HEART

Editorial

Lipid lowering in the young

Hyperlipidaemia of sufficient severity to cause symptoms and signs in childhood is a rare occurrence. The "commonest" rare cause is homozygous familial hypercholesterolaemia (FH), with a frequency of one in a million, which gives rise to cutaneous and tendon xanthomas, corneal arcus, and atherosclerotic involvement of the aorta and coronary arteries by the age of 15.[1] Equally rare are children with inherited deficiency of lipoprotein lipase (type I hyperlipidaemia) who present with attacks of acute pancreatitis and severe hypertriglyceridaemia, sometimes accompanied by eruptive xanthomas. Rarer still are those manifesting mixed hyperlipidaemia and palmar striae (type III hyperlipidaemia), the expression of which in childhood indicates an underlying dominant mutation of the apolipoprotein E gene.[2]

The most commonly recognised and best understood cause of inherited hyperlipidaemia in childhood is heterozygous FH, which has a prevalence of 0·2% in most populations. This is usually asymptomatic until adult life and pathognomonic tendon xanthomas develop in very few cases before the age of 19.[3] However, there is a steep increase in both the prevalence of tendon xanthomas and the incidence of fatal coronary heart disease (CHD) between the ages of 20 and 39.[4] It seems reasonable to speculate that lipid-lowering treatment during adolescence would reduce this risk.

Association between dyslipidaemia and atherosclerosis in youth

There is convincing pathological evidence that atherosclerosis starts by the age of 6 and is commonly associated with abnormalities of serum lipids, albeit less marked than those which occur in FH. In both the PDAY[5 6] and Bogalusa[7] studies about a fifth of children and young adults dying suddenly from non-cardiac causes showed evidence of coronary and aortic atherosclerosis, especially the latter. The severity of lesions was more marked in males and in those who were smokers. Fatty streaks were the commonest finding but raised lesions occurred in the abdominal aorta and right coronary artery in a minority of those aged 15–19.[6] The presence and extent of lesions was positively correlated with serum concentrations of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) cholesterol and was negatively correlated with high density lipoprotein (HDL) cholesterol. Non-genetic determinants of serum lipids in childhood and adolescence are similar to those seen in adults including age, dietary intake of saturated fat, and use of oral contraceptives.[8] The need to detect and modify risk factors in early life if adult CHD is to be prevented seems obvious, including widespread education in healthy eating habits and avoidance of smoking. Specific dietary recommendations by the National Cholesterol Education Program (NCEP) in the USA were that all children and adolescents over the age of two should limit their intake of total and saturated fat to not more than 30% and 10% respectively of total calories and dietary cholesterol to less than 300 mg/day.[9]

Screening for cardiovascular risk during childhood

Studies of 63 families where the father had developed CHD by the age of 50 showed increased concentrations of triglyceride or LDL cholesterol and/or decreased concentrations of HDL cholesterol in 65% of affected fathers and 51% of their children.[10] Similar results were obtained in a study of over 800 adolescents in whom serum cholesterol, triglyceride, and apolipoprotein B concentrations were higher in boys with a family history of death from myocardial infarction before the age of 55 and in girls with a paternal history of a cerebrovascular accident.[8]

These findings suggest that early detection of children at increased risk of developing CHD in adult life on account of inherited or acquired familial traits is feasible by selective screening, as promulgated by the NCEP.[9] Specific recommendations were to measure serum cholesterol in all children whose parents or grandparents developed evidence of CHD before the age of 55, or where one of the parents has a serum cholesterol of ⩾ 6·2 mmol/l. Those children found to have a total cholesterol of ⩾ 5·2 mmol/l should go on to have a fasting lipid profile measured (total and HDL cholesterol and triglyceride), which enables LDL cholesterol to be calculated.

A selective approach to the prevention of CHD was also proposed by Porkka and Viikari,[11] although neither they nor the NCEP advocated general screening. However, even selective screening of children with a family history of CHD or hypercholesterolaemia was opposed by Hulley and Newman[12] on the grounds that it would do more harm than good. This nihilistic attitude would exclude screening even the children of parents with FH, in whom there is a 1 in 2 chance of a positive result, and is impossible to justify in families where one of the parents has died prematurely from CHD.

Treatment of hyperlipidaemia in childhood

NCEP guidelines for the treatment of children with a family history of hypercholesterolaemia or premature CHD are based on total and LDL cholesterol concentrations and the presence or absence of additional risk factors. The borderline category of risk encompasses children with total and LDL cholesterol concentrations of 4·4–5·1 and 2·8–3·3 mmol/l respectively and is treated with a Step One diet—that is, not more than 30% of calories from fat, with

Table 1 Classification of risk category for children and adolescents with familial hypercholesterolaemia[13]

Risk	Cholesterol (mmol/l)	Sex of child	Family history of CHD*
Low	5·3–6·9	M	No
		F	Only in M
	7·0–9·9	F	No
Moderate	5·3–6·9	M	Yes
		F	In F
	7·0–9·9	M	No
	≥ 10	F	No
High	≥ 10	M	No
	≥ 7	M and F	Yes

*Early CHD in a family with FH is defined as CHD occurring before age 40 in men and before age 50 in women. Reprinted with permission from Ose L, Tonstad S. The detection and management of dyslipidaemia in children and adolescents. *Acta Paediatr* 1995; 84: 1213–5.

