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HEMOCHROMATOSIS: A COMMON (YET PREVENTABLE) CHRONIC DISEASE

A 52-YEAR-OLD, previously active, white male with a great tan presented with acute congestive heart failure. His previous medical history was significant for a 10-year history of diabetes, hypothyroidism, and hypogonadism. Examination revealed pulmonary edema, hepatomegaly, impaired liver function, and a dilated, hypokinetic heart. After standard heart failure therapy, he was transferred to a tertiary care medical center for heart transplant evaluation. There, additional tests eventually revealed an iron of 179 µg/dl (normal 50-180), a total iron binding capacity (TIBC) of 195 µg/dl (normal 195-370), transferrin saturation of 92%, and a ferritin of 4720 ng/ml (normal <400). A liver biopsy showed mild fibrosis with abundant stainable iron. After repeated phlebotomization, his symptoms began to improve. During the next two years, over 140 units of blood were removed, and the patient resumed a normal, active lifestyle. Recent DNA analysis has confirmed that the patient carried a mutant gene.

ABOUT HEREDITARY HEMOCHROMATOSIS

To be specific, the man was homozygous for the C282Y mutation in the newly-described[1] hemochromatosis gene. Although unappreciated by many physicians, hereditary hemochromatosis (HH) is by far the most common genetic disease in America, affecting 1 of every 200-300 persons—or as many as 16,000 Oregonians.[2,3] Far from being yet another rare, untreatable genetic disease, HH is not only common but, when detected early, quite amenable to treatment.

HH is an autosomal recessive disease, and homozygotes with two defective HH genes have an uncontrolled increase in the intestinal absorption of dietary iron. Tissue damage occurs as excess iron accumulates in the liver, pancreas, heart, pituitary, and other organs. The common clinical consequences of this iron burden are variable but can be numerous, including cirrhosis, diabetes, heart failure, impotence, amenorrhea, and arthritis. Less severe (albeit often disabling) symptoms include fatigue, weakness, arthralgias, and/or hyperpigmentation. These nonspecific symptoms, together with a long presymptomatic phase and lack of physician awareness, contribute to the multitude of mis- or undiagnosed cases.

DIAGNOSIS

Hemochromatosis should be considered in patients with persistent elevations in serum ferritin levels and transferrin saturation (the ratio of serum iron to TIBC). In the not-too-distant past, the diagnosis, suspected on clinical and laboratory grounds, was often confirmed by liver biopsy. Although liver biopsy remains diagnostically useful (to assess tissue iron stores and provide valuable prognostic information on the presence or absence of cirrhosis), those reluctant to pursue this invasive option can now be evaluated by a direct DNA test for HH. Over 80% of those with HH have recently been shown to carry two mutated copies of a gene called HLA-H (or HFE) that has a single, hemochromatosis-specific, DNA substitution.[1] Direct identification of this homozygous C282Y HLA-H mutation—available with a simple DNA-based blood test—now allows a definitive diagnosis of HH in those with clinical symptoms, family histories, and/or elevated iron parameters. Although now available in only a few specialized labs, this direct DNA test should be considered in everyone with an elevated screening transferrin saturation. As family members (symptomatic or not) may have inherited the same genes, consanguineous relatives of affected individuals should also be tested (about $80-$300, depending on the lab).

Bear in mind, however, that although as many as 10-15% of those with clinical hemochromatosis may appear to have no direct mutations, they nonetheless may still benefit from therapeutic phlebotomy.

POPULATION SCREENING

Although screening persons based on symptoms or familial history yields a higher proportion of HH cases, a growing number of experts feel that more widespread or even universal screening may be the best route to detect (and treat) patients before symptoms develop. In many respects, HH is a model disease for which population-based screening may be worthwhile, because 1) it is common (affecting ~0.4% of the population), 2) it can be screened for with an inexpensive and reasonably sensitive* test, transferrin saturation (TS); 3) there is a long, asymptomatic stage preceding chronic end-organ damage, and 4) early detection can be followed up with safe and effective therapy.

