This case of a 44-year old European woman illustrates the importance of recognizing hereditary hemochromatosis as a possible cause of vague presenting symptoms, in particular fatigue. It also stresses the need to identify less common mutations leading to the condition in the context of high clinical suspicion in susceptible populations. Students should pay special emphasis to normal iron metabolism, as well as the genetic defects, inheritance pattern, variety of presenting features and pathophysiology of the disease (particularly the hepatic manifestations).

Hereditary hemochromatosis (HH) is an \textit{autosomal recessive} disorder that causes an \textit{abnormally increased iron absorption} in the body resulting in progressive \textit{iron overload} and subsequent \textit{organ damage}.

\textbf{GENETICS:}
Two main mutations, C28Y & H63D, are responsible for majority of the cases or HH. Other less common mutations (TFR-2 and HAMP-related Juvenile Hemochromatosis genes) have also been identified in some groups of patients. Over 80\% of affected individuals are homozygous for the C282Y mutation. Four to 7\% are compound heterozygous (one allele each of C282Y and H63D). H63D homozygous patients make up about 1\% of the population whereas 3-10\% are heterozygous for either C282Y or H63D.

\textbf{EPIDEMIOLOGY:}
Previously thought to be a rare disorder, HH is not being regarded as one of the most common genetic mutations in Caucasians. Prevalence of the heterozygous state is thought to be up to 10\% in the US and European Caucasian population whereas the frequency of homozygote state is about 5 in 1000 (0.5\%).

\textbf{PATHOPHYSIOLOGY:}
The main genetic defect in most patients is a mutation in the HFE gene located on the short arm of chromosome 6. The normal HFE gene product, a single polypeptide with three extracellular domains, by its interaction with the transferrin receptor, modulates cellular iron uptake and decreases ferritin levels. In HH, the influence of the HFE protein on ferritin levels is abated resulting in increased accumulation of iron in tissue parenchyma. The excess free iron in the tissue produces free radicals (hydroxyl and superoxide moieties), which cause cell injury and fibrosis.
CLINICAL FEATURES:
Symptoms can be present for 10 years or more before diagnosis and most frequently include fatigue (46%), arthralgia (44%) and loss of libido (26%). The classic triad, “bronze diabetes” (cirrhosis, diabetes and skin pigmentation) occurs late in the disease. Parenchymal iron deposition can lead to dysfunction of many different organ systems including the liver (elevated liver enzymes, hepatomegaly and cirrhosis), skin (bronze pigmentation), pancreas (diabetes), joints (especially the 2nd and 3rd MCP joints), heart (dilated cardiomyopathy, conduction abnormalities), pituitary gland (hypogonadism, loss of libido and impotence) and thyroid gland (hypothyroidism). Patients with HH are also susceptible to uncommon infections caused by siderophillic (iron-loving) organisms like listeria, yersenia enterocolitica and vibrio vulnificus.
In heterozygous patients, liver disease due to HH alone is uncommon but viral hepatitis and alcohol use increases the risk. These patients are also thought to be at increased risk for diabetes, colon cancer and hematological malignancies but have a normal life expectancy.

DIAGNOSIS & TREATMENT:
Serum transferring saturation alone or in combination with iron and fasting ferritin levels can be used as initial screening tests in suspected cases, or first-degree relatives of patients with HH that are more than 18 years old. The diagnosis can be confirmed by testing for the C282Y and H63D mutations. If required, the less common mutations can also be tested but usually require specialized centers.
Treatment is with serial phlebotomies to reduce total body iron content. Some of the manifestations of the disease (e.g., left ventricular dysfunction) can be reversed with successful treatment whereas others (e.g., arthropathy) are not affected to a significant extent.

LEARNING OBJECTIVES:
1. Recognize that hereditary hemochromatosis (HH) can present with vague symptoms.
2. Understand basic iron metabolism.
3. Understand the genetic defects leading to iron overload in HH.
4. Describe the pathophysiology of multiorgan damage from iron overload in HH.
5. Learn about the complications of HH.
6. Recognize the indications and importance of screening family members of individuals with HH.
Hebe Haralampidou is a 44-year old professor of Mathematics who recently moved to the US from Athens, Greece as part of an international scholar exchange program through the local university.

