Primary Hemachromatosis:
Pumping Iron

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Hereditary hemachromatosis (HH) is an inherited disease characterized by excess iron deposition in various organs, leading to eventual fibrosis and functional organ failure.

Inappropriate and excessive iron absorption from the small bowel leads to overload, with deposition in and damage to the cells of the liver, heart, pancreas and pituitary gland. It is inherited as an autosomal recessive, with only homozygotes manifesting the clinical features of the disease.

How does HH occur?

HH is due to a mutation in the gene HFE on the short arm of chromosome 6. The normal HFE protein is expressed in the small intestine and is thought to play a role in the regulation of iron absorption. HLA-A3, B7 and B14 occur with increased frequency, compared to the general population.

What is the epidemiology?

HH is one of the most common inherited diseases in those of European descent, occuring in about 1 in 400 people, with approximately 10% of the population being carriers. Recently, it has become prevalent in the Hispanic population, yet the Celtic population is most frequently affected.

Men are affected more often than women, with an estimated ratio of 1.8:1. Women with the disease tend to present approximately 10 years later, due to slower iron accumulation because of increased physiologic blood loss (*e.g.*, pregnancy, menstruation).

Philip's Fatigue

- Philip, 48, has recently moved to Alberta from Newfoundland after accepting a job in the oil plants.
- He presents quite frustrated with his extreme tiredness, which has been ongoing for the last few years. He is concerned that it may cause him to lose his job.
- His fatigue started approximately five years ago and gradually increased. It is also associated with artherlagia, mainly affecting his hands. Philip also complains of decreased libido.
- He has been investigated by many doctors and was given the diagnosis of fibromyalgia and depression.
- Philip is concerned about the possibility of liver tumours, as his father died from this in his late sixties.

For more on Philip, go to page 98.

More on Philip

- Philip does not feel depressed; in fact, he is very happy with his new job.
- He denies any recent change of bowel habits, rectal bleeding, urinary symptoms and shortness of breath, or orthopnea. He does not notice any recent weight changes.
- His mother is healthy and his two brothers and sisters are all fit and in good health.
- His past medical history is unremarkable, apart from having an uncomplicated right inguinal hernia repair six years ago.
- Philip smokes five to six cigarettes a day and drinks alcohol socially.
- His exam reveals a healthy-looking appearance; he is neither pale nor jaundiced.
- He has bilateral equal good volume radial pulses of 72 bpm.
- Heart auscultation: Normal double rhythm with no added sounds.
- JVP: Not elevated.
- Abdominal exam: Unremarkable, apart from the palpable and soft liver edge.
- He has noticeable testicular atrophy with no associated gynecomastia.

How do you advise Philip? Go to page 99 to find out.

JVP: Jugular venous pressure

In regards to age, HH usually becomes apparent after age 40 in men (median age: 51 years) and after age 50 in women (median age: 66 years).

What are the clinical features?

Symptoms usually begin between ages 30 and 50, but they may occur much earlier. Clinical manifestations of HH include:

- skin pigmentation,
- diabetes mellitus,
- artheropathy,
- impotence in males and
- cardiac enlargement, with or without heart failure or conduction defects.

Table 1

The symptoms of diabetes mellitus and cirrhosis

Diabetes mellitus (48%): This is due to progressive iron accumulation in the pancreas. The defect appears to be relatively selective for the pancreatic beta cells. Most patients with hemachromatotic diabetes have other signs of hemachromatosis, such as liver disease or skin pigmentation.

Cirrhosis: This is one of the most common disease manifestations of the tissue damage caused by hemachromatosis, and it may progress to liver cancer years later (risk > 200-fold). It is also the most common cause of death in patients with hereditary hemachromatosis.

- It is due to progressive iron deposition in the liver parenchyma.
- Reversibility with iron removal has been reported even with development of varices, but this is more likely early in the course of liver disease.
- All patients with cirrhosis should undergo diagnostic endocscopy 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.
- Hepatocellular carcinoma is one of the most serious complications of hemachromatosis.
- Most hepatologists recommend periodic screening with serum alpha-protein (AFP) every six months in patients with cirrhosis.
- The most cost-effective imaging test used to supplement serum AFP screening is ultrasound. The sensitivity is approximately 80% when serum AFP and ultrasound are combined for the screening of hepatocellular carcinoma.
- Liver transplant may be used to treat patients with hepatocellular carcinoma, but careful patient selection is advised. Particularly, these patients should have a single tumour of 5 cm or smaller in diameter. If multiple tumours are present, the acceptable number is three or less smaller than 3 cm. The four-year survival rate can be approximately 90%, if these criteria are respected.