Projections suggest that—even if one ignores the health benefits to patients—total health care costs would likely be reduced by widespread screening efforts.[4,5] Several pilot programs to detect presymptomatic HH have been carried out with predictable success.[4,5] In response, both the College of American Pathologists[5] and an expert panel convened by CDC/NIH have recently recommended universal iron screening of all Americans over 18 years old. Armed with the information in this *CD Summary* Oregon physicians now have the opportunity to get the jump on their colleagues elsewhere by beginning to screen for HH.

At a minimum, screening for HH should now be done on all patients with potential symptoms of iron overload, including all patients with unexplained liver disease, adult-onset diabetes, unexplained arthropathy/arthralgia, unexplained cardiac disease (cardiomyopathy, heart failure, or arrhythmia), unexplained weakness or fatigue, impotence, amenorrhea, hypogonadism, hyperpigmentation, infertility, or those with a family history of these syndromes. The prevalence of HH in

* Sensitivity is high (>90% in most studies) but specificity for TS is poor (i.e., many false positives), necessitating confirmatory testing with ferritin and DNA.

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these symptomatic patients is significantly higher than in the general population.

The consensus first-line screening test is quantitation of transferrin saturation, defined as serum iron divided by TIBC. If the screening transferrin saturation is elevated, it should be repeated after fasting (and after iron and vitamin C supplements have been discontinued). Although a transferrin saturation above 55% in females or 60% in males is a sensitive marker for HH, its biologic variability is high, and it can be falsely decreased by infections or inflammation.[4] To confirm true iron overload, those with a high screening transferrin saturation should have serum ferritin levels determined. In the absence of a toxic or inflammatory cause, a high serum ferritin (above 200 ng/ml in females or 400 ng/ml for males) is highly suggestive of iron overload and requires further consideration. A hemochromatosis DNA test (and/or liver biopsy) should be performed on those with elevated screening tests for transferrin saturation and/or serum ferritin.

TREATMENT AND COUNSELING

As this disease is curable when detected early, therapeutic phlebotomy should be considered for all HH homozygotes with an elevated transferrin saturation and serum ferritin (regardless of signs or symptoms of end organ damage). The excess iron burden can be relieved with a lifelong program of therapeutic phlebotomy. Initially, a unit of blood is removed 1–2 times per week. Once iron depletion is induced (target ferritin of 10 - 50 ng/ml without anemia), the frequency of bleeding is reduced (to typically ~2-6 times per year) to maintain a serum ferritin level below ~100 ng/ml. When initiated before the onset of cirrhosis or diabetes, such a program both restores normal life expectancy and alleviates many of the cardiac and hepatic symptoms.[6] Although phlebotomy treatment is ideally started before the onset of symptoms, considerable benefit is available at almost any stage of illness, as in the introductory example.

Diet plays a miminal role. The savings afforded by a low-iron diet are probably not worth the effort considering that the patient will need to be bled regardless. However, HH patients should definitely avoid iron supplements, vitamin C (which enhances iron absorption), and Geritol®.

Increased utilization of the HH DNA test will identify heterozygotes carrying one copy of the C282Y mutation—who may comprise a whopping 13% of the population. As these HH heterozygotes have (on average) slightly elevated iron stores,[7] they may benefit from periodic clinical and laboratory evaluation.

Importantly, known carriers and consanguineous family members of homo- and heterozygotes are obviously at increased risk for HH, and should be offered genetic counseling regarding their risk, as well as confirmatory iron and/or DNA testing.

In summary, HH is a common (yet treatable) chronic disease for which early detection and treatment can prevent serious sequelae. Identification of many of these individuals will require both a high index of suspicion and a widespread screening program. Starting today, the groups that should be screened include those with diabetes, arthropathy, cardiac disease, unexplained liver disease, impotence, fatigue, or hypogonadism. Remember, when in doubt, think iron!

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The Health Division does not claim any particular expertise with hemochromatosis. In a rare deviation from our "in-house" and anonymous authorship policy, we are happy to acknowledge that this article was contributed by two OHSU physicians, to whom additional questions can be directed:

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Double Issue

DUE TO AN unfortunate confluence of mishaps, the July 22 issue of the *CD Summary* was inadvertently delayed. To save mailing costs, it is bundled with this issue. This is *not* a new look and feel that you should get used to.