Clinical Burden of Liver Disease From Hemochromatosis at an Academic Medical Center

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Hereditary hemochromatosis (HH) can cause cirrhosis and hepatocellular carcinoma (HCC), but the frequency of these complications is controversial. To address this question, we reviewed the experience with HH at an academic medical center that is the sole liver transplantation center in a state with a population that is >90% Caucasian. The records of all subjects with International Classification of Diseases, Ninth Revision, code 275, "disorders of iron metabolism" seen at the University of Iowa Hospitals and Clinics between January 1, 2004 and December 31, 2014 were reviewed, and *HFE* C282Y homozygotes and C282Y/H63D compound heterozygotes were identified. Clinical, pathologic, and laboratory data from these subjects were examined in detail. We identified 118 C282Y homozygotes and 44 compound heterozygotes; 22 of the former and 3 of the latter had advanced hepatic fibrosis (bridging or cirrhosis). Male patients predominated in both groups. Most of the C282Y homozygotes and all compound heterozygotes had causes of chronic liver disease in addition to iron overload. Together, these accounted for 0.42% of cases of cirrhosis seen at the University of Iowa Hospitals and Clinics during this period. Two male patients with cirrhosis attributable solely to iron overload presented with cardiac dysfunction and atrial fibrillation; this classical presentation was rare, representing approximately one per 3,000 cases of cirrhosis. Eight homozygotes were diagnosed with HCC, representing 1.8% of patients with HCC. *Conclusion*: Despite the expected high prevalence of HH mutations in our state and the referral bias inherent in our study, serious hepatic manifestations of HH were uncommon. These data support claims that the penetrance of frank clinical hemochromatosis is low. (*Hepatology Communications* 2017;1:453–459).

Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism that leads to iron accumulation and end-organ damage in a proportion of affected subjects. Until relatively recently, HH was regarded as a highly penetrant and progressive condition such that the majority of affected individuals were expected to develop clinical manifestations of iron overload if not diagnosed and treated in a timely fashion. This view is summed up by a quote from the late 1990s, "Although the time required to become iron loaded is variable, it is clear that most homozygotes will eventually become symptomatic."[1]

The basis for the claim that untreated HH invariably leads to morbidity is obscure. For years prior to the identification of the *HFE* mutations responsible for the most common form of hemochromatosis, HH was known to be highly prevalent among whites of Northern European ancestry, with a homozygote frequency of ~1:250.[2,3] At the same time, the condition was thought to be frequently overlooked and therefore to go untreated. Studies done prior to the availability of

Abbreviations: HCC, hepatocellular carcinoma; HH, hereditary hemochromatosis; ICD9, International Classification of Diseases Ninth Revision; UIHC, University of Iowa Hospitals and Clinics.

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genetic testing reported that cirrhosis and hepatocellular carcinoma (HCC) are the most common causes of death in HH patients.[4-6] Consequently, one would expect HH to cause substantial liver-related morbidity and mortality; yet a study that analyzed data from death certificates found that hemochromatosis was noted as an underlying or contributory cause of death at a much lower rate than expected based on the prevalence of HH in the general population.[7] It is possible that this discrepancy reflects lack of recognition of HH rather than low frequency of disease manifestations, but that explanation cannot account for the HH patients without significant liver damage from iron overload detailed in case series from experts on the disease.[8,9] The relative infrequency of serious liver pathology in the latter circumstance may be credited to early detection and treatment, but it remains the case that if many individuals with HH are not diagnosed, early diagnosis and treatment cannot account entirely for a lower than expected number of deaths resulting from HH.

More recently, various lines of evidence have challenged the concept that HH is a common cause of morbidity. In a study involving over 40,000 subjects, Beutler and colleagues[10] concluded that less than 1% of C282Y homozygotes manifest clinical evidence of HH. Three studies from Europe showed no decrease in the proportion of C282Y homozygotes among elderly versus younger subjects, suggesting no adverse selection of HH homozygotes from the population, as would be expected if HH led to shortened life expectancy.[11-14] With specific regard to liver pathology, low rates of biopsy-proven cirrhosis were found among newly diagnosed HH patients identified in a population screening program from Norway, in a review of previously diagnosed HH cases from Wales, and in a screening study from North America.[15-17] In contrast, the HealthIron study from Australia suggested a higher rate of iron overload-related liver disease, particularly in male C282Y homozygotes, as assessed by the prevalence of aminotransferase elevations or a history of liver disease in this group.[18] It is evident that estimates of the frequency of iron overload-related disease are dependent on the definition of disease. Furthermore, although screening studies are less susceptible to several types of bias, the extent of clinical evaluation of individual subjects in these types of investigation is typically limited, making it difficult to discern, for example, whether aminotransferase elevations or liver disease history are attributable to HH or to some other condition.

