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Hemochromatosis

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Overview

Practice Essentials

Hemochromatosis is the abnormal accumulation of iron in parenchymal organs, leading to organ toxicity.[1] It is the most common autosomal recessive genetic disorder[2] and the most common cause of severe iron overload.[3]

Signs and symptoms

Patients with hereditary hemochromatosis may be asymptomatic (75%) or may present with general and organ-related signs and symptoms. Early symptoms include severe fatigue (74%), impotence (45%), and arthralgia (44%). The most common signs at the time of presentation are hepatomegaly (13%), skin pigmentation, and arthritis.[4]

See Clinical Presentation for more detail.

Diagnosis

Clinical manifestations of hemochromatosis include the following:

- Liver disease (hepatomegaly, 13%; cirrhosis, 13%, usually late in the disease)
- Skin bronzing or hyperpigmentation (70%)
- Diabetes mellitus (48%)
- Arthropathy
- Amenorrhea, impotence, hypogonadism
- Cardiomyopathy
- Osteopenia and osteoporosis[5]
- Hair loss
- Koilonychia (spoon nails)

Lab tests

The diagnosis of hemochromatosis is based on clinical features of the disease. Most patients are asymptomatic and are diagnosed when elevated serum iron levels are noted on a routine chemistry screening panel or when screening is performed because a relative is diagnosed with hemochromatosis.

Laboratory studies used in evaluating suspected hemochromatosis include the following:

- Genetic testing: Examination of HFE mutations (C282Y, H63D) is pivotal for diagnosis of hemochromatosis

- Transferrin saturation levels
- Serum ferritin studies
- Hepatic iron concentration

Supraventricular arrhythmias are often revealed on ECGs.

Imaging studies

Chest radiography and echocardiography may be helpful in the evaluation of patients with hemochromatosis and cardiac disease.

CT scanning is neither sensitive nor specific for the detection of mild hepatic iron overload. MRI may be more sensitive than CT scanning, but this modality has not been validated as a diagnostic test to help confirm hemochromatosis. Hepatic iron quantification with MRI might be helpful.[6]

Procedures

The following are procedures that may be used to assess patients with hemochromatosis:

- Diagnostic endoscopy
- Skin biopsy
- Liver biopsy, with biochemical determination of hepatic iron concentration and calculation of the hepatic iron index and histologic evaluation with iron staining (Perls Prussian blue)

Indications for liver biopsy

The use of liver biopsy in hereditary hemochromatosis can be restricted to those patients with a high probability of severe fibrosis or cirrhosis.

The American Association for the Study of Liver Diseases (AASLD) guidelines include the following indications for liver biopsy[7] :

- All homozygotes with clinical evidence of liver disease
- All homozygotes with serum ferritin greater than 1,000 ng/ml
- All homozygotes older than 40 years with other risk factors for liver disease
- Compound or C282Y heterozygotes with elevated transferrin saturation, particularly those who have had abnormal liver enzyme levels or clinical evidence of liver disease

See Workup for more detail.

Management

Clinical suspicion and early diagnosis are essential in hemochromatosis. The goal of therapy in patients with iron overload disorders is to remove the iron before it can produce irreversible parenchymal damage.[8]

Phlebotomy

Once diagnosed, hemochromatosis is treated by phlebotomy to rid the body of excess iron and to maintain normal iron stores. Phlebotomy remains the sole recommended treatment for hereditary hemochromatosis and should be undertaken in a case-specific manner.

Chelation therapy

In patients with hemochromatosis and heart disease, anemia, or poor venous access, treatment with iron chelation agents is recommended and includes the following agents:

- Deferoxamine

- Deferasirox
- Deferiprone
- Iron-binding dendrimers

Surgery

Surgical procedures are used to treat 2 important complications of hemochromatosis: end-stage liver disease and severe arthropathy. Orthotopic liver transplantation is the only therapeutic option when end-stage liver disease progresses despite iron-reduction therapy.[9] This intervention is also indicated in cases with the development of hepatocellular carcinoma.

Surgical arthroplasty is considered if joint destruction becomes severe despite medical therapy.

See Treatment and Medication for more detail.

What is hemochromatosis? Hemochromatosis is a genetic disorder where the body isn't able to regulate its iron absorption. Iron levels in the body build up over time and damage the liver as well as other organs, through the generation of free radicals. Courtesy of Osmosis.org (https://www.osmosis.org/).

Background

Hemochromatosis is the abnormal accumulation of iron in parenchymal organs, leading to organ toxicity. This is the most common inherited liver disease in white persons and the most common autosomal recessive genetic disorder.

Two mutations in the HFE gene have been described. The first, C282Y, comprises the substitution of tyrosine for cysteine at amino acid position 282. In the second, H63D, aspartic acid is substituted for histidine in position 63. C282Y homozygosity or compound heterozygosity C282Y/H63D is found in most patients with hereditary hemochromatosis. The discovery of the C282Y mutation in the HFE gene has altered the diagnostic approach to hereditary hemochromatosis. Cases of homozygotic C282Y without hepatic iron overload may occur, but the clinical outcome of some of these cases requires further study and adds to the controversy on whether systematic population screening should be made available (See Screening under Clinical).

Italian investigators report that alterations in sympathetic nerve traffic may occur in those with genetic hemochromatosis before and after iron depletion therapy.[10] There may be an association with an hyperadrenergic state and a baroreflex alteration, which are reversed by iron depletion and which may increase cardiovascular risk.[10]

Secondary hemochromatosis is caused by disorders of erythropoiesis and treatment of the diseases with blood transfusions.[11] After damage of transfused erythrocytes by macrophages, iron freed from heme is accumulated in the body (liver, heart, skin). Secondary hemochromatosis is mainly induced by diseases of erythropoiesis, including thalassemia, sickle cell anemia, X-linked sideroblastic anemia, pyruvate kinase deficiency, hereditary spherocytosis, and congenital dyserythropoietic anemia (CDA).

See also Neonatal Hemochromatosis, Dermatologic Manifestations of Hemochromatosis, Hereditary Hemochromatosis and HFE, Hemochromatosis Imaging, and Transfusion-Induced Iron Overload.

Pathophysiology

Hereditary hemochromatosis is an adult-onset disorder that represents an error of iron metabolism characterized by inappropriately high iron absorption resulting in progressive iron overload.[1] This disease is the most common cause of severe iron overload.[3] The organs involved are the liver, heart, pancreas, pituitary, joints, and skin.[12]

Mutations in least 5 different genes (HFE, HJV, TFR2, SLC40A1, HAMP) in hereditary hemachromatosis have been recognized as being involved in hepcidin production/activity, which may disrupt regulation of systemic iron homeostasis.[13] Relatively recent studies suggest that newly identified heterozygous missense pro-peptide

mutations in bone morphogenetic protein 6 (BMP6), which affects upregulation of hepcidin gene transcription, may contribute ot late-onset moderate iron overload in patients with hereditary hemochromatosis.[13]

Excess iron is hazardous, because it produces free radical formation. The presence of free iron in biologic systems can lead to the rapid formation of damaging reactive oxygen metabolites, such as the hydroxyl radical and the superoxide radical. These can produce DNA cleavage, impaired protein synthesis, and impairment of cell integrity and cell proliferation, leading to cell injury and fibrosis.[14]

Derangement of iron homeostasis is also linked with susceptibility to infectious diseases. Studies performed on Hfe knockout mice (the hemochromatosis model) showed an attenuated inflammatory response induced by lipopolysaccharide and Salmonella. Secretion of tumor necrosis factor-alpha (TNF-alpha) and interleukin (IL)-6 by macrophages was lowered. However, ferroporin, the macrophage iron exporter, was upregulated. This phenomenon was linked with the presence of a decreased level of iron in macrophages. Thus, the iron level in macrophages was reported to play the regulatory role in the inflammatory response.[15]

men lose 1 mg/day, women 2 mg/day due to menstruation, 500 mg w each pregnancy. Additional fecal loss of 0.3 mg/day.

Daily iron losses and absorption

Adults preserve a constant level of body iron by efficient conservation, maintaining rigorous control over absorption to balance losses. An adult man loses approximately 1 mg of iron daily, mostly in desquamated epithelium and secretions from the gut and skin. During the childbearing years, healthy women lose an average of an additional milligram of iron daily from menstrual bleeding (40 mL blood loss) and approximately 500 mg with each pregnancy. In addition, normal daily fecal loss of approximately 0.7 mL of blood (0.3 mg of iron) occurs. Only a small quantity of iron is excreted in urine (<0.1 mg/d).

