Familial hypercholesterolaemia in children

D PAUL NICHOLLS

Abstract

Familial hypercholesterolaemia (FH) affects about one in 500 in the UK population. There are no symptoms or signs of raised cholesterol in children and so individuals can only be identified by screening, usually as a 'cascade' from known probands. Once identified, such children should be treated to prevent premature atherosclerosis.

Key words: familial hypercholesterolaemia, children, genetic testing, statins.

Br J Cardiol 2006;**13**:191–4

Introduction

Familial hypercholesterolaemia (FH) is probably the commonest single gene disorder, with an assumed prevalence in the UK population of about one in 500. This means that the average secondary school probably has three or four pupils with FH. Compared with FH, the other lipid disorders found in childhood (table 1) are all very rare.

The clinical diagnosis of FH is confirmed by the clustering of high cholesterol levels (> 7.5 mmol/L) in first- or second-degree relatives and the presence of tendon xanthomata (TX; figure 1) in at least one member of the family.[1,2] Alternatively, identification of a functional genetic defect can be used.[3]

Without effective treatment, FH males aged 20 to 40 years are 100 times more likely to develop coronary artery disease than unaffected normals,[1] compared with a risk ratio of three to six for diabetes[4] and two to three for cigarette smoking.[5] Clearly the identification and treatment of FH at a younger age would be of benefit, but random screening of the population would not be cost-effective. Cascade targeted screening from known affected individuals has been recommended in the 2003 White Paper *Our Inheritance, Our Future.* It is likely that increasing numbers of children will be found to be affected, and this raises management and treatment issues.

Royal Victoria Hospital, Grosvenor Road, Belfast, BT12 6BA.
D Paul Nicholls, Consultant Physician and Honorary Professor of Medicine
Correspondence to: Professor DP Nicholls
(email: paul.nicholls@royalhospitals.n-i.nhs.uk)

D Paul Nicholls

Table 1. Lipid disorders in childhood

Atherogenic
- Familial hypercholesterolaemia
- Familial combined hyperlipidaemia
- Remnant (type III) hyperlipidaemia
- Apolipoprotein A1-CIII deficiency
- Lecithin:cholesterol acyl transferase (LCAT) deficiency
- Hyperapobetalipoproteinaemia

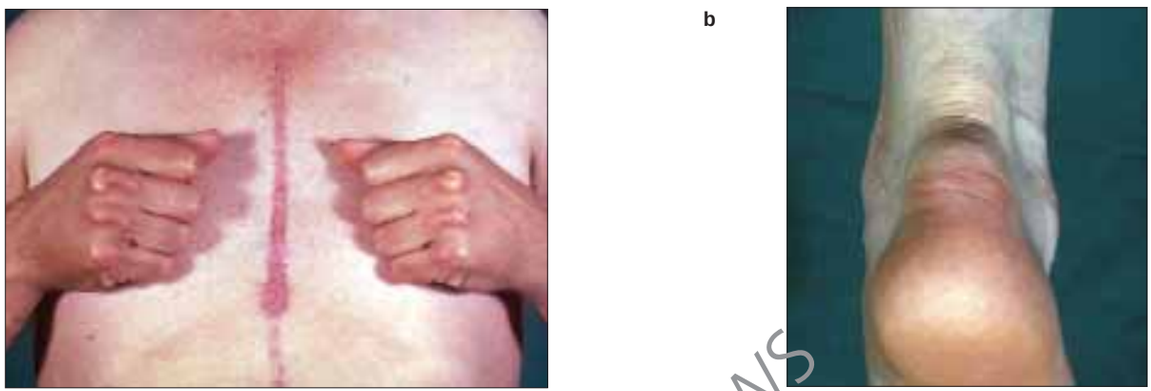
Non-atherogenic
- Tangier disease
- Fish-eye disease
- Lipoprotein lipase deficiency
- Apolipoprotein CII deficiency

Possibly protective against atherosclerosis
- A- or hypobetalipoproteinaemia
- Hyperalphalipoproteinaemia

