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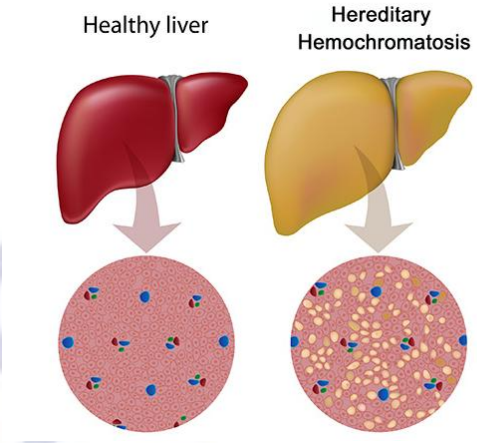
Hemochromatosis (Hereditary Iron Overload)

Background:

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

Definition:

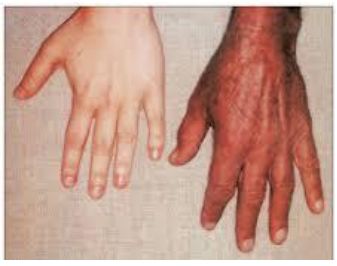


Hereditary hemochromatosis (HH) is defined as an inherited disorder of iron metabolism that leads to progressive, parenchymal, cellular iron overload in many tissues of the body–in particular in the liver, pancreas, and heart. When the degree of iron overloading reaches a critical level, structural and functional damage to these organs may become apparent, and these constitute the phenotypic evidence for HH. The genotypic definition is based on a single Messene mutation, the so-called C282Y mutation, of the HFE gene on the short arm of chromosome 6, which has a major role in the regulation of iron metabolism. When this mutation is present in both copies of the gene, homozygous HH is said to be present. Furthermore, there are other hereditary forms of iron overload based on alternative mutations of the HFE gene or mutations of other genes that may also play a role in the regulation of iron metabolism.

Excess iron is hazardous, because it facilitates 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.

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. Although the mutation underlying most cases of hereditary hemochromatosis is now known, considerable uncertainty exists in the mechanism by which the normal gene product regulates iron homeostasis.

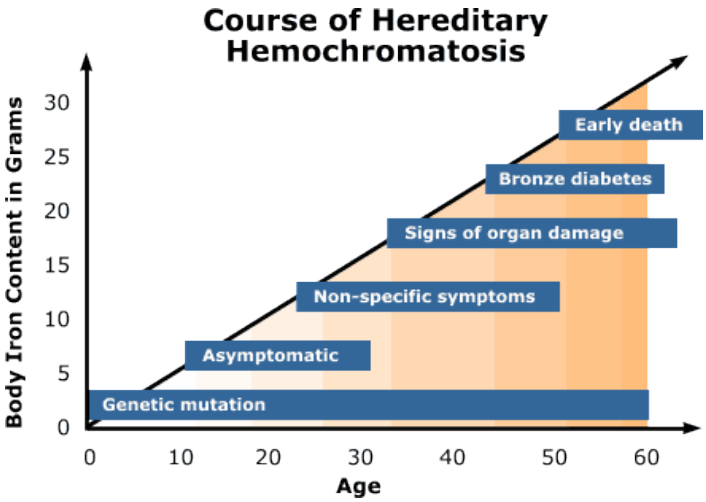
Pathophysiology:



During the childbearing years, healthy women lose an average of an additional milligram of iron daily from menstrual bleeding 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.

The normal HFE protein is expressed predominantly in the crypt cells of the upper intestine where, in association with the transferrin receptor, it may play a role in sensing the iron status of the body. Evidence has suggested that the mutant HFE protein is unable to provide this sensing, therefore “misinforming” the villous cell of the small intestine that iron deficiency

might be present. This may lead to up regulation of the iron transport protein normally expressed on the villous cell, thereby explaining inappropriate intestinal absorption of dietary iron.



Although the genetic predisposition to increase iron absorption is present at birth, the disease may take 40 to 50 years or longer to progress to significant organ damage. Therefore, it is useful to think of the evolution of this clinical condition as a series of stages that begins with clinically insignificant iron accumulation based on the genetic abnormality (from 0 to 20 years of age, 0 to 5 g parenchymal ironstorage). Subsequently, this evolves to a stage of iron overload without evident disease (at approximately 20 to 40 years of age, 5 to 20 g parenchymal iron storage). If this case left untreated, the condition may progress to the stage of iron overload with organ damage (usually at 40 years of age or older, and with more than 20 g of parenchymal iron storage).

