Familial hypercholesterolemia in childhood: diagnostics, therapeutical options and risk stratification
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Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia

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Chapter 3

Abstract

Patients with familial hypercholesterolaemia have severe coronary-artery disease early in adult life. Whether lipid-lowering treatment should be started in childhood remains to be established. We therefore assessed 201 children heterozygous for familial hypercholesterolaemia and 80 unaffected siblings (both age ranges 8–18 years) with B-mode ultrasound to measure carotid wall intima-media thickness. Mean combined carotid intima-media thickness of heterozygotes was significantly greater than that of unaffected siblings (0.494 mm [SD 0.051] vs 0.472 [SD 0.049], P=0.002). A significant deviation in intima-media thickness was noted from age 12 years in children with familial hypercholesterolaemia. Findings on multivariate analysis showed LDL cholesterol, age, and sex to be strong and independent predictors of intima-media thickness. Since raised LDL cholesterol concentrations can be lowered efficiently, clinical studies are needed to investigate long-term safety and effectiveness of statin treatment in children with familial hypercholesterolaemia.
Atherogenesis starts in early childhood, and a strong association exists between raised LDL cholesterol concentrations in young adults and risk of subsequent coronary-artery disease. Familial hypercholesterolaemia is the theory behind this relation. B-mode ultrasound can reliably assess intima-media thickness of the arterial wall, and pathological findings on carotid scans have been reported in some young patients with familial hypercholesterolaemia. Therefore, we postulated that carotid intima-media thickness might serve as a marker of atherosclerotic burden in children with this disorder and might assist with the decision of whether or not to start lipid-lowering treatment. Here, we aimed to estimate the effect of age, sex, LDL cholesterol, and other characteristics on this arterial-wall variable in children with familial hypercholesterolaemia and normolipidaemic siblings matched for age and sex.

Between July, 1997, and March, 2001, we investigated all consecutively referred children aged 8–18 years, from families who had at least one child with a molecular diagnosis of heterozygous familial hypercholesterolaemia. Families were identified mostly from paediatricians. We also included as controls unaffected siblings in whom familial hypercholesterolaemia was excluded by DNA analysis. We obtained institutional review board ethics approval and written informed consent of both the child and their parents. We obtained venous blood samples from all participants and ascertained fasting and plasma lipid concentrations with routine procedures.

**Figure 1** Difference in mean carotid intima-media thickness (ΔIMT: thick line) and 95% confidence interval (CI: thin lines) between FH children and unaffected siblings plotted versus age, adjusted for family relations.
One sonographer (JG) did carotid B-mode ultrasound examinations with an Acuson XP128 ultrasound machine equipped with an L75–10MHz transducer and extended frequency software (Acuson-Siemens, Mountainview, CA, USA). Images of the distal common, bulb, and internal far-wall carotid segments were saved as JPEG stills on minidiscs. An image analyst measured intima-media thickness while masked to all clinical information.

We assessed differences in baseline variables between groups by logistic regression analysis with generalised estimating equations in the SAS procedure GENMOD to account for correlations within families. Variables with a skewed distribution were log-transformed. We used the same SAS procedure- allowing for clustering within families- to explore univariately the relation between mean carotid intima-media thickness and baseline variables, with linear regression analysis. With multivariate models, we identified independent predictors after stepwise backward selection. An equation for change in intima-media thickness (ΔIMT) was derived by subtracting the equation for children with familial hypercholesterolaemia-(if GROUP=1), IMTFH=β1AGE+β2GROUP+β3AGE+3GROUP=β1AGE+2β+3βAGE- from the equation for their siblings: (if GROUP=0), IMTSIB=1AGE. This calculation resulted in: ΔIMT=β2+β3AGE. Betas and SEs were derived from the output of a linear regression analysis for the whole group (n=281).

