CASE REPORT

A tale of two sisters

D R Gaya, A L C McLay, K A Oien, R J Spooner, T G Reilly

J Clin Pathol 2004;57:439–441. doi: 10.1136/jcp.2003.012013

Hereditary haemochromatosis is the most common inherited disorder in white populations, whereas non-alcoholic steatohepatitis (NASH) is becoming the most common reason for referral for investigation of abnormal liver function tests (LFTs). This report describes two sisters, from similar environments, who were referred to the clinic after being found to be C282Y homozygotes and to have abnormal LFTs. One sister had developed features of haemochromatosis and the other had developed NASH. These cases illustrate the potential non-penetrance of HFE gene mutations and the need to investigate abnormal LFTs fully, even when there is a positive genetic test at the outset.

The two sisters both presented to the gastroenterology clinic at a district general hospital.

CASE 1

ER, a 48 year old woman, was referred to the clinic for the investigation of abnormal LFTs. Her father had died from a hepatoma; he had no previously known liver complaints, but had developed diabetes and a tanned complexion in his last years. After his death, ER investigated his medical history with the help of the internet, and becoming concerned that her father might have died from complications arising from undiagnosed haemochromatosis, consulted her general practitioner.

She had no relevant past medical history, was taking no medication and, apart from her father's history, had no risk factors for liver disease. In addition, she had a normal menstrual history.

On examination she appeared well. Her body mass index (BMI) was 24 and there were no stigmata of chronic liver disease.

Investigations revealed mildly deranged LFTs, with the only abnormalities being an aspartate aminotransferase (AST) of 55 U/litre (normal, < 25) and γ glutamyl transpeptidase (γ GT) of 57 U/litre (normal, < 50). Autoantibody screening and viral serology were both negative. Both serum ferritin and transferrin saturation were raised at 981 μ g/litre (normal range, 18–300) and 73 μ g/litre (normal range, 15–45), respectively. Genotyping revealed that she was homozygous for the C282Y mutation of the HFE gene (and wild-type for the H63D mutation). Liver biopsy (fig 1) revealed features in keeping with haemochromatosis; the calculated hepatic iron index was 2.62 μ mol/g/year (normal, < 1.9), supporting the overall diagnosis of genetic haemochromatosis.

CASE 2

CR, a 53 year old woman and elder sister of ER, was subsequently referred to the same clinic. Both sisters had lived on the same street since leaving their childhood home. After being alerted by her sister's problems, she visited her general practitioner and was found to have abnormal LFTs

and to be homozygous for the C282Y mutation (and wild-type for the H63D mutation).

She had a past history of ischaemic heart disease, type 2 diabetes, hypothyroidism, and osteoarthritis of the hip. Her current medications were aspirin, isosorbide mononitrate, lisinopril, metformin, thyroxine, and dihydrocodeine. She consumed less than 10 units of alcohol each week, had no risk factors for viral hepatitis, and had a normal past menstrual history.

On examination she was obese with a BMI of 39. There were no stigmata of chronic liver disease.

Investigations revealed abnormal LFTs with an AST of 56 U/litre (normal, < 25), alanine aminotransferase of 75 U/litre (normal, < 50), alkaline phosphatase of 348 U/litre (normal, 240), γ GT of 65 U/litre (normal, < 50), bilirubin of 19 μ mol/litre (normal, < 18), and albumin of 42 g/litre (normal range, 34–48). Viral serology and autoantibodies were negative. Ferritin was within the normal range at 235 μ g/litre (normal range, 18–300), although transferrin saturation was borderline at 45% (normal range, 15–45%). Liver biopsy revealed pronounced steatohepatitis but no fibrosis. There was minimal siderosis (fig 2) and the hepatic iron index was 0.22 μ mol/g/year (< 1.9). The underlying diagnosis in this patient was thus non-alcoholic steatohepatitis (NASH).

DISCUSSION

We have presented the cases of two sisters who both lived in similar environments and both inherited the C282Y mutation. Despite their genotypes, only one sister expressed the disease and showed phenotypic haemochromatosis. The other sister had developed an entirely different spectrum of liver disease in the form of NASH, probably related to her obesity and type 2 diabetes mellitus.