The aim of this study was to examine the frequency of hemochromatosis-related liver disease from a real-world perspective, reviewing our institutional experience with HH. The University of Iowa Hospitals and Clinics (UIHC) is a public teaching hospital. It is the only academic tertiary care center in the state of Iowa and is home to the state's only liver transplantation program. According the U.S. Census Bureau's 2014 estimate, approximately 92% of Iowa's population of 3.1 million is white.[19] Based on the expectation that *HFE* mutations are common among Iowans and that C282Y homozygotes who develop clinical manifestations of HH, particularly liver disease, are likely to be referred to UIHC, we examined the burden of liver disease related to HH in patients seen at our institution over a 10-year period.

Patients and Methods

The Institutional Review Board of the University of Iowa approved this study. A list of patients seen at the UIHC between January 1, 2004 and December 31, 2014 with the International Classification of Diseases, Ninth Revision (ICD9), code 275 "disorders of iron metabolism" as a primary or secondary diagnosis was obtained from the Joint Office of Compliance at UIHC. From this same source, we obtained numbers of unique patients seen at UIHC during the study period with diagnoses of liver cirrhosis or liver cancer.

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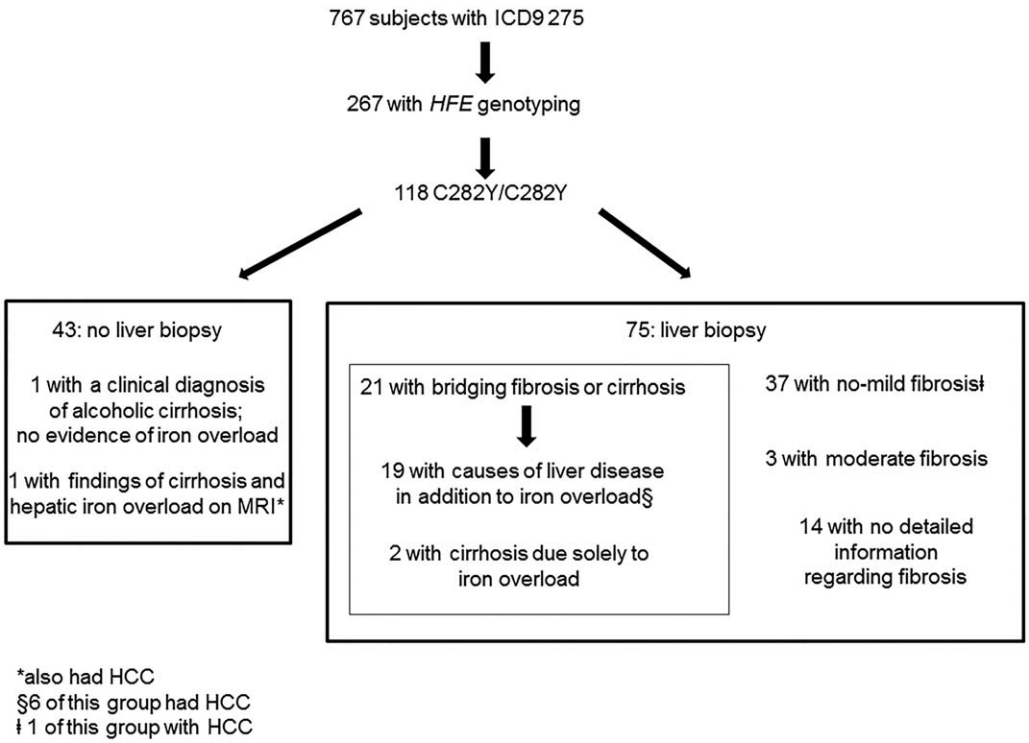

FIG. 1. Identification of C282Y homozygotes and their liver biopsy results. Abbreviation: MRI, magnetic resonance imaging.

The electronic medical records of all patients with ICD9 275 were reviewed. Patients with iron deficiency anemia or no mention of hemochromatosis, iron overload, or related disorders in their record were considered miscoded and excluded from further study, as were subjects without documentation of *HFE* genotyping.

We restricted our analysis to C282Y homozygotes and C282Y/H63D compound heterozygotes. Medical records of C282Y homozygotes and compound heterozygotes were reviewed by both authors with specific attention paid to the presence/absence of risk factors for additional forms of liver disease and reports of liver biopsies and liver imaging.

