Familial chronic fatigue

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A 53-year-old woman presented to her general practitioner with a long history of profound lethargy associated with insomnia and arthralgia mainly affecting her knees. The patient dated her symptoms to a 'flu-like' illness six months previously. Medical history was of hypertension treated with an angiotensin-converting enzyme inhibitor and thiazide diuretic. She had also been taking oestrogen replacement since the menopause two years earlier. She had been a blood donor until 13 years previously, donating a total of 24 units of blood. She drank four units of alcohol per week but did not smoke. Physical examination was normal. Initial investigations performed were full blood count, urea and electrolytes, liver function tests, thyroid function tests, random glucose, cholesterol, calcium and urate. All were normal. Rheumatoid factor was negative and viral serology showed a raised IgG antibody titre to Epstein Barr virus, indicative of a past infection. X-Rays of the knee joints were normal.

A diagnosis of chronic fatigue syndrome was made. Over the following months her symptoms impaired her ability to work, shop and perform household tasks. Further medical consultations revealed no new features or abnormal tests and she took early retirement on the grounds of poor health.

Two years after her initial presentation, her brother, who had also been suffering from longstanding fatigue, was diagnosed as having liver disease.

Questions

- 1 Could liver disease account for the patient's illness, and if so, what is the most likely diagnosis?
- 2 What tests would you request to investigate your suspected diagnosis?
- 3 How would you confirm the diagnosis and manage her condition?

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Answer

QUESTION 1

Fatigue is a common symptom of liver disease which may be disabling and is often overlooked. Whilst arthralgia is not a typical feature of chronic liver disease in general, fatigue and arthralgia are the commonest presenting symptoms of genetic haemochromatosis.

QUESTION 2

Unlike virtually every other type of acute or chronic liver disease, liver function tests are often normal in haemochromatosis. Ultrasound scanning is usually not helpful in making the diagnosis, though hepatomegaly may be present. Fasting transferrin saturation and serum ferritin should be performed if the diagnosis is suspected. An elevated fasting transferrin saturation (males >60%, females >50%) and an elevated serum ferritin suggest the diagnosis of haemochromatosis,² though the serum ferritin can be normal early in the disorder before significant iron overload develops. Serum iron may be elevated but is often normal and is not useful in establishing the diagnosis. If serum ferritin but not transferrin saturation is elevated, then haemochromatosis is unlikely. Serum ferritin can be elevated in inflammatory and carcinomatous conditions, as well as liver diseases other than haemochromatosis, such as alcoholic liver disease.

This patient had a fasting transferrin saturation of 84% (normal <50%) and serum ferritin of 2823 ng/ml (normal <200).

QUESTION 3

The diagnosis is confirmed by liver biopsy. Histology of sections stained with Perls' stain shows the characteristic pattern of parenchymal iron overload. Measurement of the dry liver iron weight, if available, is also valuable as the 'hepatic iron index' can be calculated.

$$\text{Hepatic iron index} = \frac{\text{dry liver iron weight } (\mu\text{mol/g})}{\text{age (years)}}$$

A value >2 reliably differentiates haemochromatosis from other conditions associated with increased hepatic iron stores.³

HLA typing can be used to confirm the diagnosis in siblings of an index case. The patient was HLA identical to her brother who had had haemochromatosis diagnosed by liver biopsy. However, if iron indices are elevated, it is still important to perform liver biopsy to establish the presence or absence of cirrhosis, the most important prognostic factor in haemochromatosis.¹

Treatment is with regular venesection, usually once per week, until iron stores are depleted. To achieve this, venesection should be continued until serum ferritin levels fall below 100 ng/ml and anaemia develops. Maintenance venesection is then required, usually two to four times per year. If cirrhosis is present then there is a 200-fold increase in risk of the patient developing a hepatocellular carcinoma, even if iron stores are depleted.¹ Serum α -fetoprotein levels are often not elevated in hepatocellular carcinoma associated with haemochromatosis but regular ultrasound scanning in combination with α -fetoprotein testing, particularly in male cirrhotics, may detect tumours small enough for treatment.² Dietary restrictions are not generally necessary but patients should be told to avoid vitamin preparations containing iron and vitamin C.

