Hemochromatosis

More common than you think

Mark Ram Borgaonkar, MD, MSC, FRCPC

ABSTRACT

OBJECTIVE To review current knowledge of the genetics, presentation, diagnosis, and management of hereditary hemochromatosis.

QUALITY OF EVIDENCE MEDLINE was searched from January 1966 to June 2002, and references of relevant papers were reviewed. Most articles were reviews, practice guidelines, or observational studies. Several randomized controlled trials were identified but none studied primary therapy for hemochromatosis.

MAIN MESSAGE Hemochromatosis, the most common genetic disease in white populations, has a prevalence of one in 200, yet is still underrecognized. This disease of unregulated iron absorption leads to generalized iron overload that can eventually impair organ systems and lead to cirrhosis, diabetes, and cardiomyopathy. Symptoms are often nonspecific and patients are identified by mild abnormalities in routine laboratory testing. Transferrin saturation, ferritin levels, and genotyping can often establish the diagnosis. Iron depletion therapy with phlebotomy is helpful if initiated before organ damage occurs.

CONCLUSION Family physicians should be aware that hemochromatosis can be treated effectively if diagnosed early.

RÉSUMÉ

OBJECTIF Faire une revue des connaissances sur la génétique, les symptômes révélateurs, le diagnostic et le traitement de l'hémochromatose héréditaire.

QUALITÉ DES PREUVES Les articles et les références bibliographiques pertinentes ont été répertoriés dans Medline entre janvier 1966 et juin 2002. La plupart des articles retenus étaient des revues, des directives de pratique et des études d'observation. Plusieurs essais randomisés ont été identifiés, mais aucun ne traitait du traitement primaire de l'hémochromatose.

PRINCIPAL MESSAGE L'hémochromatose est la maladie génétique la plus fréquente chez les gens de race blanche. Malgré une prévalence de un sur 200, elle est encore sous-diagnostiquée. Cette maladie, qui résulte d'un défaut du contrôle de l'absorption du fer, entraîne une surcharge généralisée en fer qui peut éventuellement entraver le fonctionnement de certains systèmes organiques et entraîner une cirrhose, un diabète et une cardiomyopathie. Les symptômes sont souvent non spécifiques, et l'identification des patients repose sur l'observation de légères anomalies dans les examens de laboratoire de routine. La mesure de la saturation de la transferrine et des niveaux de ferritine ainsi que le génotypage permettent souvent de confirmer le diagnostic. Une réduction des réserves en fer par un traitement à base de phlébotomies est efficace à condition d'être commencée avant que les organes ne soient atteints.

CONCLUSION Le médecin de famille devrait se souvenir que l'hémochromatose peut être traitée de façon efficace à la condition d'être diagnostiquée tôt.

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Hereditary hemochromatosis (HH), the most common genetic disorder in white populations, has a prevalence of up to one in 200 among certain people of northern European ancestry.[1,2] Many still consider it rare, and it remains an underdiagnosed, though easily treated, disease.[3] Recent discovery of the gene defect that accounts for most cases has revolutionized our understanding of HH and allowed for early detection through screening of specific groups, such as family members of known cases.[4] It is important that family physicians recognize the various presentations, understand the diagnostic approach, and be familiar with appropriate therapy for patients with HH.

Quality of evidence

Articles were identified from a MEDLINE search from January 1966 to June 2002. All subheadings of the search term hemochromatosis were exploded, and 4442 citations were identified. The limits, randomized controlled trial, clinical trial, controlled clinical trial, practice guideline, meta-analysis, multicentre study, review literature, review academic, and scientific integrity review, were applied, and only review articles published after 1995, when the *HFE* gene was discovered, were assessed. The references of every relevant article were cross-checked to ensure that all pertinent papers were identified.

Only two relevant clinical trials were identified; neither assessed the therapeutic efficacy of phlebotomy. Most citations were reviews or practice guidelines based upon existing data (level III evidence). Retrospective and observational studies provided the best available data on the genetics, natural history, prognosis, and response to therapy of patients with HH (level II evidence). Findings and recommendations from these papers were synthesized to produce this update.

