

Screening for hyperlipidaemia in childhood

RECOMMENDATIONS OF THE BRITISH HYPERLIPIDAEMIA ASSOCIATION

ABSTRACT—Children with familial hypercholesterolaemia are at high risk of developing coronary artery disease in early adulthood. The diagnosis should therefore be made in childhood. Population screening identifies a small number of children with major genetically determined disorders of lipid metabolism and a large number with polygenic hypercholesterolaemia of uncertain prognostic significance. Selective screening based on a family history of familial hypercholesterolaemia or premature coronary artery disease is an appropriate strategy for identifying most children with familial hypercholesterolaemia. A non-fasting total cholesterol measurement is a suitable screening test: if the concentration exceeds 5.5 mmol/l, a fasting measurement of total cholesterol, high-density lipoprotein cholesterol and triglyceride is required. The diagnosis in a child under 16 years should be based on finding a total cholesterol concentration greater than 6.7 mmol/l and a low-density lipoprotein cholesterol concentration above 4.0 mmol/l on at least two measurements taken more than one month apart. Children should not usually be screened before the age of two years, but the aim should be to diagnose heterozygous familial hypercholesterolaemia before the age of 10 years. Affected children should be referred for specialist care.

Hypercholesterolaemia in childhood is common in westernised countries with high rates of coronary heart disease [1]. The indications for lowering cholesterol in childhood are less well defined than in adults, and there are differences between the recommendations for screening by the US National Cholesterol Education Program Expert Panel on Blood Cholesterol Levels in Children and Adolescents [2] and usual practice in the UK. In the UK, selective testing in childhood is used principally to identify major inherited disorders of lipoprotein metabolism, in particular familial hypercholesterolaemia, while the US

recommendations favour a more comprehensive screening policy. This article presents the recommendations of the British Hyperlipidaemia Association and briefly reviews the evidence on which they are based.

Rationale for identifying hyperlipidaemia in childhood

Homozygous familial hypercholesterolaemia is a monogenic autosomal dominant condition in which plasma cholesterol levels are markedly increased due to the accumulation of low-density lipoprotein (LDL) particles resulting from defective LDL receptor function [3]. About one child in a million in the UK is affected, and clinically manifest coronary artery disease (CAD) almost invariably develops in childhood. The rationale for identifying other causes of hyperlipidaemia in childhood is that some affected children are also at increased risk of developing CAD in early adulthood. Autopsy studies of young men killed in war have demonstrated that atherosclerotic lesions can be present at an early age [4], and a recent study reported that 7% of children aged 10–15 years had raised and potentially progressive coronary artery lesions [5]. Moreover, studies of flow-related endothelium-dependent reactive hyperaemia (a non-invasive surrogate marker for endothelial dysfunction) have demonstrated abnormalities in children with heterozygous familial hypercholesterolaemia as young as 10 years old [6].

Account should be taken, however, both of the uncertainty concerning the pathophysiology of atherogenesis in childhood [7] and of the imprecision of prediction of CAD risk. For patients with heterozygous familial hypercholesterolaemia, which has a gene frequency of about one in 500 [3], the risk of developing clinically manifest CAD in childhood is low but, without treatment, the cumulative incidence of myocardial infarction by the age of 50 years is about 50% in men and 10% in women [8,9]. By contrast, the long-term outlook is unclear for the estimated 1% of children with familial combined hyperlipidaemia and the much larger number with polygenic hypercholesterolaemia. This uncertainty is partly explained by the imperfect tracking of serum cholesterol concentrations (the relative stability between subsequent measurements). From birth to two years, tracking is inconsistent; medium-term tracking from early childhood to late adolescence may be better but the estimates vary in different studies ranging from a 12-year tracking

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coefficient of about 0.7 [10], indicating a reasonably good predictive value, to only 0.48–0.58 in a recent much larger study of 3,596 healthy subjects [11].

Screening strategies in childhood

Population screening identifies a large number of children with polygenic hypercholesterolaemia and a small number with major genetically determined disorders. This poses problems because the prognosis of children with polygenic hypercholesterolaemia is uncertain. Although an elevated total cholesterol level in childhood is a risk factor for an elevated level in adulthood, moderately elevated cholesterol levels are not a good predictor of individual risk of CAD in adulthood [12] unless other cardiovascular risk factors are also present [13]. Furthermore, no longitudinal studies have determined the effect of lipid-lowering therapy during childhood on the development and progression of coronary atherosclerosis. In addition, labelling a child as being at increased risk of CAD may sometimes have harmful effects on both the child and the family [14,15].

