Published in final edited form as:

JAMA. 2014 August 20; 312(7): 743–744. doi:10.1001/jama.2014.302.

Elevated Serum Ferritin

Lisa B. VanWagner, MD, MS and Richard M. Green, MD

Departments of Preventive Medicine and Medicine, Division of Gastroenterology & Hepatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (VanWagner); Department of Medicine, Division of Gastroenterology & Hepatology, Section of Hepatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Green).

An elevated ferritin level was discovered during an anemia evaluation in a 46-year-old man with inflammatory arthritis. The patient reported pain in multiple joints for which he took indomethacin. He also consumed 2 alcoholic beverages daily. His mother had inflammatory arthritis and his sister had lupus. On physical examination, the patient's blood pressure was 148/82 mm Hg, pulse was 92/min, and body mass index was 28. The liver was 7.0 cm and slightly firm. He was anicteric with no stigmata of chronic liver disease and the spleen was not palpable. Physical examination findings were otherwise unremarkable. The results of laboratory tests are shown in the Table.

Test Characteristics

Ferritin is an iron-binding protein that indicates total body iron stores. Ferritin is an acute-phase protein that increases in response to inflammatory states, including malignancy, infection, and in liver, renal and autoimmune diseases.¹ The likelihood of having hereditary hemochromatosis depends on the degree of ferritin elevation and is affected by sex and weight.^{2,3} A ferritin level of 200 µg/mL or higher (in women) or 300 µg/mL or higher (in men) has a sensitivity of 66% and a specificity of 85% to detect hereditary hemochromatosis, whereas a ferritin level of 500 µg/mL or higher (in men) or 400 µg/mL or higher (in women) has a sensitivity of 45% and specificity of 97%.³ The transferrin saturation is the ratio of serum iron to total iron-binding capacity. A transferrin saturation of 60% or higher (in men) or 50% or higher (in women) has a sensitivity greater than 90% to detect C282Y homozygosity in the presence of abnormal liver enzyme levels.⁴ In patients younger than 35 years, a ferritin level lower than 200 µg/mL and transferrin saturation lower than 45% have a negative predictive value around 97%.^{5,6} However, the positive predictive value of these thresholds is only 20%; thus, confirmatory testing with gene analysis or liver biopsy with the hepatic iron index may be needed. The Medicare midpoint reimbursement for a ferritin assay is \$25.31 and for transferrin saturation is \$23.72 (<http://www.cms.gov/>

Copyright 2014 American Medical Association. All rights reserved.

Corresponding Author: Lisa B. VanWagner, MD, MS, Fellow, Division of Gastroenterology & Hepatology, and Preventive Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, 680 N Lake Shore Dr, Ste 1400, 14-079K, Chicago, IL 60611 (lvw@northwestern.edu).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Green reports receiving consulting fees from Gilead for work unrelated to this article. No other disclosures were reported.

Additional Contributions: We thank the patient for providing permission to share his information.

[Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/clinlab.html](#)). The cost of genetic analysis ranges from \$150 to \$500.⁷

Research demonstrates that a ferritin level higher than 1000 µg/L is associated with a high prevalence (20%–45%) of advanced fibrosis and cirrhosis in hereditary hemochromatosis.^{6,8} Thus, liver biopsy is recommended to stage the degree of liver disease in *C282Y* homozygotes or compound heterozygotes if liver enzymes are elevated or if the ferritin level is above 1000 µg/L.⁶ The risks of liver biopsy have been previously reviewed and most commonly include pain and mild bleeding.⁹ The mortality rate associated with liver biopsy is less than 1:10 000.^{6,9}

Application of Test Result to This Patient

This patient has several potential causes of an elevated ferritin level, including inflammatory arthritis, obesity, and alcohol use.¹ However, the concurrent elevations of transferrin saturation and aminotransferases in addition to the magnitude of the ferritin elevation may make hereditary hemochromatosis the most likely cause. *HFE* analysis was ordered for confirmation and liver biopsy was performed to evaluate for cirrhosis and exclude additional causes of aminotransferase elevation.⁶

Hereditary hemochromatosis is an autosomal recessive disorder associated with increased iron absorption, resulting in iron deposits that may lead to arthritis, diabetes, endocrinopathy, heart disease, cirrhosis, and hepatocellular carcinoma. Nonhereditary causes of iron overload include excess iron supplementation, frequent blood transfusions, obesity, alcohol consumption, and several hematologic disorders. The most common form of hereditary hemochromatosis is caused by homozygous *C282Y* mutations of the *HFE* gene with a prevalence of 1:200 in white individuals.³ The frequency of *C282Y/C282Y* homozygosity is less than 1:3500 in black and Hispanic persons.³ Another mutation not associated with iron loading is *H63D* unless seen with *C282Y* as a compound heterozygote (*C282Y/H63D*).⁶ Men are 3 times more likely to develop iron overload–related disease than women and often at a younger age.¹⁰ Patients may be asymptomatic (75%) or may present with fatigue, arthralgias, abdominal pain, or impotence.⁶

What Are Alternative Diagnostic Testing Approaches?

