CLINICAL RESEARCH STUDY

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Hereditary Hemochromatosis: Missed Diagnosis or Misdiagnosis?

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ABSTRACT

BACKGROUND: Hereditary hemochromatosis is a disorder that can cause iron overload and organ damage. Hereditary hemochromatosis is characterized by mutations in the *HFE* gene. *HFE* C282Y homozygotes and compound heterozygotes (C282Y/H63D) are at risk of developing manifestations of hemochromatosis. Abnormal iron study results also occur in many liver and hematologic diseases. The aim of this study was to evaluate the accuracy of diagnosis of hereditary hemochromatosis.

METHODS: Pertinent clinical and laboratory data, including *HFE* genotype, were tabulated from the electronic medical records of patients with the International Classification of Diseases 9th Revision code 275, "disorders of iron metabolism," who were seen at a tertiary referral center between January 2002 and May 2012.

RESULTS: *HFE* genotyping was obtained in only 373 of 601 patients (62%); 200 were C282Y homozygotes or compound heterozygotes. Of the 173 patients with nonhereditary hemochromatosis genotypes, 53% were misdiagnosed with hereditary hemochromatosis and 38% underwent phlebotomy. In two thirds of these cases, the misdiagnosis was made by a nonspecialist. In the remaining 228 patients who were not genotyped, 80 were diagnosed with hereditary hemochromatosis and 64 were phlebotomized. Of patients misdiagnosed with hemochromatosis, 68% had known liver disease and 5% had a hematologic cause of abnormal iron study results.

CONCLUSIONS: Abnormal iron study results in patients with nonhereditary hemochromatosis genotypes commonly lead to a misdiagnosis of hereditary hemochromatosis and inappropriate treatment with phlebotomy. This error often is seen in the setting of elevated iron study results secondary to chronic liver diseases. Furthermore, hereditary hemochromatosis is commonly diagnosed and treated without *HFE* genotyping. We suggest that phlebotomy centers require a documented *HFE* genotype before initiating phlebotomy.

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KEYWORDS: Hereditary hemochromatosis; Iron overload; Liver disease; Phlebotomy

Elevated iron study results are a frequent laboratory finding that can be a clue to a common genetic disorder. Hereditary hemochromatosis is an inherited disorder of iron metabolism that can cause organ damage from the accumulation of excess iron.[1,2] The most common form of hereditary hemochromatosis ("hemochromatosis type 1") results from mutations in the gene known as *HFE*. The specific mutations associated with hereditary hemochromatosis are the substitution of a tyrosine for cysteine at amino acid 282 (C282Y) and the substitution of aspartic acid for histidine at amino acid 63 (H63D).[1,2] Individuals who are homozygous for the C282Y mutation or who have single copies of both the C282Y and H63D mutations (compound heterozygotes) are susceptible to developing iron overload, with 85% to 90% of hemochromatosis cases occurring in C282Y homozygotes and the remainder occurring in compound heterozygotes.[1,3,4] In contrast, simple C282Y heterozygotes and H63D heterozygotes and homozygotes are not at risk for hereditary hemochromatosis.[2,4,5] Additional forms of primary iron overload (hemochromatosis types 2-4) caused

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by mutations in iron-regulatory genes other than *HFE* are now recognized,[1,2] but genetic testing for these rare conditions is not routinely available.

Multiple conditions can be associated with abnormal iron study results in the absence of an inherited defect in iron metabolism.[6] Secondary abnormalities of iron tests are frequently seen in the context of hematologic diseases, in particular hemolytic anemias, anemia secondary to ineffective erythropoiesis, and disorders treated with multiple transfusions, and in several common types of chronic liver disease. Among the latter group, increased iron studies are seen in up to 50% of patients with alcoholic liver disease, nonalcoholic fatty liver disease, or chronic viral hepatitis.[4] In this setting, elevations in transferrin saturation or serum ferritin levels do not invariably reflect the presence of excess iron in the liver or other organs. The clinical significance of elevated iron study results and hemosiderosis in liver disease—and whether this condition requires treatment—remains controversial.[6] This contrasts with hereditary hemochromatosis and transfusional iron overload, in which there is consensus that heavy iron loading causes organ damage and that removal of excess iron can prevent these complications.[7-9] Thus, correct identification of the cause of iron test abnormalities is required to determine appropriate treatment.

