Hereditary dyslipidaemias and combined risk factors in children with a family history of premature coronary artery disease

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Abstract

***Aim*—Schoolchildren aged 10–11 with a family history of premature coronary artery disease (CAD), were examined in order to identify children with genetically determined dyslipidaemias and a combination of risk factors.**

***Methods*—A total of 4000 questionnaires were distributed by the school; 55% of the families answered and returned the questionnaire. Blood lipids, apolipoprotein B, and Lp(a) lipoprotein were analysed in high risk children and their parents.**

***Results*—A family history of premature CAD in parents or grandparents was identified in 208 families; 175 agreed to take part in a clinical examination and laboratory tests. Normal blood lipid tests were found in 89 children. Another 48 had an isolated increase of Lp(a) lipoprotein of minor clinical importance. Of the remaining 38 children, 23 had non-hereditary abnormalities of low (LDL) or high density lipoprotein (HDL) cholesterol or apolipoprotein B. Fifteen children were suspected to have genetically determined dyslipidaemias or a combination of risk factors: in four, possible familial hypercholesterolaemia (FH); in five, possible familial combined hyperlipidaemia; in three, hereditary low HDL cholesterol; and in three a combination of high LDL cholesterol and Lp(a) lipoprotein concentrations. In addition, possible FH was detected in eight of the parents.**

***Conclusion*—It is worthwhile asking parents about the occurrence of premature CAD among their child's closest relatives.**

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Serum lipoproteins are related to vascular atherosclerotic changes early in life and the extent of the lesions is dependent on serum lipoprotein concentrations determined before the fatal event.[1] If prevention of premature atherosclerosis should start as early as possible, a high risk strategy may be justified to identify children with hereditary lipid disorders and those with several coronary artery disease (CAD) risk factors.[2] During childhood and adolescence a low fat diet, optimal physical activity, and the avoidance of smoking may reduce the CAD risk.[3 4] We have developed a family therapeutic method that effectively promotes lifestyle changes required to prevent severe obesity.[5] Therefore we have a potentially safe and effective method of changing dietary habits and physical activity in children with a high risk of CAD, so the key issue was to identify children at greatest risk. A family history of heart disease is an important determinant of CAD risk with implications not only for the patient but also for other family members.[6] We decided to ask parents of 10–11 year olds whether they or the child's grandparents had suffered premature CAD. A previous study indicated that about 7% of 7 year olds had a family history of premature CAD, defined as CAD before age 50 years in the father or grandfathers and 55 years in the mother or grandmothers.[7]

We hypothesised that many children with genetically linked dyslipidaemias and with a combination of risk factors might be identified in 10–11 year old schoolchildren who had a family history of premature CAD in any parent or grandparent. The dyslipidaemia and risk factors were identified by analyses of low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein B, and Lp(a) lipoprotein.

Materials and methods

For two years, 10–11 year old schoolchildren and their families were invited to take part in voluntary screening of families with high risk CAD family history. Families were given written information about the purpose of the study and a questionnaire. The questions concerned the occurrence of CAD in the mother or female grandparents before 55 years of age or in the father or male grandparents before 50 years of age. About 4000 questionnaires were distributed and 2199 were answered and returned. A total of 208 families gave a family history of CAD, and 182 agreed to participate in the study. A blood sample was obtained from 175 of the children.

After an overnight fast, blood samples were collected from the high risk child and parent or parents. After centrifugation serum was separated and frozen at −20°C for later analysis.

