

The Significance of Liver Enzyme Elevations

Paper III. Liver Enzyme Elevations and Hemochromatosis in the Insurance Population.

Background

The first two papers of this series reported data on the relationship between liver homeostasis, Hepatitis C and alcohol. Hepatitis C and alcohol represent external agents that affect normal liver function. In the third paper, iron's effect on liver function is reviewed. Iron is required for the catalytic action of many enzymes, for the binding of oxygen to hemoglobin, and in electron transfer in the mitochondrial respiratory chain. Excess levels, however, carry an increased risk for liver, endocrine, immune and cardiovascular diseases.

The clinical manifestations of iron overload are easily understood if you have knowledge of iron metabolism. With no specific method for elimination of iron, the body level is closely maintained by regulation of absorption. The average daily Western diet contains about 20 milligrams of iron, with the actual amount linked to total caloric intake. Normally, only 1 to 2 milligrams of iron are absorbed per day. When excess amounts are absorbed, the body stores the iron in the liver. After liver parenchymal cells become saturated, iron is stored in other organs including the heart. In adults, inherited and acquired disorders of iron overload are common. The genetic basis of the familial disease has been described.(1) While mutations in HFE gene family identify most cases of hemochromatosis, other iron-responsive element-binding gene mutations have been implicated.(2)

Hemochromatosis is a progressive disease requiring decades before the onset of clinical symptoms. 90% of symptomatic patients have hepatic fibrosis or cirrhosis of the liver. While the liver bears the bulk of iron's insult, the heart does not escape injury, which most commonly results in congestive heart failure. Other secondary injuries occur to the endocrine system, with 71% of cirrhotic hemochromatosis patients and 20% of non-cirrhotic patients developing diabetes. Other clinical manifestations include arthropathy, abnormal skin pigmentation, and increased susceptibility to infection. Early diagnosis and treatment of iron overload reduces the risk of development of these clinical diseases.

Liver storage of excess iron results in progressive damage to the organ. Serum transaminases, AST and ALT, elevations occur in about 50% of affected individuals, with hepatomegaly a common clinical finding. Applicants with hemochromatosis have a lifetime excess risk of 220 times for the development of hepatocellular carcinoma. In the symptomatic hemochromatosis population, 69% have cirrhosis, 21% have fibrosis, and only 10% have neither. Hemochromatosis is treated by repeated phlebotomy to deplete iron stores. Symptoms of hemochromatosis are non-specific resulting in an average of ten clinical visits prior to correct diagnosis.

The genetic basis of hemochromatosis has been described. The protein product is a member of the HLA (human leukocyte antigen) family responsible for the binding of

foreign antigens to white cells. The 3D structure of the hemochromatosis protein, HFE, is one with a deep cleft characteristic of the major histocompatibility antigens.(3) HFE is a membrane bound protein that binds both beta-2-microglobulin and the transferrin receptor protein binding.(3-7) The association with the transferrin receptor may provide one mechanism of disease development. But, penetrance of the HFE gene mutation at nucleotide 845 is incomplete (approximately 50%) and some people without this mutation develop the disease.(8) Due to an incomplete penetrance and with hemochromatosis present in some individuals without the mutation, the current medical consensus is not to use genetic screening for this disease.(8)

Serum iron is transported by the serum protein transferrin. Transferrin binds one or two atoms of iron. Normally transferrin is only 30% saturated with iron, indicating that many of the available sites are unoccupied. A diagnosis of hemochromatosis is suspected in all individuals with a high serum iron, saturation of serum transferrin greater than 59%. The diagnosis is established by liver biopsy. In this paper a presumptive diagnosis of hemochromatosis is based on a serum iron greater than 1500 micrograms per liter, with transferrin iron saturation greater than 59%. For brevity, the term hemochromatosis is used in the text of this article to describe this group.

The Study Population:

The prevalence of iron overload and Total Iron Binding capacity was determined in a random group of 2,317 insurance applicants. The group was 37.3% female, 62.7% male, with a mean age of 43 years and a range of 13 to 89 years.

Tests:

A standard insurance blood profile plus iron and unsaturated iron binding capacity (UIBC) was performed on each sample. All chemistries were analyzed on a Hitachi 747-200 using BMC Roche reagents without modification. The total iron binding capacity and transferrin saturation were calculated from the iron and UIBC.

Total Iron Binding Capacity = Serum Iron + UIBC

% Transferrin Saturation = (Serum Iron/Total Iron Binding Capacity) X 100

Results:

Hemochromatosis is very prevalent in the insurance population. The prevalence of iron overload in the insurance buying population is 1.4%. When 2,317 insurance applicant samples were screened, the range of iron saturation was 3% to 98%. Thirty-three applicants have iron saturation greater than 59%; the gender distribution was 11 females and 22 males.