Haemochromatosis is a disorder of iron overload in which the excess iron accumulates in the parenchymal tissue, causing damage if untreated. Genetic haemochromatosis is the most common inherited disorder in white populations, particularly affecting those of Northern European or Celtic descent; the genetic prevalence ranges from 1 in 200 to 1 in 400 in Western countries.¹

The identification of the HFE (high iron) gene on the short arm of chromosome 6 in 1996 represented an advance in the understanding of genetic haemochromatosis.² The exact pathophysiology leading to increased intestinal iron absorption continues to be unravelled, but it is clear that about 95% of cases of genetic haemochromatosis in the UK are associated with mutations in this gene, via an autosomal recessive mode of inheritance. Of those patients, over 90% are homozygous for the missense mutation C282Y (substitution of tyrosine for cysteine at position 282).³ A second mutation

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; γ GT, γ glutamyl transpeptidase; LFT, liver function test; NASH, non-alcoholic steatohepatitis

Figure 1 High power view of liver stained with Perls Prussian blue for iron. The hepatocytes, which occupy most of the field, show moderate haemosiderosis in the form of blue granules. The portal tract, located at the top left, does not contain hepatocytes and therefore lacks blue granules; instead it is demonstrated only by the pink counterstain.

in the HFE gene, H63D (substitution of aspartate for histidine at position 63), when associated with the C282Y mutation in the other chromosome 6 (the “compound heterozygote”), accounts for a much smaller proportion (approximately 10%) of patients with genetic haemochromatosis.⁴ In recent years, increasing numbers of non-HFE related genes have been discovered, which accounted for a small proportion of cases; these are beyond the scope of this discussion.

“Despite the high population prevalence of genetic haemochromatosis, clinical expression of the disorder appears much less common”

Interest has recently focused on the penetrance of the condition. It has become clear that environmental stimuli that predispose to hepatic iron deposition (such as hepatitis C infection, alcohol excess, and repeated blood transfusion) make the expression of disease and earlier presentation far more likely; indeed, numerous reports describe HFE heterozygotes expressing disease in the context of one of the above mentioned cofactors.^{5–6} Despite the high population prevalence of genetic haemochromatosis, clinical expression of the disorder appears much less common. It is unclear whether this represents simple underdiagnosis or true lack of penetrance. To date, no study has prospectively followed up asymptomatic C282Y

Figure 2 High power view of liver stained with Perls Prussian blue for iron. This is within normal limits because only the pink counterstain is seen and the blue granules are absent.

Take home messages

- We describe two sisters, from similar environments, who were C282Y homozygotes and had abnormal liver function tests (LFTs): one had developed haemochromatosis and the other had developed non-alcoholic steatohepatitis
- These findings illustrate the occurrence of non-penetrance of genetic haemochromatosis in the context of C282Y homozygosity, and suggest that other, yet to be described, genes might affect the expression of the disorder
- Abnormal LFTs should be investigated fully, even when there is a positive genetic test at the outset

homozygotes without venesection to ascertain the proportion developing symptoms or complications of haemochromatosis. However, within the past 18 months several studies have shown that, although biochemical evidence of some degree of iron overload is present in most adult C282Y homozygotes, the clinical penetrance of the phenotypic condition is extremely low.^{7–9} Thus, despite the HFE mutation being common, clinical haemochromatosis remains a relatively rare disease.

The liver biopsy of the sister who did not express the disease suggested that NASH was the probable cause of her deranged LFTs. Until recently, this condition was thought to be a relatively rare disorder with a benign prognosis. However, it has become apparent that NASH is extremely common,¹⁰ and has become one of the most common reasons for referral for investigation of abnormal LFTs.¹¹ The increased incidence of NASH seems to mirror the epidemic of obesity and type 2 diabetes currently being seen in Western societies; it seems to be a disease of “affluence”, with insulin resistance being central to the pathogenesis.¹² In addition, the condition does not always have a benign prognosis¹³ and NASH may account for most, if not all, cases of “cryptogenic” cirrhosis.^{14–15} The hepatic prognosis in NASH appears to be related to the degree of fibrosis on the index liver biopsy;¹³ the absence of fibrosis on CR’s liver biopsy placed her in a good prognostic category.