Serum concentrations of total cholesterol (TC) and triglycerides (TG) were measured enzymatically, and HDL cholesterol (HDLC) after precipitation of very low density lipoproteins with dextran sulphate and magnesium chloride. The details and reliability of the methods have been described previously.[8]

Concentrations of apolipoprotein B in serum were assayed by electroimmunoassay, using calibration standards from Behringwerke.[8]

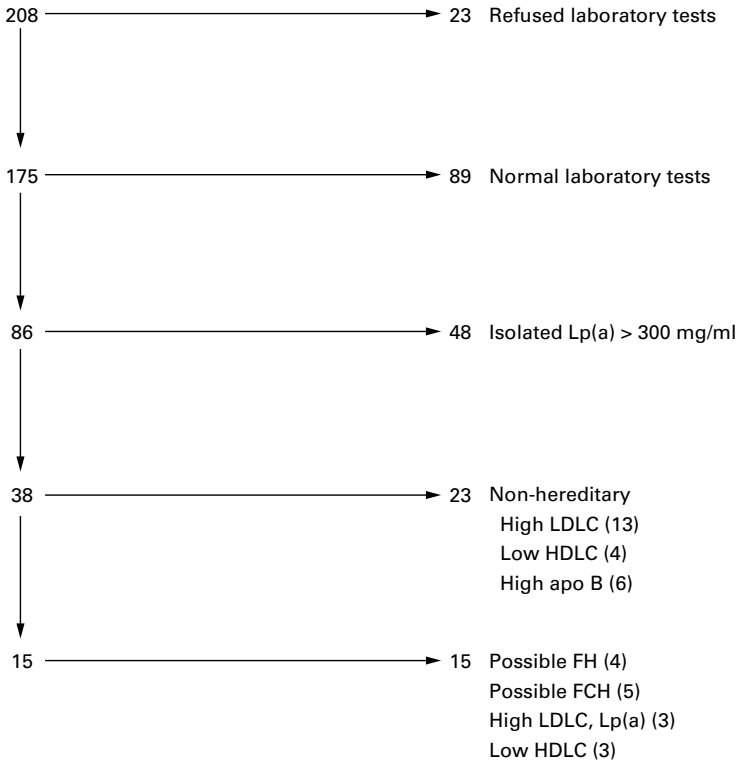

Figure 1 Children with a family history of premature CAD.

Serum Lp(a) lipoprotein concentrations were measured by a radioimmunoassay system (Pharmacia, Sweden), details of which have been described previously.[8]

The clinical examination included a routine physical examination, measurement of height, weight, and blood pressure, and completion of the hereditary background regarding CAD in the family.

The genetically linked dyslipidaemias are defined as: (1) Possible familial hypercholesterolaemia (FH) if the child has LDL cholesterol (LDLC) greater than 4.9 mmol/l, and the parent has hypercholesterolaemia or died of premature CAD. Possible FH in the parent is defined either as above, or if TC is greater than 7.5 mmol/l and myocardial infarction occurred before 50 or 55 years of age in a first degree male or female relative respectively. (2) Possible familial combined hypercholesterolaemia if the child has an increase of LDLC and apolipoprotein B or only apolipoprotein B, and a parent with hypercholesterolaemia and/or hypertriglyceridaemia.

Results

Of the 175 children who participated in both the clinical examination and blood tests, 89 had normal test results defined as serum LDLC $\leqslant$ 3.40 mmol/l, HDLC $\geqslant$ 0.90 mmol/l, TG $\leqslant$ 1.40 mmol/l, apolipoprotein B $\leqslant$ 1.00 g/l, and Lp(a) $\leqslant$ 300 mg/l. Hypercholesterolaemia in parents was defined as serum TC > 6.20 mmol/l. Figure 1 summarises the number of children taking part in the study.

The children with one or more abnormal blood test results were divided into four main groups: (1) Moderately increased LDLC (3.40–4.20 mmol/l). (2) Highly increased LDLC (> 4.20 mmol/l). These two groups include those with other concurrent abnormal blood lipid or lipoprotein test results. (3) Isolated increase of apolipoprotein B (> 1.00 g/l). (4) Isolated hypo-HDL-cholesterolaemia (< 0.90 mmol/l).