When the data for liver enzyme levels and iron saturation were compared, 11 of 33 (33%) applicants with hemochromatosis have enzyme levels greater than the upper limit of

normal. Therefore, most applicants with a presumptive diagnosis of hemochromatosis either do not have or have not yet developed liver disease. Female gender is under-represented in the group of applicants with high liver enzymes with only one female detected. The single female is most likely post-menopausal at age 64 years. Menses protects young females with periodic loss of blood. For females with iron overload, 9.1% (1/11) had abnormal serum liver enzyme levels. In comparison, 45% (10/22) of males with iron overload had high liver enzymes. Of the applicants with hemochromatosis with abnormal liver enzymes, the average age is 40 years with a range of 23 to 64 years.

Table I. Gender of Insurance Applicants and Hemochromatosis

	All Applicants	Iron Overload	Elevated Liver Enzymes and Iron Overload
Female	36.8%(846/2299)	1.3%(11/846)	9.1%(1/11)
Male	63.2%(1453/2299)	1.5%(22/1453)	41%(10/22)
Total	2299	1.4%(33/2299)	33%(11/33)

Table II. Liver Enzyme Elevations and Hemochromatosis

Enzyme	Liver Enzyme Elevations In 2317 Random Insurance Applicants	Applicants with Liver Enzyme Elevations and Iron Overload
ALT	10.8% (251/2317)	10
AST	4.1% (95/2317)	5
GGT	8.1% (189/2317)	6
Total	345/2317 (14.9%)	11/33 (33%)

Discussion:

Blood testing to identify risk factors is a frequently used screening tool for the insurance applicant population. The standard blood profile includes a group of proteins, the liver enzymes, which have a substantial concentration in the liver. If the liver is damaged, these escape into the blood where they are measured as surrogates of liver homeostasis. In iron overload, the cells of the liver are progressively damaged by iron. The prevalence of iron overload is 1.4% (33/2317) in the insurance population, using 1500ug/L and 59% Transferrin saturation as the upper limit of normal. The insurance prevalence is higher than that reported for the most common genetic form of HFE; the prevalence of HFE is reported to be 0.5% in the general Caucasian population.(9,10) The difference in reported prevalence is due to iron overload occurring in individuals heterozygous (10-15% of the population) for the HFE mutation that were not included in the homozygous population.(11) While genetic testing for HFE remains controversial, serum transferrin saturation remains the most effective test to identify people at risk for the development of both genetic and secondary iron overload.(12)

Liver enzyme elevations are common in insurance applicants, with 14.9% having at least one enzyme above the upper limit of normal. The prevalence of hemochromatosis in the same population is 1.4%. The prevalence of the hemochromatosis in applicants with liver enzymes above the ULN is 2.9%. Therefore, in applicants with abnormal liver enzymes, the risk of having hemochromatosis is twice that of an unselected population. While the pattern of enzyme elevations is complex, ALT was elevated in 10 of 11 applicants with iron over load. With early diagnosis and prudent medical management, significant complications of this disease can be avoided.

References:

- 1) Feder JN, et al. A novel MHC class I-like gene is mutated in-patients with hereditary hemochromatosis. *Nature Genetics* 1996;399-408.
- 2) Flanagan PR, Hajdu A, Adams PC. Iron-responsive element-binding protein in hemochromatosis liver and intestine. *Hepatology* 1995;22:828-832.
- 3) Lebr`on JA, et al. Crystal structure of the hemochromatosis protein HFE and the characterization of the interaction with transferrin receptor. *Cell* 1998;93:111-123.
- 4) Feder JN, et al. The hemochromatosis founder mutation in HLA-H disrupts B2-microglobulin interaction and cell surface expression. *J Biol Chem* 1997;272:14025–28.
- 5) Feder JN, et al. The hemochromatosis gene product complexes with the transferrin receptor and lowers its affinity for ligand binding. *Proc Natl Acad Sci USA* 1998;95:1472-1477.
- 6) Parkkila S, et al. Association of the transferrin receptor in human placenta with HFE,
- 7) the protein defective in hereditary hemochromatosis. *Proc Natl Acad Sci USA* 1997;94:13198-202.
- 8) Parkkila S, et al. Immunohistochemistry of HLA-H, the protein defective in patients with hereditary hemochromatosis, reveals unique pattern of expression in gastrointestinal tract. *Proc Natl Acad Sci USA* 1997;94:2534–9.
- 9) Burke W, et al. Hereditary hemochromatosis. Gene discovery and its implications for population-based screening. *JAMA* 1998;280:172-178.
- 10) Bradley LA, Haddow JE, and Glenn E Palomaki. Population screening for hemochromatosis: expectations based on a study of relatives of symptomatic probands. *J Med Screening* 1996;3:171-177.
- 11) Edwards CQ, et al. Prevalence of hemochromatosis among 11,065 presumably healthy blood donors. *N Engl J Med* 1988;318:1355–62.
- 12) Bulaj ZJ, et al. Clinical and biochemical abnormalities in people heterozygous for hemochromatosis. *N Engl J Med* 1996; 335:1799–1850.
- 13) McLaren CE, et al. Distribution of transferrin saturation in an Australian population: relevance to the early diagnosis of hemochromatosis. *Gastroenterology* 1998;114:543-549.