In healthy adults, losses are balanced by absorption of sufficient dietary iron (1-2 mg) to maintain a relatively constant amount of body iron throughout life. Although excretion is quantitatively as important as absorption in the maintenance of iron balance, absorption usually plays the more active regulatory role. In hereditary hemochromatosis, dysregulation of intestinal iron absorption occurs, wherein iron continues to be efficiently absorbed even in the face of substantial elevation of body iron stores.[16]

HFE gene missense mutations

The gene most recognized as responsible for the disease is called HFE, and it is located within the human leukocyte antigen (HLA) class I region on chromosome 6 between the genes coding for HLA-A and HLA-B. This gene is mutated in most individuals with hereditary hemochromatosis, and the 2 missense mutations (C282Y and H63D) of the HFE gene are responsible for most cases of hereditary hemochromatosis in patients of European descent.

HFE protein, the product of the HFE gene, is homologous to major histocompatibility complex (MHC) class I proteins. However, HFE does not present peptides to T cells, and transferrin receptor (TfR) is a ligand for the HFE protein.[17] HFE interacts with THR and causes a clear decrease in the affinity with which the receptor binds transferrin; thus, there's a direct association of the HFE protein and the TfR-mediated regulation of iron homeostasis, and this interaction may also modulate cellular iron uptake and decrease ferritin levels. When a mutant or nonfunctional variant of the HFE gene is present, ferritin levels are not under influence of a normal and functional HFE gene, which leads to enhanced accumulation of iron in peripheral tissues.

Although the mutation underlying most cases of hereditary hemochromatosis is now known, considerable uncertainty exists in the mechanism by which the normal gene product, the HFE protein, regulates iron homeostasis. Findings suggestive of increased iron transport at the basolateral membrane of enterocytes in hemochromatosis have emerged from numerous studies of HFE -related hemochromatosis in humans[18] and in mice.

Knockout mice models of the HFE gene confer the hereditary hemochromatosis phenotype. However, studies on HFE expressed in cultured cells have not clarified the mechanism by which HFE mutations produce increased dietary iron absorption. There have been data that implicate other genes, including those encoding a second TfR and the circulating peptide hepcidin, which may participate in a shared pathway with HFE in the regulation of iron absorption.

Hemochromatosis types 2 and 3

The gene for hemochromatosis type 1 (HFE1), the result of the C282Y and H63D mutations, is located at band 6p22 and encodes a protein containing 343 amino acids. However, 2 other types of hemochromatosis have been identified: juvenile hemochromatosis (JH) or type 2 (gene HFE2), which has been mapped to band 1q21,[19, 20] and an adult form defined as hemochromatosis type 3 (HFE3), which results from mutations of the transferrin

receptor 2 gene (TfR2) located on band 7q22. The clinical appearance of different types of hemochromatosis could be similar. This speculation also relates to JH with late onset. Therefore, patients with hemochromatosis without HFE mutations should be evaluated for other possible types of hemochromatosis.

Hepcidin deficiency

All types of hemochromatosis have been found to originate from the same metabolic error: disruption of tendency for circulatory iron constancy. Severe iron overload was found in patients with mutations of genes encoding hemojuvelin. These changes correlated with a low level of hepcidin.[21] Hepcidin is a human antimicrobial peptide synthesized in the liver[22] that plays a key role in the downregulation of iron release by enterocytes and macrophages (inhibits iron absorption in the gut and iron mobilization from the hepatic stores). The degradation of cellular iron exporter (ferroportin) caused by hepcidin is the mechanism of cellular iron efflux inhibition. The absence of this peptide is associated with severe, early-onset, iron-loading phenotype. It is also inappropriately low in adult-onset HFE -related disease.[23]

Hepcidin synthesis remains under the regulatory influence of hemojuvelin, which is a member of the repulsive guidance molecule (RGM) and is the coreceptor of the bone morphogenetic protein (BMP). De-arranged BMP signaling in hemojuvelin mutants associated with hemochromatosis disturbs hepcidin synthesis in hepatocytes. Thus, decreased BMP signaling by hemojuvelin disfunction lowers hepcidin secretion. The hepcidin deficiency due to mutations of hepcidin gene or genes of hepcidin regulators is supposed to be the main factor leading to different types of hemochromatosis.

SLC11A3 gene missense mutation and autosomal dominant hemochromatosis

A large family was described with autosomal dominant hemochromatosis not linked to HFE and distinguished by early iron accumulation in reticuloendothelial cells.[24] This form of the disease was mapped to band 2q32. The gene encoding ferroprotein (SLC11A3), which is a transmembrane iron export protein, is within a candidate interval defined by highly significant logarithm of odds (lod) scores.

The iron-loading phenotype in autosomal dominant hemochromatosis was shown to be associated with a nonconservative missense mutation in the ferroprotein gene. This missense mutation, converting alanine to aspartic acid at residue 77 (A77D mutation), was not identified in samples from 100 unaffected control subjects. Montosi and associates proposed that partial loss of ferroprotein function leads to an imbalance in iron distribution and a consequent increase in tissue iron accumulation.[24]

Etiology

Hereditary hemochromatosis is a genetic heterogeneous disorder inherited as an autosomal recessive trait.[20] The gene is tightly linked to the human leukocyte antigen (HLA)-A region on the short arm of chromosome 6. HFE, a specific gene for hemochromatosis, has been identified.[25, 26] (See Pathophysiology.)

HFE missense mutations

Homozygosity for a missense mutation, with substitution of a cysteine residue for a tyrosine residue at amino acid position 282 (C282Y) of HFE is found in 70-100% of clinically diagnosed patients.[27] A second missense mutation, with substitution of histidine for aspartate at amino acid 63 (H63D), has also been identified. The clinical effects of this mutation appear to be limited.[28]

C282Y homozygotes and, possibly, C282Y/H63D compound heterozygotes, appear to be at risk for clinical iron overload.[29] The clinical significance of other rarer forms of compound heterozygosity, such as heterozygosity for C282Y and a mutation in which cysteine replaces serine at position 65 (S65C) or heterozygosity for H63D and S65C, is controversial.[30]

The precise mechanism by which mutations in the HFE gene lead to iron overload is unknown. The outcome is increased intestinal iron absorption and predominantly hepatocellular accumulation of hepatic iron.

Although relatively few cases have been described to date, the iron-overload phenotype associated with mutations in the gene encoding transferrin receptor 2 (TfR2) appears to be very similar to that of classic HFE -related hemochromatosis.

Elevated iron storage is related to the development of metabolic syndrome, diabetes, and obesity, which are themselves associated with hypertriglyceridemia. When Solanas-Barca et al investigated whether HFE mutations that cause hereditary hemochromatosis can be linked to the development of primary hypertriglyceridemia, the investigators these mutations may be important factors in the development of several primary hypertriglyceridemia phenotypes.[31]

Furthermore, in the hypertriglyceridemia group, the genetic predisposition to hereditary hemochromatosis was 5.9 and 4.4 times greater than in subjects who were normolipidemic and in those with familial hypercholesterolemia, respectively.[31] Moreover, 16.8% of persons (35 cases) in the hypertriglyceridemia group had iron overload, compared with 6.5% of individuals (14 cases) who were normolipidemic and 5.6% of patients (9 cases) with familial hypercholesterolemia.[31]

HAMP gene mutation and juvenile hereditary hemochromatosis

Rare cases of juvenile hereditary hemochromatosis have been linked to a homozygous mutation in the HAMP gene, which encodes hepcidin, a peptide that plays a key role in human iron metabolism.[32, 33] However, most juvenile-onset cases have been mapped to chromosome 1q, where the gene that produces hemojuvelin, HJV (originally called HFE2), has been identified.[19, 20]

Hepcidin deficiency

Evidence indicates that certain forms of hereditary hemochromatosis are caused by hepcidin deficiency.[34] Studies suggest that TfR2 is a modulator of hepcidin production in response to iron; hepcidin was low or undetectable in most cases of patients homozygous for TfR2 mutation.[35, 36, 37]

Epidemiology

United States statistics

Prevalence of hereditary hemochromatosis in the United States is 1 case in 200-500 individuals. Most are of northern European origin.[38] Frequency of the C282Y mutation is 5.4% and that of the H63D mutation is 13.5%. Prevalence of C282Y homozygosity has been estimated to be 0.26%, the H63D homozygosity was estimated to be 1.89%, and compound heterozygosity was estimated to be 1.97%.[39] The carrier state is estimated to be approximately 10%.