All children had normal blood pressure defined as systolic pressure $\leqslant$ 140 and diastolic pressure $\leqslant$ 90 mm Hg. No child had symptoms of hypothyroidism and all had grown normally. We defined obesity in 11 year old children as body mass index (BMI) greater than 23 and in adults as BMI greater than 30 kg/m^2. In a second control LDLC and HDLC concentrations were checked; those which were normalised are mentioned in the text. Serum TSH and triiodothyronine were also analysed, and all had normal test results.

All parents mentioned in tables or text are those with a family history of premature CAD.

MODERATELY INCREASED SERUM LDLC

Sixteen children had LDLC concentrations in the 3.40–4.20 mmol/l range. Nine of them also had increased serum cholesterol (> 5.20 mmol/l). The abnormal LDLC test result was combined with an increased apolipoprotein B concentration in nine children and an increased Lp(a) concentration in six. Serum TG was normal in all 15 children. A familial occurrence of hyperlipoproteinaemia was found in six families (table 1).

Before testing, no parent (families 1–6) with hyperlipoproteinaemia was aware of their high risk CAD constitution.

HIGHLY INCREASED SERUM LDLC

Seven children had LDLC concentrations greater than 4.20 mmol/l. All also had increased TC and apolipoprotein B concentrations. One family had high Lp(a) concentration. Three of

Table 1 Children with moderately increased concentrations of LDL cholesterol (3.40–4.20 mmol/l) and a parent with serum cholesterol > 6.20 mmol/l

Family	*Age*	*Sex*	*TC (mmol/l)*	*HDLC (mmol/l)*	*LDLC (mmol/l)*	*TG (mmol/l)*	*apoB (g/l)*	*Lp(a) (mg/l)*
1	11	F	6.01	1.48	4.18	0.76	1.04	840
1	Died from coronary heart disease							
2	11	F	5.48	1.23	3.82	0.9	1.07	17
2	38	F	6.54	1.34	4.34	1.90	1.55	< 17
3	11	F	5.14	1.16	3.78	0.44	1.00	682
3	43	M	7.39	0.89	5.98	1.13	1.59	137
4	11	M	5.40	1.27	3.73	1.00	1.10	80
4	45	M	6.34	1.11	4.30	2.06	1.39	45
5	11	F	5.17	1.06	3.67	0.96	1.07	202
5	40	M	6.46	0.94	4.84	1.48	1.35	< 17
6	11	F	5.38	1.44	3.69	0.54	1.35	84
6	39	F	6.59	1.07	4.98	1.20	1.35	306

Table 2 Children with highly increased concentrations of LDL cholesterol (> 4.20 mmol/l) and a parent with serum cholesterol > 6.20 mmol/l

Family	Age	Sex	TC (mmol/l)	HDLC (mmol/l)	LDLC (mmol/l)	TG (mmol/l)	apoB (g/l)	Lp(a) (mg/l)
7	11	M	8.35	0.97	7.15	0.5	1.81	139
7	34	M	7.37	0.58	5.58	2.64	1.74	—
8	11	M	7.93	0.97	6.56	0.87	1.71	89
8	60	M	Residency unknown					
9	11	M	7.50	0.91	6.29	0.66	1.58	840
9	37	M	7.12	1.13	5.59	0.87	1.47	> 840
10	11	M	7.17	1.67	5.27	0.50	1.25	124
10	42	F	6.72	1.27	4.92	1.15	1.30	89

Table 3 Children with isolated abnormal levels of apoB (≥ 1.0 g/l, families 11–12) or HDL cholesterol (< 0.90 mmol/l, families 13–15)) and a parent with dyslipoproteinaemia