Results

A total of 767 subjects with a primary or secondary diagnosis of disorder of iron metabolism (ICD9 code 275) were seen at UIHC between January 2004 and December 2014. *HFE* genotyping was available in 267 (35%) of these individuals. Among those who underwent *HFE* genotyping, there were 118 C282Y homozygotes and 44 compound heterozygotes (C282Y/H63D).

Of the 118 C282Y homozygotes, 43 subjects had not undergone liver biopsy (Fig. 1). Female individuals predominated in this group (25 versus 18), and most of these subjects had been diagnosed with HH by a nonhepatologist (i.e., internist, family practitioner, hematologist, rheumatologist). Only 1 of these patients had a known liver disease based on review of the records; this was a 55-year-old man with a past history of heavy alcohol use and reported alcoholic cirrhosis. He was diagnosed with HH in the course of evaluation of joint complaints that led to a diagnosis of HH arthropathy. His liver disease was not evaluated further at UIHC, but as he was not previously known to have HH and his ferritin was normal at the time of his initial HH diagnosis, iron overload can be excluded as its cause.

Liver biopsies had been performed in the remaining 75 C282Y homozygotes, more than two thirds of whom were male subjects (53 versus 22). Most of the liver biopsies were performed at UIHC. In one case, liver histopathology was obtained from UIHC autopsy records of a male C282Y homozygote. Liver biopsies

TABLE 1. CHARACTERISTICS OF C282Y HOMOZYGOTES WITH ADVANCED FIBROSIS ON LIVER BIOPSY (EXCLUDING SUBJECTS WITH HCC)

	Sex	Age*	Fibrosis	Iron	Other
1	M	44	Cirrhosis	"Massive"	HCV, alcohol
2	M	49	Cirrhosis	"Marked"	Alcohol
3	M	42	Bridging	2+	Steatohepatitis
4†	M	57	Cirrhosis	4+	–
5	M	41	Cirrhosis	"Significant"	Alcohol
6	M	42	Cirrhosis	2+/3+	HCV, alcohol
7	M	33	Bridging	3+	HIV+
8†	M	45	Cirrhosis	4+	HCV, alcohol
9	M	45	Bridging	3+	HCV, alcohol
10	M	61	Bridging	3+/4+	Steatosis
11	M	42	Cirrhosis	"Dense"	Alcohol
12	M	54	Cirrhosis	4+	Steatohepatitis
13†	M	27	Cirrhosis	"Severe"	–
14	F	56	Bridging	"Marked"	Steatohepatitis
15	M	61	Cirrhosis	"Prominent"	Steatosis

*Age at time of biopsy
†Patients with cardiomyopathy and atrial fibrillation
Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

done at other institutions were reviewed by UIHC pathologists in several instances, and formal histopathologic interpretation was available in the electronic medical record. In a smaller number of cases, the findings of the external pathology report were summarized in the clinical notes or were based on patient reports. In 11 cases, the report included either no statement regarding fibrosis stage, a general comment such as "no cirrhosis," or a description of noncirrhotic fibrosis in a pattern indicative of an injury process other than HH (i.e., sinusoidal fibrosis or central sclerosis). Finally, the records of 3 male homozygotes indicated that liver biopsy had been done elsewhere, but no information regarding the biopsy results was available in the records. None of the latter patients had evidence of significant liver disease as far as could be determined from the available clinical and laboratory data.

Information regarding the fibrosis stage was therefore available in 61 patients. Twenty-one subjects had advanced hepatic fibrosis (bridging fibrosis or cirrhosis), 3 had moderate fibrosis without bridging, and in 37 cases fibrosis was rated as absent, minimal, or mild. In addition to the patients with histologically proven bridging fibrosis or cirrhosis, 1 patient was diagnosed with cirrhosis based on imaging studies, bringing the total number of C282Y homozygotes with advanced fibrosis and hepatic iron deposition to 22.

Most of the C282Y homozygotes with advanced fibrosis had risk factors for causes of chronic liver injury in addition to iron overload (Table 1). Heavy alcohol use, obesity, and features of metabolic syndrome were common in this group, and steatosis or steatohepatitis was present on many of the biopsies. In addition, 4 patients had chronic hepatitis C infection and 1 had human immunodeficiency virus infection. However, there were 2 male patients, ages 53 and 27 years at diagnosis, whose cirrhosis appeared to be due solely to iron overload based on clinical, laboratory, and histologic findings. Interestingly, both of these patients presented with cardiac dysfunction with atrial fibrillation and a severely depressed left ventricular ejection fraction. (Although the age of the latter patient suggested coexisting juvenile hemochromatosis, this possibility was not formally evaluated.) In both cases, HH was diagnosed only after the presentation with cardiac involvement.

