Lipoprotein (a) concentrations as risk indicators for atherosclerosis

G M Kostner, A Czinner, K H Pfeiffer, M Bihari-Varga

Abstract
The plasma concentration of different lipoproteins were measured in 102 control children, in 42 children with a parent suffering from coronary heart disease (CHD), and in 50 children with a parent with cerebrovascular disease (CVD). Significant differences between controls and children in the other two groups were found for apolipoprotein A I, apolipoprotein B, and high density lipoprotein-cholesterol. Children of parents with CHD differed from controls in total cholesterol and apolipoprotein A II concentrations. A highly significant difference furthermore was found in lipoprotein (a) concentrations from children of parents with CHD in comparison with controls, but not between children of parents with CVD and controls. The difference in lipoprotein (a) concentrations (children of parents with CHD compared with controls) were only noticed in children above the age of 10 years. This could be explained by the observed rise of lipoprotein (a) between age 2 and 13 years, which was much more pronounced in the group with parents who had CHD. Plasma glycosaminoglycan concentrations were also measured in the three groups. They were significantly higher in children of parents with CHD and CVD compared with controls; they also varied with age.

The pathophysiological events leading to atherosclerosis are known to originate already in early childhood. In numerous reports multivariate analysis of prospective morbidity and mortality studies strongly suggest a family history for coronary heart disease (CHD) and cerebrovascular disease (CVD). In fact it appears that genetic and familial factors contribute most to the risk of atherosclerosis. As the causes for atherosclerosis are multifactorial, there is no single parameter that would allow prediction of the individual risk with sufficient certainty. Evidence is accumulating, however, that raised plasma lipoprotein (a) concentrations contribute to a great extent to atherogenesis especially if low density lipoprotein-cholesterol is increased in addition. In a previous study we investigated 1500 young soldiers and based on a questionnaire they were divided into two groups: positive and negative family history of myocardial infarction. It was found that parents of children with premature myocardial infarction had significantly higher plasma lipoprotein (a) concentrations compared with healthy controls.

In this study we extended our previous work by investigating the children of people suffering from CHD and CVD separately. The data are not based on a questionnaire but derive from blood analysis of the children of affected patients directly.

Previous in vitro experiments in our laboratory, aimed at sheding more light on the possible molecular mechanism of the atherogenicity of lipoprotein (a), demonstrated that this lipoprotein avidly complexes with glycosaminoglycan, and this in turn is recognised by the scavenger receptors on macrophages. Such a process may favour the complex formation of lipoprotein (a) with intracellular matrices of arteries, followed by triggering of the onset of early lesions. As it is known that glycosaminoglycan is present in a variable concentration in circulating blood even in healthy people, we measured glycosaminoglycan concentrations in the serum of children and correlated them with age and familial atherosclerosis risk.

Subjects and methods
Ninety six children with an established familial risk for atherosclerosis between 2 and 15 years of age were investigated and compared with 102 control children matched for age and sex. This control group consisted of children who were admitted to hospital for various reasons not connected with acute diseases or metabolic defects, for example, tonsillectomy.

The children at risk for atherosclerosis were divided into two groups: (1) those with a parent suffering from CHD (a myocardial infarction at <45 years of age) (n=46) and (2) those with a parent suffering from CVD who had had a stroke and apoplexia (n=50).

Blood was collected from children during a period of absence of any virus or other infection, after an overnight fast, and it was allowed to clot at room temperature for 1 hour. The serum was separated by centrifugation at 1500×g for 15 minutes.

The concentration of plasma lipids was measured enzymatically by routine laboratory methods. Lipoproteins and apolipoproteins were quantified immunohchemically as described previously. Lipoprotein (a) was quantified using ready to use Laurell plates, as well as standards from Immuno Diagnostica. The concentration of glycosaminoglycan in serum was estimated by measuring the hexuronic acid concentration.

STATISTICAL ANALYSIS
For comparison of all three groups with each
Table 1  Mean (SD) concentrations of different parameters measured in the serum of high risk children of parents with CHD and CVD in comparison with age and sex matched controls

<table>
<thead>
<tr>
<th>Total cholesterol (mmol/l)</th>
<th>Triglyceride (mmol/l)</th>
<th>High density lipoprotein-cholesterol (mmol/l)</th>
<th>Apolipoprotein A I (g/l)</th>
<th>Apolipoprotein A II (g/l)</th>
<th>Apolipoprotein B (g/l)</th>
<th>Glycosaminoglycan (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD (n=46)</td>
<td>4.87 (0.93)*</td>
<td>0.94 (0.26)</td>
<td>1.01 (0.27)*</td>
<td>1.41 (0.22)*</td>
<td>0.41 (0.06)*</td>
<td>0.61 (0.19)*</td>
</tr>
<tr>
<td>CVD (n=50)</td>
<td>4.36 (0.78)</td>
<td>0.88 (0.21)</td>
<td>1.04 (0.25)*</td>
<td>1.40 (0.17)*</td>
<td>0.42 (0.06)</td>
<td>0.63 (0.21)*</td>
</tr>
<tr>
<td>Controls (n=102)</td>
<td>4.35 (0.65)</td>
<td>0.94 (0.23)</td>
<td>1.15 (0.22)</td>
<td>1.49 (0.17)</td>
<td>0.44 (0.05)</td>
<td>0.50 (0.14)</td>
</tr>
</tbody>
</table>

Significantly different from controls: *p<0.05 and **p<0.01.

