Site of principal metabolic defect in idiopathic haemochromatosis: insights from transplantation of an affected organ

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Idiopathic haemochromatosis is an inherited defect of iron metabolism characterised by excessive iron absorption and deposition in the tissues leading to damage in the liver and other organs.¹ The nature of the fundamental metabolic abnormality remains unknown, but the liver and the gut have both been proposed as the principal site of expression of the metabolic defect.¹

We recently had the opportunity to study this question when a liver was transplanted from a donor who subsequently proved to have had presymptomatic idiopathic haemochromatosis into a young woman with normal iron metabolism. We describe here the changes in iron status observed in our patient in the first 29 months after liver transplantation.

Patient, methods, and results

A 16 year old girl underwent orthotopic liver transplantation for subacute hepatic failure caused by presumed non A, non B viral hepatitis. Extensive investigation had shown no specific cause.

A liver biopsy performed on the donor organ after reperfusion showed grade 3 stainable iron within hepatocytes without significant fibrosis. Further needle biopsies in the next six weeks confirmed grade 3 or 4 hepatocyte iron staining with only a small amount of iron seen in macrophages and sinusoidal cells. The hepatic iron concentration on day 42 was 152 $\mu\text{mol/g}$ dry weight (normal 5-40), and the hepatic iron index (donor age 48 years) was 3.17. These findings suggested idiopathic haemochromatosis.

The donor was a 48 year old woman who drank virtually no alcohol and who had no history of liver disease, anaemia, or blood transfusions. The donor's HLA haplotype included the A3 allele, which is known to be strongly associated with idiopathic haemochromatosis.¹ In addition, two siblings of the donor were found to have significantly raised serum ferritin concentrations and on liver biopsy showed greatly increased iron stores, confirming the diagnosis of idiopathic haemochromatosis in the donor family.

Findings on the recipient's iron studies before operation were as follows: iron 33 $\mu\text{mol/l}$ (normal 13-30), total iron binding capacity 38 $\mu\text{mol/l}$ (45-73), and serum ferritin 106 $\mu\text{g/l}$ (9-190). The serum ferritin

concentration was measured regularly as a guide to iron stores, and by the 42nd day after transplantation, it had risen to 1585 $\mu\text{g/l}$. It subsequently fell progressively, until by 29 months it was normal (figure). At this point the serum iron concentration had fallen to 14 $\mu\text{mol/l}$. Four estimates of dry weight liver iron showed a progressive reduction from 152 $\mu\text{mol/g}$ immediately after transplantation to normal (30 $\mu\text{mol/g}$) at 29 months. The iron indices returned to normal in the absence of abnormal blood losses.

Comment

Intuitively it seems reasonable to seek the expression of the metabolic defect of idiopathic haemochromatosis in the gut since increased assimilation of dietary iron is the major abnormality leading to increased body iron stores.¹ In patients with idiopathic haemochromatosis a larger than normal proportion of the iron taken up by the enterocyte is transferred into the body.² Further support for the epithelial cell as the site of the defect comes from immunohistochemical findings; these show a failure of downregulation of the enterocyte transferrin receptor by iron overload in patients with idiopathic haemochromatosis.³

Some evidence exists for hepatic control of iron metabolism, however, and hence of tissue iron accumulation in haemochromatosis. Patients with idiopathic haemochromatosis who have been "de-ironed" have a significantly higher hepatic iron uptake after intravenous infusion than controls.⁴ The influence of the liver on iron absorption has been shown in a study in rats,⁵ in which the transplanting of iron loaded livers into normal animals significantly reduced iron absorption in the graft recipients.

In our study, in which a liver from a patient with idiopathic haemochromatosis was transplanted into a recipient with normal iron metabolism, liver iron concentrations and serum ferritin concentrations returned to normal in the absence of any abnormal source of iron loss. This case provides strong evidence against a primary hepatic defect in idiopathic haemochromatosis.

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Serum ferritin concentrations after transplantation

Increased concentrations of serum lipoprotein (a) in response to growth hormone treatment

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Premature death from cardiovascular disease has been reported in patients with adult growth hormone deficiency.¹ The treatment of such patients with

growth hormone lowers serum cholesterol concentrations and has positive effects on body fat distribution.² We recently reported that treating patients with gall stone disease with growth hormone stimulates hepatic low density lipoprotein receptors while at the same time reducing serum low density lipoprotein cholesterol concentrations.³ In light of interest in expanding the indications for growth hormone treatment beyond that of growth retardation in childhood² it is important to evaluate the effects of growth hormone treatment on lipoprotein metabolism.

A high serum concentration of lipoprotein (a), especially combined with raised concentrations of low

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density lipoprotein, increases the risk of premature coronary heart disease.⁴ Lipoprotein (a) concentrations are relatively resistant to most forms of conventional hypolipidaemic therapy, but recent studies have indicated that the lipoprotein (a) concentration is drastically reduced by oestrogen therapy.⁵ Since growth hormone seems to mediate some of the effects of oestrogen on lipoprotein metabolism,³ we hypothesised that growth hormone treatment might also lower lipoprotein (a) concentrations. This hypothesis was tested by analysing the concentration of lipoprotein (a) before and during short term growth hormone treatment in healthy humans.

