CASE 2

A tanned man with diabetes mellitus

Mr Peter Black, a 50-year-old engineer, went to his family doctor complaining of fatigue for at least a year, which was slowly increasing. He said he could only sleep for a few hours and woke early in the morning. He also complained of intermittent pain in the joints of his right hand.

Q1 What are the possible explanations for his complaints?

A Early-morning waking may suggest depression. More information is needed regarding his sleeping pattern and activity levels during the day.

On further questioning, Peter mentioned that he had gone to another doctor, with the same symptoms, 6 months previously. He had been under a lot of pressure at work and the first doctor felt that his symptoms were stress related. He had been prescribed sleeping tablets, which he felt were not helping.

Q2 What further information is needed?

A More information about his joint pain. A history of trauma, swelling or redness of the joints should be sought. One should also enquire about associated symptoms such as weight loss, fevers, night sweats or recent infections.

He revealed that he drank two gin and tonics in the evening and two glasses of wine with his dinner. He is a non-smoker.

On examination Peter is tanned and overweight. His liver is slightly enlarged. His second metacarpophalangeal joint is tender but not red or swollen.

Q3 What else in his history may be contributing to his symptoms and signs?

A His consumption of 28 units of alcohol weekly.

Although alcohol often helps people fall asleep, it also fragments the sleep pattern.

Key point

Guidelines for sensible drinking suggest that a man should not drink more than 21 units/week (one glass of beer or wine or one spirit measure). Many people who abuse alcohol can continue to function at quite a high level.

Q4 What blood tests should be done and why?

A A full blood count (Table 2.1), to see if the fatigue is caused by anaemia; a biochemistry profile and blood glucose (Table 2.2), to find the reason for the enlarged liver.

Table 2.1 Full blood count

	Patient's results	Normal range (male)
Hb	16.5 g/dl	13.5–18.0 g/dl
MCV	100 fl	83–99 fl (μm^3)
WBC	6.0 × 10^9/l	4–11.0 × 10^9/l (10^3/μl)
Platelets	160 × 10^9/l	140–450 × 10^9/l (10^3/μl)

The white cell differential was normal.

Table 2.2 Biochemical results

	Patient's results	Normal range
AST (SGOT)	60 IU/l	7–40 IU/l
Alkaline phosphatase	140 IU/l	40–120 IU/l
GGT	80 IU/l	10–55 IU/l
Random blood glucose	13.0 mmol/l	<11.1 mmol/l (<200 mg/dl)

Mr Black returned to the surgery 2 weeks later. He was still fatigued, despite stopping the sleeping tablets and reducing his alcohol intake. He mentioned that he was impotent, which he had been too embarrassed to mention initially.

Q5 How can the blood results be interpreted?

A The elevated blood glucose suggests diabetes mellitus. His liver blood tests are also slightly abnormal. Although his haemoglobin is normal, his red cells are slightly larger than normal (elevated MCV).

Q6 What other information might add to the interpretation of the blood tests?

A The reticulocyte count, serum vitamin B_{12} and red cell folate level (Table 2.3).

Table 2.3 Reticulocytes and vitamins

	Patient's results	Normal range
Reticulocyte count	75 × 10^9/l	50–100 × 10^9/l (0.5–1.5%)
Serum B_{12}	600 ng/l	150–1000 ng/l (pg/ml)
Red cell folate	250 µg/l of packed red cells	150–1000 ng/l (pg/ml)

Q7 How can these results be interpreted?

A Large red cells (high MCV) could be reticulocytes due to haemolysis. The vitamin levels are normal and therefore are not the cause of the high MCV. In liver disease lipid accumulates on the red cell membrane causing a macrocytosis.

Q8 In view of these findings, what other information should be sought from the patient?

A A detailed family history should be obtained because some types of liver disease are familial.

He said his father had diabetes mellitus, but also had many other medical problems and had died from cirrhosis of the liver. He said this always surprised him, as his father was a non-drinker.

Q9 What should be done next?