By contrast, selective screening aims to identify patients who may benefit from early treatment: those with marked elevation of serum cholesterol due to major inherited disorders of lipoprotein metabolism, in particular familial hypercholesterolaemia. Most patients identified in childhood by selective screening based on a positive family history of either premature CAD or hypercholesterolaemia will require dietary therapy, but drug therapy will often be necessary later in adolescence and adulthood [16]. Selective screening will miss an estimated 12% of children with familial hypercholesterolaemia [17], although this may be an overestimate since in this study cases were referred from primary care physicians and were not a representative sample. Selective screening would be likely to miss children with heterozygous familial hypercholesterolaemia with LDL receptor mutations not sufficiently penetrant to produce marked hypercholesterolaemia. These children would be unlikely to develop significant CAD in the first three decades of life, and there is now clear evidence that, even if diet and drug therapy are not initiated until middle age, progression of coronary atheroma can be slowed or even reversed and morbidity and mortality reduced [18].

Interpretation of serum lipid levels in childhood and adolescence

Age- and sex-related population data are available for lipid and lipoprotein levels in childhood and adolescence [19], although there are few published data for the UK except in adults. The mean concentration of total cholesterol in cord blood is about 1.7–2.0 mmol/l, rising in the first year of life to a

mean of 4.1 mmol/l (95th centile 5.2 mmol/l) which persists until the early teens. Levels are similar in boys and girls until adolescence when they both fall slightly; thereafter they are higher in boys, but increase by about 0.5 mmol/l in both sexes by the mid-20s.

The 95th percentile for the mean serum cholesterol concentration varies little in childhood and adolescence [19] despite its fluctuations with age. The relative constancy of the upper centiles for serum cholesterol concentrations allows a diagnostic threshold for childhood familial hypercholesterolaemia to be defined, and explains why a total serum cholesterol concentration above 6.7 mmol/l correctly identifies 95% of heterozygotes and misclassifies as false positives only 2.5% of the affected children [20]. To meet current diagnostic criteria used in studies such as that by the Simon Broome Register group [21], the LDL cholesterol concentration should also exceed 4.0 mmol/l in a child under 16 years. Interpretation of these measurements is not usually a problem because most children with heterozygous familial hypercholesterolaemia will have total cholesterol concentrations considerably higher than 6.7 mmol/l. Uncertainty may, however, occur with concentrations in the range of 5.5–7 mmol/l, particularly if the family is already on a cholesterol-lowering diet. The diagnosis cannot then be made or excluded with complete confidence, and repeated measurements over time are required.

Hypertriglyceridaemia in childhood may be defined on the basis of the 95th percentile, which corresponds to a fasting triglyceride concentration of 1.15 mmol/l in the first decade of life and 1.5 mmol/l in the second decade [19]. Although the prevalence of familial combined hyperlipidaemia has been estimated to be three times higher than that of familial hypercholesterolaemia [22], its inheritance pattern does not follow simple Mendelian rules and may be polygenic in aetiology. The phenotype is usually not expressed until adulthood, and even then the diagnosis can be a problem. There is therefore a risk of being falsely reassured by normal levels measured in childhood, and screening for this condition is not indicated at present.

The rare inherited chylomicronaemia syndrome may present in childhood with a constellation of symptoms, including pancreatitis and triglyceride concentrations usually in excess of 20 mmol/l [23]. The siblings of affected children should be screened.

Target groups for selective screening

Children at highest risk of developing premature CAD are those with familial hypercholesterolaemia. Those most likely to have inherited the gene can usually be identified by a family history of hypercholesterolaemia or CAD (but not peripheral vascular disease which is not associated specifically with familial hypercholesterolaemia [24]). Two groups of patients should be screened:

Children with a relative with familial hypercholesterolaemia

The principal indication for screening is a diagnosis of familial hypercholesterolaemia in a first- or second-degree relative. By definition, it is an autosomal dominant condition, so 50% of children of index cases will be affected. Family tracing is therefore the most efficient form of selective screening. The diagnosis should be based on at least two measurements taken more than a month apart to avoid potential misclassification due to biological and analytical variation. If there is diagnostic uncertainty, with a total cholesterol concentration in the range 5.5–7 mmol/l, repeated measurements over time should be obtained.