Subjects, methods, and results

Two groups of subjects were studied. The first was nine otherwise healthy patients (including two post-menopausal women) with uncomplicated gall stone disease; they had a mean (SEM) age of 51 (5) years and a relative body weight of 105 (3)%. They were given 12 IU somatotropin (Kabi Pharmacia, Sweden) daily for five days. The second group comprised nine healthy male controls aged 32 (2) with a relative body weight of 103 (2)%. They received somatotropin 0.1 IU/kg daily for seven days. All somatotropin was given in single subcutaneous doses. Informed consent was obtained before each subject entered the study, which was approved by the ethical committee of the Karolinska Institute. Fasting blood samples were analysed for serum cholesterol and triglycerides, lipoprotein lipids, and lipoprotein (a) concentrations.⁶ Low density lipoprotein cholesterol concentrations fell significantly in both study groups (see table). In contrast, lipoprotein (a) levels increased after treatment in all but three subjects.

Comments

In contrast to oestrogen treatment,⁵ and contrary to our original hypothesis, growth hormone administration had opposing effects on low density lipoprotein cholesterol and lipoprotein (a) concentrations. The difference appeared to be more pronounced in the older subjects (the patients with gall stones).

The results of these two open studies underline the complexity of lipoprotein (a) metabolism.⁴ Clearly the twofold to threefold upregulation of hepatic low density lipoprotein receptors that occurs during growth hormone treatment³ is not sufficient adequately to clear lipoprotein (a). Thus, it seems reasonable to assume that an enhanced hepatic production of lipoproteins and lipoprotein (a) occurs, possibly as a

Lipoprotein concentrations before and during treatment with growth hormone. Values are means (SEM).

Study group	Baseline	After treatment
<i>Patients with gall stones</i>		
Cholesterol (mmol/l):		
Total	6.8 (0.5)	5.3 (0.5)‡
Low density lipoprotein	4.7 (0.4)	3.2 (0.3)‡
High density lipoprotein	1.4 (0.1)	1.2 (0.2)
Very low density lipoprotein	0.7 (0.1)	0.9 (0.2)
Triglycerides (mmol/l)	1.7 (0.2)	2.4 (0.4)
Lipoprotein (a) (mg/l)*	225 (6-605)	280 (7-692)‡
<i>Healthy controls</i>		
Cholesterol (mmol/l):		
Total	5.1 (0.3)	5.0 (0.2)
Low density lipoprotein	3.7 (0.2)	3.4 (0.2)‡
High density lipoprotein	1.0 (0.1)	1.1 (0.1)
Very low density lipoprotein	0.4 (0.1)	0.5 (0.1)
Triglycerides (mmol/l)	1.0 (0.1)	1.2 (0.1)
Lipoprotein (a) (mg/l)*	191 (12-714)	295 (13-896)‡

*Mean (range). †p < 0.05; ‡p < 0.01 compared with baseline (Wilcoxon test).

consequence of the increased lipolytic activity induced by growth hormone. Furthermore, the fact that insulin-like growth factor-1 levels are increased during growth hormone treatment but reduced during oestrogen therapy may indicate that this factor has a role in the regulation of lipoprotein (a) metabolism. Other metabolic adaptations to the hormonal treatment, such as hyperinsulinaemia, may also be important.

The increase in lipoprotein (a) concentration is a clinically undesirable effect of growth hormone treatment. Although only long term controlled studies can evaluate the overall advantages and disadvantages of growth hormone treatment in various conditions, these results call for caution in considering growth hormone treatment in patients other than children with growth hormone deficiency.

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SOUND BITES

Spectacular problems

When I was a mixed infant the world beyond about two metres away was gently blurred about the edges. It didn't trouble me because it never occurred to me that this was anything out of the ordinary. In class we were seated in alphabetical order, so I was in the front row and could see the blackboard. If I had been an Underwood or a Wilberforce I might never have passed the scholarship or qualified in medicine.

When a responsible school nurse arranged for eye tests for all I was told I would need spectacles. I can still recall the day I got them. The world had sharp edges. This was what other people had been seeing all the misty years of my mixed infancy.

When I went to the secondary school bigger boys hit me for wearing specs and broke them. I knew it cost seven and sixpence to get them mended and I went home contrite, but there was not a lot I could do about it. We were a

soccer school. If I took my specs off I couldn't see the ball. If I kept them on they got broken.

In my 50s I was promoted to bifocals. In my mid-60s I found that I could no longer see to thread a trout fly on to a cast unless I took my specs off. I took them off and dropped them in the river. Much, much more than seven and sixpence.

"You've got presbyopia," the optician told me." I knew. "It's something elderly people get," the optician told me. I knew that, too. Now I had to take my specs off to see properly to cut my nails or to read small print, but when I took them off I couldn't look for them until I had them on. I tried hanging them round my neck but forgot I had done so. Sometimes I pushed them up over my head where I never thought to look.

I feel rather like a mixed infant once again.—DENIS CASHMAN is a retired general practitioner in Cullercoats