Genetics of FH

FH is inherited as an autosomal co-dominant disorder, which means that the sex distribution is equal. Affected individuals inherit a defective allele from one parent (i.e. heterozygous FH [HEFH]) and will pass on the defective gene to one in two of their offspring. Unaffected individuals cannot pass it on and the disorder cannot 'skip' a generation. In certain populations of the

Figure 1. **a**: shows tendon xanthomata and a coronary artery bypass grafting scar in an adult with heterozygous familial hypercholesterolaemia due to an intron splicing defect in the LDLR gene, c.1845+11c>g;[3] **b**: shows Achilles tendon thickening in the same patient. Note that in children, these signs are only observed in homozygous familial hypercholesterolaemia



world in whom the gene pool is more restricted, such as Afrikaaners, French Canadians and Lebanese, the prevalence of FH is much greater, up to one in 50 of the population being affected. In the majority of cases, the fault lies in the gene encoding for the low-density lipoprotein receptor (LDLR) which is responsible for the catabolism of ApoB-containing particles.[6] With only half the normal number of functioning LDLRs available, circulating plasma cholesterol levels are approximately doubled and there is a marked predisposition to premature coronary artery disease.

The gene encoding the LDLR is on chromosome 19p.13.2, and nearly 800 mutations have been described (http://www.ucl.ac.uk/fh; http://www.umd.necker.fr). The precise defect varies but can be identified in 70–90% of FH families.[3] In about 10% of families, the problem is a missense mutation in the ligand for the LDLR, ApoB (R3500Q).[7] In some families, no genetic abnormality can be defined, despite the presence of tendon xanthomata (TX) in the family.[3]

Homozygous FH

In theory, if an individual with HeFH meets by chance another individual with HeFH, then one in four of their offspring would have homozygous FH (HoFH). This would give a prevalence of one in 500 x 500 x 4 in the population, i.e. 1 in 10^6. In practice, HoFH is much rarer than this in the UK and there are currently no individuals with HoFH in Ireland (population > 5 million). In other areas with restricted gene pools, such as Lebanese Christians in whom first-cousin marriages are common, HoFH becomes a real possibility.[8]

HoFH is a serious disease, with a virtual absence of functioning LDLRs, cholesterol levels of > 20 mmol/L, premature atherosclerosis, TX in childhood, and death in the second or third decade if untreated. Drug treatment is unsatisfactory except for the cholesterol absorption inhibitor ezetimibe,[9] and LDL-apheresis is the mainstay of treatment.[10] Liver transplantation has been used to donate LDLRs,[11] and direct injection into the portal vein of LDLR-encoded recombinant retroviruses has also been performed.[12]

Diagnosis of FH in childhood

In children with HeFH, there are no symptoms or signs, and so the diagnosis can only be made by blood testing. Although normal ranges for total and LDL-cholesterol in children have been published,[13] there is considerable variability and hence overlap between affected and unaffected individuals.[14] Genotyping is much more satisfactory, when the LDLR defect for the family has been characterised, but the test is not as yet widely available. This may change in the near future with the increasing availability of 'chip' technology.

Individual children with HeFH are exposed to inappropriately high cholesterol levels from birth or before but, in practice, treatment is rarely possible before school age. At that stage, when a child is aged four to five, it is very helpful to know whether he/she is affected as there is an opportunity to teach healthy eating (see below). Alternatively, knowing that the child is not affected can be very reassuring. Research has shown that there are no negative psychological features associated with this knowledge, either in the child or the parents.[15]

Treatment of FH in children

Treatment of HeFH in childhood is recommended because the adverse long-term effects of severe hypercholesterolaemia have been well described.[1] In addition, there is direct evidence that there is endothelial dysfunction in young people with HeFH,[16] which is reversible,[17] and evidence of carotid artery damage,[18] and so the process of atherosclerosis has already started. The

treatment of affected children should be supervised by a lipid clinic in view of the complex issues involved.[19]

As with adults, initial advice is on diet but this can be problematic in childhood, not least because of school meals! Very low fat or low cholesterol diets are inappropriate and potentially harmful. The best that can be achieved in terms of cholesterol reduction with a 'healthy diet' is about 15%, and this is not enough to normalise levels in patients with FH. Nevertheless, this is a good time to teach children the principles of a healthy diet, with more emphasis on cereals and fruit, and viewing fries, sweets, crisps and so on as occasional treats rather than the mainstay of their diet.

