Can Individuals with Latent (Precirrhotic) Hemochromatosis be Accepted at Standard Rates?

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A rational evaluation by insurance medical directors of an applicant for life or health insurance requires not only adequate information from a prospective insuree, but current knowledge concerning a common genetic disorder such as genetic hemochromatosis (GH), and the routine use of an appropriate screening test for GH of all applicants. Such an evaluation could make a vital difference in prognosis for life of an “apparently-healthy” applicant who statistically might have GH.

GH is a disorder of iron metabolism which is now known to be more prevalent than previously believed. Until the mid-1970’s, GH was considered to be rare, affecting about 200,000 Americans. Recent estimates, however, based on population and pedigree studies of GH families in Europe, Australia and North America (Utah), indicate a gene frequency of 0.05 to 0.088, corresponding to a heterozygote frequency of 10% to 16%, and a disease frequency of 3 to 8 per 1,000 Caucasians.* In terms of current U.S. population statistics, there may be 500,000 to 1,600,000 affected Americans (truly an epidemic unrecognized!) and 24 to 32 million carriers.

Sad to write, too many practicing physicians in all disciplines still consider the earlier estimate to be valid. And, as pointed out in a recent, significantly-entitled article “The neglected diagnosis”, GH is often not diagnosed during life because it mimics other common diseases: diabetes mellitus, congestive heart failure, “idiopathic” cardiomyopathy, rheumatoid arthritis, alcoholic cirrhosis, or hypogonadism.

This neglect in diagnosis of GH is especially tragic inasmuch as effective treatment (phlebotomies) is available. An early diagnosis in the precirrhotic stage before symptoms or organ damage occur is now possible, even in adolescence and younger ages; and early phlebotomy treatment can prevent iron-accumulation, tissue damage and its inevitable complications, and early death.*

The fundamental defect in GH, although not precisely understood, leads to an increase in iron absorption inappropriate to the level of body iron requirement. This results in a gradual accumulation of iron over many years, in the liver, pancreas, heart, pituitary and other organs, including joints, because excess iron cannot be excreted.

It is now generally accepted that tissue damage and eventual organ failure in all forms of iron overload (primary and secondary forms) are caused by the excess iron, possibly by lysosomal injury and the release of lysosomal enzymes; and, in the liver, this leads to periportal fibrosis and eventually to cirrhosis and hepatocellular failure. The major cause of death in the preinsulin era was diabetic coma. Sheldon’s classic 1934 monograph was the first compilation of a world series of 345 cases of hemochromatosis diagnosed mainly at autopsy. Life expectancy then was about 18 months. Of the 119 cases in which cause of death could be determined, 61 had died of diabetic coma, 15 of cirrhosis of the liver (8 hematemesis, 7 of hepatic failure), 8 carcinomas of the liver, 11 pneumonias, 10 of tuberculosis, the remainder of various unrelated “intercurrent conditions” and myocardial failure. Sheldon predicted that with the availability of insulin, the majority of deaths will be of the effects of liver cirrhosis.

Phlebotomy therapy to remove excess body iron in GH was introduced in the early 1950’s by Dr. Clement A. Finch. Although the beneficial effect of phlebotomy has never been proved by controlled studies, there is convincing evidence from several studies that clinical improvement occurs and that the prognosis for life is significantly improved. In addition, vital information was obtained of the relationship of hepatic iron concentration in liver damage with the reduction of liver iron and improvement with iron depletion.

Without therapy and removal of excess iron, the five-year survival rate after diagnosis is 18%, the 10-year survival

* The current estimates of GH became possible following the discovery of an association between hemochromatosis and the histocompatibility locus antigens (HLA), the subsequent mapping of the hemochromatosis gene on the short arm of chromosome 6 in tight linkage with the HLA region, and the use of HLA data in studies of pedigrees of families with GH. A summary of the studies contributing to the understanding of the genetics of GH is contained in a recent review.
rate 6%. Death before removal of iron can be completed occurs more frequently among alcoholic subjects. The incidence of hepatomas remains high. Controversy exists concerning the occurrence of malignancies in other organs.

Hepatomas have not been reported in precirrhotic hemochromatosis.

Cardiomyopathy is completely reversible. Early arthropathy is reversible. Hypogonadism and impotence is restorable.

A retrospective study of 163 GH patients phlebotomized included 49 precirrhotics, of whom 15 were asymptomatic. Five of the symptomatic precirrhotic patients were diagnosed in hematology clinics and a number through family screenings of diagnosed relatives. The significant finding in this study was that GH individuals diagnosed in the precirrhotic stage and treated by phlebotomy have a normal life expectancy. Although cirrhotic patients have a shorter life expectancy, phlebotomy improved their life expectancy by five years.

The Niederau study adds emphasis to the need of identifying GH individuals in the precirrhotic stage before tissue damage, and the value of routine screenings wherever possible (insurance exams, preemployment physicals, routine physicals, clinics, etc.)

A timely 1986 study from Queensland has just been published, reporting on its two-decade study of the families of 179 probands and the phenotypic manifestations of 114 asymptomatic precirrhotic relatives. Briefly, the Australian group has noted: (1) a correlation between age (duration of iron accumulation) and the hepatic iron concentration (HIC); (2) the toxic threshold above which fibrosis occurs (400 micromoles per gram); and (3) the hepatic iron concentration, when corrected for age (ratio of HIC to age), will distinguish early GH from alcoholic siderosis and heterozygotes.

SCREENING TESTS

The least expensive one, recommended by the Utah researchers, is the transferrin saturation test. A saturation above 62% accurately predicts homozygosity in 92% of the cases. (This test may be available under $10 through a national laboratory).

An alternate test is a combination of the transferrin saturation and serum ferritin. The predictive accuracy of the combination of increased transferrin saturation over 50% and an elevated serum ferritin concentration (over 200 μg/l in men; over 150 μg/l in women) was 94% sensitive and 86% specific to determine the young GH.

The definitive test is the liver biopsy; and determinations of the hepatic iron concentration (HIC) and hepatic iron index (ratio of HIC to age) are recommended.

CONCLUSION

Studies and data have been presented to show that precirrhotic GH individuals have a full life expectancy, provided that they are diagnosed early and are prevented from accumulating a body iron burden by phlebotomy treatment; and they are, therefore, good candidates to obtain standard insurance coverage.

GH heterozygotes are good candidates for standard insurance coverage. About 30% have increased iron absorption; but insufficient iron accumulates to develop tissue damage.

GH patients with cirrhosis, diabetes and other complications require, of course, a case by case evaluation of their application for insurance.

The old adage of “an ounce of prevention is worth a pound of cure” applies especially to GH. Although it is not possible to prevent inheriting the hemochromatosis gene, it is possible to prevent the complications of GH by early diagnosis through routine screening wherever possible, and referral for treatment. FINDING ONE INDIVIDUAL WITH GH IS USUALLY REWARDED IN ADDITION WITH IDENTIFICATION OF OTHER AFFECTED MEMBERS, unaware of their genetic inheritance.

The cost benefit ratio: The cost of screening applicants must be weighed against the cost of premature deaths and the payment of death benefits arising from premature deaths. It is a matter of conjecture how much insurance companies have paid out in death benefits to beneficiaries for deaths secondary to GH, such as diabetes, heart and liver disease and other GH complications.

BIBLIOGRAPHY


Note: A M.D. booklet with bibliography to aid in the diagnosis and monitoring the treatment of GH is available from The Hemochromatosis Research Foundation, Inc. P.O. Box 8569, Albany, N.Y. 12208. A self-addressed and stamped envelope is appreciated.
BIBLIOGRAPHY (continued)


