**Insurance Testing**

**HEMOCROMATOSIS 1991**

**WHAT WILL INCREASED CLINICAL SCREENING MEAN FOR MEDICAL DIRECTORS?**

DAVID L. WITTE, MD PHD
Director of Clinical Laboratories
Laboratory Control, Ltd.
Ottumwa, Iowa

BRIAN R. KAY, MD
Formerly Associate Medical Director
Principal Financial Group
Des Moines, Iowa

Hereditary hemochromatosis (HH) was last discussed in this journal in 1986. The papers by Krikker and Iacovino presented differing views of the prevalence of disease and the utility of testing for the disease. We review recent data and discuss the currently growing consensus regarding these subjects.

Hereditary hemochromatosis has an autosomal recessive inheritance pattern. The homozygous diseased state occurs in 50 of 10,000 and the heterozygous non-diseased carrier state in 1000 of 10,000 caucasians. The typical case has two unaffected heterozygote carrier parents. However, HH can occur in consecutive generations owing to the chance mating between an as-yet-undiagnosed homozygote and a heterozygote.

Hereditary hemochromatosis (HH) is frequently difficult to recognize owing to the subtlety of early presenting findings and the underestimation of disease prevalence by many physicians. In a 1985 study the average time between presentation with symptoms of HH to diagnosis of HH was 5.2 years, and 10% of cases were seen by more than five physicians before the diagnosis was made. As Krikker noted, this delay is "tragically" since early phlebotomy therapy prevents morbidity and postpones mortality. Insurance medical directors review many records of patients with as-yet-undiagnosed HH. The early findings are variable and subtle. Unexplained arthralgia and endocrine abnormalities occur in 40% of cases. Lethargy is the most frequent symptom (83%). The overt signs of disease occur later in the course with hepatomegaly in 83% and high liver enzymes in 50%. A separate study of consecutive liver clinic patients with persistent unexplained elevation of serum transaminase found 3.5% of them to be caused by HH.

Krikker stated HH prevalence to be 30-80 per 10,000 caucasians, while others state 1 per 10,000 in the U.S. In 1991, the consensus is strong that the prevalence of HH among caucasians is about 50 per 10,000. This is supported by 11 studies in seven countries.

Recent publications have strongly advocated population screening. Early detection and prevention of iron accumulation prevents morbidity and postpones mortality. Balancing the costs of testing against the costs of caring for cases discovered after symptoms develop has been studied by Phatak.

He modeled the epidemiology and identifies a net savings in health care for a screened population, even after allowing for the variability in expression among different kindreds with HH.

Serum tests of iron (Fe), iron binding capacity (IBC), percent transferrin saturation (TS), and ferritin have been widely studied in homozygous hereditary hemochromatosis, heterozygous carriers, and normal populations. Dependable sensitivity, specificity, predictive values, and likelihood ratios have been developed from these data. The most studied predictive test is transferrin saturation. Recent meals are a major confounding factor and samples following a 12-hour fast are most useful.

Transferrin saturation (TS) has been measured in two large populations. Olsson studied 4,098 inpatients, 3,340 outpatients and 1,311 blood donors. Edwards studied 11,165 blood donors. Both studies conclude TS was an effective test to find HH. A careful analysis of Edwards's larger study of blood donors reveals the potential for ambiguity if TS were used to search for HH among insurance applicants. The prevalence of homozygous HH in the total population is 41 of 11,165 or 0.4%. The initial screening sample was nonfasting. Donors with nonfasting TS above 50% were then fasted, restested, and called positive if TS was above 62% (Dadone showed 62% the appropriate reference value). A 6% prevalence of HH was observed in the 688 individuals with nonfasting TS values above 50%. Among those 58 with fasted TS above 62%, 41 were homozygous HH and 17 heterozygous carriers. Clearly, fasted TS effectively finds HH.