A He should be re-examined for evidence of complications of diabetes mellitus.

His blood pressure is normal. He has gynaecomastia (enlargement of the breast tissue) (Fig. 2.1). His liver span is 18 cm (normal 12–15 cm) (Fig. 2.2). There is no evidence of a peripheral neuropathy. Retinal examination is normal. Urinalysis shows glucose but no protein.

Key point

As the blood glucose estimation was carried out on a random sample, Mr Black was advised to have the test repeated when he was fasting (Table 2.4).

Table 2.4 Fasting blood glucose

	Patient's results	Normal range
Fasting blood glucose	9 mmol/l	<7.0 mmol/l (<125 mg/dl)

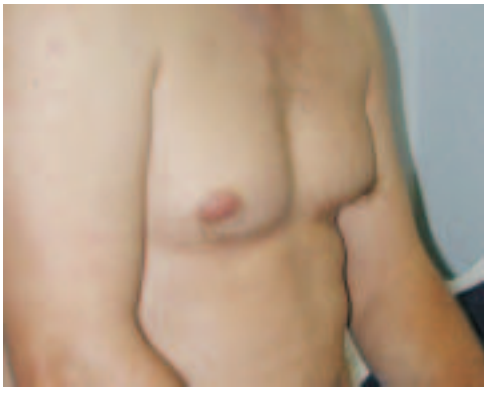


Figure 2.1 Enlargement of the breast tissue in a male, known as gynaecomastia.

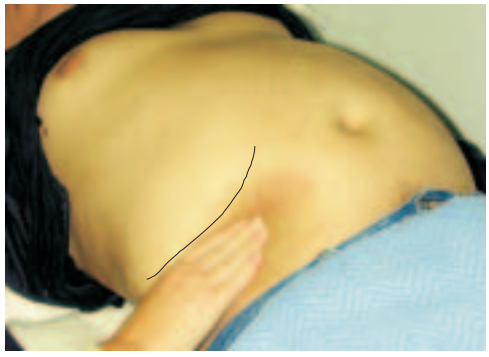


Figure 2.2 Palpation of an enlarged liver. The liver is not normally palpable. In this case, the lower edge is easily felt 3 cm below the costal margin.

Q10 Based on the blood results is a diagnosis possible, and if so what is it?

A Diabetes mellitus, because of the combination of an elevated fasting blood glucose (9.0 mmol/l or greater) and glycosuria. The impotence could be related to a diabetic neuropathy but the gynaecomastia and arthritis are probably not related to the diabetes. The complications of diabetes and the follow-up care and diet should be explained.

He returned in 2 months' time. He had started an exercise programme, modified his diet and lost 5 kg (11.0 pounds). However, he was still complaining of fatigue and a sore hand. The impotence had not improved.

On re-examination, he is pigmented. His liver remains enlarged. He has loss of body hair and the gynaecomastia is more pronounced.

Key point

He mentions that his cousin was recently diagnosed as having liver problems and was told his iron levels were too high.

Q11 What is the relevance of Mr Black's family history to his diagnosis?

A It is probably very relevant. His cousin has liver disease and was told he had 'too much' iron in his blood. Mr Black's father also had liver disease and diabetes mellitus.

Q12 What connection, if any, can be made between the diabetes mellitus, the liver disease, which appears to be familial, and the clinical findings?

A A genetically inherited disorder in which the body absorbs more iron than is required for daily use is called haemochromatosis.

Because the body has no effective mechanism for excreting iron, other than bleeding, the clinical manifestations of haemochromatosis are much more common in men than women until after the menopause (when monthly blood loss ceases).

Q13 How could a diagnosis of haemochromatosis be confirmed?

A By measuring the serum ferritin and transferrin saturation (Table 2.5).

The serum ferritin concentration is a good measure of body iron stores, but can, however, be non-specifically elevated in inflammatory conditions. The serum transferrin saturation is the most sensitive and cost-effective screening test.

