload (10% of cases) (Table 2) [18-20].

Table 1: Causes of raised serum ferritin without iron overload [19].

Recent illness	Check for acute infection.
Chronic alcohol intake	Check alcohol excess.
Chronic liver disease, cirrhosis	Check for Abnormal liver function. Check liver by US.
Viral hepatitis	Serology for hepatitis B and C.
Acute or chronic inflammatory conditions	Erythrocyte sedimentation rate or C reactive protein, or both.
Metabolic syndrome (obesity, type 2 diabetes, dyslipidemia, hypertension)	Check body mass index, blood pressure, blood glucose, lipid studies.
Renal failure	Check renal function.
Malignancy	Check for weight loss, anorexia. Do Imaging as appropriate.

Table 2: Causes of raised serum ferritin with iron overload [19].

Personal history of iron overload	Heavy oral, intravenous iron supplements or many transfusion history.
Chronic Anemia with ineffective erythropoiesis (thalassemia intermedia, sideroblastic anemia, chronic hemolytic anemia	Full blood count, blood film, haemoglobinopathy studies.
Hereditary haemochromatosis	Check for fatigue, lethargy, arthralgia, diabetes, loss of libido, impotence, amenorrhoea, right upper quadrant abdominal pain, hepatomegaly, cirrhosis, chondrocalcinosis, skin hyperpigmentation, heart failure.
Family history of iron overload	Check for positive family history.
Porphyria cutanea tarda	Check for cutaneous photosensitivity. Check for liver dysfunction.

Guideline in Clinical Assessment of Hyperferritinemia in Primary Care [4,18,21-24]

1. It is mandatory to ask about alcohol and iron over load in each hyperferritinemia presentation.
2. Check the body mass index, blood pressure, blood sugar and blood lipid , if suspecting metabolic syndrome.
3. Check the blood count and inflammatory markers (C reactive protein or erythrocyte sedimentation rate) in order to detect occult inflammatory disorders.
4. Check serum creatinine and electrolytes for renal function.
5. Check liver function tests: Abnormal results should prompt consideration of viral hepatitis screening and abdominal ultrasonography.
6. Check the transferrin saturation: the level of transferrin saturation > 45% has a sensitivity of 94% and a positive predictive value of 6% for hereditary hemochromatosis (check for C282 Y homozygotes/ H63D).
7. Refer the patient to Hematology and Hepatology if:

a. The patient has a confirmed iron overload with ferritin level of > 1000 µg/L or abnormal liver function, regardless of the cause.

b. The patient has a positive HFE mutation results.

c. The patient has a high ferritin level need for frequent venesection (Phlebotomy) or iron chelation; the aim is to lower the serum ferritin concentrations to a level < 50 µg/L.

d. Check for genetic and iron overload in siblings of the hemochromatosis patient.

e. Refer the patient for direct assessment of liver iron stores, for instance Magnetic Resonance Imaging (MRI) or liver biopsy.

f. Refer the patient to Hepatology; if viral hepatitis or inflammatory disorder are suspected.

8. Consider interventions in patient with metabolic Hyperferritinemia (SF range 300-1000 µg/L), in whom iron overload is unlikely (transferrin saturation ≤ 45) by reducing SF (alcohol abstinence, improved glycemic control, weight reduction, and lowering triglyceride concentrations) [24].

Conclusion

Mostly, an increased ferritin with normal transferrin saturation is often found in patients with hepatic steatosis. The simultaneous disorder of iron and glucose and/or lipid metabolism may occur in metabolic hyperferritinaemia. Patients present with positive hepatitis profile indicate combined infective and metabolic hyperferritinaemia.

Recommendation

- Elevated S.F is usually due to acute/chronic inflammation, heavy alcohol ingestion, acute/chronic liver, kidney, metabolic syndrome and rarely malignancy.
- Initial tests are full CBC, liver/renal function and inflammatory markers.
- Normal fasting serum transferrin saturation will exclude iron overload.
- Unexplained very high levels of SF ≥ 1000 µg/L warrant specialist referral.
- Consider HFE gene study, if hereditary hemochromatosis is considered (SF ≥ 1000 µg/L and raised serum transferrin saturation is ≥ 45%).

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