International statistics

The worldwide frequency of the C282Y is about 1.9% and that of the H63D mutation is about 8.1%.[40] Hemochromatosis has the same prevalence in Europe, Australia, and other Western countries, with the highest prevalence being noted in people of Celtic origin.[41] Hemochromatosis is less common among patients of African descent.[42]

Marked geographical disparity in the distribution of the C282Y mutation has been noted. Non-HFE- associated hereditary hemochromatosis was found in Mediterranean countries.[43]

In populations of northern European ancestry, hereditary hemochromatosis is closely linked to mutations in HFE.[41] In one study, more than 93% of Irish patients with hereditary hemochromatosis were homozygous for the HFE C282Y mutation, providing a reliable diagnostic marker of the disease in this population.[41] However, the prevalence of the C282Y mutation and that of the second HFE mutation, H63D, have not been determined in the Irish population.

In a population of white adults of northern European ancestry, 0.5% were homozygous for the C282Y mutation in HFE.[44] However, only half the homozygotes had clinical features of hemochromatosis, and one quarter had serum ferritin levels that remained within the reference range over a 4-year period. The G320V mutation seems to be widely distributed among juvenile hemochromatosis patients from central Europe and Greece.[45] Therefore, detection of the G320V mutation could be a noninvasive method to identify most of the patients from these regions.

Racial differences in incidence

Marked racial disparity in the distribution of the C282Y mutation has been noted. Prevalence of hemochromatosis is 6 times higher in white persons than in black persons. In the Irish, the frequency of the C282Y mutation was 10%, whereas in Australian aboriginal, African, and Asian populations, the mutation has not been found.

10% prevalence of mutation in Irish (homocygotes)?

C282Y homozygotes account for 82-90% of clinical diagnoses of hereditary hemochromatosis among persons of northern European descent[46] ; in a report, 1 in 227 white individuals were homozygotes for the HFE C282Y mutation.[47] The highest reported prevalence for C282Y homozygosity is one in 83 people and was described in Ireland.[48]

The frequency of the C282Y heterozygosity is much lower among Hispanic persons (0.27 per 1000 population), Asian Americans (<0.001 per 1000 population), Pacific Islanders (0.12 per 1000 population), and black persons (0.14 per 1000 population) than among persons of northern European descent. The frequencies of the C282Y and H63D mutations vary in black individuals from different geographic regions of the United States as a result of white admixture.[39]

HFE mutations in black women with diabetes

In a study that compared the frequency of HFE mutations in black women who had type 2 diabetes mellitus to the frequency of mutations in control subjects, the frequencies of the C282Y and H63D mutations were not significantly different between patients with type 2 diabetes mellitus and control subjects.[49] The C282Y mutation was noted in 0.59% of patients and in 1.41% of control subjects, whereas the H63D mutation was seen in 2.99% of patients and in 3.08% of control subjects.

All of the patients with type 2 diabetes mellitus with either a C282Y or H63D mutation had levels of serum ferritin, serum iron, and transferrin saturation in the reference range.[49] One woman who inherited the C282Y mutation also had human leukocyte antigen A3 (HLA-A3) and human leukocyte antigen B7 (HLA-B7), which are considered part of the ancestral haplotype containing the gene predisposing whites to hemochromatosis.

Sexual differences in incidence

Men are affected with hemochromatosis nearly 2-3 times as often as women, with an estimated ratio of 1.8:1 to 3:1.

Disease related to iron overload commonly develops in men (but not in women) who are homozygous for the C282Y mutation, especially when serum ferritin levels are 1000 mcg/L or more. The increased prevalence of iron-overload –related disease in C282Y homozygous men, as compared with that in women, is frequently ascribed to recurrent physiologic blood loss and the resultant slower accumulation of iron in women.[50, 51]

However, disparate frequencies of HLA A*03B*07 haplotypes in men and women have also been reported in hereditary hemochromatosis probands, which may be relevant to sex-specific phenotypic expression of this disease.[52]

Studies of iron regulatory pathways in black persons have suggested that serum ferritin levels may be genetically determined by sex differences as well as environmental factors.[53]

In a study of relatives of patients with hereditary hemochromatosis who are homozygous for the C282Y mutation, expression of the iron overload phenotype was noted in 85% of males and 69% of females.[54]

expression 85% in males and 69% in females.= NOT in 15% of males and 31% of females

Olynyk et al reported that one quarter of patients who are homozygotes for the C282Y mutation did not express clinical or biochemical symptoms of disease, all of whom were women of reproductive age.[44]

Men have also been reported to have a higher incidence of serious complications of hereditary hemochromatosis, primarily diabetes mellitus and cirrhosis.[55] In men, the incidence of cirrhosis was 25.6% (13.8% in women), and the incidence of diabetes mellitus was 15.9% (7.4% in women). Women complained more often of fatigue 64.8% (42% in men) and skin hyperpigmentation 48% (44.9% in men).[55]

Age-related differences in incidence

Hemochromatosis usually becomes apparent after age 40 years in men (median age, 51 y)and after age 50 years in women (median age, 66 y). In women, onset of hereditary hemochromatosis begins later because menstruation causes physiologic blood loss, which increases iron removal.

However, in juvenile hemochromatosis, which is unrelated to HFE mutations, symptoms appear in persons aged 10-30 years. Neonatal hemochromatosis, which is more correctly termed neonatal iron overload, is a disease with unknown etiology that progresses rapidly to death after birth.

Prognosis

Sharpened diagnostic awareness has improved early diagnosis of hereditary hemochromatosis and increased the diagnostic frequency of clinical hemochromatosis. Early detection and treatment of this common iron overload disorder can guarantee a normal lifespan in patients with hemochromatosis.

The most important prognostic factor at the time of diagnosis is the presence or absence of hepatic fibrosis or cirrhosis. Patients without significant hepatic fibrosis may be expected to have a normal life expectancy with phlebotomy therapy. Adequate phlebotomy treatment is the major determinant of survival, and it markedly improves prognosis. Early diagnosis and therapeutic phlebotomy to maintain low normal body stores is crucial and can prevent all known complications of hemochromatosis. If untreated, hemochromatosis may lead to death from cirrhosis, diabetes, malignant hepatoma, or cardiac disease.[56, 57]

Potential complications of hemochromatosis include the following:

- Liver cirrhosis
- Hepatocellular carcinoma
- Congestive heart failure
- Cardiac arrhythmias
- Diabetes mellitus
- Hypogonadism
- Impotence
- Arthropathy
- Thyroid dysfunction
- Sepsis

Mortality is estimated to be 1.7 cases per 10,000 deaths. This number increases to 3.2 cases per 10,000 deaths in autopsy series. The death rate associated with hemochromatosis increased from 0.5 persons per million population in 1968 to 0.9 persons per million population in 1992 due to improved recognition of the disease. Mortality is higher in infants and in adults older than 50 years as well as higher in men and in white persons than in women, black persons, and other groups.[58]

In a study from Denmark, investigators evaluating the incidence and course of hereditary hemochromatosis in white Danish patients with clinically overt hemochromatosis found that survival duration was significantly reduced in patients with liver cirrhosis, diabetes mellitus, or both.[57] In contrast, survival rate in patients without cirrhosis or diabetes was similar to rates expected in the general population. In addition, survival rates in patients with arthropathy were higher than in patients without arthropathy.[57] Patients adequately treated with phlebotomy also had a higher survival rate than patients treated inadequately. The primary causes of death were hepatic failure due to cirrhosis (32%) and cirrhosis with liver cancer (23.1%).[57]

After liver transplantation, 1-year survival rates are 58% and 5-year survival rates are 42%, which are significantly lower than those for all other indications. Poor survival and increased posttransplant mortality are predominantly due to infectious and cardiac complications. Sepsis causes most early posttransplant mortality, whereas congestive heart failure accounts for most deaths 1 year or longer after transplantation.

When Bathum et al studied the significance of heterozygosity and mortality, the investigators found that in a population with high carrier frequency, such as the Danish, mutations in HFE show an age-related reduction in the frequency of heterozygotes for the C282Y mutation. This suggests that carrier status is associated with shorter life

expectancy.[59] In the same study, genotyping for mutations in exons 2 and 4 of the HFE gene showed a trend toward fewer heterozygotes for the C282Y mutation in exon 4 mutations.

Presentation

History and Physical Examination

Patients with hereditary hemochromatosis may be asymptomatic or may present with general and organ-related signs and symptoms.

Symptoms from hemochromatosis usually begin between age 30 years and age 50 years, but they may occur much earlier in life.[60] Most patients are asymptomatic (75%) and are diagnosed when elevated serum iron levels are noted on a routine chemistry screening panel or when screening is performed because a relative is diagnosed with hemochromatosis.