Serum ferritin is only part of the algorithm used to detect hereditary hemochromatosis.⁶ Elevated ferritin occurs later in the course of iron overload than elevated transferrin saturation and the sensitivity of ferritin alone is poor for the detection of hereditary hemochromatosis. Therefore, both assays are important screening tests in a patient with suggestive symptoms, clinical findings, or family history of hereditary hemochromatosis.⁶ If transferrin saturation is 45% or greater or ferritin is elevated, then *HFE* analysis should be considered.⁶ Other laboratory testing typically includes measurement of liver enzymes and platelet count to assess the presence of hepatocyte damage and portal hypertension (Table).

Patient Outcome

In this patient, *HFE* analysis confirmed *C282Y/C282Y* homozygosity. A liver biopsy demonstrated grade 3 hemosiderosis and mild portal fibrosis. He underwent weekly phlebotomy for 15 months and is now receiving maintenance phlebotomy. Nine years later, he remains well without evidence of disease progression.

Acknowledgments

Funding/Support: Dr VanWagner is supported by an NIH grant (1F32HL116151-01) and an American Liver Foundation Postdoctoral Research Fellowship Award, and Dr Green is supported by an NIH R01 grant.

Role of the Sponsors: The funding agencies played no role in the preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Moore C Jr, Ormseth M, Fuchs H. Causes and significance of markedly elevated serum ferritin levels in an academic medical center. *J Clin Rheumatol*. 2013; 19(6):324–328. [PubMed: 23965472]
2. McKinnon EJ, Rossi E, Beilby JP, Trinder D, Olynyk JK. Factors that affect serum levels of ferritin in Australian adults and implications for follow-up. *Clin Gastroenterol Hepatol*. 2013 Jul.30
3. Adams PC, Reboussin DM, Barton JC, et al. Hemochromatosis and Iron Overload Screening (HEIRS) Study Research Investigators. Hemochromatosis and iron-overload screening in a racially diverse population. *N Engl J Med*. 2005; 352(17):1769–1778. [PubMed: 15858186]
4. Pippard MJ. Detection of iron overload. *Lancet*. 1997; 349(9045):73–74. [PubMed: 8996414]
5. Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2006; 145(3):209–223. [PubMed: 16880463]
6. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011; 54(1):328–343. [PubMed: 21452290]
7. Chandrasekharan S, Pitlick E, Heaney C, Cook-Deegan R. Impact of gene patents and licensing practices on access to genetic testing for hereditary hemochromatosis. *Genet Med*. 2010; 12 suppl(4):S155–S170. [PubMed: 20393306]
8. Powell LW, Dixon JL, Ramm GA, et al. Screening for hemochromatosis in asymptomatic subjects with or without a family history. *Arch Intern Med*. 2006; 166(3):294–301. [PubMed: 16476869]
9. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. American Association for the Study of Liver Diseases. Liver biopsy. *Hepatology*. 2009; 49(3):1017–1044. [PubMed: 19243014]
10. Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in *HFE* hereditary hemochromatosis. *N Engl J Med*. 2008; 358(3):221–230. [PubMed: 18199861]

HOWDO YOU INTERPRET THESE TEST RESULTS?

- A.** Obesity and alcohol consumption are the most likely primary causes of the elevated ferritin level.
- B.** Hereditary hemochromatosis is the most likely primary cause of the elevated ferritin level.
- C.** Inflammatory arthritis is the most likely primary cause of the elevated ferritin level.
- D.** Excess iron consumption is the most likely primary cause of the elevated ferritin level.

Answer

- B.** Hereditary hemochromatosis is the most likely primary cause of the elevated ferritin level.

Clinical Bottom Line: Elevated Ferritin Level

- Disease progression in hereditary hemochromatosis can be slowed or prevented by decreasing iron stores through therapeutic phlebotomy, followed by maintenance phlebotomy with a goal ferritin of 50–100 µg/L.⁵
- Patients without hepatic fibrosis may have a normal life expectancy with phlebotomy. The main causes of death in untreated hereditary hemochromatosis are cirrhosis (32%) and hepatocellular carcinoma (30%).⁶
- Patients with cirrhosis should be screened for hepatocellular carcinoma and esophageal varices.⁶ Although phlebotomy is indicated in cirrhosis, it may not prevent clinical decompensation or need for liver transplantation.

Table**Serum Laboratory Tests**

Test	Patient's Value	Reference Range
Ferritin, µg/mL	2556	24–336
Iron, µg/dL	253	40–140
Transferrin saturation, %	88	20–50
Alanine aminotransferase, U/L	52	0–48
Aspartate aminotransferase, U/L	41	0–40
Alkaline phosphatase, U/L	76	30–115
Total bilirubin, mg/dL	0.9	0–1.3
International normalized ratio	0.9	0.9–1.1
Platelet count, $\times 10^3$ cells/ μ L	211	140–390