Etiology and pathogenesis

Hereditary hemochromatosis is an autosomal recessive disorder characterized by increased and inappropriate absorption of iron that results in tissue deposition and end organ damage.[5] The gene responsible for HH resides on the short arm of chromosome 6 and has been designated *HFE*.[1] The gene mutation seen in most cases of HH results in substitution of tyrosine for cysteine at the 282 amino acid position of the protein product (C282Y).[6] A second mutation that appears to play a role is substitution of aspartic acid for histidine at position 63 (H63D).[6]

Approximately 90% of patients with HH are homozygous for the C282Y mutation (C282Y/C282Y). There is substantial regional variation, however; 95% of Canadian patients are C282Y homozygotes compared with only 64% of Italian patients.[7,8] The compound heterozygous state (C282Y/H63D) comprises about 4% of all HH cases.[9] Most studies suggest that the genotypes C282Y/wild, H63D/wild, and H63D/H63D do not cause clinically significant iron overload,[10] although they are associated with elevated iron indices of unknown importance.[11]

The precise molecular mechanisms by which mutations of the *HFE* gene result in excessive iron absorption are unclear. Some suggest that the C282Y mutation leads to a false signal that intracellular iron stores are low, leading to inappropriately high iron absorption.[9] Future research will undoubtedly shed more light on the molecular mechanisms underlying HH.

Clinical manifestations

Presentation. Hereditary hemochromatosis was first described in 1865 when Trousseau noted an association between cirrhosis, diabetes, and increased skin pigmentation.[9] The misconception that most HH patients present with this classic triad has persisted despite the fact that fewer than 15% of patients do.[12]

Patients with HH are usually diagnosed between age 40 and 60. They sometimes have several symptoms, although many are diagnosed without symptoms (**Table 1**). The most common symptoms include fatigue (54%), abdominal pain (48%), and palpitations

Table 1. Hereditary hemochromatosis patients' symptoms and physical findings at presentation

SYMPTOMS
Fatigue
Abdominal pain
Arthralgias
Palpitations
Impotence (men)
Weight loss
Depression
PHYSICAL FINDINGS
Skin pigmentation
Hepatomegaly
Arthropathy
Cardiomegaly
TEST RESULTS
Elevated transaminases
Hyperglycemia

Dr Borgaonkar *is an Assistant Professor of Medicine at Memorial University of Newfoundland in St John's.*

(37%).[5] Increased skin pigmentation (71%), hepatomegaly (56%), and arthropathy (48%) are sometimes found on physical examination.[5] Patients sometimes present initially with liver disease, diabetes, or cardiac disease (cardiomyopathy or arrhythmias) that are incorrectly assumed to be sporadic cases of common diseases rather than manifestations of iron overload.[12]

Increased awareness and the availability of genetic testing have resulted in diagnosis of HH in many patients before they have symptoms. Most patients (90%) diagnosed through screening are asymptomatic, and most have no abnormal physical findings.[5] In the future, it seems likely that an even greater proportion of HH patients will be diagnosed at a preclinical stage.

Underrecognition. Many studies indicate that HH is diagnosed less frequently than expected based upon the known high genetic prevalence.[13] One possible explanation is a lack of penetrance of the gene in some people such that clinically significant iron overload never develops.[14] This position is supported by a large, population-based study where only one of 152 C282Y homozygotes had classic signs of HH.[15] Forty-five patients, however, had abnormal iron indices and no clinical disease, suggesting that the disease had been diagnosed at a preclinical stage.

A more likely explanation for this discrepancy is that physicians do not recognize HH. An international survey of 2851 HH patients supports this contention.[3] Patients visited an average of 3.5 physicians for their symptoms and had a mean delay from symptom onset to correct diagnosis of 10 years. More encouraging was the fact that primary care physicians diagnosed 56% of patients, and 45% were diagnosed by routine laboratory testing before symptoms developed. This suggests that some physicians had developed a greater awareness of HH.