Early symptoms include severe fatigue (74%), impotence (45%), and arthralgia (44%); fatigue and arthralgia are the most common symptoms prompting a visit to a physician. The most common signs at the time of presentation are hepatomegaly (13%), skin pigmentation, and arthritis.[4]

Clinical manifestations include the following:

- Liver disease (hepatomegaly, 13%; cirrhosis, 13%, usually late in the disease)
- Skin bronzing or hyperpigmentation (70%)
- Diabetes mellitus (48%)
- Arthropathy
- Amenorrhea, impotence, hypogonadism
- Cardiomyopathy

Liver disease

Liver function abnormalities occur in 35-75% of patients. Among organ-related symptoms, hepatomegaly is seen in more than 95% of patients and can be accompanied by signs of chronic liver disease, such as abdominal pain and cutaneous stigmata of liver disease (palmar erythema, spider angioma, or jaundice), and liver failure (ascites or encephalopathy). Right upper quadrant tenderness with hepatomegaly or splenomegaly may be present.

Cirrhosis is due to progressive iron deposition in the liver parenchyma, and it is one of the most common disease manifestations of the tissue damage caused by hemochromatosis. Cirrhosis may be complicated by liver cancer years later (risk >200-fold). This condition is also the most common cause of death in patients with hereditary hemochromatosis.

Cirrhosis reversibility after iron removal has been reported, usually early in the course of liver disease, although reversal of advanced liver disease with varices has also been reported.

Some studies show that HFE mutations in patients with hepatitis C infection are associated with higher frequencies of fibrosis and cirrhosis.[61, 62] Increased fibrosis was also found in patients with nonalcoholic steatohepatitis (NASH) who had the C282Y mutation.[63, 64]

Skin bronzing or hyperpigmentation

A combination of iron deposition and melanin causes the skin bronzing or hyperpigmentation that is typical of the disease. The classic triad of cirrhosis, diabetes mellitus, and skin pigmentation occurs late in the disease, when total iron body content is 20 g (ie, >5-times normal).

Diabetes mellitus

Diabetes, often requiring insulin therapy, occurs due to progressive iron accumulation in the pancreas. The damage appears to be relatively selective for the pancreatic beta cells. Most patients with hemochromatotic diabetes have other signs of hemochromatosis, such as liver disease or skin pigmentation.

Diabetes mellitus can be seen in 30-60% of patients with hereditary hemochromatosis; therefore, polyuria, polydipsia, and high blood and urine glucose levels may be found. In one study, the prevalence of diabetes mellitus was 21.9% in patients with hereditary hemochromatosis.[65] The type of mutations for hereditary hemochromatosis, ferritin level, or the presence of cirrhosis were not predictive for diabetes mellitus development. In the majority patients, the insulin requirements or glucose level was not influenced by iron depletion.[65]

Arthropathy

Arthropathy is due to iron accumulation in joint tissues. It is associated with characteristic radiologic findings, that is, squared-off bone ends and hooklike osteophytes in the metacarpophalangeal (MCP) joints, particularly in the second and third MCP joints. Symptoms usually do not respond to iron removal.

Chondrocalcinosis, which involves the knees and the wrists, may occur and may be asymptomatic.

The most commonly affected joints include the following:

- MCP joints
- Proximal interphalangeal joints
- Knees
- Feet[66]
- Wrists
- Back
- Neck

Amenorrhea, impotence, hypogonadism

Amenorrhea, loss of libido, impotence, and symptoms of hypothyroidism can be seen in patients with hereditary hemochromatosis. Although amenorrhea can occur in women, it is less frequent than hypogonadism in men.

Hypogonadism is the most common endocrine abnormality causing decreased libido and impotence in men. It usually is due to pituitary iron deposition. Primary hypogonadism, presumably due to testicular iron deposition, also can occur but is much less common.

Cardiomyopathy

Cardiac enlargement, with or without heart failure or conduction defects, is another mode of presentation, particularly in younger patients. Hereditary hemochromatosis C282Y/C282Y, C282Y/H63D, and C282Y/wild-type genotypes have not been associated with ischemic heart disease or myocardial infarction.[67]

Dilated cardiomyopathy is characterized by the development of heart failure and conduction disturbances, such as sick sinus syndrome. In the past, cardiac disease was the presenting manifestation in as many as 15% of patients; therefore, the absence of other manifestations of hemochromatosis should not preclude the diagnosis. Signs of fluid overload are seen with congestive heart failure.

Other manifestations

Osteopenia and osteoporosis[5] as well as hair loss and koilonychia (spoon nails) may occur in patients with hemochromatosis.

Of patients with hereditary hemochromatosis, 25% have osteoporosis, while 41% are diagnosed with osteopenia.[5] The osteoporosis is independent of genetic background and is associated with hypogonadism, increase in alkaline phosphatase, increase in body weight, and the severity of iron overload.[5]

Partial loss of body hair is evident in 62% of patients. The pubic area is affected most commonly, although total loss of body hair is seen in about 12% of patients. Hair loss and thinning may be reversed by therapy in some patients.

Koilonychia, usually of the thumb and index and middle fingers, is seen in almost half of patients. Overall, one fourth of patients with hemochromatosis have prominent spoon nails.

Screening

As the most common autosomal recessive disorder in populations of northern European descent, hereditary hemochromatosis may be an almost ideal disease for which to perform population screening.[2] The advent of genetic testing for hereditary hemochromatosis focuses concern on informed consent and the ethical, legal, and social implications of screening, particularly in relation to medical and general discrimination.

The American Association for the Study of Liver Diseases (AASLD) guidelines recommend screening of high-risk groups such as those with suggestive organ involvement, a familial history of hereditary hemochromatosis, and those with biochemical or radiologic abnormalities suggestive of the possibility of iron overload.[7] See Guidelines for detailed information.

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Diagnostic Considerations

When evaluating a patient with suspected hemochromatosis, alcoholic liver disease, ineffective erythropoiesis with marrow hyperplasia, iron overload associated with chronic anemia, multiple transfusions, and porphyria cutanea tarda should also be considered. In addition, patients may have susceptibility to certain bacterial infections, such as Yersinia enterocolitica liver abscess, Y pseudotuberculosis sepsis, Vibrio vulnificus sepsis, and Listeria monocytogenes meningitis.[68] Also, take note of the increased risk of hepatoma in cirrhotic livers of patients with hemochromatosis.

Distinguishing hemochromatosis arthropathy from rheumatoid arthritis is important for several reasons. For example, patients with hereditary hemochromatosis do not require corticosteroid treatment. In addition, if a diagnosis of rheumatoid arthritis is made incorrectly, treatment with phlebotomy is not started early, and familial genetic counseling is not considered.[69]

Alcoholic liver disease

Patients with alcoholic disease include those who are heavy drinkers, perhaps of iron-containing fortified wines, who have cirrhosis. Liver biopsy in these patients may show a modest increase in iron; however, contrary to patients with hemochromatosis, the hepatic iron levels are relatively normal and iron stores are less than 4 g.

Ineffective erythropoiesis with marrow hyperplasia

Patients with hyperplastic erythroid marrow absorb an increased amount of iron to the point where they may have clinical iron overload. Examples include the hereditary sideroblastic anemias, severe alpha and beta thalassemia, and the myelodysplastic syndrome variants, such as refractory anemia with ringed sideroblasts (RARS).

Iron overload associated with chronic anemia

Patients who have iron overload due to chronic anemia have increased effective erythropoiesis and increased iron absorption. Examples include hereditary spherocytosis and acquired sideroblastic anemia.

Multiple transfusions

Hypertransfusion is performed in patients with beta thalassemia major, sickle cell anemia, refractory aplastic anemia, and myelodysplastic syndrome. Such patients may receive as many as 100 units of red blood cells, which contain as much as 20-25 g of iron, similar to or more than the amount retained in many symptomatic patients with hereditary hemochromatosis.

Porphyria cutanea tarda

Porphyria cutanea tarda is primarily a skin and liver disease that occurs in familial and sporadic forms. The cause of liver siderosis in sporadic porphyria cutanea tarda has not been established, but it may be related to a mutation in the HFE gene in most patients.

Differential Diagnoses

- Beta Thalassemia
- Biliary cirrhosis
- Hemolytic Anemia

Workup

Workup

Approach Considerations

The diagnosis of hemochromatosis is based on clinical features of the disease; these features include diffuse hyperpigmentation, hepatomegaly, and diabetes mellitus accompanied with biochemical abnormalities of iron metabolism and genotypic investigation.[69] Perform early genetic testing or liver biopsy to avoid the complications of hemochromatosis.