This procedure was used to account for correlations within families. We also did a sib-pair analysis. Every child with familial hypercholesterolaemia was matched for age

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<td>Univariate analysis</td>
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<td>Regression coefficient (SE)</td>
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<tr>
<td>Age (y)</td>
<td>0.0035 (0.0011)</td>
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<td>Male sexe</td>
<td>0.0116 (0.0060)</td>
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<td>LDL-cholesterol (mmol/L)</td>
<td>0.0052 (0.0014)</td>
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<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>-0.0237 (0.0116)</td>
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<tr>
<td>Triglycerides (mmol/L)</td>
<td>-0.0025 (0.0077)</td>
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<td>Mean arterial pressure (mm Hg)†</td>
<td>0.0002 (0.0004)</td>
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<tr>
<td>Body Mass Index (kg/m2)</td>
<td>0.0018 (0.0011)</td>
</tr>
<tr>
<td>Premature disease in first degree</td>
<td>0.0102 (0.0077)</td>
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*log transformed. † Mean arterial blood pressure = (systolic blood pressure + [2xdiastolic blood pressure])/3
and sex with an unaffected sibling, and we adjusted differences in age and sex within pairs in a matched multiple regression model. For statistical analyses, we used SAS release 8.02 (SAS Institute, Cary, NC, USA).

Of 148 families, 201 children heterozygous for familial hypercholesterolaemia were recruited. From 69 of these families, 80 unaffected siblings served as controls. Heterozygotes and controls were similar with respect to age, sex, smoking status, body-mass index, and blood pressure. Mean combined intima-media thickness (all three carotid segments) was 0.494 mm (SD 0.051) in children with familial hypercholesterolaemia versus 0.472 mm (0.049) in unaffected siblings (p=0.002), which remained significant after adjustment for family history of premature cardiovascular disease, HDL cholesterol, or triglycerides.

69 sib-pairs were available for analysis; mean difference of carotid intima-media thickness between children with familial hypercholesterolaemia and unaffected siblings was 0.022 mm (95% CI 0.005–0.031, P=0.006), which was closely similar to that in the whole study cohort. Adjustments for differences in age and sex within pairs in a matched multiple regression model did not change these results.

When the difference in carotid intima-media thickness between children with familial hypercholesterolaemia and unaffected siblings (ΔIMT) was plotted against age (figure), patients showed at least five times more rapid increase in intima-media thickness during childhood than did controls (0.005 mm/year vs <0.001 mm/year). The table shows the effect of individual baseline variables on carotid intima-media thickness and findings of the multivariate analysis. Age, LDL cholesterol, and sex were identified as independent predictors of carotid intima-media thickness. Although HDL cholesterol concentrations were significant on univariate analysis, this finding was not seen on multivariate analysis.

Analyses were also done in boys and girls separately. Boys with familial hypercholesterolaemia had a significantly thicker mean carotid artery wall than did girls (mean difference 0.017 mm [95% CI 0.003–0.031], P=0.02). LDL cholesterol and age were the main contributors to this difference in boys). In analyses restricted to children with familial hypercholesterolaemia, age was significantly associated with increase in intima-media thickness (0.005 mm/year [0.003–0.008], p<0.0001).

We have shown that carotid arterial wall atherosclerosis rapidly progresses during childhood in individuals heterozygous for familial hypercholesterolaemia. Moreover,
age, sex, and LDL cholesterol contributed significantly to this progression. Our findings highlight the important role of LDL in development of premature vascular disease. When children heterozygous for familial hypercholesterolaemia reach adulthood, their atherosclerotic burden has risen significantly as a result of one factor: amplified LDL cholesterol. A nearly 100-fold increase in risk for coronary-artery disease has been noted in patients with familial hypercholesterolaemia between ages 20 and 40 years. Therefore, researchers now need to establish at what age lipid-lowering intervention should be initiated before clinical sequelae become inevitable and what the results of such treatment are in terms of safety and efficacy.

Clinical research in individuals heterozygous for familial hypercholesterolaemia should focus on treatment of this disorder, initiated possibly before puberty to preserve normal arterial-wall composition, since these children face a high risk for future premature coronary-artery disease when untreated.

References