Although she does not have any major health concerns, she admits to being overly fatigued and lethargic for the past year or so. The symptoms last most of the day and are not relieved even after adequate sleep and rest. She is still able to carry out her professional responsibilities and daily chores but thinks that this feeling of “being tired all the time” has started to affect her productivity. A nurse friend had told her that she might be depressed or have fibromyalgia. She denies any mood symptoms and from what she has read about fibromyalgia on the internet, she is convinced that is not the case either. She does complain, though, of joint pains especially in the knuckles and knees but thinks its just “age”.

At the age of 37, she had her uterus and ovaries removed for multiple fibroids. Two years earlier, she had a bout of severe diarrhea and was hospitalized for intravenous fluids and antibiotics. She was told that she had “yersinia” infection in her blood. She has not seen a physician since then as her health has generally been good.

Her father had cirrhosis and died of liver cancer at the age of 68 with no history of excessive drinking. Her mother, two younger brothers and a 19 year old son are relatively healthy.

She takes an over-the-counter allergy medication, a multivitamin with iron, and an occasional Tylenol for minor headaches. After smoking a pack a day for 10 years, she quit 3 years ago. Her alcohol intake is limited to a single drink of wine on weekends.
On exam, HH is a slightly overweight (BMI = 28.5) Caucasian lady, who appears her stated age. The skin, especially the sun-exposed area, appears tanned although the patient denies significant sun-exposure. HEENT, neck and cardiopulmonary examination is unremarkable. Abdomen is soft, non-tender and bowel sounds are normal. A smooth and non-tender liver edge is palpable below the costal margin and the liver span is 16cm on percussion. No other masses or splenomegaly are noted. Mild swelling and tenderness is noted at the 2nd and 3rd MCP joints of both hands. Neurological exam reveals normal strength, sensations and cognition.

**Labs:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>13.5 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>90 CU micL</td>
</tr>
<tr>
<td>Na+</td>
<td>139 mEq/L</td>
</tr>
<tr>
<td>K+</td>
<td>4.7 mEq/L</td>
</tr>
<tr>
<td>Cl-</td>
<td>107 mEq/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>112 mg/dL</td>
</tr>
<tr>
<td>BUN</td>
<td>14 mg/dL</td>
</tr>
<tr>
<td>Cr</td>
<td>0.6 mg/dL</td>
</tr>
<tr>
<td>Fasting Lipids</td>
<td>WNL</td>
</tr>
<tr>
<td>TSH</td>
<td>1.5 uIU/mL</td>
</tr>
<tr>
<td>AST</td>
<td>83 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>101 U/L</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>40 U/L (0-120)</td>
</tr>
<tr>
<td>BR</td>
<td>0.6 mg/dL (0.2-1.2)</td>
</tr>
<tr>
<td>Anti-HC-Ab</td>
<td>Non-reactive</td>
</tr>
<tr>
<td>HbsAg</td>
<td>Non-reactive</td>
</tr>
<tr>
<td>Anti-HBcAb</td>
<td>Non-reactive</td>
</tr>
<tr>
<td>Anti-HBsAb</td>
<td>&lt;3 mIU/mL (&lt;9=Non-reactive)</td>
</tr>
<tr>
<td>Total Iron</td>
<td>173 mcg/dL (50-150)</td>
</tr>
<tr>
<td>TIBC</td>
<td>278 mcg/dL (270-440)</td>
</tr>
<tr>
<td>% Saturation</td>
<td>62% (20-50%)</td>
</tr>
</tbody>
</table>

Chest X-Ray shows normal lung fields and a slightly enlarged cardiac shadow. Electrocardiogram shows a first degree AV-block and non-specific ST-segment changes.
The serum iron studies are repeated and are found to be consistent with the previous reports. Ferritin level is elevated at 1254 ng/mL.