Epidemiology:

Men have also been reported to have a higher incidence of serious complications of hereditary hemochromatosis, primarily diabetes mellitus and cirrhosis. Women complained more often of fatigue 64.8% (42% in men) and skin hyperpigmentation 48% (44.9% in men). Hemochromatosis usually becomes apparent after age 40 years in men (median age, 51 years) and after age 50 years in women (median age, 66 years).

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.

Causes

Transfusion dependence due to the following is among the causes of transfusion-induced iron overload:

- Sickle cell disease
- Hemolytic anemia
- Leukemia
- β-thalassemia major
- Blackfan-Diamond syndrome
- Aplastic anemia
- Myelodysplastic syndrome

Diagnostic Considerations

The exact number of blood transfusions that lead to significant iron overload varies with the patient's underlying disease and the duration of their transfusion dependence. Hepatitis C is prevalent in patients who undergo long-term transfusions (>35% of sickle cell patients), especially those who have undergone transfusions before screening began. Transfusion-induced iron overload superimposed on hepatitis C would accelerate the development of cirrhosis.

Treatment

A) Phlebotomy

- It remains the sole recommended treatment for hereditary hemochromatosis and should be undertaken in a case-specific manner.

- 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). 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.
- Avoid excessive phlebotomy and the risk of hypovolemia and dehydration.

B) Chelation Therapy

- In patients with hemochromatosis and heart disease, anemia, or poor venous access, treatment with iron chelation agents is recommended
- **Deferasirox** (Exjade) is the oral iron chelator that should be taken once daily as an adjunct to phlebotomies. Deferasirox is very efficacious in liver iron removal. During treatment with deferasirox, kidney function should be controlled.

Dendrimers; This family of iron-selective chelators, have been synthesized. Therefore, the application of Dendrimers in the treatment of iron overload diseases is considered.

Dietary Considerations and Prevention

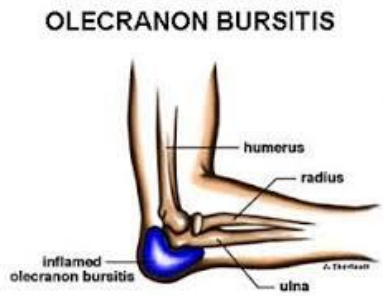
Patients should not consume foods that contain large concentrations of bioavailable iron, such as red meats and organ meats. In addition, they should not use iron supplements. In addition, vitamin C supplements should be avoided. Substances in foods and drinks, including tannates, phytates, oxalates,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

http://emedicine.medscape.com/article/1389732-overview#a5
http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hepatology/hemochromatosis/.

Terminology

Olecranon bursitis

The olecranon bursa is located between the pointy bone at the back of elbow - called the olecranon - and the overlying skin. This bursa helps the elbow to bend and straighten smoothly.Bursitis is an inflammation of small sacs of fluid (bursae) that help joints move smoothly. Olecranon bursitis, which affects the olecranonbursa at the back of the elbow, is sometimes called Popeye elbow. This is because the bump that develops at the back of the elbow looks like the cartoon character Popeye's elbow.



Source:http://www.webmd.com/pain-management/tc/olecranon-bursitis-popeye-elbow-topic-overview

Complementary Medicine

Safflower

Order: Asterales
Family: Asteraceae
Genus: Carthamus
Species: C. tinctorius
Botanical Source: Northwest India; North Africa & North America.
Botanical Name: *Carthamustinctorius*
Common names: false saffron, dyer's saffron and zaffer,

Description: Safflower is an annual herb, It has long, spiny leaves and yellow or reddish flowers on a stiff, upright stem. The seeds produce edible oil. Safflower grows to a height of about 3 feet (1 m) in poor, dry soils in full sun.

Nutritional Values and constituents:

The major constituents are triterpenesaponins (2–10%) based on oleanolic acid (i.e. calendulosides) and flavonoids (3-O-glycosides of isorhamnetin and quercetin), including astragalin, hyperoside, isoquercitrin and rutin. Other constituents include essential oil, sesquiterpenes (e.g. caryophyllene) and triterpenes (e.g. α- and β-amyrins, lupeol and lupenone). Polysaccharides have also been reported.

