

Familial hypercholesterolaemia: a look back, a look ahead

We still have no national program for detecting this potentially lethal disorder

In 1985, Brown and Goldstein were awarded the Nobel Prize in Physiology and Medicine for unravelling the regulation of cholesterol metabolism in man. A key feature of their work was the elucidation of the molecular mechanism for autosomal dominant familial hypercholesterolaemia (FH), a potentially lethal disorder caused by defective endocytosis of low-density lipoprotein (LDL) cholesterol by its receptor (LDLR).¹ This, in turn, led to the development of “statin” drugs, which potently lower plasma LDL cholesterol and reduce coronary heart disease (CHD) mortality. But, 20 years later, what have we achieved in detecting and treating FH?

FH is characterised by lifelong marked hypercholesterolaemia (LDL cholesterol >5 mmol/L) that leads to tissue cholesterol deposition — in such forms as tendinous xanthomata (particularly involving the Achilles), corneal arcus and palpebral xanthomas — and greatly increased risk of fatal CHD.² Unfortunately, most people with FH are at present undiagnosed or only diagnosed after their first coronary event. We estimate that, of the roughly 40 000 cases of FH in Australia, about 20% are diagnosed and less than 10% are being adequately treated.

Atherosclerosis in FH begins in early childhood. Children with FH are known to have endothelial dysfunction (the earliest phase of atherosclerosis) and increased carotid intima media thickness (CIMT), both surrogate markers of cardiovascular disease.^{3,4} Carotid atherosclerosis in FH rapidly progresses during childhood, at a rate proportional to plasma LDL cholesterol levels.⁴

FH typically involves mutations in the *LDLR* gene, with homozygotes having a more severe phenotype than heterozygotes. To date, about 1000 mutations have been identified in the *LDLR* gene (www.ucl.ac.uk/fh), most being unique, which makes the search for an unknown mutation challenging and expensive. Although heterozygous FH affects about 1 in 500 people overall,² it occurs much more frequently in some populations such as Afrikaners, Christian Lebanese and French Canadians² because of “founder” effects that occur when a few members of a population migrate and start a new colony.

FH can be caused by mutations in genes other than *LDLR*. A mutation in the apolipoprotein B gene (*APOB*) may result in a clinical and biochemical picture that is indistinguishable from classic FH, although cholesterol levels are generally not as elevated and tendon xanthomas are less common.⁵ An autosomal recessive form of FH has also been described.⁶ The clinical picture of this condition is similar to that of homozygous FH, although it is generally less severe and more variable, with greater responsiveness to therapy. Except in “founder” populations, homozygosity for any of these conditions is exceedingly rare (about 1/1 000 000 people), and, without special intervention, such as LDL aphaeresis and liver transplantation, is typically lethal at an early age.

Early statin treatment in children with FH improves endothelial function.³ A recent 2-year randomised controlled trial of pravastatin treatment (40 mg daily) in 214 children aged 8–18 years with FH showed regression of carotid atherosclerosis with no adverse effects on growth, sexual maturation, hormone concentrations, or serum liver and muscle enzyme levels.⁷ Despite this, the long-term safety and efficacy of statin use in children with FH is yet to be established.

The Atorvastatin versus Simvastatin on Atherosclerosis Progression trial compared the effect of “aggressive” lipid-lowering treatment in FH with “conventional” lipid-lowering therapy.⁸ Over 2 years, LDL cholesterol lowering by high-dose atorvastatin resulted in regression of CIMT, whereas reduction with conventional-dose simvastatin did not. Moreover, the change in CIMT was proportional to the reduction in LDL cholesterol. These results support the concept that intensive lowering of LDL cholesterol levels in patients with CHD is beneficial.

Although heterozygous FH patients are responsive to statins, additional treatment in combination with statins (for example, statin plus cholestyramine) is often required to achieve the desired LDL-cholesterol-lowering target.⁹ Moreover, combination therapy often permits use of a lower statin dose, which can benefit patients in whom adverse effects have occurred. Ezetimibe, a new drug that specifically inhibits intestinal cholesterol absorption alone, can reduce plasma LDL cholesterol concentrations by about 18%. Used in combination with a statin, it can achieve a further 25% reduction in LDL cholesterol levels over statin alone, by reducing both cholesterol supply to the liver and cholesterol biosynthesis.¹⁰ The long-term effects of ezetimibe on FH cardiovascular morbidity and mortality are unknown.

The most cost-effective strategy for finding subjects with FH is to screen close relatives of patients already diagnosed with FH. Screening involves measurement of plasma LDL cholesterol, combined with either a clinical examination and family history or molecular genetic testing.¹¹ Children born to an affected parent have a one in two risk of inheriting FH, and should be screened, at least biochemically, after the age of 2–3 years, when a cholesterol-lowering diet can be safely implemented.¹² It is important to appreciate that a normal lipid profile does not rule out heterozygosity for an FH-causing mutation, particularly in early childhood.¹³ International experience shows that a family screening program must incorporate ethically acceptable protocols for approaching and interacting with relatives, follow-up communication with family members and their health care practitioners, as well as access to genetic counselling services, if required.

Despite all these advances, it remains a tragedy that after 20 years of burgeoning knowledge about FH and the parallel development of powerful cholesterol-lowering drugs, Australia does not have a national program for detecting the vast majority of patients with FH in our community, let alone diminishing their risk of CHD.

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EDITORIALS

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- 1 Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science* 1986; 232: 34-47.
- 2 Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest* 2003; 111: 1795-1803.
- 3 de Jongh S, Lilien MR, op't Roodt J, et al. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol* 2002; 40: 2117-2121.
- 4 Wiegman A, de Groot E, Hutten BA, et al. Arterial intima-medial thickness in children heterozygous for familial hypercholesterolaemia. *Lancet* 2004; 263: 369-370.
- 5 Whitfield AJ, Barrett PHR, van Bockxmeer FM, Burnett JR. Lipid disorders and mutations in the *APOB* gene. *Clin Chem* 2004; 50: 1725-1732.
- 6 Garcia CK, Wilund K, Arca M, et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science* 2001; 292: 1394-1398.
- 7 Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia. A randomized controlled trial. *JAMA* 2004; 292: 331-337.
- 8 Smilde TJ, van Wissen S, Wollersheim H, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised double blind trial. *Lancet* 2001; 357: 577-581.
- 9 Kane JP, Malloy MJ, Ports TA, et al. Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. *JAMA* 1990; 264: 3007-3012.
- 10 Davidson MH, Toth PP. Combination therapy in the management of complex dyslipidemias. *Curr Opin Lipidol* 2004; 15: 423-431.
- 11 Marks D, Wonderling D, Thorogood M, et al. A cost effectiveness analysis of different approaches to screening for familial hypercholesterolaemia. *BMJ* 2002; 324: 1303-1306.
- 12 Civeira F, on behalf of the International Panel on Management of Familial Hypercholesterolemia. Guidelines for the diagnosis and management of heterozygous hypercholesterolemia. *Atherosclerosis* 2004; 173: 55-68.
- 13 Thorsson B, Sigurdsson G, Gudnason V. Systematic family screening for familial hypercholesterolemia in Iceland. *Arterioscler Thromb Vasc Biol* 2003; 23: 335-338. □