Familial hypercholesterolaemia: Pilot study to identify children at risk


Abstract

Aims—To evaluate a more effective method of identifying children with familial hypercholesterolaemia by screening a population at high risk.

Methods—Domiciliary measurement of random cholesterol concentration was made in 200 children who were first or second degree relatives of subjects with premature onset coronary artery disease. Measurements were taken by a health visitor using a portable analyser.

Results—Twelve new cases of familial hypercholesterolaemia were identified during the first nine months of the study. Random cholesterol concentrations were within the normal range (<5-2 mmol/l) in 70-5% of samples tested. Forty two (21%) of patients tested had a borderline cholesterol (5-2-5-9 mmol/l) but 50% of these fell within the normal range when fasting capillary samples were analysed. Children with significant hypercholesterolaemia on random testing (concentrations of >5-9 mmol/l) (8-5%) also had fasting venous blood assayed for high density lipoprotein (HDL) cholesterol and tri-glyceride in the laboratory. Results indicated that 6-5% of patients screened were at high risk of cardiovascular disease (ratio of total: HDL cholesterol of >4-5), and 1% had a moderately increased risk (ratio 3-5-4-5).

Conclusions—Children with familial hypercholesterolaemia can be identified from a selected “high risk” population by measuring random capillary cholesterol concentration.

(F J Clin Pathol 1993;46:730–733)

Familial hypercholesterolaemia is the commonest significant autosomal dominant disorder with a gene frequency of about 1 in 500. The condition causes accumulation of low density lipoprotein cholesterol in the plasma leading to premature atherosclerosis. An estimated 51% of male and 12% of female heterozygotes will sustain fatal or non-fatal coronary heart disease by the age of 50. There is good evidence that atheroma in these patients begins to form in early life, and because a reduction in cholesterol may be seen after treatment with a low fat diet, it seems prudent to screen for the condition and to introduce dietary modification as early as possible. Once someone in a family with familial hypercholesterolaemia has been identified, the case for screening these “at risk” families is strong because the likelihood of serious vascular disease is so high.

There are extensive published findings on various forms of screening for hypercholesterolaemia. Opinions differ as to whether a selective approach identifying families at “high risk” or a form of universal screening should be used. Screening initiatives have included neonatal screening, using cord blood, or by integration with screening for phenylketonuria and blood testing at school entry. DNA technology is of limited value in screening for familial hypercholesterolaemia but may be of use in differentiating those hypercholesterolaemic subjects who have defective apo-β-100.

All universal systems of screening by blood cholesterol determination have the disadvantage that the overlap between the upper range of normal and the disease range leads to a high false positive rate. It would, therefore, be more effective to attempt to identify children from families at high risk of familial hypercholesterolaemia. A programme based on screening individuals with premature atherosclerosis could identify most families at risk and allow the children and adolescents to be screened while reducing the likelihood of false positive results.

Calculations suggest there are at least 300 children in Sheffield with familial hypercholesterolaemia, yet at the inception of this study fewer than 10 cases were known to the paediatric services. Two of these families were referred to their general practitioners by the Coroner following the premature deaths of their fathers from coronary artery disease (Taitz LS, personal communication). An attempt was therefore made to identify and treat all children systematically within this population group by targeting such at risk families.

Methods

Individuals with premature atherosclerosis, defined as evidence of coronary artery disease (previous myocardial infarction or angina) in men under 50 years and women under 55 years were considered as index cases and their families approached by a health visitor through their general practitioners. A detailed family history was obtained and cases with hypercholesterolaemia associated with other conditions, such as renal disease, diabetes, and hypothyroidism, were excluded. Index
cases were identified from hospital and general practitioner records, review of patients admitted to coronary care units, scrutiny of death certificates and referrals from adult lipid clinics.