Disease expression. Clinical manifestations of HH are different in women and men. Women tend to be older than men at diagnosis; when matched for age, 6.2% of women with HH had normal serum ferritin and transferrin saturation levels compared with 0% of men.[16] The reason for this difference could be that physiologic blood loss through pregnancy or menstruation mitigates the degree of iron overload. There are also sex differences in clinical symptoms: women are more likely to present with fatigue, increased pigmentation, or arthritis; men more often present with cirrhosis or diabetes.[16]

The nature of clinical symptoms is strongly related to the degree of iron overload. In a study of 410 HH patients, the concentration of hepatic iron was significantly associated with cirrhosis, diabetes, and pigmentation.[17]

Alcohol consumption is another factor that can influence disease expression. A review of 105 HH patients found that 44% of those who consumed more than 80 g of ethanol daily had cirrhosis compared with only 10% of those who did not drink heavily.[18] Long-term survival rates were significantly lower among heavy drinkers also.

Diagnosis

Diagnosis of HH has been revolutionized by the discovery of etiologic genetic mutations in 1996. It is essential that primary care physicians understand the diagnostic approach to evaluating suspected HH patients (**Figure 1**).

A diagnosis of HH should be suspected in any patient presenting with unexplained, nonspecific symptoms, such as fatigue or arthralgia.[19] It should also be considered in evaluating patients with cardiac disease, diabetes, hepatomegaly, impotence, or elevated liver enzymes,[1] and in patients with a family history of liver disease or a family member known to have HH.

Screening tests. The preferred screening test for HH is transferrin saturation (TS) administered after an overnight fast.[1,20] Sensitivity, specificity, positive predictive value, and negative predictive value vary depending on population prevalence, cutoff used to determine abnormal results, and sex (more sensitive in men, more specific in women). In a study of 3011 healthy adults, a TS of ≥45% had a sensitivity and specificity of 94% and a positive predictive value of 6%.[2] Using statistical modeling techniques, others have confirmed that this is the optimal TS value for screening.[21]

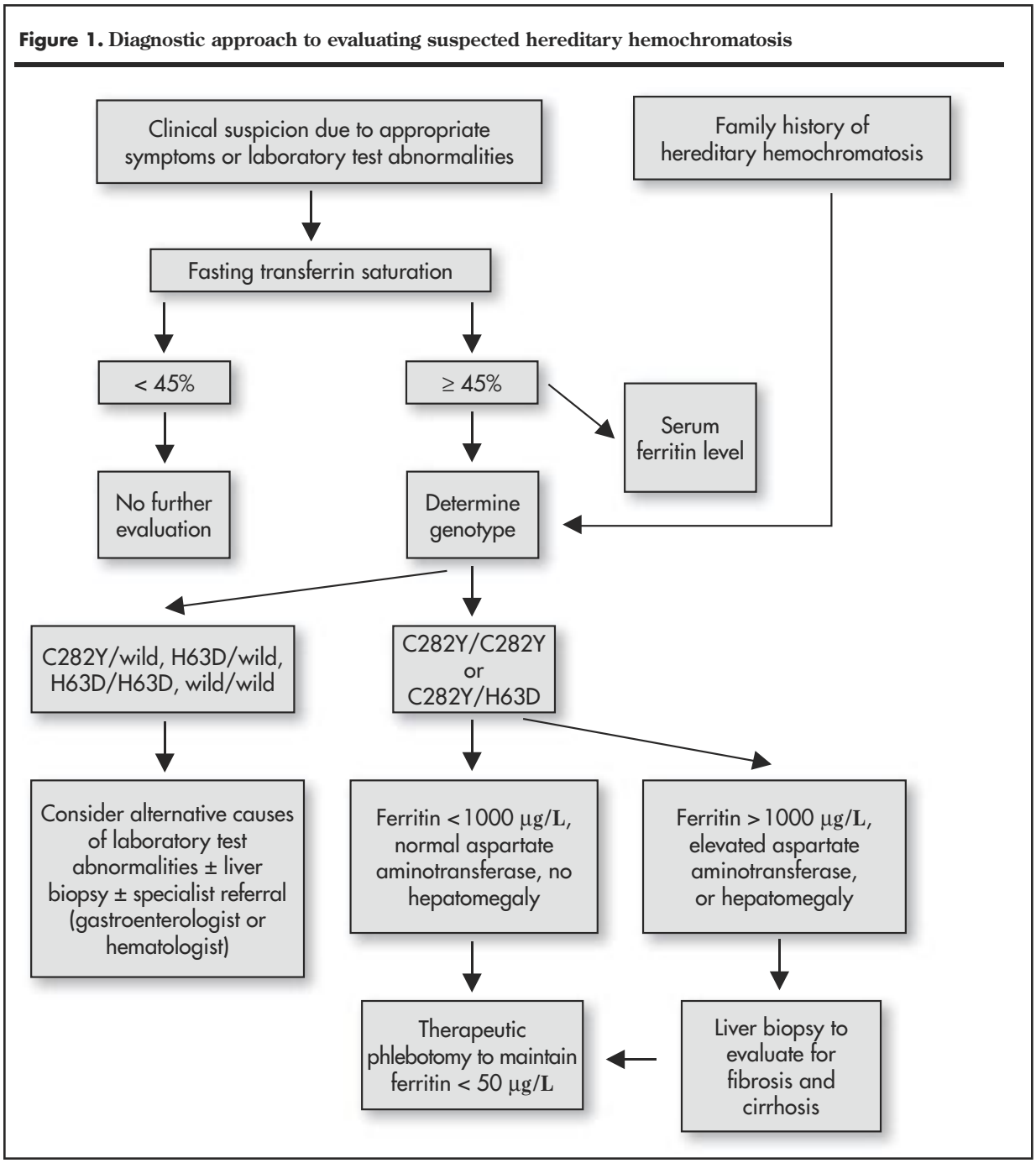
If a patient has a fasting TS of ≥45%, serum ferritin levels should be tested. Unlike TS, which is a measure of iron transport kinetics, ferritin is a marker of total body iron stores.[22] If the ferritin level is normal, annual follow up with reassessment of TS and ferritin is appropriate to monitor for signs of progressive iron overload.[19] An alternative approach would be to proceed directly to genotyping.

