Idiopathic Hemochromatosis: An Assessment of Mortality

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The purpose of this paper is to assist the medical director and underwriter in the mortality assessment of Idiopathic Hemochromatosis (IH). Although a relatively rare disorder with a frequency of 1:10,000 in the United States, we will undoubtedly be requested to underwrite more cases with the advent of multiphasic screening. We must be knowledgeable in underwriting both those with established disease as well as those diagnosed on screening in an asymptomatic state. Finally, those applicants with a family history may have to be considered for insurability.

Hereditary transmission of IH is by an autosomal recessive gene. Partial biochemical expression has been noted in heterozygotes whose gene frequency is 1:50 in the United States. Fifty percent of siblings of a source case can have hypersideremia and thus are at risk for development of IH. Disease susceptibility is linked to the major histocompatibility complex HLA (A3, B14) on the sixth chromosome; however, cases of an absent or variable HLA linkage have been described. Alcohol can affect development and progression by both accelerating iron absorption from the gastrointestinal tract and a synergistic fibrogenic effect with iron.

Laboratory diagnosis of IH can be difficult. Serum iron levels with a sensitivity of 68 percent and a positive predictive value of 61 percent are unreliable for screening probands as well as the detection of early stages of the disease. The serum ferritin and transferrin saturation have higher degrees of predictability, with the sensitivity and specificity being 85%–95% and 82%–88% respectively. The combination of ferritin and transferrin saturation is recommended for screening with a positive predictive value of 94%. Conclusive diagnosis can only be established by a liver biopsy.

Serum iron is usually greater than 200 mcg/dL in affected individuals. Total iron binding capacity is characteristically reduced and fully saturated. Plasma transferrin is greater than eighty percent saturated. Serum ferritin is usually elevated above 200 mg/dL; a level beyond 700 mg/dL is essentially diagnostic of patients with superimposed cirrhosis.

Using liver function tests to screen for hepatic involvement in IH can be misleading, as up to two-thirds of cases, at presentation with an abnormal liver histology, can be normal. Conversely, those without cirrhosis can have laboratory evidence of liver dysfunction.

The preponderance of current mortality from IH is related to the fibrogenic effect of iron deposition in the liver. In the past, 30 percent of the deaths were cardiac, usually cardiomyopathies with congestive heart failure at a young age; with treatment this complication has been reduced to 9 percent. At present, the leading cause of death in treated patients is the late development hepatocellular carcinoma.

The key to the mortality of IH is the presence of cirrhosis at biopsy. Cirrhosis is present in 40 to 80 percent of liver biopsies on initial evaluation in symptomatic patients as well as in a number of those without symptoms. There is controversy in the literature concerning the reversibility of cirrhosis and its progenitor, fibrosis. Clearly the latter, if mild and without nodular regeneration, can resolve in most cases with phlebotomy. However, often the histologic presentations of fibrosis and cirrhosis merge; thus one must not underwrite with the assumption of resolution. Moreover fibrosis can progress to cirrhosis during the phlebotomy period which can take from 6 months to 2 years (mean 18 months). Deironing cannot reduce the degree of cirrhosis once it is present but it can significantly improve mortality. To prevent the development of cirrhosis, phlebotomy must continue for the lifetime of the patient; otherwise the iron will reaccumulate.

Hepatocellular carcinoma is currently the leading cause of death in IH comprising nearly 30 percent of the mortality in treated patients whereas in untreated patients the major cause of death is hepatic failure. Hepatomas occur in about 30 percent of patients who have cirrhosis at presentation despite adequate iron removal. At an age greater than sixty five, 50 percent will die from hepatoma if cirrhosis was present on the initial biopsy. Whether there is an increased incidence of extrahepatic malignancies is controversial.

Complete deironing in the precirrhotic state is essential to remove the risk of hepatocellular carcinoma. Hepatomas do not appear to have an increased incidence when fibrosis and cirrhosis are absent on the biopsy.
conversely all patients who did develop hepatomas had cirrhosis on their initial liver biopsy. Total deironing of cirrhotic livers does not remove the risk of malignancy. Hepatomas have developed up to 18 years after maintenance phlebotomy. The mean interval from the completion of deironing to the development of hepatomas is 9 years with a range of 3 to 19 years.