Examination of HFE mutations is pivotal for diagnosis of hemochromatosis; the discovery of the HFE gene allows easy differentiation of hereditary hemochromatosis from other forms of hepatic iron overload, including dysmetabolic hepatosiderosis. Liver biopsy and histologic evaluation of tissue iron accumulation was believed to be the criterion standard for diagnosis of hereditary hemochromatosis until testing of the HFE gene was introduced.[43]

The prevalence of the C282Y and H63D mutations in patients with alcoholic liver disease and in those with chronic hepatitic C (HCV) is the same as in the control population, whereas, in patients with nonalcoholic steatohepatitis (NASH), the prevalence of HFE mutations is higher. Moreover, 40% of patients with porphyria cutanea tarda are homozygous or heterozygous for the C282Y mutation (shown in patients from the United States, the United Kingdom, and Australia but not in Italian patients).

Measuring serum iron has no value in the diagnosis, but measuring transferrin saturation is necessary. The American College of Physicians found insufficient evidence to recommend for or against the use of transferrin saturation and serum ferritin levels to help identify the early stages of hereditary hemochromatosis.[70]

Serum abnormalities of iron metabolism can be seen in 50% of patients with alcoholic liver disease, NASH, or chronic viral hepatitis.[71] These abnormalities comprise an increased ferritin level, which is sometimes accompanied with elevated transferrin saturation. Hepatic iron concentration (HIC) could be slightly elevated, but the level of HIC in patients with hereditary hemochromatosis is much higher. Patients with chronic hepatitis C virus infection (HCV) who do not respond to interferon therapy usually have higher HIC than responders.

Development of noninvasive measures of hepatic iron content has generated significant interest. Many studies are focusing on the role of computed tomography (CT) scanning or magnetic resonance imaging (MRI) in the evaluation of total iron body stores.

Portable hemoglobinometers may provide a quick and simple measurement of hemoglobin for evaluating the follow-up of tolerance for phlebotomies in patients with HFE-associated hereditary hemochromatosis.[72] In a study of 122 patients, hemoglobin levels were measured by a portable hemoglobinometer and a cell counter device. Compared to the cell counter device, the portable hemoglobinometer had a 100% sensitivity and 98.1% specificity for anemia

(hemoglobin Supraventricular arrhythmias are often revealed on electrocardiograms (ECGs).All patients with cirrhosis should undergo diagnostic endoscopy to document the presence of varices and to determine their risk of variceal hemorrhage. Patients at risk for variceal hemorrhage should be considered for primary prophylaxis with propranolol or nadolol.

Transferrin Saturation

Transferrin saturation corresponds to the ratio of serum iron and total iron-binding capacity (TIBC). The screening threshold for hemochromatosis is a fasting transferrin saturation of 45-50%. If transferrin saturation is greater than 45%, the presence of the C282Y or H63D mutation may be evaluated to confirm the diagnosis of hemochromatosis.

Hemochromatosis is suggested by a persistently elevated transferrin saturation in the absence of other causes of iron overload. This is the initial test of choice. However, similar to iron studies, transferrin saturation is influenced by liver disease (other than hemochromatosis) and inflammation; therefore, it has limitations in the diagnostic workup.

High transferrin saturation is the earliest evidence of hemochromatosis; a value greater than 60% in men and 50% in women is highly specific. However, approximately 30% of women younger than 30 years who have hemochromatosis do not have elevated transferrin saturation.

Serum iron concentration in patients with hereditary hemochromatosis is greater than 150 mcg/dL. TIBC ranges from 200 to 300 mcg/dL in hemochromatosis-affected patients (normal range, 250-400 mcg/dL). Hepatic iron concentration in hemochromatosis-affected patients ranges from 5000 to 30000 mcg/g (normal values, 100-2200 mcg/g).[73]

Serum Ferritin Studies

Ferritin levels are less sensitive than transferrin saturation in screening tests for hemochromatosis. Ferritin concentration can also be high in other conditions, such as infections, inflammations, and liver disease. Ferritin concentration higher than 1000 mcg/L suggests liver damage with fibrosis or cirrhosis.[74]

Recognize that a high ferritin level may be an indicator of iron overload, not just a sign of nonspecific inflammation, especially if accompanied with elevated liver enzymes.

Serum ferritin levels elevated higher than 200 mcg/L in premenopausal women and 300 mcg/L in men and postmenopausal women indicate primary iron overload due to hemochromatosis, especially when associated with high transferrin saturation and evidence of liver disease.

Genetic Testing

Genetic tests for the C282Y and H63D mutations are widely available. Detection of hemochromatosis-associated mutations is conducted to confirm the diagnosis or to discover asymptomatic patients.

Genetic testing for the HFE mutation is indicated in all first-degree relatives of patients with hemochromatosis and also in patients with evidence of iron overload[75] (eg, elevated transferrin saturation, high serum ferritin levels, excess iron staining or iron concentration on liver biopsy samples). This is particularly indicated in patients with known liver disease and evidence of iron overload, even if other causes of liver disease are present.[76]

Such testing is accomplished by searching for the 2 HFE gene mutations, C282Y and H63D. This is the next step in diagnosis after increased biochemical iron indices are present and other causes of iron overload have been excluded.

The finding of heterozygosity for C282Y is expected in 10% or more of subjects with hemochromatosis of northern European extraction and in approximately 15-20% of patients for the H63D mutation; thus, this finding is common in any white population studied.

At present, only homozygosity for C282Y and compound heterozygosity for C282Y/H63D should be considered indicative of hereditary hemochromatosis. C282Y heterozygosity may contribute to iron overload due to other conditions, but it should not be considered the sole cause of iron overload and it should not be considered diagnostic of hereditary hemochromatosis.

HFE genotyping cannot provide information about the degree of increased body iron stores or organ damage. DNA-based testing cannot replace liver biopsy to confirm the presence of end-stage liver damage.[77] The use of DNA-based tests alone may fail to identify 20-40% of white patients and most black patients with clinical evidence of hemochromatosis but without the C282Y mutation.

Imaging Studies

Radiographs demonstrate cardiomegaly and increased pulmonary vascular markings in patients with hemochromatosis. On echocardiograms, features of restrictive cardiomyopathy are visible.

Heart diseases are associated with hereditary hemochromatosis in one third of patients. Cardiac disease is mainly manifested by congestive heart failure accompanied by supraventricular arrhythmias. On radiographs, cardiomegaly with increased pulmonary vascular markings are seen. Echocardiography reveals the features of the restrictive type of cardiomyopathy.

Computed tomography (CT) scanning is neither sensitive nor specific for the detection of mild hepatic iron overload. Magnetic resonance imaging (MRI) may be more sensitive, but this modality has not been validated as a diagnostic test to help confirm hemochromatosis. However, in cases of elevated ferritin levels in the absence of homozygosity for C282Y/compound heterozygosity for C282Y/H63Asp, hepatic iron quantification with MRI might be helpful.[6] Nonetheless, consensus has not yet been reached regarding the technique or the possibility to reproduce the same method of calculus in different machines.

Biopsies and Histologic Features

A skin biopsy specimen may confirm the diagnosis of hereditary hemochromatosis. Any cutaneous site, hyperpigmented or not, may be selected for biopsy, but avoid performing cutaneous skin biopsies on the legs, because iron deposition in that area may be due to stasis. In healthy people, iron deposition may be evident only around apocrine glands and not around eccrine glands.

Liver biopsy with biochemical determination of hepatic iron concentration and calculation of the hepatic iron index (HII) as well as histologic evaluation with iron staining (Perls Prussian blue) was previously considered the criterion standard for diagnosis. The HII is calculated by dividing body weight in pounds by the hepatic iron concentration (HIC) in micromoles per gram of dry weight. An HII of greater than 1.9 can accurately differentiate homozygous hemochromatosis from heterozygous hemochromatosis, alcoholism, and normal controls. When the HII is 1.5-1.9, the diagnosis of hemochromatosis is equivocal.

Currently, the diagnosis can be confidently based on genetic testing for the C282Y mutation; thus, liver biopsy is no longer essential for diagnosis in many cases. However, liver biopsy may not only be useful to identify liver disease and to determine the presence or absence of cirrhosis, which directly affects prognosis, but it may also be helpful in patients with cirrhosis, which is the primary risk factor for hepatocellular carcinoma.

Indications for liver biopsy

According to guidelines that were developed for the diagnosis and management of hereditary hemochromatosis (on behalf of the Dutch Institute for Healthcare Improvement) (which is mainly expert opinion based), a liver biopsy is indicated in the following cases[6] : (1) elevated liver enzymes in combination with hereditary hemochromatosis, and (2) serum ferritin levels greater than 1000 mcg/L.