Family	Age	Sex	TC (mmol/l)	HDLC (mmol/l)	LDLC (mmol/l)	TG (mmol/l)	apoB (g/l)	Lp(a) (mg/l)
11	11	F	4.69	1.09	3.10	1.10	1.19	202
11	38	M	6.30	0.99	4.87	0.97	1.45	21
12	11	F	4.87	1.14	3.16	1.26	1.04	59
12	38	M	6.75	1.42	4.46	2.25	1.33	325
13	11	F	3.28	0.85	2.09	0.74	0.59	89
13	39	M	5.67	0.68	4.09	1.97	1.18	89
14	11	F	4.03	0.80	2.45	1.72	0.92	106
14	43	F	7.98	0.77	6.79	0.92	1.90	186
15	11	F	4.75	0.84	3.09	1.79	0.85	319
15	48	M	5.55	0.86	3.63	2.33	1.17	428

them had parents with normal blood lipid test results and had normal blood lipids when re-examined after changing to a low fat diet. The remaining four children had a familial occurrence of hyperlipoproteinaemia (table 2).

Neither children nor parents of families 7–10 were aware of their high risk CAD constitution before the present investigations.

ISOLATED INCREASED SERUM APOLIPOPROTEIN B CONCENTRATION

Eight children had apolipoprotein B greater than 1.00 g/l, the other blood test results being within the normal range. Two of them had a parent with increased lipoproteins (table 3).

ISOLATED DECREASED SERUM HDLC CONCENTRATION

Seven children had HDLC concentrations below 0.90 mmol/l and three of them also had a parent with abnormal lipoprotein test results (table 3). In one of the families (no. 15), both the parent and his daughter were obese.

Of the parents with a high risk family history but a child with normal lipoproteins, 16 had TC greater than 6.20 mmol/l (in the range 6.20–7.50 in 11 subjects, and greater than 7.50 mmol/l in five).

Thus possible FH was found in four children and three of their tested parents (families 7–10). Of the parents with normal children, five had possible FH. Possible familial combined hyperlipidaemia (FCH) was suspected in seven children (families 2–6, 11–12).

Discussion

An important motive for preventive paediatric cardiology is the fact that vascular atherosclerotic lesions may develop in early life.[9] A high risk strategy has been advocated to identify children with hypercholesterolaemia both in the United States (US National Cholesterol Education Program for Children and Adolescents, NCEP-Peds) and European countries including Sweden.[10 11] The major indicators for lipoprotein screening are a family history of premature CAD and/or a parental serum cholesterol concentration 6.20 mmol/l or greater. A major problem is that the parents are usually quite young and that many children live in one parent households. Thus, most of the children selected for screening are identified by the occurrence of premature CAD in a grandparent.[7] Another problem is that a high risk CAD family history is relatively common among the children. If the NECP-Peds guidelines are applied, about one in five children will have at least one major screening indicator.[12 13] It was therefore mainly for practical reasons that we chose to define premature CAD as symptoms of CAD occurring before or at age 50 years in men and 55 in women (cf 55 years for both men and women in the NCEP-Peds guidelines) both in the present and previous study.[7] Lessons from previous studies also indicated that few parents were aware of their cholesterol concentration. We thus decided to exclude parental cholesterol 6.20 mmol/l or greater as a major screening indicator. About 4000 questionnaires were distributed to families with 10–11 year old schoolchildren. Of the responders, 201 children had a high risk family history and about 90% of them decided to take part in the clinical and laboratory examinations.

In the information to parents we stressed that the main purpose of the investigation was to identify children with hereditary lipid disorders, particularly familial hypercholesterolaemia (FH) and FCH. In addition families with a cluster of risk factors were of special interest. The motives behind these limited aims were the following. Firstly, hyperlipoproteinaemia is just one of many CAD risk factors, top quintile cholesterol concentrations only contributing to one fifth of all CAD deaths.[14] Secondly, moderately increased childhood cholesterol is a poor predictor of adult cholesterol.[15] Thirdly,

cholesterol intervention may be effective even if started in middle age.[16] Fourthly, psychosocial effects may outweigh the benefits of intervention.[17]

