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Mild liver enzyme abnormalities: eliminating hemochromatosis as cause

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Chronic mild liver enzyme abnormalities are attributable to hereditary hemochromatosis in at least 3% of cases. Hemochromatosis formerly was diagnosed late with diabetes and hepatic and cardiac failure. Only recently have the autosomal recessive inheritance and subtle early presentations been understood. However, patients still wait many years and see many physicians before receiving a correct diagnosis. Increased serum transferrin saturation is currently the best test for detection of those likely to accumulate iron. Serum ferritin identifies those requiring treatment. When liver biopsy (controversial in asymptomatic individuals) is indicated, chemical measurement of liver iron content is helpful and therapeutic phlebotomy is the only effective treatment. Caucasian-type hemochromatosis (prevalence of 0.005) is associated with genetic abnormalities in HLA-H but also occurs in other ethnic groups. Those of African descent may have a different but also heritable iron-loading disease. Caucasian-type and to a lesser extent African iron loading are detectable early by laboratory testing. Early treatment restores normal expectations of length and quality of life in the Caucasian disease. Long-term treatment data are not yet available in African iron loading. Laboratory-initiated screening programs using unsaturated iron-binding capacity can eliminate symptomatic hemochromatosis.

INDEXING TERMS: iron metabolism • hemochromatosis • iron-binding capacity • ferritin • screening • HLA-H

Mild liver function abnormalities are a frequent problem in the evaluation of primary care patients. These abnormalities have a wide variety of causes including fatty liver, viral, and alcoholic hepatitis plus the less likely inherited metabolic liver diseases and muscle leakage of aspartate and alanine aminotransferases after excessive exercise. Mild persistent increases of serum transaminases have been evaluated in several studies. The causes are multiple and constitute the differential diagnosis of liver diseases. Results of four studies combined include 369 cases with 168 attributable to fatty liver, 100 to viral hepatitis, 30 to alcohol, 12 to hemochromatosis, and 59 to a long list of other causes *[1–4]*.

Data are presented that can be used to direct the design of a laboratory-initiated system that should eliminate hemochromatosis as a cause for abnormal liver function. Also presented is the advocacy position for hemochromatosis testing of both asymptomatic individuals and those who encounter the healthcare system for any reason.

Hemochromatosis

Hemochromatosis was historically described as a rare disorder associated with diabetes mellitus, bronze skin, hepatic cirrhosis, and cardiomyopathy, all attributable to abnormal accumulation and storage of iron. These patients died prematurely, usually from cardiac failure or hepatocellular carcinoma arising in a cirrhotic liver *[5]*.

Now, hemochromatosis is known to be inherited in an autosomal recessive pattern and associated with a gene tightly linked to the HLA locus on chromosome 6. A specific abnormality, named HLA-H, has been associated with 83–100% of cases *[6]*. The exact molecular mechanism of the abnormality remains a mystery. Homozygous individuals absorb iron at an increased rate and accumulate excess iron in parenchymal organs, leading to organ failure. The normal iron absorption rate of 1 mg/day in males and 2 mg/day in females may increase to as much as 10 mg/day in homozygotes *[5]*. No excretory mechanism for excess iron exists. Therefore accumulated iron causes tissue damage resulting in diabetes mellitus, hepatic failure, cardiomyopathy, arthritis, and pituitary siderosis with secondary decreased gonadal function.

The variety and severity of symptoms lead patients to all types of healthcare providers. Diagnosis can commonly be delayed 5 years from sentinel symptoms and occur after encountering multiple physicians *[7, 8]*.