Medicinal actions and uses:

Safflower flower has been used in **traditional Chinese medicine**. It is used to treat menstrual disorders. Safflower flower is an emmenagogue, It is used to treat menstrual **pain**, to firm up the uterus after **childbirth**. It relieves stiffness and pain in the joints. Safflower flower is a blood regulator. It invigorates and harmonizes the blood and dissolves **blood clots**. Chinese practitioners use safflower oil in*tuina* massage. Safflower has other non-medicinal uses. The flowers were dried and ground together with finely powdered talc to produce cosmetic rouge.

Safflower seed oil is used for preventing heart disease, atherosclerosis and stroke. It is also used to treat fever, tumors, coughs, breathing, clotting conditions, pain, chest pain, and traumatic injuries. It also used as a laxative, stimulant, antiperspirant, and expectorant to help loosen phlegm.
In foods, safflower seed oil is used as cooking oil.
In manufacturing, safflower flower is used to color cosmetics and dye fabrics. Safflower seed oil is used as a paint solvent.

Safety and Toxicity:

Because safflower flower brings on menstruation, it should not be used by pregnant women. Large doses can cause spontaneous abortion. In addition, because safflower may prolong blood clotting time, it should not be given to patients with peptic ulcers or hemorrhagic illnesses.

Side effects

The unprocessed oil of safflower seed can cause severe **diarrhea**.

http://herbalinformation.awardspace.com/?cm=c&fn=carthamus_tinctorius
http://www.webmd.com/vitamins-supplements/ingredientmono-96-safflower.aspx?activeingredientid=96&

Test Your Knowledge

1. You are evaluating a 35-year-old woman who presents with an acute lithium overdose. Which one of the following statements concerning lithium overdosing is true?

A) Aggressive diuresis is needed to augment lithium excretion.
B) Hypocalcemia can be seen as a side effect of lithium.
C) Lithium cannot be removed by dialysis.
D) It is recommended that you avoid the use of saline in lithium intoxication.
E) You should evaluate thyroid function in anyone taking lithium.

2. Which one of the following is the treatment for a heparin overdose?

A) Vitamin K
B) Fresh frozen plasma
C) Protamine sulfate
D) Desmopressin acetate (DDAVP)
E) Cryoprecipitate

3. In controlling the synthesis and secretion of aldosterone, which of the following factors is least important?

A) Renin
B) Angiotensin II
C) Concentration of plasma Na^+
D) Concentration of plasma K^+
E) Adrenocorticotrophic hormone (ACTH)

4. When a patient presents with a fall and a blackout:

A) The incident has to be investigated
B) The patient has epilepsy
C) The incident should raise the alarm only if it occurs in paediatric patients

ASK the Nutritionist

What are the main differences between PROBIOTICS and PREBIOTICS?

PREBIOTIC VS PROBIOTIC	
PREBIOTICS	**PROBIOTICS**
Are special form of dietary fiber that acts as a fertilizer for the good bacteria in your gut.	Are live bacteria in yogurt, dairy products and pills. There are hundreds of probiotic species available.
Their powders are not affected by heat, cold, acid or time.	Bacteria must be kept alive. They may be killed by heat, stomach acid & with time.
Provide a wide range of health benefits to the otherwise healthy person. Most of these have been medically proven.	Are still not clearly known to provide health benefits to the otherwise healthy. Some are suspected but still not proven.
Prebiotics nourish good bacteria that everyone already has in his gut.	Probiotics must compete with the over 1000 bacteria species already in the gut.
May be helpful for several chronic digestive disorders or inflammatory bowel disease.	Helpful for childhood diarrhea, irritable bowel disease and for recurrence of certain bowel infections.

http://www.webmd.com/vitamins-and-supplements/nutrition-vitamins-11/probiotics

Real Enquiries

At the "Drug Information Center", we respond to enquiries from the professional healthteam as well as from others. Here's one of the enquiries received at the center:

Enquiry received from: Ph. Lamiaa Mohamed, AssiutUniversity Hospital.

Enquiry: Is the use of Unasyn antibiotic safe during lactation?

Summary of the answer: Unasyn isAntibacterial; β-lactam antibiotic; fixed combination of ampicillin (an aminopenicillin) and sulbactam (a β-lactamase inhibitor) the use of Unasyn during lactation is not recommended. Low concentrations of ampicillin and sulbactam are excreted in the milk. This should be considered as the neonate may be exposed, particularly since renal function is not fully developed in neonates. So it must used with caution.