A recent study from the Simon Broome Association[20] identified male sex and cigarette smoking as the two most important factors in determining prognosis in patients with HeFH. Affected children should be left in no doubt that it is imperative that they *never* start smoking, whatever the peer pressures to do so. Apart from this, though, they should regard themselves as being normal in every way. HeFH, particularly if well treated, is no bar to any sport, no matter how intense – most of the sudden deaths on sports fields are due to cardiomyopathy rather than premature coronary artery disease.[21]

There remains controversy on when to initiate drug treatment. It is important to consider all the variables before making such a decision. In particular, if there is a very strong history of premature coronary artery disease in the family, then it is reasonable to start treatment early, as soon as dietary intervention has been given a chance. If, on the other hand, the family history is relatively benign then drug treatment can be deferred until later.

Resins were used in children in the past, but they are unpalatable in the quantity required to effect a significant cholesterol reduction, and are now outmoded. Fenofibrate in the low-dose preparation (Lipantil Micro 67®) is licensed for use in children but is only moderately effective. The most effective drugs by far are the statins. Studies in children have confirmed effective cholesterol reduction without any observed effects on growth or development.[22-26] In the UK, pravastatin is licensed for use in children with HeFH from the age of eight years at the reduced dose of 10–20 mg daily, and from 14 years at 10–40 mg. Atorvastatin is licensed from ages 10–17 years at the 10–20 mg dose. Other statins are not yet licensed for use in children with HeFH. Girls should be told not to conceive whilst on a statin. The cholesterol absorption inhibitor ezetimibe is not recommended for children under 10 years, unless they have HoFH.[9]

Conclusions

HeFH should be actively sought and treated in children. As it is thought that the main risk in HeFH derives from the inappropriate elevations of LDL cholesterol, and children have been exposed to such increases from or before birth, then it is hoped that early aggressive treatment will prevent the development of premature atherosclerosis. If cholesterol levels are normalised, then there is no reason why the individual should be barred from active jobs or sports, and no reason why they should not be accepted for life insurance at standard rates. By an active screening policy the threat of FH could be greatly reduced.

Key messages

- Familial hypercholesterolaemia (FH) affects about one in 500 of the UK population
- Affected children have evidence of premature atherosclerosis
- Affected children should be identified and treated
- The cardiovascular risk of FH can be reduced by effective treatment

Conflict of interest

None declared.

