Familial hypercholesterolemia in childhood

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Family History of Cardiovascular Events and Endothelial Dysfunction in Children with Familial Hypercholesterolemia

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Abstract

Objectives: In patients with familial hypercholesterolemia (FH), the propensity towards atherosclerosis may vary considerably. In the general population, a positive family history is associated with an increased risk for cardiovascular events. Since endothelial dysfunction is predictive for future cardiovascular events, we evaluated whether FH-children with a positive family history of premature cardiovascular disease have more pronounced endothelial dysfunction compared to children with a negative family history.

Study design: Fifty FH children, 10 to 18 years, participated in this study. Thirty-one children had a positive family history for cardiovascular events (fh+) and 19 children had no events in the family (fh-). Nine-teen matched siblings participated as controls. Endothelial function was assessed by testing the flow-mediated dilatation (FMD) of the brachial artery.

Results: Baseline characteristics were comparable for fh+, fh- and controls. Lipid levels were significantly higher in FH children. In FH, FMD was impaired compared to controls (11.7 ± 4.4% vs. 15.6 ± 6.8%, p<0.03). In addition, FMD was significantly lower in fh+ compared to fh- (10.7 ± 9.9% versus 13.3 ± 4.6%, p<0.05).

Conclusion: In FH children, endothelial function is impaired compared to matched controls. This impairment is most pronounced in FH children with a positive family history of premature cardiovascular disease.
Introduction

Familial Hypercholesterolemia (FH) is an inherited autosomal dominant disorder of lipoprotein metabolism caused by mutations in the low density lipoprotein (LDL) receptor gene. The disorder has a frequency of one in 400 persons and is therefore the most common inborn error of metabolism in the Dutch population\(^1\). FH is associated with elevated levels of LDL-C and premature atherosclerosis. Affected persons show symptoms of atherosclerotic cardiovascular disease at relatively young age, sometimes before the age of 30. In the general population autopsy reports of healthy adolescents, 15 to 19 years of age, have shown a prevalence of 3.2% of coronary stenosis \(^2\). In view of the aggressive nature of vascular disease in adult FH patients one can safely assume that atherosclerotic changes begin in early childhood \(^3\);\(^4\). Early detection of abnormal arterial function could therefore assist in early institution and optimization of cardiovascular preventive strategies.

The endothelium constitutes the first line of defence against atherosclerosis\(^5\). Accordingly, all major risk factors for atherosclerosis are characterized by endothelial dysfunction\(^6\). Recently, data have emerged to show that impaired endothelial function, assessed as acetylcholine-induced coronary vasodilatation and/or flow mediated dilation of the brachial artery can predict future cardiovascular disease \(^7\);\(^8\).

In the general population, a positive family history for cardiovascular disease has a major impact on the cardiovascular risk of an individual and has been associated with endothelial dysfunction \(^9\);\(^10\). In FH families, the additional effect of familial traits on top of elevated LDL-C is less clear. In the present study we evaluated whether children from FH families with a positive history of cardiovascular events are characterized by a more pronounced impairment of endothelial function compared to children with a negative family history.

Patients and methods

Patients

A total of 50 heterozygous FH patients 10 to 18 years of age were enrolled in this study. The following criteria were designed to select children with heterozygous FH: plasma LDL-C levels above 95\(^{th}\) percentile for age and gender; a documented family history of hyperlipidemia with LDL-C levels above the 95\(^{th}\) for age and gender before treatment or a personal diagnosis of FH by detection of a mutation
in the LDL receptor gene. Exclusion criteria were smoking; current use of any vaso-active medications; and concomitant conditions such as serious illness, hypertension or diabetes mellitus.

Nine-teen age- and gender-matched siblings participated in the study as healthy controls. Each child or child’s parents gave written informed consent for his or her participation in the study, which was approved by the local Ethical Committee.

**Family history of cardiovascular disease**

From the 50 FH children, 31 children had a family history of cardiovascular events in first-or second-degree relatives (fh+) and 19 FH children had no events in the family or only events in distant family members (fh-). All parents of the children were investigated by a standard questionnaire based on the questionnaires used in the Health Family Tree study. It provided information about each parent and other family members. The questionnaire included the age of onset, and age of death of cardiovascular events in the family. Smoking habits of the FH affected parents were defined as pack-years (1 pack-year = 20 cigarettes per day for 1 year). Premature cardiovascular events were defined for males and females when they occurred before the age of 60. Events were defined as Myocardial Infarction (MI), Coronary Angioplasty Bypass Graft (CABG) and Percutaneous Transluminal Coronary Angioplasty (PTCA).