With a provisional diagnosis of iron overload and a differential of Hereditary Hemochromatosis, HH is tested for the C282Y and H63D mutations. They are reported to be normal. Because of continued high suspicion for the condition, and the mutation prevalence pattern in the Greek population, a blood specimen is sent to a specialized center where testing is done for the less frequent TFR2 and HAMP-related Juvenile Hemochromatosis gene mutations. She raises the concern that her insurance may not cover the genetic tests.
The results are received after a week and are positive for the TFR2 mutation. A diagnosis of Hereditary Hemochromatosis is made and treatment is started with weekly removal of 0.5 to 1 unit of blood using outpatient phlebotomies. She is switched to a multivitamin preparation without iron. Over the next few months, even though her arthralgias persist, most of her fatigue is resolved and her transaminase levels are normalized. It is recommended to her that all her 1\textsuperscript{st} degree relatives over the age of 18 be screened for HH with transferrin saturation, ferritin levels and genetic testing.
CUES, HYPOTHESES & LEARNING ISSUES

**Cues Page 1:**
- 44-year old Greek woman
- Recently moved to the US
- Fatigue & lethargy for 1 year, not relieved with sleep or rest
- Productivity affected by symptoms
- Denies mood symptoms
- Knuckle & knee pain
- s/p hysterectomy & oophorectomy at age 37
- h/o Yersinia infection (sepsis)
- No regular healthcare since age 37
- Father died of cirrhosis & liver cancer
- Takes OTC allergy meds, MV with Iron & occasional acetaminophen
- Former smoker, quit 3 years ago
- No excessive alcohol use

**Hypotheses Page 1:**
- She is depressed
- She has chronic fatigue secondary to a systemic disorder
- She has chronic fatigue syndrome
- She has an autoimmune disorder
- She has osteoporosis from early menopause
- She has an inheritable liver disease
- She has a susceptibility uncommon infections

**Learning Issues Page 1:**
- What major diseases and disorders cause fatigue?
- Which patients are susceptible to Yersinia infections?
- What are the major inheritable liver disorders that can cause cirrhosis?
- How can her OTC medications and postmenopausal status be contributing to her symptoms?

**Cues Page 2:**
- Overweight (BMI = 28.5)
- Tanned appearance of sun-exposed skin
- Enlarged palpable liver
- 2nd/3rd MCP swelling & tenderness (bilateral)
- Slightly elevated glucose
- Elevated transaminases
- High total iron & transferrin saturation
- Enlarged cardiac shadow
- 1st degree AV-block and nonspecific ST changes

**Hypotheses Page 2:**
- She has NAFLD
- She has hepatitis
- She has a metabolic disorder with systemic manifestations
- She has coronary artery disease or another cardiac disorder

**Learning Issues Page 2:**
- Which liver diseases can manifest as dermatologic and/or arthritic symptoms?
- What are the common causes of hepatomegaly?
- What is the mechanism of transaminase elevation?
- How do you work up a patient with elevated transaminases?
- How is Iron metabolized in the body? How are “iron studies” interpreted?
- Which conditions can lead to iron-overload?
- Can liver diseases have cardiac manifestations?

**Cues Page 3 (if required):**
- Elevated ferritin
- Diagnosis of iron overload
- C282Y and H63D mutations are negative
- Less frequent gene testing ordered
- Patient concerned about insurance coverage

**Learning Issues Page 3/4:**
- What is the mechanism of iron overload?
- How does iron overload lead to the various systemic manifestations of hereditary hemochromatosis?
- How is hemochromatosis different from other iron overload syndromes?
- How are various genetic mutations manifested as hemochromatosis? What is the inheritance pattern?
- How is hemochromatosis diagnosed? What are the implications for family members of a patient with HH?
STIMULUS QUESTIONS

1. How is iron metabolized in the body?
2. What is the genetic defect in hereditary hemochromatosis that leads to abnormalities of iron metabolism?
3. How does iron cause damage to tissue and organs?
4. What is the role of “iron studies” in the diagnosis of various pathological disorders?
5. What are the positive predictive value, sensitivity and specificity of “iron studies” in the diagnosis of hemochromatosis?
6. What makes patients with hemochromatosis prone to certain bacterial infections?
7. Are there other forms of iron overload? How is their pathophysiology different from that of hereditary hemochromatosis?
8. What are the major extrahepatic systemic manifestations of hemochromatosis?
9. Who should be screened for hemochromatosis gene mutations? What are the recommended screening tests?
10. What is the risk of developing hepatoma in patients with hereditary hemochromatosis? How should cancer surveillance be conducted for these patients?
11. How effective is phlebotomy in the treatment of HH? What is the impact of treatment on symptoms and organ damage?