Children with a family history of premature onset coronary disease

A family history of premature onset coronary disease (angina or myocardial infarction) in first- or second-degree relatives is also a clear indication for screening. The age cut-off chosen to define this is to some extent arbitrary. The occurrence of CAD in men before 50 years and in women before 55 years [25] is more specific but less sensitive than the corresponding recommendation of 55 years and 60 years respectively [21]. Using the former criteria, familial hypercholesterolaemia was diagnosed in 6% of 200 children screened in a pilot study [25].

Appropriate age for screening in childhood

The age at which testing to identify heterozygote patients is undertaken must take account of the wishes of the parents and the age of onset of CAD in the index family. Even within a monogenic autosomal dominant condition such as heterozygous familial hypercholesterolaemia there is heterogeneity in the age of onset of clinically significant CAD, with much greater concordance *within* than *between* families [26]. A strong argument can therefore be made for screening at a commensurately younger age children of families with a particularly early onset of CAD.

The diagnosis will not influence management unless the child is two years or older, when dietary modification becomes practicable. An earlier diagnosis may be important to allay parental anxiety if an affected parent has already developed CAD. Testing may be delayed if the whole family is already adhering to an appropriate diet, but ought to be undertaken before the age of 10 years because drug therapy may be indicated in older children in some circumstances [2]. However, it should be recognised that there is evidence that an earlier diagnosis is associated with better long-term compliance [27]. In exceptional circumstances, neonatal screening by measurement of cord blood may be needed to exclude homozygous familial hypercholesterolaemia. This will not, however, reliably exclude the heterozygous form; the LDL concentration is relatively

low in cord blood, so variations in high-density lipoprotein (HDL) cholesterol have more impact on total cholesterol concentration [28].

Laboratory measurements

An initial random total cholesterol measurement may be made using a capillary or venous sample. If the concentration is above 5.5 mmol/l, a fasting venous blood sample should be assayed for concentration of total and HDL cholesterol and triglyceride. The LDL cholesterol can then be calculated using the Friedewald equation [29]:

$$\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \frac{\text{triglycerides}}{2.19 \text{ mmol/l}}$$

Measurement of HDL cholesterol in children, as in adulthood, avoids the misclassification of 5–15% of children with normal LDL and increased HDL cholesterol concentrations who would otherwise be labelled as hypercholesterolaemic [30,31]. Apolipoprotein measurement offers some theoretical advantage in determining CAD risk, but routine clinical measurement cannot yet be recommended [32]. Similarly, it is not clear whether there is any clinical advantage in measuring the lipoprotein Lp(a) in childhood [32].

Genetic screening based on DNA tests for mutations causing familial hypercholesterolaemia remains a research procedure. It offers theoretical clinical advantages because there is some overlap in serum cholesterol concentrations between familial hypercholesterolaemia heterozygotes and the general population. However, putative LDL receptor mutations not sufficiently penetrant to produce marked hypercholesterolaemia may not result in premature CAD. Knowledge that a child has such a mutation would not be of practical significance and might have potential harmful effects for both the child and the family [14,15]. To date, more than 150 different LDL receptor mutations have been identified [33]; methods for more rapid mutation screening will have to be developed before this can become a routine diagnostic procedure.

SUMMARY OF RECOMMENDATIONS

- 1 The principal aim of screening should be to identify children with familial hypercholesterolaemia.
- 2 A selective screening strategy should be used.
- 3 Selection should be based on a family history of familial hypercholesterolaemia or premature coronary disease.
- 4 A non-fasting total cholesterol measurement is a suitable screening test.
- 5 If the cholesterol concentration is above 5.5 mmol/l, fasting measurement of total cholesterol, HDL cholesterol and triglycerides is required.

- 6 The diagnosis of familial hypercholesterolaemia in a child under 16 years should be based on finding a total cholesterol concentration above 6.7 mmol/l and an LDL cholesterol concentration above 4.0 mmol/l, and requires at least two measurements to be made more than one month apart.
- 7 Children should not usually be screened before the age of two years, but the aim should be to diagnose heterozygous familial hypercholesterolaemia before the age of 10 years.
- 8 Affected children should be referred for specialist care.

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