Hemochromatosis is not rare. Among individuals of Northern European descent ~5 per 1000 are homozygous. The frequency of heterozygotes is 8% to 13%. The het-

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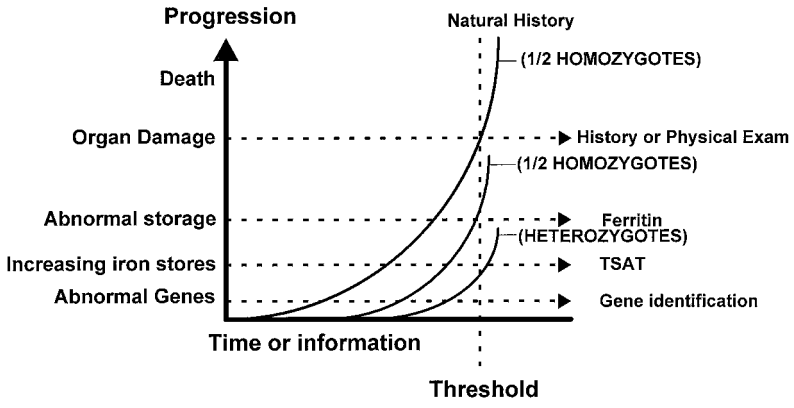

Fig. 1. Hemochromatosis natural history for 50% of homozygotes who develop more serious symptoms, homozygotes with less serious symptoms, and heterozygotes without any other risk for iron loading.

The upper 1/2 of the homozygotes are the more seriously affected, the lower 1/2 are less affected. Historical or physical examination is effective later in the progression. Serum TSAT, ferritin, and gene identification are effective earlier in the progression. The *threshold* refers to the presence of enough information to confirm the diagnosis and/or initiate treatment.

erozygotes rarely experience organ damage but have 10–20% likelihood of mildly abnormal serum transferrin saturation (TSAT)[1] and ferritin *[9]*. The expression of disease in homozygotes is quite variable, probably in response to other genetic as well as dietary or menstrual factors. Most estimates of symptom frequency in homozygotes are near 50% *[10, 11]* (see Fig. 1).

Hemochromatosis male predominance is a misconception. Symptoms and severity tend to be more prevalent in males, but with earlier detection now more frequent, the male to female ratio of cases is 1.6:1 in recent studies *[5]*.

The difficult clinical differential is between homozygotes, heterozygotes, and alcoholic liver diseases. Those patients with alcoholic liver disease who accumulate enough iron to cause organ damage most likely are also homozygotes for hemochromatosis *[5, 12]*.

Liver biopsy with chemical quantitation of hepatic iron content is helpful. Iron accumulates with age, and iron content is best interpreted as the hepatic iron index, i.e., hepatic iron content in micromoles per gram dry weight of liver divided by the patient's age. Healthy subjects, heterozygotes, and patients with alcoholic liver disease have an hepatic iron index <2, whereas homozygotes are >2 *[5]*. As homozygotes continue to be detected earlier, these decision points may need to be revised.

Early Detection

Detection of hemochromatosis before development of cirrhosis or diabetes followed by removal of iron by therapeutic phlebotomy is associated with length and quality of life identical to age-matched controls *[13, 14]*. These data indicate that an early detection program using TSAT *[5]* would prevent morbidity and postpone mortality. Phatak et al. *[15]* have modeled the costs of testing plus preventative treatment vs awaiting symptoms before treatment, assuming a prevalence of only 3 per 1000, with 40% developing symptoms. Their model indicates that screening males in their 30s with an initial test charge of $12 is less costly to society than postponing treatment until symptoms appear; i.e., society saves money and quality-adjusted life years. A similar analysis by Buffone and Beck *[16]* suggested screening would cost $605 per quality-adjusted life year saved. These estimates of cost for quality-adjusted life years saved for hemochromatosis compare with cardiac intervention strategies with costs of $7124 to $37 000 per quality-adjusted life year saved *[15–18]*. If the hemochromatosis screening test costs were $<$$12, then cost savings in a screening program would increase.

To date no randomized trial of screening vs not screening has been performed. Available data strongly support the benefits of early detection through screening. Several nonrandomized trials have been begun or reported *[11]*.

Screening programs for Caucasian-type hereditary hemochromatosis on the basis of serum TSAT as the first test will also uncover other types of abnormal iron metabolism. African-Americans are reported to experience an iron overload disease that is inherited but more dependent on environmental factors, particularly excess dietary iron *[19]*. Secondary causes of abnormal iron loading interact with hereditary hemochromatosis. Most suspect that iron overload in the conditions listed in Table 1 is related to the presence of one hemochromatosis allele *[5]*.