If insurance applicants were tested, accurate classification would require fasting specimens. Edwards's data for nonfasted samples indicate 23 false negatives and 186 false positives. If the Edwards strategy of initial nonfasting TS above 50% followed by fasted TS above 62% were used, 688 of 11,165 (6%) donors require retesting. Of the 688, 41 are homozygous HH and 17 heterozygous carriers. If one supposes a million insurance applicants were tested, then 3,672 homozygous HH and 1,522 unaffected heterozygous carriers would be detected. Of those detected, many might be new diagnoses. There may be secondary gain from making these new diagnoses. Costs for initial testing are expected to be low, but inconvenience and cost of retesting may preclude initiation of such a program. A more thorough actuarial and cost analysis may be indicated.
Mortality studies from the 1970s and 1980s showed that homozygous HH patients no longer died of diabetic coma as they did in the 1930s, but instead died of hepatocellular cancer, cardiomyopathy, and liver failure.17-20 These mortality statistics reflect a homozygous HH patient group detected after significant symptoms had developed secondary to massive iron accumulation. Life expectancy was reduced if patients presented with cirrhosis, diabetes, or required more than 18 months for iron removal by phlebotomy. All three of these mortality associated variables reflect later stages of disease with larger iron stores.

Nowadays, the diagnosis of HH is made more frequently at an earlier stage with lower total iron stores and less severe organ dysfunction. Recently, Adams et al.21 reported results from 56 probands and 37 of their relatives. Thirty percent of probands were discovered incidentally while being managed for other illness and 10% during a periodic health examination. This is testimony to physician awareness and laboratory testing. Abdominal pain (16%), joint pain (11%) and weakness (9%) were the most frequent presenting complaints. Hepatomegaly (43%), abnormal enzymes (26%), and arthritis (11%) lead physicians to the diagnosis. A longer term survival study of 85 phlebotomy treated homozygous HH patients revealed that life expectancy for patients presenting without cirrhosis was no different than an age/sex-matched local population.23 However, patients presenting with cirrhosis had a 15-year survival rate of about 50%, compared to about 95% for the comparative population. Phlebotomy prevents morbidity and postpones mortality if begun at early stages of disease.

Mortality outcomes are also dependent on the severity of expression of homozygous HH. Muir21 studied nine unrelated HH kindreds and described four different degrees of expression. Some families followed an aggressive course, others a more indolent course. Some families followed an aggressive course, others a more indolent course. However, patients presenting with cirrhosis had a 15-year survival rate of about 50%, compared to about 95% for the comparative population. Phlebotomy prevents morbidity and postpones mortality if begun at early stages of disease.

All the survival studies corroborate the higher mortality risk if cirrhosis is present. Phlebotomy has been shown to reverse cirrhosis to fibrosis in a few cases.23,24 Hepatocellular carcinoma was thought to only develop in the HH patients with cirrhosis. However, recent reports describe one patient with hepatocellular carcinoma after reversal of cirrhosis24 and two patients with hepatocellular carcinoma and no cirrhosis.25 The 67-year-old male who developed hepatocellular cancer after reversal of cirrhosis was phlebotomized only 10 units during the first four years of therapy. To be effective, phlebotomy must be vigorous initially with one unit removed per week. This must be continued, maintaining a slight anemia (hematocrit 40%) to facilitate iron mobilization into erythrocytes.3 Evaluation of patient records by insurance medical directors should include a determination that phlebotomy therapy is adequate, as described above.

In addition to hepatocellular carcinoma, incidence of extrahepatic carcinoma has been studied among homozygous HH patients.18,23-26,27 Three reports,18,23,26 including 218 patients, suggest an increase in extrahepatic carcinomas. Therapy is not well described in all these patients and at least 26 were untreated. Bradbear's report27 included 208 patients, described neither the stage at diagnosis nor phlebotomy schedules, and found no increase in extrahepatic carcinomas. Bradbear discussed different study designs as the possible reason for his different results. As clinicians continue to find more heterozygous HH cases earlier, larger cohorts will be followed for longer times and the frequency of extrahepatic carcinomas can be addressed with greater statistical certainty.

Clinicians are becoming increasingly aware of HH and more frequently discovering patients at earlier stages. Patients without iron-induced cirrhosis who receive adequate and lifelong phlebotomy therapy should have a normal life expectancy.22 The growing understanding of the genetics, prevalence, detection, management, and natural history of HH will facilitate appropriate action by insurance medical directors.

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