Table 2.5 Iron studies

	Patient's results	Normal range
Transferrin saturation	77%	<38%
Ferritin level	4250 µg/l	20–300 µg/l (mg/ml)

There is no absolute abnormal value, but transferrin saturations of >55–60% in a man or >45–50% in a woman are very suggestive of haemochromatosis.

In 1996, mutations in the *HFE* gene were described and subsequently found in the majority of patients with hereditary haemochromatosis (HH). Two separate mutations have been described; the most common is the C282Y defect where a cysteine residue is replaced by a tyrosine residue. 90% of patients with HH are homozygous for the C282Y mutation. The second defect is H63D where aspartate replaces histidine. These gene mutations can be detected by a DNA-based test.

Mutation analysis showed he was homozygous for C282Y mutation. Figure 2.3 shows DNA, which has been amplified, from normal controls and homozygotes and heterozygotes for the HFE mutant alleles.

Multiplex site-directed mutagenesis PCR plus BbrPI digest for simultaneous detection of the two common hereditary haemochromatosis mutations C282Y and H63D

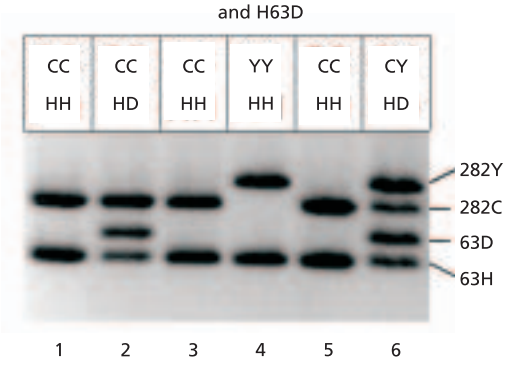


Figure 2.3 PCR (polymerase chain reaction) is used to amplify normal and mutant DNA. Lanes 1, 3 and 5 are normal. Lane 2 is a heterozygote for the H63D mutation. Lane 4 is homozygous for the C282Y mutation (haemochromatosis) and lane 6 is a heterozygote for the two different mutations. Reproduced with kind permission from Caitriona King, National Centre for Medical Genetics, Our Lady's Hospital for Sick Children, Dublin.

Key point

The carrier rate for HH in people of northern European descent is between 10–15%, making it the commonest genetic disorder in this population.

Dietary iron is transported into the enterocyte (cells lining the gut) by the divalent metal transporter DMT_1, among others. The amount of iron absorbed and transported to body stores is regulated by a number of proteins including HFE (the *HFE* gene is on chromosome 6) found in enterocytes and liver cells. The precise mechanism whereby the mutated protein increases iron absorption is unknown but HFE works in conjunction with β2-microglobulin.

Q14 How might the diagnosis of hereditary haemochromatosis (HH) explain Mr Black's symptoms?

A Increased absorption of dietary iron leads to organ dysfunction, especially of the liver, heart, skin and pancreas. This would account for the skin pigmentation, diabetes and abnormal liver blood tests.

Disruption of hypothalamic–pituitary function due to iron deposition leads to hypogonadism, gynaecomastia and impotence.

Arthropathy, due to iron deposition, is a common feature and occurs in 25–50% of patients. The joints of the hands, especially the 2nd and 3rd metacarpophalangeal joints, are usually the first joints involved.

Q15 How should Mr Black be treated?

A Phlebotomy should be performed until his ferritin level falls below 50 μg/l (mg/ml), followed by life-long maintenance phlebotomy.

Mr Black should be referred to a hepatologist to be assessed for evidence of cirrhosis. Once cirrhosis develops, there is >200-fold increased risk of developing liver cancer. Phlebotomy is effective at improving a sense of well-being, normalising the skin pigmentation and liver enzymes. The effect on arthralgia, diabetes and hypogonadism is more variable.

Key point

Death is most commonly due to cardiac and liver iron overload. If aggressive phlebotomy is initiated before end-organ damage occurs, life expectancy of patients with hereditary haemochromatosis can be normal.