FDA News

FDA Approves Epclusa for Treatment of Chronic Hepatitis C Virus Infection

Epclusa is a new First regimen to treat all six major HCV genotypes FDA approved Epclusa to treat adult patients with chronic (HCV) with and without cirrhosis. For patients with moderate to severe cirrhosis,FDA approved for use in combination with the drug ribavirin. Epclusa is a fixed-dose combination tablet containing sofosbuvir, and velpatasvir.

There are at least six distinct HCV geno-types, or strains, Approximately 75 % of Americans with HCV have genotype 1; 20-25 %has genotypes 2 or 3; and a small numbers of patients are infected with genotypes 4, 5 or 6. According to the Centers for Disease Control and Prevention, HCV infection becomes chronic in approximately 75 to 85 % of cases. The safety and efficacy of Epclusa for 12 weeks was evaluated in three Phase III clinical trials of 1,558 subjects without cirrhosis or with compensated cirrhosis (mild cirrhosis). Results demonstrated that 95–99 % of patients who received Epclusa had no virus detected in the blood 12 weeks after finishing treatment, suggesting the patients' infections had been cured. The safety and efficacy of Epclusa was also evaluated in a clinical trial of 267 subjects with decompensated cirrhosis, of whom 87 subjects received Epclusa in combination with ribavirin for 12 weeks, and 94 % of these patients had no virus detected in the blood 12 weeks after finishing treatment.

The most common side effects of Epclusa include headache and fatigue. Epclusa and ribavirin combination regimens are contraindicated for patients for whom ribavirin is contraindicated. Epclusa carries a warning for patients with bradycardia and cases requiring pacemaker intervention have been reported, whenamiodarone is used with sofosbuvir in combination with another HCV direct-acting antiviral. Co-administration of amiodarone with Epclusa is not recommended. It also carries a warning not to use with certain drugs that may reduce the amount of Epclusa in the blood which could lead to reduced efficacy of Epclusa.

Epclusa was reviewed under the FDA's priority review program, in safety or effectiveness. Epclusa is manufactured and marketed by Gilead Sciences, Inc., of Foster City, California.
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm508915.htm

Answers:

1. **E)** Thyroid function tests should be obtained in anyone taking lithium. The woman needs intravenous saline to facilitate lithium excretion [Choice (D) is incorrect]. Never use diuretics; in fact, volume depletion and dehydration can increase the risk of lithium toxicity. Other metabolic effects of lithium include hypercalcemia, hypothyroidism or hyperthyroidism, and diabetes insipidus. Lithium can be removed by Dialysis.

2. **C)** Protamine sulfate is the only used for **heparin overdose**. Both of Vitamin K and fresh frozen plasma used for warfarin overdose. Cryoprecipitate is another type of clotting factor high in vWf and Factor VIII. Desmopressinacetate can be used to treat bleeding in somepersons with von Willebrand's disease.

3. **E)** Aldosterone is part of a group of linked hormones, which form the renin-angiotensin-aldosterone system. Activation of this system occurs when there is decrease in blood flow to the kidneys following loss of blood volume or a drop in blood pressure or decrease in plasma sodium concentration. Renin is an enzyme that leads to a series of chemical reactions resulting in the production of angiotensin II, which in turn stimulate aldosterone release. Aldosterone causes an increase in salt and water reabsorption into the bloodstream from the kidney thereby increasing the blood volume, restoring salt levels and blood pressure. Once salt levels and blood pressure are corrected and the body becomes rehydrated, the level of renin in the bloodstream falls and therefore the amount of aldosterone in the blood also falls, meaning more water is excreted in the urine. The other two main regulators of aldosterone secretion are increase in the plasma potassium concentration and adrenocorticotrophic hormone (ACTH), which can act via either positive or negative feedback mechanisms, depending on the extent of changes in the levels of these two regulators and it seems to be the least important in this case.

4. **A)** the incident has to be investigated
   When there is temporary loss of consciousness leading to a fall, it may indicate a brief cerebral hypoxia, which could be caused by a number of factors including emotional stress, vascular pooling in the legs, diaphoresis or a sudden change in body position. Such an incident may also indicate serious disease states, such as brain tumors. The patient should be assessed and medical and drug histories should be reviewed.