Mortality of IH can be reduced by phlebotomy. Sherlock noted a mean survival time with phlebotomy of 8.2 years, without treatment 4.9 years. McLaren’s group noted similar results with survival from the onset of symptoms of 7 years, treated and 4.4 years, untreated.

A life table analysis by Bomford showed the 5 and 10 year survival after diagnosis at onset of symptoms to be 66 and 32 percent respectively in treated patients. This corresponds to a mean survival time for those treated of about 6 years, those untreated about 2 years.

In each of the preceding, the mean age at which the patients became symptomatic and were initially diagnosed as having IH was about 55 years. All three study groups included subjects who had advanced disease on presentation.

Neiderau recently published the most comprehensive mortality study of IH. The mean age of his study group was 46 and mean follow-up period was 10.5 ± 5.6 years. Compared to previous studies the 10 year lower mean age was attributed to the inclusion of asymptomatic individuals as well as those identified by family screening; thus the group was similar to our applicant pool. Unfortunately, the population used for comparison was not totally applicable to an insurable group, it being similar to the United States general population.

Multiple group survival comparisons are available. The mortality rate of the IH patients, at each 5 year interval, was approximately twice that of the normal population. Those without cirrhosis were shown to have a standard mortality. The cirrhotic group was then compared to the noncirrhotic. The mortality ratios at 5, 10 and 15 years, were 400, 180 and 180 percent for those with cirrhosis. If we exclude, as an insurable risk, those diagnosed in the first 5 years then mortality is approximately 200% at 10 and 15 years after initial diagnosis. The group that could not be completely deironed in the first 18 months had the highest mortality at each interval.

Discussion: Idiopathic Hemochromatosis produces a reduction in survival, despite treatment, after onset of the histological demonstration of cirrhosis. As noted previously, liver function tests are unreliable in screening for the existence of liver disease. Total removal of iron from the involved liver will neither produce a reversal in the cirrhosis with its attendant mortality nor decrease the high risk of hepatocellular carcinoma in later years. Newer therapies such as the chelating agent desferrioxamine are not likely to be any more effective than phlebotomy.

Underwriting of established IH requires an initial liver biopsy even in asymptomatic individuals with normal liver function tests. Since cirrhosis can develop during the acute phlebotomy period (up to two years) a repeat liver biopsy is highly advisable, in fact probably necessary at the completion of therapy. The follow-up biopsy is also required to document total iron removal. If the liver histology is normal then, provided maintenance phlebotomy is continued, this group appears to be a standard risk. An exception to the follow up biopsy might be the individual who has mild iron loading, has no fibrosis on the initial biopsy and whose deironing phlebotomy time is short as documented by laboratory studies.

For those applicants, who on screening have blood studies indicative of IH, a liver biopsy is also required to rule out asymptomatic hepatic involvement. A negative biopsy will place them in a standard mortality group, provided phlebotomy is initiated and maintained to prevent iron-induced cirrhosis.

The judgement of the medical director is tested in those cases where cirrhosis is present on the biopsy. Those who are overtly symptomatic with signs of cardiac or hepatic decompensation are obviously not insurable. Also those who cannot be deironed within one and one-half years have an unacceptable mortality.

It appears prudent to postpone any applicant with IH and cirrhosis for the first 5 years unless very mild disease is present. Somewhere between the fifth and tenth years those with asymptomatic, histologic cirrhosis become insurable at 200%. This rating assumes maintenance phlebotomies and is feasible due to the age of this group at diagnosis, about 55 years, and the long tail, about 10 years, until the potential development of hepatocellular carcinoma.

Cardiac abnormalities and Diabetes Mellitus contribute to the mortality of IH. However, both of these are almost invariably associated with large iron overloads and associated cirrhosis. By eliminating those with advanced hepatic disease their contribution to mortality should be minimal. Where diabetes is present, and unimproved by phlebotomy, an additional rating may be appropriate. One may also want to rate for associated electrocardiographic abnormalities. However, since further iron
overload is prevented by continued phlebotomy neither problem is likely to progress in severity.

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REFERENCES