**Lipids**

All lipid measurements were performed in a central laboratory (Clinical Research Laboratories, Zaventem, Belgium). Samples for lipoproteins were collected in ethylene-diaminetetraacetate (1 mg/ml) and centrifuged within 30 minutes; the plasma was separated, kept at 4°C and shipped overnight to the central laboratory. Total cholesterol (TC) and triglycerides (TG) were analyzed by enzymatic methods (Hitachi 747 analyzer) high-density lipoprotein (HDL-C) was isolated with heparin-2M manganese chloride. Lipids levels were measured on three separate occasions in the FH children: once before the assessment of FMD and twice 6 weeks prior to this visit.

**Flow-mediated dilatation**

The flow-mediated dilatation (FMD) was performed as published previously. In summary, all FMD’s were performed during the morning in a fasting state. All children refrained from alcohol and caffeine containing beverages. A blood
pressure cuff was placed just below the elbow of the right arm. After a 10-15 minutes rest, the diameter of the brachial artery in the right ante-cubital fossa was measured using the 7.5 MHz transducer. By inflation of the blood pressure cuff to 200 mmHg, ischemia is applied to the forearm, distal to the location of transducer. Upon release of the cuff the brachial artery will dilate through endothelial NO-release. Ultrasonography continues for 5 minutes to allow for lumen diameters measurements at 20 seconds intervals. Wall track measurements are stored digitally and analyzed off-line by a blinded observer using wall track system software analysis package. Endothelial function is expressed at each examination as \( \frac{\text{lumen diameter after ischemia} - \text{diameter at baseline}}{\text{diameter at baseline}} \). Intra and inter-session variation coefficient for baseline diameter are 1.1 and 3.8 % respectively. The total duration of this investigation is approximately 30 minutes. All measurements were performed by the same observer, unaware of clinical details and the stage of the experiment.

**Statistical Analysis**
The mean vessel diameter and percent dilatation for each patient were obtained by averaging the measurements taken over all occasions on which that patient was studied. The presented lipid levels of the FH children are the average of three measurements. Differences between groups were tested by using student t test for continuous data. Non parametric testing (Mann-Whitney test) was used for triglycerides and pack-years since the distribution of these data are skewed. A p value < 0.05 was considered significant.

**Results**
Family history was obtained in all FH children (n=50). Evidence of cardiovascular disease (CVD) was present in 15 parents (30%; all fathers with FH) The mean age of onset of CVD of these parents was 33.3 years. Seven fathers with FH (14% of the parents with FH) had died due to CVD (age 44.9 ± 7.0 years). No mothers with FH had died due to CVD. The parents with FH was the father in 20 cases (65%) in the fh+ group and 16 cases (84 %) in the fh- group. The remaining still living FH parents had an average age of 44.4 ± 4.6 years in the fh+ group (n=24) compared to 43.0 ± 4.3 years of the fh- group (n=19), (p=0.310). In the fh- group, 8 (42 %) parents were smokers or former smokers.
compared 24 (77%) in the fh+ group. Parents of the fh- group smoked a median of 4.0 (1.0-32.0) pack-years compared to 16.8 (1.0-31.0) pack-years in the fh+ group (p=0.06).

Baseline characteristics of the children showed no significant difference between FH children and controls with regard to age, body mass index, blood pressure or baseline vessel size. Total cholesterol and LDL-C were higher in the FH group. There was a trend towards a lower HDL-C in the FH group. The healthy siblings had lipid levels within the normal range. The FMD was significantly impaired in the total FH group compared to the controls: 11.7 ± 4.4 versus 15.6 ± 6.8; p<0.028 (table 1).