If the ferritin level is elevated (≥200 μg/L in premenopausal women or ≥300 μg/L in postmenopausal women or in men), the possibility of HH must be strongly considered.[19] Further evaluation should include clinical assessment for symptoms or signs of end organ dysfunction, measurement of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and genotyping. Keep in mind that the

serum ferritin level is an acute-phase reactant that might be elevated in association with acute inflammation, infection, or cancer.[19]

Genotyping. The next step in evaluation is genotyping. If a patient has elevated TS and ferritin levels and is homozygous for the C282Y mutation, diagnosis is definite, and therapy should be initiated.[1] For patients with genotypes less clearly associated with clinical HH (ie, C282Y/H63D, C282Y/wild, or H63D/H63D) and abnormal iron indices, diagnosis is more difficult to establish. For these patients, further evaluation with liver biopsy might be necessary.[1] If diagnosis remains in doubt, a trial of phlebotomy could be considered. It is generally agreed that clinically significant iron overload is present if 4 g of iron (16 500-mL phlebotomies) can

Figure 1. Diagnostic approach to evaluating suspected hereditary hemochromatosis



be mobilized without inducing iron deficiency. This approach, known as "quantitative phlebotomy," can be used for both therapeutic and diagnostic purposes.[19] Occasionally patients appear to have HH clinically and biochemically but test negative for both the C282Y and H63D mutations. Such patients might carry a novel mutation for HH and should be considered for liver biopsy.

Liver biopsy. The role of liver biopsy in establishing the diagnosis of HH has been supplanted somewhat by genetic testing. Liver biopsy is still useful to quantify the amount of hepatocellular iron when diagnosis is uncertain.[23] Liver biopsy is also helpful for establishing presence or absence of cirrhosis, an important prognostic indicator. A useful guide is to biopsy patients who have ferritin levels >1000 µg/L, or elevated AST, or hepatomegaly.[24] Patients with none of these can be safely assumed to have no serious liver disease and can forego biopsy.

Population screening. Population screening for HH using genetic testing is controversial. Some advocate it because of the high prevalence of HH and because early treatment is usually successful.[25] As yet, the optimal screening method, target population, and cost remain unclear.[26,27] Hence, population screening for HH is not currently recommended.

Therapy

Iron depletion using therapeutic phlebotomy is the treatment of choice for HH (**Table 2**).[28] Phlebotomy of 500 mL weekly (250 mg of iron) should be initiated as soon as diagnosis is secure. Some patients can tolerate removal of 500 mL twice weekly; elderly patients or those with small body mass might only tolerate biweekly sessions.[28] Some patients have total body iron stores >30 g and require weekly phlebotomy for more than 2 years for adequate depletion.[1]

Before each phlebotomy, hemoglobin should be measured to ensure it has returned to baseline. Serum ferritin should be monitored after every 10 venesections with a target of <50 µg/L.[1] Once the target is achieved, phlebotomy is usually required every 3 to 4 months for maintenance.