Eight patients with HCC were identified among the C282Y homozygotes (Table 2). All but 1 of these patients were male, and all but one of the HCCs occurred in the context of cirrhosis. Additional risk factors for liver disease were present in all the subjects with HCC, several of whom had been depleted of excess iron for extended periods (over 20 years in one case) prior to the diagnosis of HCC.

Forty-four compound heterozygotes were identified during the study interval. These patients were disproportionately male (73%). Nineteen had undergone liver biopsy. In 12 cases, histopathologic findings unrelated to iron excess were documented, most commonly steatosis or steatohepatitis (11 cases) and chronic hepatitis C infection (one case). Fibrosis was reported as absent, minimal, or mild in most cases; however, 3 compound heterozygotes had biopsy-proven cirrhosis (attributed to nonalcoholic steatohepatitis in two cases and alcoholic liver disease in a third). There were no patients with advanced fibrosis attributable to iron overload alone in this group and no cases of HCC among the compound heterozygotes.

During the period of study, a total of 5,934 patients with a diagnosis of liver cirrhosis were seen at UIHC. Considering all 22 subjects with advanced fibrosis and evidence of iron overload irrespective of concomitant causes of chronic liver disease, C282Y homozygotes constituted 0.37% of the patients with cirrhosis seen at our institution during this time interval. This proportion remains very low (0.42%) with the addition of the 3 compound heterozygotes. If only those cases of cirrhosis attributable to iron overload alone are considered, the proportion attributable to HH is 0.03%, i.e., one of every 3,000 cases of cirrhosis. During this same period, there were 447 cases of liver cancer. If all

TABLE 2. FEATURES OF C282Y HOMOZYGOTES WITH HEPATOCELLULAR CARCINOMA

	Sex	Age at HCC diagnosis	Age at HH diagnosis	Cirrhosis?	Phlebotomy?	Other causes of chronic liver disease	Comment
1	M	50	50	Yes	No	Obesity, alcohol	Initial presentation with metastatic HCC
2	M	71	71	Yes	No	Obesity	Diagnosis of cirrhosis based on imaging
3	M	64	56	Yes	Yes	Chronic HCV, alcohol	
4	F	70	48	Yes	Yes	Obesity, alpha1-antitrypsin deficiency	Biopsy 4 years before HCC diagnosis showed cirrhosis due to NASH and alpha1-AT deficiency with no stainable iron
5	M	65	41	Yes	Yes	Obesity, alcohol, DM	
6	M	58	39	Yes	Yes	Alcohol	
7	M	53	49	No	Yes	Obesity	Lobectomy showed mild portal fibrosis
8	M	56	33	Yes	Yes	Obesity, alcohol	Explant (24 years after HH diagnosis) showed near-complete regression of cirrhosis

Abbreviations: AT, anti-trypsin; DM, diabetes mellitus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

patients with HCC and homozygosity for C282Y are considered irrespective of concomitant causes of chronic liver disease (n = 8), HH is implicated in 1.8% (8/447) of HCC cases. There were no cases of HCC among the patients with cirrhosis due to HH alone. The single case of HCC in an iron-loaded but noncirrhotic liver accounts for 0.2% (1/447) of all cases of HCC seen during this interval at our institution, in keeping with the characterization of HCC in noncirrhotic HH as a rare entity.[20]

Discussion

The aim of this study was to assess the frequency of clinically significant liver disease in HH homozygotes and compound heterozygotes evaluated at our institution over a 10-year period. This approach afforded the ability to examine the records of patients with these HH mutations in granular detail, including in the majority of cases, liver biopsy data concerning the presence or absence of hepatic fibrosis and additional causes of liver pathology. Because the population of Iowa is overwhelmingly Caucasian, *HFE* mutations are presumed to be common among our patients. Furthermore, because our institution is home to both the only academic hepatology section in the state and the sole liver transplantation program, a significant proportion of the state's residents who have advanced liver disease are seen at UIHC. Taking this inherent referral bias into account, the low frequency of advanced fibrosis and HCC attributable to HH at our institution is particularly striking.