Table 1. Baseline characteristics and FMD of the FH group compared to controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FH children</th>
<th>Controls</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>50</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>No (%) male</td>
<td>26 (52)</td>
<td>11 (58)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>14.6 ± 2.2</td>
<td>14.2 ± 3.1</td>
<td>0.597</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>21.3 ± 3.8</td>
<td>21.5 ± 5.4</td>
<td>0.886</td>
</tr>
<tr>
<td>Systolic bloodpressure (mmHg)</td>
<td>125 ± 15</td>
<td>121 ± 17</td>
<td>0.309</td>
</tr>
<tr>
<td>Diastolic bloodpressure (mmHg)</td>
<td>67 ± 8</td>
<td>66 ± 11</td>
<td>0.885</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>7.02 ± 1.32</td>
<td>4.32 ± 0.85</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.32 ± 0.26</td>
<td>1.42 ± 0.31</td>
<td>&lt; 0.231</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>5.27 ± 1.27</td>
<td>2.51 ± 0.66</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>0.84 (0.43-1.77)</td>
<td>0.76 (0.50-1.38)</td>
<td>0.225</td>
</tr>
<tr>
<td>Baseline vessel size (mm)</td>
<td>3.14 ± 0.49</td>
<td>3.10 ± 0.53</td>
<td>0.540</td>
</tr>
<tr>
<td>FMD (%)</td>
<td>11.7 ± 4.4</td>
<td>15.6 ± 6.8</td>
<td>&lt; 0.028</td>
</tr>
</tbody>
</table>

Values are given as means (SD) except for no male (percentage) and TG (median and range). FH= familial hypercholesterolemia, TC= total cholesterol, HDL= high-density lipoprotein, LDL= low-density lipoprotein, TG= triglycerides, FMD= flow-mediated dilatation.

Table 2 shows the baseline characteristics and FMD of the FH children with cardiovascular events in first or second degree relatives (fh+) compared to FH children with no events or only in distant family members (fh-). Except for BMI and triglycerides there were no significant differences between these two groups. It is evident that the baseline vessel size is similarly distributed in both groups. However, there is a significant difference in FMD between both groups. The FMD impairment was significantly more pronounced in the fh+ group compared to fh- group (10.7 ± 3.9 versus 13.3 ± 4.6; p< 0.035) (figure 1). The FMD in the fh- group compared to the controls was no longer significantly different (p = 0.239).
Table 2. Baseline characteristics of the FH children with a positive family history of cardiovascular events and FH children with a negative family history of cardiovascular events.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>fh+</th>
<th>fh-</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>31</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>No (% ) male</td>
<td>15 (48)</td>
<td>11 (58)</td>
<td>0.523</td>
</tr>
<tr>
<td>Age (y)</td>
<td>14.6 ± 2.3</td>
<td>14.5 ± 2.1</td>
<td>0.829</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>22.1 ± 4.1</td>
<td>20.0 ± 3.0</td>
<td>0.037</td>
</tr>
<tr>
<td>Systolic bloodpressure (mmHg)</td>
<td>127 ± 15</td>
<td>122 ± 15</td>
<td>0.231</td>
</tr>
<tr>
<td>Diastolic bloodpressure (mmHg)</td>
<td>68 ± 8</td>
<td>65 ± 9</td>
<td>0.205</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>7.21 ± 1.16</td>
<td>6.71 ± 1.52</td>
<td>0.194</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.29 ± 0.21</td>
<td>1.39 ± 0.32</td>
<td>0.238</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>5.46 ± 1.11</td>
<td>5.00 ± 1.48</td>
<td>0.189</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>0.96 (0.43-1.77)</td>
<td>0.75 (0.48-1.48)</td>
<td>0.021</td>
</tr>
<tr>
<td>Baseline vessel size (mm)</td>
<td>3.18 ± 0.50</td>
<td>3.10 ± 0.49</td>
<td>0.549</td>
</tr>
</tbody>
</table>

Values are given as means (SD) except for no male (percentage) and TG (median and range), fh+ =FH children with cardiovascular events in first or second degree relatives, fh- = FH children without cardiovascular events or only in third degree relatives, TC= total cholesterol, HDL= high-density lipoprotein, LDL= low-density lipoprotein, TG= triglycerides.