There are no randomized controlled trials demonstrating the efficacy of phlebotomy in HH. A retrospective review of 111 HH patients is compelling, however.[29] Mean survival of the 85 treated patients was 67.4 months compared with 15.5 months for the 26 untreated patients ($P < .001$). Based on such observational data, it is accepted that phlebotomy prolongs survival in HH.

Early treatment, before organ damage occurs, results in improved outcomes. Niederau and colleagues found that the 10-year survival rate of 251 HH patients was 77%, significantly lower than that of controls.[30,31] Patients who began therapy before development of cirrhosis or diabetes, however, had identical survival rates to controls; patients diagnosed later had a substantially higher mortality rate. These data provide strong motivation for early diagnosis and treatment of HH.

Once therapy is initiated, some complications of HH can be expected to improve (**Table 3**). Liver enzymes normalize in 50% to 90% of patients, and approximately 33% experience improved glycemic control.[5,29] Nonspecific symptoms, such as weakness and fatigue, might improve.[5] One case report describes reversal of congestive heart failure after 33 venesections, although this does not represent the norm.[32] Men with hypogonadism do not experience improvement in sexual function.[33] The effect of phlebotomy on arthralgia varies: about a third of patients improve, a third worsen, and a third experience no change in symptoms.[34]

Cirrhotic patients who deteriorate are eligible for liver transplantation. Unfortunately, 1-year post-transplant survival was only 54% for HH patients compared with 79% for all patients in a cohort of 5180 liver transplant recipients between 1982 and 1991.[35] Reasons for the poor outcome of liver transplantation in HH is unclear.

Dietary recommendations

Patients with HH may follow regular diets but are advised to consume in moderation food rich in iron, such as red meats and organ meats (eg, liver).[28] Iron

Table 2. Management of hereditary hemochromatosis

THERAPEUTIC PHLEBOTOMY
Removal of 500 mL of blood every week
Check hemoglobin before each phlebotomy; defer for 1 week if anemic
Check serum ferritin after every 8 to 10 phlebotomies
Goal is a ferritin level of <50 µg/L and transferrin saturation <50%
Once achieved, continue phlebotomy every 3 to 4 months to maintain ferritin <50 µg/L
DIETARY THERAPY
Reduce ingestion of foods rich in iron (eg, organ meats)
Avoid iron supplements
Avoid vitamin C supplements
Minimize alcohol consumption; abstain if underlying liver disease
Regular tea drinking might reduce accumulation of iron

Table 3. Expected outcome of clinical symptoms and signs with therapy

CLINICAL FEATURE	EXPECTED OUTCOME
Fatigue	Some improvement to complete resolution
Abdominal pain	Some improvement to complete resolution
Palpitations	Some improvement to complete resolution
Increased liver enzymes	Some improvement to complete resolution
Skin pigmentation	Usually resolves
Hepatomegaly	Usually resolves
Arthralgias	Improvement in one third of patients
Diabetes	Improvement in one third of patients
Impotence	Improvement is rare
Cardiomyopathy	Might improve but rarely resolves
Cirrhosis	No improvement
Increased risk of hepatocellular carcinoma	No improvement

supplements should be avoided. Further dietary therapy to limit the amount of ingested iron is unnecessary. A recent study suggested that removal of iron fortification in food might reduce the frequency of phlebotomy required for HH patients.[36] These results should be viewed with caution until they are replicated in a larger sample.

Alcohol could worsen HH by increasing intestinal absorption of iron or by its direct hepatotoxic effects.[37] It is known that HH patients who drink heavily have higher rates of cirrhosis and mortality compared with those who do not.[18,38] For patients with known liver disease, complete abstinence is recommended.

Vitamin C enhances gastrointestinal absorption of iron.[39] Hence, HH patients are advised to limit vitamin C supplementation to 500 mg/d.[28] There is no need to curtail the amount of citrus fruits and vegetables in the diet, however.