Family trees were drawn up through three generations and all individuals under 16 years of age were entered into the study protocol (fig 1). Random capillary blood samples were screened in the home for total cholesterol using a portable reflectance photometer (Lipotrend, Boehringer Corporation Ltd). Fasting capillary cholesterol and triglyceride concentrations were assayed enzymatically by Reflotron (Boehringer Corporation Ltd). The performance of these analyses was maintained and all borderline results checked in the laboratory using a centrifugal analyser (Cobas Bio, Roche Diagnostics Ltd). Interbatch analytical imprecision was assessed using commercially available quality assurance material on a weekly basis. The Lipotrend photometer showed a coefficient of variation (CV) of 4·2% at a concentration of 4·4 mmol/l; the Reflotron, a CV of 3·2% at a concentration of 4·0 mmol/l, and the Cobas Bio, a CV of 3·0% at a concentration of 2·8 mmol/l. The accuracy of the Reflotron was assessed by participation in a nationally organised external quality assurance scheme (Wolffson Research Laboratories extra laboratory assay survey); in all cases the returns were within 7% of the target value. The accuracy of the laboratory based analyser was monitored by participation in the national external quality assessment scheme for clinical chemistry. In all cases the returns were within 6% of their designated value. The non-laboratory methods showed good correlation with the laboratory based analyser: Lipotrend v Cobas Bio, CV r = 0·89; Reflotron v Cobas Bio CV r = 0·99.

Random cholesterol concentrations of <5·2 mmol/l were considered normal. Children with cholesterol concentrations of >5·2 mmol/l were asked to attend the Children's Hospital where a further fasting capillary sample was obtained. Confirmed cholesterol values between 5·2-5·9 mmol/l were considered outside the normal range but below that compatible with familial hypercholesterolaemia. All children in this group were seen, however, and dietary advice was given. Children with a random or fasting capillary cholesterol concentration of >5·9 mmol/l had fasting venous blood assayed for total and HDL cholesterol and triglyceride values, using a centrifugal analyser (Cobas Bio, Roche Diagnostics). LDL cholesterol was calculated from the Friedewald equation.20

Children were considered to be at high risk of familial hypercholesterolaemia if the following criteria were met: a history of early coronary artery disease in a first or second degree relative, fasting total cholesterol of >5·9 mmol/l, HDL cholesterol of <1·5 mmol/l, LDL cholesterol of >3·5 mmol/l, normal fasting triglyceride values (<2·3 mmol/l). The risk of developing ischaemic heart disease in children with confirmed hypercholesterolaemia was calculated from the ratio of total:HDL cholesterol.21

**Results**

A total of 200 children, mean age 9·6 years, range 3–16·5 years, were identified from 120 families. The flow diagram (fig 1) shows how the study population were divided according to cholesterol concentration. Random cholesterol concentrations obtained using the Lipotrend analyser are shown in fig 2. The mean random cholesterol for the whole study population was 4·7 mmol/l (range 2·9–10·7), with 70·5% of these values falling within the normal range (<5·2 mmol/l). A further fasting capillary sample was requested in the 42 (21%) of patients with an initial cholesterol between 5·2 and 5·9 mmol/l. This was analysed for cholesterol and triglyceride concentrations. No child showed an increase in cholesterol on repeat testing, but fasting cholesterol concentrations fell within the normal range (<5·2 mmol/l) in 50% of these repeat samples. Two children with a random cholesterol value of >5·2 mmol/l failed to attend

![Flow diagram of study protocol indicating percentage of patients falling into each diagnostic group.](http://jcp.bmj.com/)

*Two children with cholesterol concentrations of >5·2 mmol/l failed to attend for repeat sampling*
random cholesterol by age (n = 200)

Figure 2. Distribution of random cholesterol concentrations (mmol/l) by age at testing for entire study population. Borderline results fall within dotted lines; values of <5.2 are normal.