The most common genetic dyslipidaemias associated with premature CAD, FH and FCH, account for 5% and 10% respectively of survivors of premature CAD.[18] It is important to identify children with these genetic disorders in order to prevent or check the atherosclerotic process. However, at present we have no specific biochemical marker for those dyslipidaemias. Specific molecular diagnosis is available for FH but clusters of certain LDL receptor mutations have been identified in a few geographic regions only.[19] Children with a familial occurrence of hypercholesterolaemia and LDLC concentrations of 4.20 mmol/l or greater may be suspected of having FH, while children with LDLC concentrations of 4.90 mmol/l or greater are most likely to have FH.[20 21] Thus children of families 7, 8, 9, and 10 are most likely to have FH. None of the families were aware of their high risk constitution before this investigation. We note with interest that three children with very high LDLC and normal parents, normalised their LDLC as a result of changing their diet after being notified about their hypercholesterolaemia. Several explanations for this normalisation are possible: regression to the mean; nutritional changes of lipid and cholesterol intake; and absence of hypercholesterolaemia in the parents.[22]

Familial combined hyperlipidaemia is a common disorder occurring in about 1% of adults. The pathogenesis of this metabolic disorder is not properly known. In adults FCH is a dominantly inherited trait while its penetrance is incomplete in childhood, 16% of children compared with 50% of the adult group having hyperlipidaemia.[18] The phenotype in children is variable, 7% having high LDLC, 46% high triglyceride, and 86% high apolipoprotein B concentrations.[23] We decided that a combination of increased apolipoprotein B and LDLC and/or TG concentrations in the child and abnormal TC and/or TG in the parent makes the diagnosis of FCH highly probable. Thus FCH was suspected in five families (2–6), while the parent had died of CAD in the sixth. There is also a possibility that FCH in a child may be expressed as an isolated increase of apolipoprotein B with FCH phenotype being present in the parent.[23 24] This combination occurred in two families (11 and 12).

A low HDLC concentration is also an independent predictor of CAD.[25] The hypo-HDLC is often associated with other atherogenic lipoproteins, obesity, lack of physical exercise, and inheritance. Decreased HDLC may be a component of the insulin resistance syndrome, which may be evident even in early life.[26 27] Three children had low HDLC concentrations (families 3, 14, and 15). In one of the families both father and child were obese while in the other two, hypo-HDLC may be hereditary.

Lp(a) is a factor linked to the atherosclerotic process, and in most studies raised Lp(a) concentrations are associated with the presence or severity of CAD.[28 29] High Lp(a) concentrations together with increased LDLC exert the most significant adverse effect. That effect is removed by lowering the LDLC concentration.[30] A combined increase of LDLC and of Lp(a) above 300 mg/l was found in only three of the children with high LDLC not accounted for in the tables.

Identification of children and parents at highest CAD risk—that is, those with a combination of a family history of premature CAD and FH, FCH, or multiple lipoprotein risk factors should have priority according to our hypothesis. Few of the parents and children identified were aware of their high risk CAD situation. A prerequisite for successful management of high risk families is that they are highly motivated. In this study 84% of those reporting such a history decided to take part in the further examination. In a population of about 4000 children, about eight (one per 500) should have FH, about half of the adults expecting myocardial infarction before age 50–55 years. We found four FH children by our high risk approach. About 40 (one per 100) FCH children should be present in our population, with about seven expected to reveal the high LDLC/apolipoprotein B FCH phenotype already in childhood. We found seven children suspected of suffering from FCH. Hypo-HDLC occurred rarely in this age group (2% incidence). Isolated high concentrations of Lp(a) of minor clinical importance occurred in about one third of the children. A combination of high Lp(a) and LDLC was found in six children.

We conclude that as CAD is, to a considerable extent, a result of genetically determined dyslipidaemias it is worthwhile to reflect on the question "Has a grandparent given the child or parents a high risk CAD constitution?". About 10% of children with a positive family CAD history were suspected to have hereditary dyslipoproteinaemia (FH, FCH, or hypo-HDLC) or a combination of risk factors (increased LDLC and Lp(a) concentrations). Thus the "grandparent CAD question" should be asked routinely.

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