Quality Improvement

We decided to use the quality improvement strategy to develop a hemochromatosis detection program in a community healthcare setting. The strategy involves real-time science *[20]* by identifying the difference between desired and observed outcomes, identifying the process variables

Table 1. Other conditions associated with iron overload.

Sideroblastic anemia	Hereditary atransferrinemia
Porphyria cutanea tarda	Neonatal hemochromatosis
Transfusional iron overload	African iron overload
β-Thalassemia	Postportocaval shunt
X-linked iron-loading anemia	Chronic hemodialysis
Pyridoxine-responsive anemia	Medicinal iron overload
Pyruvate kinase deficiency	

[1] Nonstandard abbreviations: TSAT, transferrin saturation; UIBC, unsaturated iron-binding capacity; TIBC, total iron-binding capacity.

likely to remove that difference, and designing in the quality characteristics expected to improve process variables. In utilizing this strategy it is important to remember that best should not be the enemy of better and to use local data describing local patients and providers to enhance collaboration.

In the community hemochromatosis was being identified after the development of symptoms, a difference from desired outcome. The testing plan began with the outcome in mind *[21]*. Our goals were to identify both hemochromatosis before symptoms developed and individuals likely to benefit from intervention—not to find and label every individual with two hemochromatosis alleles, nor identify all homozygotes who had not yet accumulated substantially large iron stores.

The process variable most likely to alter the outcome was to initiate testing in asymptomatic people. We realized that the other stakeholders could not be expected to think of it and initiate a screening test, nor could we expect anyone to pay substantially for a screening test. In addition, discussions with care providers revealed their expectation that the positive screening tests would need high positive predictive value; thus the necessity to investigate a false positive would occur infrequently.

We decided to use unsaturated iron-binding capacity (UIBC) as the initial test *[5, 22]*. UIBC can be readily automated, and the reagent cost was pennies per test. UIBC estimates the empty sites on transferrin by adding a known amount of reagent iron to fill those empty sites and then measuring the iron in excess of the transferrin sites with a chromophore. When UIBC is low, high TSAT is very likely. Total iron-binding capacity (TIBC) is calculated by adding the UIBC to serum iron. TSAT is calculated by dividing serum iron by the sum of UIBC plus serum iron, i.e., the TIBC.

We performed UIBC with the Beckman (Brea, CA) CX-7 and Diagnostic Chemicals, Ltd. (Oxford, CN) reagents. The TIBC calculated from UIBC + serum iron compared favorably with the usual Beckman TIBC method, and the between-run precision of UIBC revealed CVs of 7–10%. The reagent cost of $0.02 per test estimates the order of magnitude of the incremental cost of performing UIBC.

We measured UIBC, serum iron, TSAT, and ferritin in the serum from 282 inpatients and 819 ambulatory patients and voluntary participants in public health screenings *[23]*. We found 14 ambulatory and 13 inpatients with UIBC 1250 μg/L or less. Only 6 of these 27 had both TSAT >50% and ferritin >90th percentile *[24]*. Conversely, we found no individual with TSAT >50% and ferritin >90th percentile who had UIBC >1250 μg/L. The six individuals with TSAT >50% and >90th percentile ferritin included one case of hemochromatosis diagnosed during and because of the study, two probable heterozygotes, one possible homozygote who was lost to follow-up, and two patients with hematologic diagnosis known to alter iron metabolism (see Table 2).

Table 2. Subjects identified in initial screening study.

Age/sex	Ferritin, μg/L	TSAT, %	Diagnosis
78/M	897	97	Sideroblastic anemia
63/M	1476	90	Hemochromatosis
40/M	624	60	Lost
56/M	329	59	Heterozygote[a]
45/M	428	54	Heterozygote[a]
96/F	732	68	Myeloproliferative

[a] Ferritin concentrations of 300–428 μg/L for several years.

We decided to act by sharing the data with all the care providers, gaining approval from institutional committees and offering UIBC with some chemistry panels at no additional charge. Also at no additional charge we performed serum iron on all samples with UIBC of 1250 μg/L or less and reported TSAT. If UIBC was 1260 μg/L or more we did nothing.