Figure 1. FMD of FH + children compared to the FH- children

Discussion

In this cohort of FH-children, being the largest to date in which endothelial function was assessed, we show that FH-children are characterized by endothelial dysfunction compared to matched control children. In addition, we show that the degree of endothelial dysfunction is associated with the presence of a family history for premature cardiovascular events. These findings underscore the importance of other factors, besides elevated LDL-C, in determining the susceptibility for cardiovascular disease in these FH children.
Endothelial dysfunction

Endothelial dysfunction is seen during early stages of atherosclerosis, clearly preceding the development of morphological changes. In the general population, various risk factors such as hypertension, diabetes, hyperlipidemia, hyperhomocysteinemia, inflammation, ageing and cigarette smoking have all been associated with impaired flow-mediated dilatation in the preclinical phase of vascular disease. Recently, Neunteufel et al. and Suwaidi et al. demonstrated that impaired FMD is correlated with prognosis in patients with chest pain and predicts which patients are at risk for cardiac events. As a consequence, FMD has been put forward as surrogate marker for cardiovascular morbidity and mortality, potentially allowing early identification of cardiovascular risk as well as monitoring of clinical benefit of instituted therapy aimed at reducing cardiovascular risk. In line with earlier data, we confirm the presence of endothelial dysfunction in asymptomatic FH-children compared to healthy controls, underscoring the onset of atherogenesis at an early age in childhood.

Family history for cardiovascular disease

Familial aggregation of coronary heart disease (CHD) is well established. In previous studies, vascular changes have been reported in young people whose parents suffered from premature myocardial infarction. The specific underlying mechanisms leading to cardiovascular events in subjects with a positive family history are not well understood. Clustering of lifestyle factors such as high fat diet, cigarette smoking, and physical activity, and factors that influence lipid metabolism have all been associated with a higher prevalence of cardiovascular disease (CVD) in both the general population and in FH. Besides classical risk factors, the specific underlying molecular defect responsible for FH may also contribute to the variation of phenotype, but even among carriers of an identical FH mutation, mortality varies to a large extent.

In the present cohort, we show a clear difference in FMD between FH children with versus without events in the family history. This difference was independent of TC, LDL and HDL levels. Notably, the triglyceride levels, although within the normal range, were slightly elevated in the fh+ children, as compared to fh- children. Earlier studies have shown that hypertriglyceridaemia is associated with impaired endothelial function. However, in the present study TG levels were all, but one, within the normal range. As such, it is highly unlikely that this minor difference in TG level can be held responsible for the significant differences in FMD response.
In addition, there was a trend towards higher BMI in the fh+ group. In a previous study, severe obesity (BMI >30) has been associated with endothelial dysfunction. However, in the present study, all BMI’s were within the (lower) normal range, whereas there was no significant difference between BMI in the fh+ compared to the fh- group. Hence, it is highly unlikely that differences in BMI have contributed to the distinct difference in FMD in fh+ compared to fh- group. Finally, in the fh+ group more parents smoked. Since parental smoking habit is only indirectly associated with the functional vessel wall properties in the FH children, this is likely to be of minor influence on the FMD differences.

In summary, the (tendencies towards) differences in the mentioned factors are unlikely to be held solely responsible for the significant differences in FMD between the fh+ and fh- group. Hence, our results imply that in FH, other risk factors besides the ‘classical risk factors’ may play an important role in determining the susceptibility towards atherogenesis.

**Clinical implications**

In the present study we show that endothelial dysfunction, the earliest stage of atherogenesis, is already present in young FH children. Normalization of endothelial function during this ‘reversible’ stage of atherosclerosis may prove to be of crucial importance in view of the limited time period before the occurrence of CVD in FH subjects. The clear relation between positive family history and early endothelial dysfunction in FH, combined with the recently reported predictive value of endothelial dysfunction for future cardiovascular risk, underscore the relevance of a positive history as an important risk factor in FH subjects. In view of the aggressive nature of atherogenesis in ‘susceptible’ FH subjects, early identification and vigorous therapy might be considered especially in FH children with a positive family history of CVD. The current therapy for FH children is a fat restricted diet and lifestyle advice. However, these diets provide a maximal LDL reduction of 10%. Whereas in adults HMGCoA reductase inhibitors are the therapy of first choice, the use of the latter in children is still under debate. Currently, trials are ongoing in our center, evaluating the safety and efficacy of statins in children with familial hypercholesterolemia.
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