< 10% from saturated fat, and cholesterol intake < 300 mg/day. High risk is defined as children with total and LDL cholesterol values of ≥ 5·2 and ≥ 3·4 mmol/l respectively and is treated with either a Step 1 or, if necessary, a Step 2 diet—that is, calories from saturated fat < 7% and cholesterol intake < 200 mg/day. A third category includes children whose LDL cholesterol remains high despite diet and is stratified into those with a concentration ≥ 4·9 mmol/l but no other risk factors, and those with a concentration of ≥ 4·1 mmol/l plus a family history of cardiovascular disease before the age of 55 or the presence of other risk factors. The use of anion exchange resins, the NCEP proposed, should be considered in children aged 10 or over who are in the third or High Despite Diet category of risk.[9]

Some European paediatricians and lipidologists would regard the NCEP guidelines on screening and treatment as over zealous. For example, Ose and Tonstad[13] recommend screening only those families where one of the parents has FH. As regards treatment all agree that the initial emphasis should be on diet, but in children with FH this is often insufficient to bring down LDL to a desirable concentration. Ose and Tonstad[13] have proposed that such children should be categorised as being at low, moderate, or high risk according to the severity of hypercholesterolaemia, gender, and whether there is a family history of very premature CHD (table 1). Depending upon which category they are in and their age, children who are insufficiently responsive to diet are then treated with either an anion exchange resin or a statin (table 2).

The efficacy and safety of a Step 2-like diet were recently assessed in a randomised trial of over 600 children aged 8–10 who were studied for 3 years.[14] Those on this diet achieved a significantly greater reduction in LDL cholesterol than the controls and showed no evidence of any nutritional insufficiency. Anion exchange resins are poorly tolerated but, being unabsorbable, have a good

safety record. An alternative drug available in Britain is fenofibrate, which is licensed for use in children. The use of statins in children remains sub judice at present but preliminary reports suggest that this approach will eventually prove to be both effective and safe.[15][16] Finally, in the few children with homozygous FH, long-term LDL apheresis or liver transplantation are the treatments of choice,[17] whereas plasma exchange is a highly effective means of rapidly controlling severe hypertriglyceridaemia in type I patients with incipient acute pancreatitis.

GILBERT R THOMPSON
*MRC Lipoprotein Team, Clinical Sciences Centre,
Royal Postgraduate Medical School, Hammersmith Hospital,
Du Cane Road, London W12 ONN*

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Table 2 Drug treatment for children and adolescents with familial hypercholesterolaemia in relation to defined risk for later coronary heart disease[13]

	Age (y)				
	7–11	12–14	15–18		
Boys			Resin → Statin		Low risk
		Resin →	Statin		Moderate risk
	Resin →		Statin →		High risk
Girls			Resin →		Low risk
			Resin →		Moderate risk
		Resin →	Statin →		High risk

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patients reported by Groves *et al.* They show, in any case, remarkable similarities in relation to the location of the block within the atrioventricular node. They all had a wide QRS which suggests a distal block within the bundle of His. Groves *et al* performed a pathological examination of the hearts of their patients and demonstrated a distal lesion of the bundle of His of the type of nodoventricular block instead of atrioventricular block.[2] This is in accordance with the pathological findings of Ho *et al*,[3] and with the clinical data presented by Frohn-Mulder *et al*[4] who noted that the QRS width was wider in a group of anti-Ro negative patients compared with a group of anti-Ro positive children.

Pathogenic mechanism of isolated congenital heart block has been related to immune mechanisms mediated by anti-Ro or anti-La antibodies. Immune mediated damage is usually located proximal to the bundle of His. Damage of the conduction system in anti-Ro negative patients seems to be located distal to the bundle of His. This may explain a lower ventricular rate which could explain the poor outcome of Groves *et al*'s patients. Further serological and familial studies of anti-Ro negative patients may give insight into the mechanism of the disease.

LUIS G GUERETA
M BURGUEROS
F MORENO
*Cardiologia Infantil, Hospital La Paz,
Madrid, Spain*

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CORRECTION

Impact of the 1991 NHS reforms on the availability and use of coronary revascularisation in the UK (1987–1995)
Black N, Langham S, Coshall C, Parker J. Heart 1996;76(suppl 4):1–31.

Data on the availability of whole-time equivalent (WTE) adult cardiac surgeons in Glasgow in 1994–95 was incorrect. There were 5·9 (not 10·9) WTE representing 3·38 (not 6·25) WTE per million population aged over 24 years (Appendix 1, page 25; fig 10, page 8). The comments on page 9 should read:

Consultant levels more than doubled in East Anglian, though the increase in South East Thames was only 27%, in Greater Glasgow only 22% and there was no increase in North Western (fig 10).

Similarly, the fifth statement on page 22 under *Objective 1* should read:

The availability of consultant surgeons showed little or no change between 1987 and 1995 in three regions but more than doubled in East Anglian.

NICK BLACK
*Professor of Health Services Research,
London School of Hygiene & Tropical Medicine,
University of London,
London WC1E 7HT, UK*

NOTICES

The First European Workshop on Hypertrophic Obstructive Cardiomyopathy under the auspices of the Working Groups on Myocardial Function and Cardiomyopathy of the European Society of Cardiology will take place on 31 October 1997 at the Imperial College School of Medicine, London, UK. Course fee (includes coffee, tea, lunch, and live teleconference) is £125. For further information please contact The Conference Centre (tel: 0171 351 8172; fax: 0171 376 3442; email a.c.allen@ac.ic.uk).

Practical Adult Cardiovascular Pathology Course will take place on 17 November 1997 at the National Heart and Lung Institute, London, UK. Course fee (includes coffee, tea, and lunch) is £125; £100 for juniors in training. For further information please contact National Heart and Lung Institute (tel: 0171 351 8172; fax: 0171 376 3442).