Our results are in line with other studies suggesting that liver-related morbidity from HH is uncommon[10,13-15,17,21]; however, it is important to recognize that it cannot be assumed that the number of cases of HH-related liver disease seen at a single center necessarily reflects the propensity of HH to cause serious liver pathology. Cases of advanced liver disease and HCC may have been prevented by timely detection and treatment of HH. Although this has not been evaluated prospectively, it is reasonable to surmise that treatment contributes to a lower than expected rate of liver disease caused by iron overload. Nonetheless, in the absence of a systematic screening program for HH, the benefit of treatment in preventing the development of liver disease is limited to those in whom the diagnosis of HH is made, while those who are undiagnosed remain at risk. It is difficult to estimate the magnitude of the impact of treatment on our results as this depends both on the proportion of HH cases that are diagnosed and treated and the probability of progression to advanced fibrosis in untreated HH, neither of which are known.

Another potential explanation for the low frequency of HH-related advanced liver disease is that these patients are cared for by community physicians and/or referred elsewhere. Although we cannot exclude this possibility, we doubt that this is a significant factor given referral patterns for other forms of chronic liver disease as demonstrated by the large volume of patients with cirrhosis seen at our center (nearly 6,000 over 10

years). It is also formally possible that cases of liver disease caused by HH were missed due to miscoding, but it seems unlikely that such errors occur with sufficient frequency as to alter our overall conclusions. "Missed" diagnoses of HH in patients with liver disease due to iron overload are likewise unlikely to account for our findings given that serum iron tests are routinely obtained in the evaluation of patients with chronic liver disease at our institution, followed by genetic testing and biopsy as indicated. In this context, it is worth noting that the number of C282Y homozygotes with advanced fibrosis identified in our study (n = 22) matches exactly the number of homozygotes that would be expected among the patients with cirrhosis if one assumes that the probability of cirrhosis in C282Y homozygotes does not differ from that of the general population, that the ethnic composition of the group with cirrhosis is the same as the state overall (i.e., 92% of 5,934), and that the C282Y homozygote frequency is 1:250. Also to this point, in a review of adults with cirrhosis autopsied at UIHC over a 10-year period, there was a single case of HH who had been diagnosed premortem.[22] Taken together, these data suggest that significant liver disease caused by HH rarely goes unrecognized at our institution.

Our finding that causes of chronic liver disease in addition to iron overload were often present in C282Y homozygotes with advanced hepatic fibrosis is consistent with previous studies showing that excess alcohol consumption, hepatic steatosis related to obesity, and chronic hepatitis C virus infection are associated with fibrosis in HH.[23-25] Because it is not feasible to perform liver biopsies routinely in large-scale studies of HH, it has been suggested that these types of studies may underestimate the prevalence of clinically silent liver disease.[26] Conversely, our data suggest that without liver biopsy, cases of advanced fibrosis could be inaccurately attributed to HH when additional causes of liver pathology are present. The contribution of HH to the fibrogenic process in these cases notwithstanding, the lack of histologic information poses a significant limitation in ascertaining the burden of liver disease caused solely by iron overload in HH.

The present study confirms the striking predominance of male subjects among HH homozygotes with advanced fibrosis, as has been reported by other investigators.[16,18,21,24,25,27] Collectively, these data suggest that it is a rare female C282Y homozygote in whom treatment is required to prevent serious liver-related morbidity, but as with the male homozygotes, the number needed to treat cannot be determined without robust data on the risk of adverse liver outcomes in HH and the magnitude of the risk reduction with treatment. Our data also confirm the greater frequency of HCC development in male versus female C282Y homozygotes. The overall rate of HH-associated HCC in the current study is lower than in earlier reports from the United Kingdom, with C282Y homozygotes representing ~2% of all patients with HCCs in our series versus 6%-9% in three studies from Willis et al.[13,21,27] It is interesting to note that there were considerably fewer HCCs in the British studies despite a much longer accrual period (over 3 decades) than in the current study. We speculate that as the incidence of HCC has increased as a result of advanced liver disease due to chronic hepatitis C virus infection and nonalcoholic steatohepatitis, HH accounts for proportionately fewer cases of HCC. However, this requires additional studies for confirmation.

In conclusion, subjects with HH accounted for less than one half of 1% of all patients with cirrhosis seen at a tertiary referral center over a 10-year period. Most of the individuals with HH and cirrhosis had causes of chronic liver disease in addition to iron overload. Only 2 male C282Y homozygotes had cirrhosis for which iron overload was the sole cause. These 2 men also had cardiac dysfunction and atrial fibrillation, but this classical presentation of HH was unusual, accounting for only one case per 3,000 cases of cirrhosis. Although some cases of HH-related liver disease may have been prevented by early diagnosis and treatment, our data suggest that morbidity due to liver disease caused by HH is uncommon in our practice environment. HH-related liver disease commonly coexists with other causes of chronic liver disease, which should be considered in suspected cases of liver damage due to iron overload. Future research should focus on identification of patients most at risk for adverse liver outcomes.

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