The cases described above illustrate two main messages. First, they highlight the occurrence of non-penetrance of genetic haemochromatosis in the context of C282Y homozygosity in two siblings; this suggests the importance of other, yet to be described, genes affecting the expression of the disorder, particularly because environmental factors were similar in both sisters. Second, they illustrate the need to maintain an open mind when investigating abnormal LFTs; one should fully investigate all potential causes even in the face of a positive genetic test at the outset.

Authors’ affiliations

D R Gaya, T G Reilly, Department of Gastroenterology, Hairmyres Hospital, Lanarkshire G75 8RG, UK

A L C McLay, Department of Pathology, Hairmyres Hospital

K A Oien, Department of Pathology, Glasgow Royal Infirmary, Glasgow G4 0SF, UK

R J Spooner, Department of Biochemistry, Gartnavel General Hospital, Glasgow G12 0YN, UK

Correspondence to: Dr D Gaya, Flat1/2, 15 Julian Avenue, Kelvinside, Glasgow G12 0RB, UK; danielgaya@aol.com

Accepted for publication 5 August 2003

REFERENCES

- 1 **Bacon BR**, Powell LW, Adams PC, *et al*. Molecular medicine and haemochromatosis: at the cross-roads. *Gastroenterology* 1999;**116**:193–207.
- 2 **Feder JN**, Gnirke A, Thomas W, *et al*. A novel MHC class-1 like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996;**13**:399–408.
- 3 **UK Haemochromatosis Consortium**. A simple genetic test identifies 90% of UK patients with haemochromatosis. *Gut* 1997;**41**:841–4.
- 4 **Crawford DH**, Jazwinska EC, Cullen LM, *et al*. Expression of HLA-linked haemochromatosis in subjects homozygous or heterozygous for the C282Y mutation. *Gastroenterology* 1998;**114**:1003–8.
- 5 **Melis MA**, Cau M, Deidda F, *et al*. H63D mutation in the HFE gene increases iron overload in beta-thalassaemia carriers. *Haematologica* 2002;**87**:242–5.
- 6 **Kazemi-Shirazi L**, Datz C, Maier-Dobersberger T, *et al*. The relation of iron status and haemochromatosis gene mutations in patients with chronic hepatitis C. *Gastroenterology* 1999;**166**:127–34.
- 7 **Thorburn D**, Cook A, Spooner R, *et al*. Genetic haemochromatosis: where are all the patients? *Gut* 2002;**50**(suppl 1):A34.
- 8 **Beutler E**, Felitti VJ, Koziol JA, *et al*. Penetrance of 845G→A(C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet* 2002;**359**:211–18.
- 9 **Waalén J**, Felitti V, Gelbart T, *et al*. Prevalence of haemochromatosis-related symptoms in homozygotes for the C282Y mutation of the HFE gene. *Mayo Clin Proc* 2002;**77**:522–30.
- 10 **Bacon BR**, Farahvarsh MJ, Janney CG, *et al*. Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology* 1994;**107**:1103–9.
- 11 **Bryon D**, Minuk GY. Profile of an urban hospital-based practice. *Hepatology* 1996;**28**:813–15.
- 12 **Marchesini G**, Brizi M, Bianchi G, *et al*. Non-alcoholic fatty liver disease. A feature of the metabolic syndrome. *Diabetes* 2001;**50**:1844–50.
- 13 **Matteoni CA**, Younossi Z, Gramlich T, *et al*. Non-alcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999;**29**:664–70.
- 14 **Caldwell SH**, Oelsner DH, Lezzoni JC, *et al*. Cryptogenic cirrhosis: clinical characterisation and risk factors for underlying disease. *Hepatology* 1999;**29**:644–70.
- 15 **Poonwala A**, Nair S, Thulavath PJ. Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: a case-control study. *Hepatology* 2000;**32**:689–92.