Association between total, HDL, LDL cholesterol, and triglyceride concentrations in 12 patients with familial hypercholesterolaemia

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<th>Triglyceride (mmol/l)</th>
<th>HDL cholesterol (mmol/l)</th>
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</tbody>
</table>

*Children under 2 years not sampled unless siblings of known patient.
†Previous total cholesterol >5-9 mmol/l.

Discussion

Although optimal strategies for identifying children with hypercholesterolaemia have not been established, the results of this pilot study indicate the value of domiciliary screening for familial hypercholesterolaemia in a selected population of children. Several authorities advocate testing of children with family histories of premature coronary artery disease.2228 The usefulness of measuring cholesterol, however, either alone or with triglyceride, as a predictor of coronary heart disease in the general population has been questioned.23 Nevertheless, the range of cholesterol concentrations observed in our study compares well with data from cross-sectional population screening (fig 4) despite random (non-fasting) sampling.

The measurement of HDL cholesterol in screening could avoid the misclassification of some children because of an unusually high or low LDL cholesterol concentration. Between 5-15% of children with normal LDL cholesterol concentrations have been identified as having hypercholesterolaemia because of increased HDL cholesterol concentrations.2425 Only two children with initial cholesterol concentrations of >5-9 mmol/l in this study had raised HDL values. Other workers have also reported little overlap with normal ranges for values above 6-8 mmol/l in close relatives of hypercholesterolaemic subjects.2627 The measurement of apoprotein B and lipoprotein (a) may also improve the detection of “high risk” cases,28 but data are limited and the analyses more complex.

The proportion of children with familial hypercholesterolaemia not identified from the low risk (ratio of <3-5). Twelve previously undiagnosed cases met the study criteria for familial hypercholesterolaemia; individual values for total, HDL, and LDL cholesterol are given in the table. Three children, who also had raised triglyceride concentrations, were felt likely to have familial combined hyperli-

diabetes and remain under review at the time of writing.

Figure 4. Comparison between study population and centile values for cholesterol concentrations in a “normal paediatric population”, derived from Kustererich PC, et al. Effect of dietary treatment on the plasma of lipids, lipoproteins cholesterol, and LDL B protein in children with type II hypercholesterolaemia. (Detection and Treatment of Lipid and Lipoprotein Disorders of Childhood. 1985:123–37 (Alan R Liss, Inc.).)
family history is unclear from this study. Stanc et al estimate that such selective testing may miss 12% of heterozygous children with familial hypercholesterolaemia29 yet their figures may overestimate the incidence compared with a normal population: data are derived from cases referred through primary care physicians. Few true cases of familial hypercholesterolaemia, however, are likely to be missed by screening for total cholesterol concentrations as random values may be expected to overestimate risk.

Hypercholesterolaemia can be treated by a combination of dietary30-32 and pharmacological methods,33 and both have been shown to lower the blood cholesterol concentration in children with familial hypercholesterolaemia.34 Concern exists, however, over the long term effects of dietary restriction in growing children,35 the difficulty in adhering to the diet, possible non-compliance with drug regimens36 and a reluctance to single out otherwise healthy children. The case for preventive treatment in childhood currently rests on anecdotal evidence and analogy with similar treatment provided over several decades. There is also no information on whether a hospital or community based programme would be the most effective method of provision. Until a properly controlled longitudinal study has been carried out to evaluate the various options these questions will not be resolved.

Patient identification is the first step in such a programme. Whole population screening yields a small return with an unacceptably high false positive rate, but the results of this study are sufficiently encouraging to warrant further investigation and assessment of at least some of these unknown factors before considering district-wide screening programmes of children "at risk".

We thank Drs TA Gray and ARW Forrest for their help and encouragement during this study.

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C J Taylor, S Olpin, J Rattenbury, A Whippey, C Lunt, N Beckles-Willson, J Higginbottom, R J Pollitt, J Bonham and L S Taitz

J Clin Pathol 1993 46: 730-733
doi: 10.1136/jcp.46.8.730

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