Q16 Mr Black says that he has three teenage children and wonders should they be tested?

A They should be tested because phlebotomy, in affected individuals, will prevent organ damage due to iron excess.

Key point

The disease is transmitted as an autosomal recessive condition; therefore, homozygotes (individuals with two mutant alleles) may have clinical manifestation of disease. Heterozygotes (individuals with a single mutant allele) are common and usually will not have evidence of disease. In HH, as in other genetic diseases, there is incomplete penetrance, which means that although two people have the same mutation there is marked variability in the level of expression of the disease (Figs 2.4–2.6).

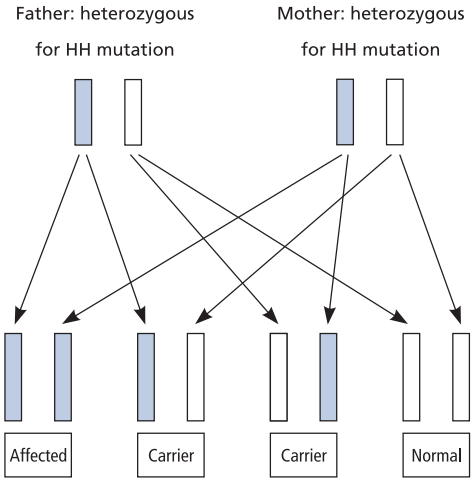


Figure 2.4 The possibilities for the children of a heterozygous mother and a heterozygous father. Blue box designates a mutant allele; white box designates a normal allele.

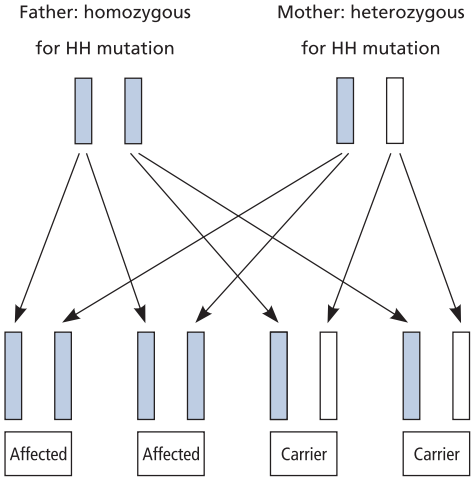


Figure 2.5 The possibilities for children of a homozygous father (haemochromatosis) and a heterozygous mother. Blue box designates a mutant allele; white box designates a normal allele.

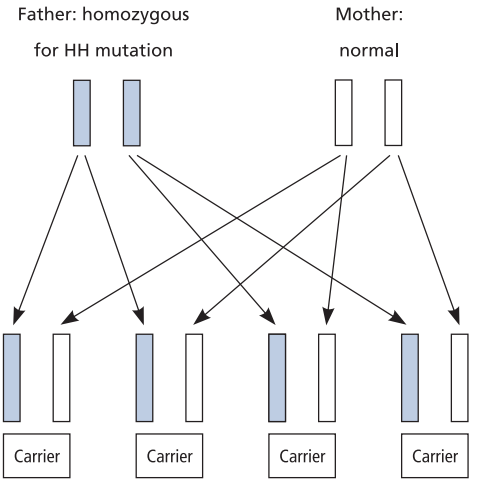


Figure 2.6 The possibilities for children of a homozygous father (haemochromatosis) and a 'normal' mother. Blue box designates a mutant allele; white box designates a normal allele.