Screening of first degree relatives with fasting serum transferrin and serum ferritin levels (with additional HLA typing in siblings) should be undertaken. The heterozygote frequency of the abnormal gene is around 10% in the general population and so sons and daughters of patients with haemochromatosis have a 5% chance of being homozygotes.

The patient had 65 units of blood (16 g of iron stores) removed with a substantial improvement in her symptoms.

Discussion

Genetic haemochromatosis is an autosomal recessive inherited disorder of iron metabolism involving an inappropriately high level of iron absorption from the small bowel. It is the commonest inherited liver disorder and one of the commonest autosomal recessive disorders, occurring in approximately 1 in 300 people in Caucasian populations.² Although not yet cloned, the gene is known to lie close to the HLA locus on the short arm of chromosome 6 and they are almost invariably inherited together. HLA A3 is the commonest HLA type associated with haemochromatosis, occurring in approximately 70% of cases. However, testing for this HLA type cannot be used to diagnose isolated cases of haemochromatosis as HLA A3 occurs in approximately 30% of the Caucasian population.⁴

Untreated, iron gradually accumulates in a variety of tissues, and can eventually result in organ failure and the protean clinical signs and symptoms of the disease. The classical triad of pigmentation, diabetes mellitus and cirrhosis, however, represents only the most severe end of a spectrum of clinical disease expression and haemochromatosis should be considered in the differential diagnosis of a wide variety of symptoms and presentations as shown in box 1. Asymptomatic cases are now often diagnosed by family screening.

Fatigue is the commonest symptom present at diagnosis regardless of whether cirrhosis is present or not. Although a symptom of liver failure and cirrhosis, fatigue is often a prominent symptom of precirrhotic haemochromatosis with normal liver function suggesting that it is iron overload *per se* that causes this

Consider genetic haemochromatosis in the differential diagnosis of:

- liver disease
- heart failure
- hyperglycaemia
- arthritis
- hypogonadism
- unexplained fatigue

Box 1

symptom. Liver function tests are often normal, with one study showing two-thirds of precirrhotic cases and one-third of cirrhotic cases having normal tests at diagnosis.¹

A number of studies have examined the usefulness of a variety of investigations in the assessment of patients presenting with chronic fatigue in general practice. In general such investigations have not proved useful as only a low yield of abnormal results has been found. However, such studies have not included screening tests for haemochromatosis and sometimes not even liver function tests.⁵

Iron stores in haemochromatosis are promoted by a diet rich in red meat and vitamin C and depleted by any cause of blood loss.² It is often wrongly thought that premenopausal women are protected from iron overload and organ damage by menstruation and the requirements of pregnancy. However this patient, who had cirrhosis due to haemochromatosis at diagnosis only four years after the menopause, illustrates that even combined blood loss due to blood donation and menstruation may not prevent iron accumulation and subsequent organ damage.

Venesection is required to deplete and maintain iron stores at the lower limit of

Summary points

- genetic haemochromatosis is a relatively common disorder protean in its manifestations
- normal liver function tests do not exclude the diagnosis
- pre- and peri-menopausal women are not exempt from clinical expression of the disease
- fasting serum transferrin saturation and serum ferritin are required to make a provisional diagnosis
- liver biopsy is required to confirm the diagnosis and assess liver architecture

Box 2

normal. Although cirrhosis cannot be reversed and the risk of hepatocellular carcinoma cannot be removed once cirrhosis has developed, liver function, cardiac function and diabetic control may all improve with venesection as can symptoms such as fatigue.¹

Final diagnosis

Genetic haemochromatosis.

Keywords: fatigue, haemochromatosis

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An unusual rectal polyp

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A 60-year-old woman underwent a flexible sigmoidoscopy for investigation of her complaint of minor rectal bleeding. The endoscopy revealed a 1-cm pale polypoidal lesion with normal overlying mucosa in mid-rectum and mild diverticular disease affecting the sigmoid colon. The polyp was snared and retrieved for histological examination. The microscopic appearance is shown in the figure.

Questions

- 1 What is the most likely diagnosis?
- 2 From which cell has this polyp originated?

Figure Haematoxylin and eosin stained section of polyp.

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