The identification of the *HFE* mutations in 1996 was a major step toward improving the accuracy of diagnosis of hereditary hemochromatosis.[7] In view of the high prevalence of conditions associated with secondary abnormalities of iron metabolism, *HFE* genotyping is a useful tool to distinguish hereditary hemochromatosis from these secondary abnormalities. The aims of this study were to investigate the approach of physicians to elevated iron study results at an academic medical center, to assess the accuracy of their diagnoses of hereditary hemochromatosis, and to identify factors that contribute to misdiagnosis.

CLINICAL SIGNIFICANCE

- A review of more than a decade's experience at a tertiary referral center suggests that diagnoses of hereditary hemochromatosis are often incorrect or inadequately substantiated.
- Failure to obtain *HFE* genotyping in suspected hereditary hemochromatosis is common.
- *HFE* genotyping is frequently misinterpreted.
- Awareness of common causes of secondary iron test abnormalities, in particular chronic liver disease, is low.

MATERIAL AND METHODS

The institutional review board of the University of Iowa approved this study. A list of patients seen at the University of Iowa between January 2002 and May 2006 and between January 2009 and May 2012 with the International Classification of Diseases (ICD) 9th Revision code 275 "disorders of iron metabolism" as a primary or secondary diagnosis was obtained. Patients seen between 2006 and 2009 were not included because transition to a new electronic medical record occurred during this period. A systematic review of the electronic medical records was then performed. Patients with iron deficiency were excluded. Subjects with no mention of iron overload and no findings in their records suggesting abnormal iron metabolism were considered to be miscoded and were likewise excluded from the study. For patients included in the study, the following data were collected: age at diagnosis, gender, family history of hereditary hemochromatosis, *HFE* genotype, history of multiple transfusions or known hematologic disease, or evidence of chronic liver disease. Diagnoses of cirrhosis or hepatocellular carcinoma based on clinical findings or imaging or pathology results, and recommendations for or records of phlebotomies were tabulated. The specialty of the diagnosing provider, the year of diagnosis, and the laboratory studies corresponding to that visit were recorded. Laboratory studies included iron levels, total iron-binding capacity, transferrin saturation, ferritin level, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, and total bilirubin.

The 2011 practice guidelines of the American Association for the Study of Liver Disease were used to assess the appropriate diagnostic strategy and management of hereditary hemochromatosis.[4] Transferrin saturation level >45% and ferritin level >250 ng/mL in women and >300 ng/mL in men were considered elevated. Aspartate aminotransferase and alanine aminotransferase >1.5 times the upper limit of normal, which corresponds to 50 U/L in our facility, were considered elevated.

An analysis was done to compare the characteristics of those diagnosed between 2002 and 2006 with those diagnosed between 2009 and 2012. Because the continuous data were not normally distributed, we presented them as medians and interquartile range and used the Wilcoxon rank-sum test to detect statistical significance. For categoric variables, the chi-square test was used. Statistical significance was set at $P < .05$. All statistical analyses were performed using SAS version 9.3 for Windows (SAS Institute, Inc, Cary, NC).

RESULTS

Patient Characteristics

There were 760 patients with ICD code 275 (disorders of iron metabolism), of whom 159 were excluded. Of the 601 patients included in the study, *HFE* genotyping was documented for 373 (62%). Of those who underwent *HFE* genotyping, 54% had genotypes consistent with hereditary hemochromatosis ("hereditary hemochromatosis genotypes"—153 C282Y homozygotes and 47 compound heterozygotes). Of those with nonhereditary hemochromatosis genotypes, 33 were simple