Tea is rich in tannates, which inhibit intestinal iron absorption.[40] A study of 18 HH patients showed that regular ingestion of black tea reduced iron absorption and the rate of accumulation of iron stores.[41] The authors suggested that regular tea drinking might reduce the frequency of maintenance phlebotomy. This has not been adopted as a universal recommendation, but might be suggested to HH patients who wish to modify their lifestyles accordingly.

Blood donation

Because HH is a genetic disorder, it cannot be transmitted through blood or blood products. The multiple venesections performed during HH therapy, therefore, present a good opportunity for supplementing chronically undersupplied regional blood banks.

At this time in the United States, blood from HH patients cannot be used for donation.[42] This position is based on ethical concerns that therapeutic phlebotomy for HH does not truly represent voluntary blood donation. In addition, data show that blood donated from purely altruistic donors is safer than that from donors who receive even small, nonmonetary incentives.[43] Whether this observation applies to HH patients is unknown.

In Canada, the situation is complex. Red Cross guidelines were revised in 1991 to allow HH patients to donate blood.[44] Donation cannot be more often then every 56 days, however. Consequently, only phlebotomies performed for maintenance therapy can be used for donation, while weekly phlebotomies performed early in the course of therapy must be discarded. We hope that this position will be revised in the future to make optimal use of this valuable resource.

Long-term management

Once HH patients' excess iron has been depleted, phlebotomy every 3 to 4 months will maintain desired levels.[1] Patients should be followed for symptoms or signs suggesting organ damage.

Patients with cirrhosis should be followed for development of hepatocellular carcinoma, which could account for up to 30% of all deaths in HH.[45] Because hepatocellular carcinoma is fatal unless detected early, surveillance for it seems reasonable, but there is no consensus regarding the optimal strategy and no evidence demonstrates that it prolongs life.[1] Nevertheless, some authors have suggested periodic ultrasound examinations as surveillance for these high-risk patients.[46]

Conclusion

Hereditary hemochromatosis is the most common genetic disorder among white populations. Patients present with mild, nonspecific symptoms; evidence of organ damage; or at a preclinical stage when mild abnormalities are detected on routine laboratory tests. The key to successful management of HH is early recognition and prompt diagnosis. Adequate therapy before irreversible organ damage occurs is essentially curative, granting patients long-term survival similar to that of the general population.

Because HH patients frequently present to and are managed by primary care physicians, it is important for these physicians to be familiar with the disease.

Competing interests

None declared

Correspondence to: *Dr Mark Borgaonkar, Department of Medicine, Memorial University of Newfoundland, St John's, NL A1B 3V6; telephone (709) 777-8072; fax (709) 777-8044; e-mail* markb@mun.ca

Editor's key points

- Hemochromatosis is the most common genetic disease in white populations. Although prevalence is one in 200, it is still underrecognized.
- Abnormal iron absorption causes iron overload in organ systems that can lead to cirrhosis, diabetes, and cardiomyopathies.
- Hemochromatosis usually presents with nonspecific symptoms, such as fatigue or subtly abnormal blood studies.
- Diagnosis is usually established by abnormal results of transferrin saturation, serum ferritin, and genetic testing, but physicians must consider hemochromatosis in the differential diagnosis of vague symptoms.
- Treatment with phlebotomy can prevent long-term complications if begun before organs are damaged.

Points de repère du rédacteur

- L'hémochromatose est la maladie génétique la plus fréquente chez les gens de race blanche. Malgré une prévalence de un sur 200, cette affection demeure sous-diagnostiquée.
- Un défaut dans l'absorption du fer entraîne une surcharge en fer dans les systèmes organiques, qui peut entraîner une cirrhose, un diabète et une cardiomyopathie.
- L'hémochromatose se manifeste habituellement par des symptômes non spécifiques tels que la fatigue ou des anomalies mineures dans les examens sanguins.
- Un test de saturation de la transferrine et une ferritine sérique anormaux de même que des tests génétiques positifs permettent habituellement d'établir le diagnostic, mais en présence de symptômes vagues, le médecin doit toujours considérer la possibilité d'une hémochromatose.
- Un traitement à base de phlébotomies peut prévenir les complications à long terme, à la condition de débuter avant que les organes soient atteints.

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