According to guidelines from AASLD: "Liver biopsy is recommended in all homozygotes with clinical evidence of liver disease, serum ferritin greater than 1,000 ng/mL, and particularly in those greater than 40 years of age with other risk factors for liver disease. Liver biopsy should also be considered in compound or C282Y heterozygotes with elevated TS, particularly those who have had abnormal liver enzyme levels or clinical evidence of liver disease."[7]

The use of liver biopsy in hereditary hemochromatosis can be restricted to those patients with a high probability of severe fibrosis or cirrhosis. A ferritin level of greater than 1000 mcg/L is a strong and independent predictor of fibrosis, but when alcohol intake exceeds 60 g/d, a significant proportion of patients may have severe fibrosis or cirrhosis, even if their ferritin levels are less than 60 g/d. Liver biopsy should be considered in these patients.

Histologic findings

Histologic evaluation liver and gallbladder biopsies with Perls Prussian blue staining shows a characteristic pattern of hepatic accumulation. In hemochromatosis, iron accumulates predominantly in hepatocytes and biliary epithelial cells, with relative sparing of Kupffer cells. Typically, a gradient of hepatocyte iron accumulation is present, with prominent involvement of periportal hepatocytes (zone 1) and decreasing intensity near the central vein (zone 3). By contrast, iron accumulation in parenteral iron overload occurs predominantly in Kupffer cells.[78]

Primary liver cancer in patients with hemochromatosis may have a wide histologic spectrum.[79] Some tumors show frequent biliary differentiation. Others arise on a nonfibrotic or cirrhotic liver and are often associated with von Meyenburg complexes and, to a lesser extent, with bile duct adenomas.

Treatment

Approach Considerations

Despite advances in the molecular understanding of hemochromatosis and the impact of C282Y on diagnosis, treatment remains simple, inexpensive, and safe.

The goal of therapy in patients with iron overload disorders is to remove the iron before it can produce irreversible parenchymal damage.[8] This is achieved via chelation therapy or venesection, depending on the underlying cause.[80] Because a normal life span can be expected if iron reduction is initiated before the development of cirrhosis, clinical suspicion and early diagnosis are essential.

The tetrad of cirrhosis, diabetes mellitus, hyperpigmentation of the skin, and cardiac failure may be evident in only a minority of patients.[81] Any patient admitted to the hospital with an isolated case of asthenia or with arthralgia or hypertransaminasemia should be examined by means of transferrin-saturation testing.

Cardiac manifestations of hereditary hemochromatosis could have sudden onset and could be poorly responsive to therapy. The hemochromatic etiology of the cardiomyopathy should be identified to ensure appropriate treatment.

A Cochrane database review of interventions for hereditary hemochromatosis found that phlebotomy remained the treatment of choice in those with hereditary hemochromatosis who required blood letting, but no data from randomized trials provided evidence of benefit from any form of blood letting in these patients. There was also insufficient evidence as to whether erythocytapheresis is beneficial or harmful compared with phlebotomy.[82] The investigators noted an overall low quality of evidence and a high risk of bias in the trials assessed, and none of the trials evaluated iron-chelating agents or provided mortality data beyond 1 year or long-term follow-up.[82]

Admission to the intensive care unit (ICU) may be warranted for patients who develop hepatic, cardiac, and infectious complications. Indications for inpatient care, preferably in an ICU, include the following:

- Gastroesophageal bleeding
- Hepatic encephalopathy
- Sepsis
- Congestive heart failure
- Arrhythmias

Transfer considerations

In case of end-stage liver disease that is refractory to all methods of medical treatment, transferring the patient to a facility experienced in liver transplantation is preferable.

When the diagnosis of hepatocellular carcinoma is being considered or if the diagnosis is confirmed, transfer the patient to a cancer institution.

Surgical Intervention

Surgical procedures are used to treat 2 important complications: end-stage liver disease and severe arthropathy.

When end-stage liver disease progresses despite iron-reduction therapy, orthotopic liver transplantation is the only therapeutic option.[9] Another indication for liver transplantation is the development of hepatocellular carcinoma.

Careful patient selection is advised for liver transplantation to treat patients with hepatocellular carcinoma. Particularly, these patients should have a single tumor of 5 cm or smaller in diameter. If multiple tumors are present, the acceptable number is 3 tumors or less, smaller than 3 cm. The 4-year survival rate can be approximately 90% if these criteria are respected.

Surgical arthroplasty is considered if joint destruction becomes severe despite medical therapy.

Phlebotomy

Once diagnosed, hemochromatosis is treated by phlebotomy to rid the body of excess iron and to maintain normal iron stores. Phlebotomy remains the sole recommended treatment for hereditary hemochromatosis and should be undertaken in a case-specific manner.

The AASLD guidelines state hereditary hemochromotosis patients who have evidence of iron overload are “strongly encouraged” to receive phlebotomy regularly until iron stores are depleted. The regular phlebotomies should continue for life, and the frequency of maintenance therapy should be based on serum ferritin levels.[7]

In the induction phase, weekly phlebotomy is made, with blood removal of 7 mL/kg per phlebotomy (not to exceed 550 mL per phlebotomy).[83] The efficacy of treatment is controlled by ferritin level evaluation in plasma once monthly until the values remain above the upper limits of normal (300 mcg/L in men; 200 mcg/L in women). The hemoglobin level must be checked before each procedure; the reference value is 12-13g/dL (120-130g/L).[83] Subsequently, evaluation of ferritin concentration should be performed bimonthly until its level is reduced below 50 mcg/L.

In the maintenance phase, the phlebotomy should be performed every 2-4 months. The interval between procedures is determined by the level of ferritin, which should be lower than 50 mcg/mL.[83, 84]

In a retrospective analysis of 12 paired patients from the Netherlands with hereditary hemochromatosis homozygous for the C282Y mutation, those who received proton pump inhibitors (PPIs) had a significant reduction in the frequency of median number of phlebotomies (0.50) compared with before the administration of PPIs (3.17), and those who received PPIs for at least 2 years required signifcantly fewer phlebotomies (1.25) than those in the paired group before they began taking PPIs (3.17).[85] Moreover, there were a significantly lower number of phlebotomies in the paired group after initiation of PPIs compared to that of patients who never received PPIs.

One study showed that phlebotomy therapy can reduce liver fibrosis, and the effects of therapy are dependent on the stage of the disease.[86] Among individuals with biopsy results positive for liver fibrosis, phlebotomy was associated with an improvement of 13-50%, with the greatest improvement among individuals with the least degree of liver fibrosis. Individuals served as their own controls, and improvement was based on qualitative histologic features. When liver cirrhosis is present and in its early stages, therapeutic phlebotomy appears to control or slow the progression of liver disease. In addition, the results of phlebotomy therapy can be predicted by the simple biochemical tests.[86]

Summary

Phlebotomy is generally a safe and efficient method of iron removal. Encourage patients to have weekly therapeutic phlebotomy of 500 mL of whole blood (equivalent to approximately 200-250 mg of iron).[87] Some patients can tolerate twice-weekly phlebotomy, but this regimen is tedious and often inconvenient. Therapeutic phlebotomy should be performed until iron-limited erythropoiesis develops, identified by failure of the hemoglobin level and/or hematocrit to recover before the next phlebotomy. It should be continued until transferrin saturation is less than 50% and serum ferritin levels are less than 50 ng/mL, preferably 20 ng/mL.

Most patients require maintenance phlebotomy in which 1 unit of blood is removed every 2-3 months. Therapeutic phlebotomy may improve or even cure some of the manifestations and complications of the disease, such as fatigue, elevated liver enzymes, hepatomegaly, abdominal pain, arthralgias, and hyperpigmentation. Other complications usually show little or no change after phlebotomy.

Avoid excessive phlebotomy and the risk of hypovolemia and dehydration.

Chelation Therapy

In patients with hemochromatosis and heart disease, anemia, or poor venous access, treatment with iron chelation agents is recommended. The therapeutic perspectives comprise compounds inhibiting intestinal absorption of iron, chelators of iron, hepcidin, or ferroportin supplementation. In disease caused by hepcidin deficiency, protein supplementation with hepcidin is advised.

Deferasirox

Deferasirox (Exjade) is the oral iron chelator that should be taken once daily as an adjunct to phlebotomies or instead of phlebotomy in patients in whom these procedures are poorly tolerated. Deferasirox is very efficacious in liver iron removal. During treatment with deferasirox, kidney function should be controlled.[88]

In an investigational study that evaluated the effects of deferasirox in Hjv-/- mice (knockout animals lacking hemojuvelin [HJV]; ie, an experimental model of hereditary hemochromatosis), a dose of 100 mg/kg markedly reduced the iron level in the liver and heart. (Note that 100 mg/kg of deferasirox is a much larger dose than is used in humans.) However, in the pancreas, deferasirox was less effective, and the splenic iron count was not influenced.[89] Deferasirox was administered once daily 5 times a week.