References

1. Betteridge DJ, Broome K, Durrington PN *et al.* Risk of fatal coronary artery disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* 1991; **303**:893-6.
2. Scientific Steering Committee on behalf of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. *Atherosclerosis* 1999;**142**:105-15.
3. Graham CA, McIlhatton BP, Kirk CW *et al*. Genetic screening protocol for familial hypercholesterolaemia which includes splicing defects gives an improved mutation detection rate. *Atherosclerosis* 2005;**182**:331-40.
4. Laing SP, Swerdlow AJ, Slater SD *et al.* The British Diabetic Association Cohort Study, I: all-cause mortality in patients with insulin-treated diabetes mellitus. *Diabet Med* 1999;**16**:459-65.
5. Tunstall-Pedoe H, Woodward M, Tavendale R *et al*. Comparison of the prediction by 27 different factors of coronary artery disease and death in men and women of the Scottish heart health study: cohort study. *BMJ* 1997;**313**:722-9.
6. Goldstein JL, Brown MS. Familial hypercholesterolaemia: identification of a defect in the regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity associated with overproduction of cholesterol. *Proc Nat Acad Sci USA* 1973;**70**:2804-08.
7. Tybjaerg-Hansen A, Humphries SE. Familial defective apolipoprotein B-100: a single mutation that causes hypercholesterolaemia and premature coronary artery disease. *Atherosclerosis* 1992;**96**:91-107.
8. Kachadurian AK. The inheritance of essential familial hypercholesterolemia. *Am J Med* 1964;**37**:402-07.
9. Gagne C, Bays HE, Weiss SR *et al*. Ezetimibe Study Group. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002;**90**: 1084-91.
10. Thompson GR, Miller JP, Breslow JL. Improved survival of patients with homozygous familial hypercholesterolaemia treated with plasma exchange. *BMJ* 1985;**295**:1671-3.
11. Bilheimer DW, Goldstein JW, Grundy S *et al.* Liver transplantation to provide low-density lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia. *N Engl J Med* 1984;**311**:1658-62.
12. Grossman M, Raper SE, Kozarsky K *et al.* Successful *ex vivo* gene therapy directed to liver in a patient with familial hypercholesterolaemia. *Nature Genet* 1994;**6**:335-41.
13. Christensen B, Glueck C, Kwiterovich P *et al.* Plasma cholesterol and triglyceride distributions in 13,665 children and adolescents: the prevlence study of the Lipd Research Clinics Program. *Pediat Res*

1980;**14**:194-202.
14. Ward AJ, O'Kane M, Nicholls DP *et al.* A novel single base deletion in the LDLR gene (211delG): effect on serum lipid profiles and the influence of other genetic polymorphisms in the ACE, ApoE and ApoB gene. *Atherosclerosis* 1996;**120**:83-91.
15. Marteau T, Senior V, Humphries SE *et al.* Psychological impact of genetic testing for familial hypercholesterolemia within a previously aware population: a randomized controlled trial. *Am J Med Genet* 2004;**128A**:285-93.
16. Sorensen KE, Celemajer DS, Georgakopoulos D *et al.* Impairment of endothelium-dependent dilation is an early event in children with familial hypercholesterolemia and is related to the Lipoprotein (a) level. *J Clin Invest* 1994;**93**:50-5.
17. De Jongh S, Lilien MR, Op't Roodt J *et al.* Early statin therapy restores endothelial function in children with familial hypercholesterolaemia. *J Am Coll Cardiol* 2002;**40**:2117-21.
18. Wiegman A, de Groot E, Hutten BA *et al*. Arterial intima-media thickness in childhood. A study in familial hypercholesterolaemia heterozgotes and their siblings. *Lancet* 2004;**363**:369-70.
19. Greene O, Durrington P. Clinical management of children and young adults with heterozygous familial hypercholesterolaemia in the UK. *J Roy Soc Med* 2004;**97**:226-9.
20. Neil HAW, Seagroatt V, Betteridge DJ *et al.* Established and emerging coronary risk factors in patients with heterozygous familial hypercholesterolaemia. *Heart* 2004;**90**:1431-7.
21. Maron BJ, Shirani J, Poliac LC *et al.* Sudden death in young competitive athletes. Clinical, demographic and pathological profiles. *JAMA* 1996;**276**:199-204.
22. Knipscheer HC, Boelen CC, Kastelein JJ *et al.* Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. *Pediatr Res* 1996;**39**:867-71.
23. Lambert M, Lupien PJ, Gagne C *et al.* Canadian Lovastatin in Children Study Group. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. *Pediatrics* 1996;**97**:619-28.
24. Stein EA, Illingworth DR, Kwiterovich PO Jr *et al.* Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999;**281**:137-44.
25. de Jongh S, Ose L, Szamosi T *et al.* Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. *Circulation* 2002;**106**:2231-7.
26. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidaemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 2003;**143**:74-80.

References: 1. Farber HW, et al. The New England Journal of Medicine; 2004; 351: 1655-65 2. Tracleer® SmPC – January 2006