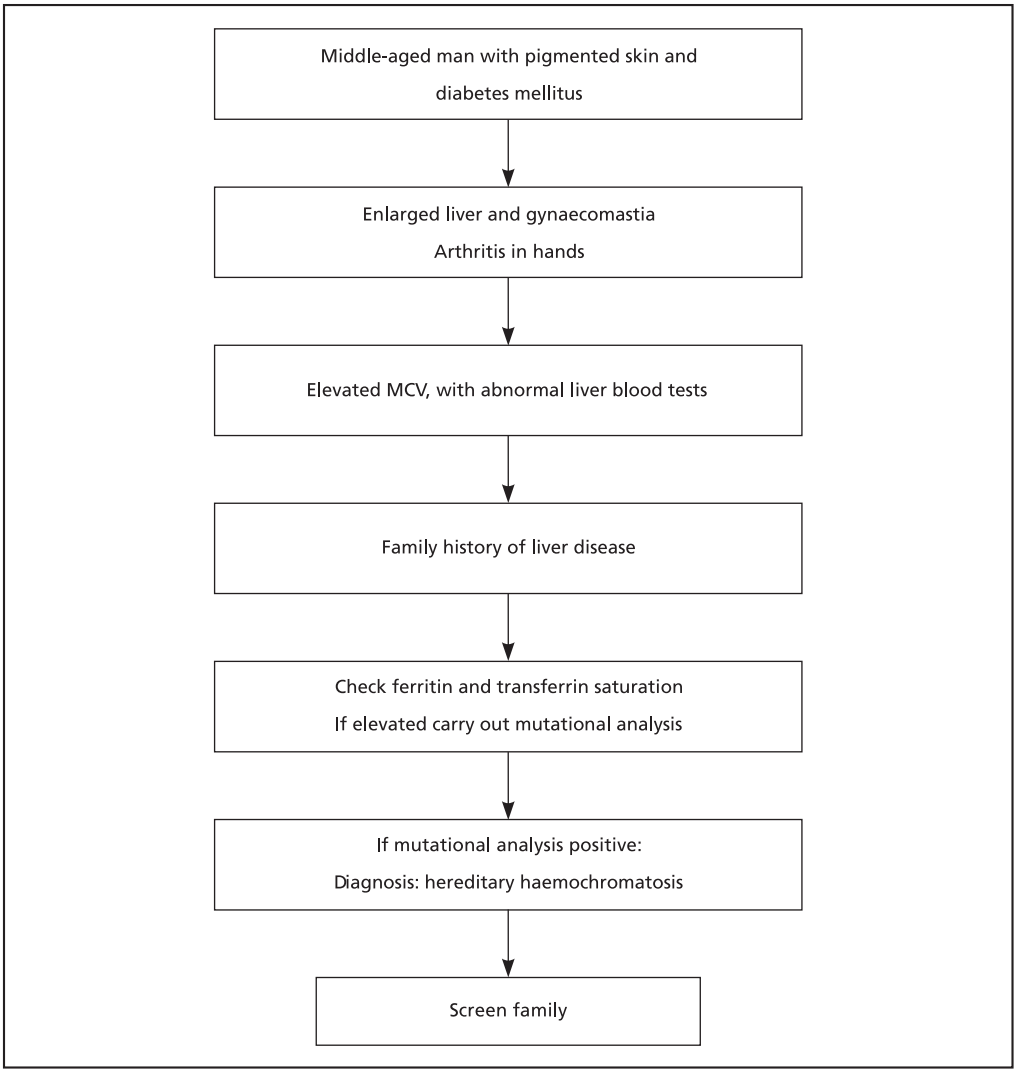
Q17 How practical is population-based screening for hereditary haemochromatosis?

A Not practical.

Variable penetrance means that not all patients with the mutations will develop evidence of iron overload. Estimates suggest that it may be as low as 1%. There are also broader issues to bear in mind, such as the use of personal genetic information for the determination of life insurance policies. Up to 40% of individuals at risk of haemochromatosis could be identified by screening of 1st-degree to 3rd-degree relatives of patients with iron overload.

Q18 Can you now construct an algorithm for a patient with pigmented skin and diabetes mellitus?

A Yes.



OUTCOME

Mr Black was started on weekly phlebotomy. He will be reviewed every 3 months and more blood removed to keep his ferritin level within the normal range.

His liver blood tests and MCV returned to normal. His blood sugar was controlled by diet. His impotence recovered but his hand remained painful.

Suggested reading

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