Investigating HH…

- Serum liver biochemistry is often normal, even with cirrhosis.
- Serum iron is elevated and total iron-binding capacity (TIBC) is reduced. The transferrin saturation (serum iron/TIBC) is > 60% (normal range is < 33%).
- Serum ferritin reflects iron stores and is usually greatly elevated (often > 500 µg/L)
- Genotyping (by polymerase chain reaction using whole blood samples) for mutation analysis of the HFE gene is performed in patients with elevated ferritin and transferrin saturation.
- A liver biopsy to document the degree of fibrosis is performed in patients who are likely to have significant hepatic injury or if the diagnosis is in doubt. Other patients with abnormal iron studies and mutations of the HFE gene may be treated without the need for biopsy.

Early symptoms include:

- severe fatigue (74%),
- impotence (45%) and
- arthralgia (44%).

Later, patients may experience skin bronzing or hyperpigmentation (70%). This reflects a combination of iron deposition and melanin.

The classic triad of cirrhosis, diabetes mellitus and skin pigmentation occurs late in the disease when total iron body content is 20 g (*i.e.*, more than five times the normal amount) (Table 1).

Regarding other symptoms:

- Fatigue and arthralgia are the most common symptoms prompting a visit to a physician.
- 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 hemachromatosis.
- Cardiomyopathy is another mode of presentation, particularly in younger patients. The patients may present with congestive heart failure or arrhythmias.

Helping Philip

- You explain your findings and reassure Philip there is nothing on examination that suggests a liver tumour.
- You arrange blood tests to discover the reason for his fatigue and you also arrange a liver ultrasound scan because he is so concerned about the possibility of a liver tumour.

Two weeks later…

- Philip's tests reveal:
  - CBC: Hb of 13.6 g/L, with normal WBC and platelet counts
  - Liver function: ALT of 58 U/L and alkaline phosphatase of 158 U/L
  - TSH: 3.76 Mu/L
  - Calcium: 2.14 mmol/L
  - Renal function: Normal
  - Hepatitis B & C serology: Negative
  - ESR: 4 mm/h
  - CRP: 3 mg/L
  - Fasting sugar: 7.2 mmol/L with normal lipid profile
  - B12 and transglutaminase antibodies: Normal range
  - Ferritin: 1,105 µg/L (normal value=12 µg/L to 300 µg/L)
  - Saturation index: 0.82 mmol/L (normal value 0.16 mmol/L to 0.60 mmol/L)

What's Philip's diagnosis? See page 100.

CBC: Complete blood cell count
Hb: Hemoglobin
WBC: White blood cell count
ALT: Alanine aminotransferase
TSH: Thyroid-stimulating hormone
ESR: Erythrocyte sedimentation rate
CRP: C-reactive protein

- 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 hemachromatosis should not preclude the diagnosis.
- Hypogonadism is the most common endocrine abnormality causing decreased libido and impotence in men. It is usually due to pituitary involvement by iron deposition. Primary hypogonadism, presumbly due to testicular iron deposition, can also occur, but is much less common.
- Amenorrhea can occur in women, but is less frequent than hypogonadism in men.
- Artheropathy is due to iron accumulation in the joint tissues. It is associated with characteristic radiologic findings (*i.e.*, squared-off bone ends and hook-like osteophytes in the metacarpophalangeal [MCP] joints, particularly in the second and third MCP joints). Symptoms do not usually respond to iron removal.
- Hypothyroidism may rarely occur.

How should HH be managed?

The aim of treatment is to remove excess tissue iron and render the patient iron deficient, while maintaining a hemoglobin > 11g/dl. This is best achieved by venesection: 500 mls of blood are removed twice weekly. This may need to be continued for up to two years. Three or four venesections per year are required to prevent the reaccumulation of iron.

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What's Wrong with Philip?

Philip is referred to a gastroenterologist for a liver biopsy.

The biopsy is uneventful, and the histologic examination confirms the diagnosis of hemachromatosis.

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