Dendrimers

The family of dendrimers, iron-selective chelators, have been synthesized.[90] Dendrimers terminated with hydroxypiridinone have high affinity to iron and reduce its absorption in the rat intestine. Therefore, the application of the dendrimers in the treatment of iron overload diseases is considered.

In experiments performed on rats compared the protective effect of 2 iron chelators, deferoxamine and deferiprone, on iron overload in the heart, deferiprone was found to reduce histopathologic changes in the heart of rats chronically loaded with iron.[91] The 2 compounds were administered individually or in combination with vitamin C (vitamin C was used as the antioxidative compound aimed at preventing heart oxidative injury). Additional administration of vitamin C improved histopathologic changes and biochemical markers in the heart.[91]

Juvenile hemochromatosis

The first patient affected by juvenile hemochromatosis was successfully treated with chelation therapy. Because of severe congestive heart failure, phlebotomy was contradicted. Simultaneous administration of deferoxamine and deferiprone reduced the myocardial dysfunction and improved the clinical status of that patient.

Anemia

Patients affected with anemia cannot be treated with phlebotomy. Thus, application of iron chelation agents (eg, deferoxamine, deferiprone, deferasirox) is recommended.[92]

Deferoxamine is administered intravenously or subcutaneously at doses ranging from 25 to 40 mg/kg. Intravenous infusion is usually 8-10 hours in duration and is repeated 5 nights per week. Similar effects can be obtained with subcutaneous bolus injections administered twice daily. The main adverse effects are inflammatory reactions at the

sites of injection, visual and auditory disturbances, bone growth disturbances, and allergic reactions, including anaphylaxis.

Deferiprone is given orally in 3 divided doses of 75 mg/kg/d. Agranulocytosis, neutropenia, arthralgia, gastrointestinal reactions, and elevation of liver enzyme levels are the main adverse effects. Cardiac iron overload is better reduced by deferiprone than deferoxamine.

Deferasirox is an oral chelation agent, administered at 10-30 mg/kg. Deferasirox adverse effects can include elevation of the creatinine level, skin exanthem, diarrhea, and visual and auditory disturbances.

Dietary Considerations and Prevention

Dietary factors may influence the phenotypic expression of hemochromatosis. Some modulate absorption of iron and may affect the variability of phenotypic penetrance. However dietary changes intended to minimize or eliminate iron ingestion are usually unnecessary and are often not feasible.

Patients should not consume foods that contain large concentrations of bioavailable iron, such as red meats and organ meats. In addition, they should not use iron supplements, including multivitamins with iron. In addition, vitamin C supplements should be avoided. Substances in foods and drinks, including tannates (in tea), phytates, oxalates, calcium, and phosphates, can bind iron and inhibit its absorption.

Alcohol abuse may accelerate disease progression. Ethanol sometimes increases iron absorption, and certain alcoholic drinks, especially red wine, contain relatively high concentrations of iron. Activity of hydroxyl free radicals is elevated by iron-containing diets combined with alcohol intake, and this is implicated in hepatocarcinogenesis.[93] Ingestion of 30 g or more of ethanol daily potentiates hepatic injury due to iron overload and increases the relative risk for primary liver cancer in persons with cirrhosis. Patients with evidence of hepatic injury should consume little or no ethanol. Other patients should consume ethanol in moderation.

Studies performed on healthy subjects living in the Spanish-Mediterranean coast showed that some genotypes (C282Y heterozygote, H63D heterozygote, and homozygote, as well as H63D/S63C compound heterozygote) together with alcohol and iron intake increased indicators of iron status; however, calcium intake decreased them.[94] These effects were not observed in S63C heterozygotes.[94]

Vitamin C (ascorbic acid) increases intestinal absorption of inorganic iron. No reason exists to discourage patients from eating fresh fruits and vegetables containing vitamin C, but advising them to limit ingestion of vitamin C in supplements to 500 mg/d is prudent. Use mineral supplements for specific deficiencies only.

Seafood from potentially contaminated waters must be cooked thoroughly. Raw or improperly cooked shellfish is sometimes contaminated with Vibrio vulnificus and can cause sepsis in patients with hemochromatosis.

Consultations

Promptly refer patients to a gastroenterologist and a liver transplant center in case of end-stage liver disease, especially if it is refractory to treatment. Most often, a gastroenterologist is required to confirm the diagnosis by liver biopsy and to assist in the management of end-stage liver diseases. A surgeon specializing in liver transplantation may be needed in cases of highly advanced liver disease.

In addition, due to the multiorgan nature of the disease and the injury or damage to many intrinsic systems, care and treatment of patients with hemochromatosis require the collaboration of other physicians in different medical or surgical specialties, such as the following:

- An endocrinologist is helpful in treating patients with diabetes mellitus or other endocrine complications, such as thyroid and gonadal dysfunction
- A cardiologist assists in the management of severe congestive heart failure and other cardiac complications, such as arrhythmias

- An infectious disease specialist can treat patients with sepsis and can also choose the appropriate antibiotic therapy for rare infectious complications
- A rheumatologist or an orthopedist is required for the management of joint complications.
- A geneticist is valuable for family screening in all first-degree relatives of newly diagnosed individuals

Long-Term Monitoring

The patient should have a primary care provider who can coordinate treatment with the other specialists involved. Physicians should be aware of the possibility of hereditary hemochromatosis, and they should perform diagnostic tests when hereditary hemochromatosis is suspected. Moreover, patient education as to the importance of early diagnosis and lifelong treatment is essential for symptom-free life.

Regular monitoring of hematocrit, hemoglobin, and serum ferritin levels is necessary in patients undergoing phlebotomy. Genetic testing for hereditary hemochromatosis should also be performed in family members of patients with hereditary hemochromatosis.

Continuous observation of patients with hereditary hemochromatosis regarding the potential complications of the disease is recommended. Regular follow-up visits should be scheduled with the gastroenterologist. Others, such as a cardiologist, an endocrinologist, or a hematologist, may be needed for serial diagnostic and therapeutic intervention. Quarterly visits with healthcare providers may be necessary depending on the severity of the symptoms or complications.

Hepatocellular carcinoma is one of the most serious complications of hemochromatosis. Most hepatologists recommend periodic screening with serum alpha-fetoprotein (AFP) every 6 months in patients with cirrhosis. The most cost-effective imaging test used to supplement serum AFP screening is ultrasonography; the sensitivity is approximately 80% when serum AFP and ultrasonograms are combined for the screening of hepatocellular carcinoma.

Guidelines

Guidelines Summary

CDC-suggested screening guidelines

The Centers for Disease Control and Prevention (CDC) does not recommend universal screening for hemochromatosis but rather suggests evaluating iron overload in individuals with a family history and in individuals who are symptomatic.[95]

Overall, the clinical expressivity of C282Y homozygosity appears to be much lower than previously thought, and the cost effectiveness of screening has been challenged, because many people must be screened in order to prevent severe disease in only a few. During a screening program conducted in a health appraisal clinic, classic multiorgan disease was detected in only 1 of 152 homozygotes.[96, 97, 98]

Screening for hemochromatosis should be considered in the following individuals[99] :

- All first-degree relatives of subjects known to have hemochromatosis: Human leukocyte antigen (HLA) typing is no longer necessary; family members identified as having C282Y homozygosity should be tested for transferrin saturation, serum ferritin, and liver enzymes; screening of young children of patients with hemochromatosis does not need to be performed if the spouse is tested and does not have the C282Y mutation
- Individuals presenting for a standard medical check: Transferrin saturation should be measured; if levels are higher than 45%, the estimation should be repeated after fasting—if the fasting level still is higher than 45%, further investigation is warranted[100]

- The general population: This group possibly should be screened, although screening is more difficult and debatable in these individuals,[101] and cost is a major consideration; a consensus stated that population screening is best performed by phenotype (using iron-binding capacity), but using genotype screening (using C282Y mutation) is considered premature until all unanswered questions are clarified
- If a proband is negative for C282Y mutation, family members must be screened by other means, such as serum iron studies or HLA typing; HLA typing or tissue typing has been used to detect homozygous hemochromatosis in a sibling of a proband who has hemochromatosis by other means, such as liver biopsy or quantitative phlebotomy—in this setting, a sibling who is HLA-A identical and HLA-B identical to the proband is considered homozygous; if only 1 haplotype is shared with the proband, the sibling is considered heterozygous

AMA-suggested screening guidelines

As a result of the high frequency of hereditary hemochromatosis–associated mutations, the American Medical Association recommended the establishment of guidelines for population screening, as follows:

- Screening tests for the general population comprise measurement of serum transferrin saturation or serum iron concentration; when transferrin saturation is greater than 60% or greater than 50% in women who are premenopausal, or when serum iron concentration is greater than 150 mcg/dL, other measurements are recommended
- Screening and diagnosis cannot be based on single-measurement transferrin saturation or serum iron concentrations, because they can be falsely increased as the result of diet, alcohol consumption, or other liver diseases
- Adams and coworkers suggested the introduction of the unbound iron-binding capacity measurement to preselect patients for genotyping[102]
- Detection of homozygosity for the C282Y mutation or compound heterozygosity for the C282Y/H63D mutations is believed to be diagnostic; however, negative results on DNA tests do not exclude hereditary hemochromatosis, which can also be the result of other mutations[103]
- Liver biopsy is not required for the diagnosis of hereditary hemochromatosis; however, liver biopsy may be useful in C282Y homozygotes with suspected liver disease, in C282Y homozygotes or heterozygotes with serum ferritin levels greater than 1000 mcg/L, in patients without C282Y mutations with unexplained iron overload, and in patients with additional risk factors for liver disease[104]
- Relatives of patients with hereditary hemochromatosis should undergo DNA testing to detect subclinical cases of hereditary hemochromatosis so that early treatment for the disease can be begun[43]

AASLD-suggested screening guidelines

Measurement of transferrin saturation after an overnight fast should be considered the initial screening of individuals with suspected iron overload and first-degree relatives of patients with hereditary hemochromatosis older than 20 years. Measurement of serum ferritin at the same time increases the predictive accuracy for diagnosis of iron overload.[7]

HFE gene mutation analysis should be performed for all individuals with abnormal iron study results and on those who are first-degree relatives of identified homozygotes. Patients younger than 40 years may be treated by therapeutic phlebotomy without the need for liver biopsy.

Medication

Medication Summary

Chelation therapy with deferoxamine-induced iron depletion is administered in people with C282Y homozygosity unable to undergo phlebotomy. However, compliance and acceptability of deferoxamine therapy in patients with nonhemochromatosis iron overload is poor.

The oral chelators, deferiprone and deferasirox, also remove iron from hepatocytes, the primary site of excess iron deposition in HFE -associated hemochromatosis, but there are no reports of the use of these drugs in people with C282Y homozygosity.[105, 106]

Antidote-iron toxicity

Class Summary

Antidotes for iron toxicity are used in patients with hemochromatosis that is associated with significant anemia or severe end-organ involvement.

Deferoxamine mesylate (Desferal)

Deferoxamine is the agent of choice used in people with C282Y homozygosity unable to undergo phlebotomy.

Questions & Answers

Overview

What is hemochromatosis?

What are the signs and symptoms of hemochromatosis?

What are the clinical manifestations of hemochromatosis?

How is hemochromatosis diagnosed?

Which lab studies are performed in the evaluation of suspected hemochromatosis?

What is the role of imaging studies in the diagnosis of hemochromatosis?

Which procedures may be performed to evaluate patients with hemochromatosis?

What are the indications for liver biopsy in the evaluation of hemochromatosis?

What is the goal of therapy in hemochromatosis?

What is the role of phlebotomy in the treatment of hemochromatosis?

Which iron chelation agents are used in the treatment of hemochromatosis?

When is surgery indicated in the treatment of hemochromatosis?

What is hemochromatosis?

Which genetic mutations are associated with hemochromatosis?

How is the nervous system affected by hemochromatosis?

What are the causes of secondary hemochromatosis?

What is hereditary hemochromatosis?

Why is excess iron dangerous in patients with hemochromatosis?

What is the role of iron regulation in the pathogenesis of hemochromatosis?

What is the role of genetics in the pathogenesis of hemochromatosis?

How do gene mutations cause hemochromatosis?

What are the different types of hemochromatosis?

What is the role of hepcidin deficiency in the pathogenesis of hemochromatosis?

What is the pathophysiology of autosomal dominant hemochromatosis?

What is hereditary hemochromatosis?

What is the main genetic cause of hemochromatosis?

Which hemochromatosis patients are at risk for clinical iron overload?

What is the mechanism by which gene mutation causes hemochromatosis?

How is the iron-overload phenotype of hemochromatosis characterized?

What is the relationship between hypertriglyceridemia and hemochromatosis?

Which gene mutations are involved in juvenile hereditary hemochromatosis?

How does hepcidin deficiency influence hemochromatosis?

What is the prevalence of hemochromatosis in the US?

What is the global prevalence of hemochromatosis?

What are the ethnic predilections of hemochromatosis?

What are the racial differences in incidence for hemochromatosis?

What is the relationship between type 2 diabetes and hemochromatosis?

How does the prevalence of hemochromatosis vary by sex?

How does the incidence of hemochromatosis vary by age?

How does early diagnosis affect the prognosis of hemochromatosis?

What is the most important prognostic factor for hemochromatosis?

What are potential complications of hemochromatosis?

What is the mortality rate for hemochromatosis?

What are the survival rates for hemochromatosis?

How does heterozygosity affect the mortality risk of hemochromatosis?

Presentation

What are the signs and symptoms of hereditary hemochromatosis?

At what age does hemochromatosis typically become symptomatic?

What are early symptoms of hemochromatosis?

What are the clinical manifestations of hemochromatosis?

How frequently is the liver involved in hemochromatosis?

How does cirrhosis develop in patients with hemochromatosis?

What is the relationship between nonalcoholic steatohepatitis (NASH) and hemochromatosis?

What are dermatologic symptoms of hemochromatosis?

How prevalent is diabetes mellitus (DM) in hemochromatosis?

How does hemochromatosis cause arthropathy?

Where can chondrocalcinosis occur in hemochromatosis?

What are the most commonly affected joints in hemochromatosis-related arthropathy?

What are endocrine symptoms of hereditary hemochromatosis?

What causes hypogonadism in hemochromatosis?

What causes cardiomyopathy in hemochromatosis?

What is the prevalence of osteopenia and osteoporosis in hemochromatosis?

What are the AASLD screening recommendations for hereditary hemochromatosis?

DDX

Which conditions should be included in the differential diagnoses of hemochromatosis?

Why is it important to distinguish hemochromatosis arthropathy from rheumatoid arthritis?

How is hemochromatosis differentiated from alcoholic liver disease?

Why are ineffective erythropoiesis with marrow hyperplasia included in the differential diagnoses of hemochromatosis?

Why is iron overload associated with chronic anemia included in the differential diagnosis of hemochromatosis?

Why must hypertransfusion be considered in the differential diagnosis of hemochromatosis?

Why is porphyria cutanea tarda included in the differential diagnoses of hemochromatosis?

What are the differential diagnoses for Hemochromatosis?

Workup

How is hemochromatosis diagnosed?

What is the criterion standard for diagnosis of hereditary hemochromatosis?

Which mutations are prevalent in hemochromatosis?

What is the role of transferrin saturation measurement in the diagnosis of hemochromatosis?

What is the role of hepatic iron concentration (HIC) in the diagnosis of hemochromatosis?

What is the importance of a portable hemoglobinometer in the diagnosis of hemochromatosis?

What is the role of electrocardiograms (ECGs) for the diagnosis of hemochromatosis?

When is endoscopy indicated in the evaluation of hemochromatosis?

What is the screening threshold of transferrin saturation for hemochromatosis?

What is the initial test of choice for evaluation of suspected hemochromatosis?

Which lab finding is the earliest evidence of hemochromatosis?

Which serum iron concentration suggests hereditary hemochromatosis?

What is the role of ferritin measurement in the diagnosis of hemochromatosis?

What is the treatment options for hemochromatosis with anemia?

What dietary modifications are beneficial in the treatment of hemochromatosis?

What are the dietary recommendations for patients with hemochromatosis?

How does alcohol abuse affect the progression of hemochromatosis?

What is the role of vitamin C in the treatment of hemochromatosis?

What precautions should patients with hemochromatosis take when preparing seafood?

When is consultation with a gastroenterologist indicated in the management of hemochromatosis?

Which medical or surgical specialties should be consulted for the management of hemochromatosis?

Who should coordinate long-term care of patients with hemochromatosis?

What monitored is needed during phlebotomy therapy for hemochromatosis?

Which physicians should conduct follow-up visits for patients with hemochromatosis?

How are patients with hemochromatosis monitored for hepatocellular carcinoma (HCC)?

Guidelines

What are the CDC recommendations for hemochromatosis screening?

What is the efficacy of hemochromatosis screening?

Which individuals should be considered for screening for hemochromatosis?

What are the American Medical Association (AMA) guidelines for population screening for hemochromatosis?

What are the American Association for the Study of Liver Diseases (AASLD) screening guidelines for hemochromatosis?

Medications

Which medications are used in the treatment of hemochromatosis?

Which medications in the drug class Antidote-iron toxicity are used in the treatment of Hemochromatosis?

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