We continue to follow the results of this program. We have reviewed all UIBC results between August 1995 and May 1996. The results of this quality review are shown in Fig. 2. Health records were reviewed in all cases with UIBC <1260 μg/L. We have identified three new cases and expect several of the five pending additional work-up will also be hemochromatosis. Thus far we have found 3 plus maybe 5 new cases and 6 known cases or ~14 in 7093 people in this cohort. This is very close to the expected frequency of individuals likely to accumulate enough iron to need intervention *[5, 10, 11]*. If 50% of 5 per 1000 are expected to accumulate iron, 17 would be expected.

The other causes of high TSAT include acute alcohol ingestion, iron therapy in hemodialysis patients, and various hematologic diseases. Caregivers have been pleased to find new asymptomatic hemochromatosis. No problems have been reported with understanding the remaining UIBC and TSAT results. As an aside, the very high UIBC values associated with iron deficiency have also been diagnostically useful.

These data represent an experience with no control

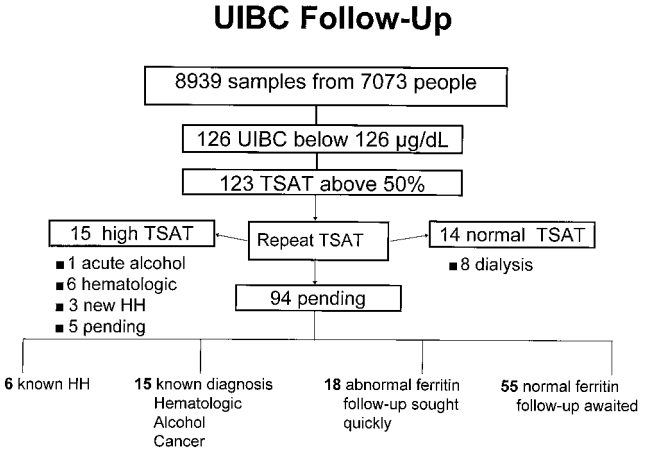

Fig. 2. Results of quality review for a cohort identified in the initial implementation period of UIBC screening program.

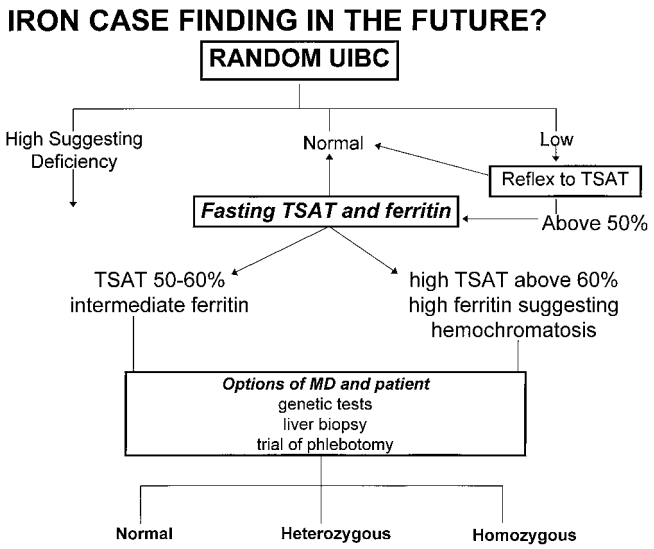

Fig. 3. Possible future developments in case finding for iron-related conditions.

population. The data also do not rule out the commonly described statistical biases in screening programs *[25, 26]*. We choose to interpret this as clinical quality improvement and trust we will prevent organ failure attributable to hemochromatosis in our community.

New genetic findings regarding iron overload in Caucasians *[6]*, African-Americans *[19]*, and those with other iron-loading diseases will initiate further improvements in our testing scheme. However, we continue to believe that UIBC will help find iron-loaded individuals likely to benefit from intervention. UIBC also identifies a portion of the much higher prevalence of iron deficiency. Future research will guide the choice of genetic tests, liver biopsy, or phlebotomy to improve the evaluation of iron overload and enhance the prevention of morbidity and premature mortality (see Fig. 3).

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