Table 2  Quartile concentrations of lipoprotein (a) in mg/l in serum of high risk children of parents with CHD and CVD in comparison with age and sex matched controls

<table>
<thead>
<tr>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD (n=46)</td>
<td>60**</td>
<td>125**</td>
<td>397**</td>
</tr>
<tr>
<td>CVD (n=50)</td>
<td>25</td>
<td>80</td>
<td>196</td>
</tr>
<tr>
<td>Controls (n=102)</td>
<td>17</td>
<td>75</td>
<td>138</td>
</tr>
</tbody>
</table>

**Significantly different from controls: p<0.01.

Results and discussion

Table 1 shows mean (SD) concentrations of some of the lipid and lipoprotein parameters of the two high risk groups of children in comparison with controls. There was no significant difference in triglyceride concentration in the two high risk groups in comparison with controls. Highly significant differences were found in the concentration of apolipoprotein B, which was higher in the two high risk groups compared with controls. Apolipoprotein A I and high density lipoprotein-cholesterol were significantly different between both high risk groups and the control group. A significant difference (p<0.05) in the apolipoprotein A II concentrations was also noticed between the group with a parent who had CHD and the control group.

Because of the non-normal distribution of lipoprotein (a) medians for serum concentration were calculated and the Kruskal-Wallis statistics were used for calculating differences. As can be seen in table 2 median lipoprotein (a) serum concentrations were highest in the group with a parent who had CHD and lowest in the control group. The differences were significant (p<0.001). There was no significant difference in median values of lipoprotein (a) between children with a parent who had CVD and control children.

In a previous study of a large family where serum lipoprotein (a) concentrations of three different generations were investigated, we showed that lipoprotein (a) increases with age. In another study we also found that newborn babies have very low lipoprotein (a) concentrations which slowly increase in the first weeks of life. In order to account for these fluctuations, lipoprotein (a) concentrations of the group with a parent with CHD and the control group were plotted against age (fig 1). Significant differences between these two groups could be established above the age of 10 years only. Maximal differences were apparent at the age of 13 years. On the basis of earlier findings of our group as well as of others, it seems well documented that lipoprotein (a) concentrations >300 mg/l are significantly correlated with premature atherosclerosis and myocardial infarction. From data in the present study it appears that this cut off concentration may be much lower in children below the age of about 10 years. We also conclude on the basis of the present study that lipoprotein (a) might be a significant discriminator for CHD only if measured in children of about 5 years or older.

We also measured the serum concentrations of glycosaminoglycan in the different groups and plotted them against age (fig 2). In all age groups the concentrations were significantly higher in both groups of high risk children in comparison with control children. As concentrations of glycosaminoglycan in both groups of...
high risk children were not significantly different from each other, they were combined in Fig 2. The highest differences were measured in children with a parent with CVD below the age of 5 years. These findings suggest that serum concentrations of glycosaminoglycan in fact correlate positively with the incidence of vascular diseases, and that individuals with extremely high serum concentrations might be prone to CVD. This hypothesis of course needs to be verified in longitudinal studies with a much larger sample size. Whether or not the differences in concentrations of glycosaminoglycan are of genetic or of environmental origin is not clear yet and this is currently under investigation in our laboratory. Another open question that awaits clarification is whether or not increased concentrations of glycosaminoglycan persist until adulthood. These questions with respect to lipoprotein (a) seem much more clear. From earlier work we know that lipoprotein (a) concentrations are genetically determined and increase with age.6 9 10 There are also indications that the patterns of plasma lipoproteins in general and that of lipoprotein (a) in particular differ between adult patients with CHD and those with CVD.11 These earlier findings are strengthened by this study.

In conclusion we have shown that children with a familial risk for atherosclerosis do in fact differ in several parameters from control children. Children of parents with CHD exhibit significantly raised concentrations of lipoprotein (a) and apolipoprotein B, reduced high density lipoprotein, and increased values of serum glycosaminoglycan. The children of parents with CVD exhibited similar changes in serum lipoproteins and glycosaminoglycan; lipoprotein (a) concentrations, however, were not different from controls.

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