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RAPID COMMUNICATION

Dyslipoproteinaemia in Children With or Without Family History of Premature Myocardial Infarction

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Summary

In order to examine the relationship between certain risk factors for atherosclerosis and family history of myocardial infarction, we compared a group of children (n=51) whose parents had survived myocardial infarction (n=34) with a control group of children (n=90) with a negative family history of atherosclerosis (62 parents). The study revealed a surprising fact that 26.7 % of control children had hypercholesterolaemia compared to 15.7 % incidence in "risk" children. "Risk" children differed from the controls most in the apo-A-I levels and a higher risk index expressed by the proportion of apo-B:apo-A-I (1.22, 1.34 g/l, p=0.001, 0.58, 0.46, p=0.05, respectively). Since the most frequent primary hyperlipoproteinaemia in myocardial infarction families was familial combined hyperlipoproteinaemia, we assume that this condition may be presented in affected children by an unfavourable proportion of apolipoproteins of the lipoprotein classes.

Key words

Hypercholesterolaemia – apo-A-I – Myocardial infarction – Children

A positive family history of premature myocardial infarction (MI) is considered as an important risk factor for atherosclerosis mostly related to hyperlipoproteinaemia (HLP). Atherosclerosis is a process developing from childhood (Stary 1989). It is thus generally accepted that the family history may be a useful tool for identifying high-risk subjects during childhood (Dennison *et al.* 1989) with the aim of providing early preventive efforts. It is well known that the manifestation of HLP is affected by age and the examination of total cholesterol and triglycerides in children reveals mainly familial hypercholesterolaemia (Kwiterovich 1986). The aim of this study in the offsprings (age less than 20 years) whose parents survived premature myocardial infarction (MI) and in the control group of children with a negative family history of MI was to evaluate: 1. parameters which characterize disturbances of lipoprotein metabolism; 2. relationship of examined risk factors with a positive or negative family history of MI; 3. analysis with respect to the type of HLP in parents and families.

Parents who survived premature MI (P-MI) and their children (CH-MI) were compared with the the control group of parents (P-C) and their children (CH-C) whose family history was free of premature atherosclerosis. Cholesterol and triglycerides were determined enzymatically (Dipro, Cobas Mira autoanalyzer), apolipoprotein-A-I (apo-A-I), apolipoprotein-B (apo-B) and lipoprotein a [Lp(a)] were measured using the immunoturbidimetric method (Immuno AG, Vienna). For the purpose of this study, Fredrickson's phenotype classification of HLP was employed. In the children and their parents, HLP was defined as follows: 1. Cholesterol levels of >5.2 and >6.2 mmol/l and/or as serum triglyceride concentrations of >2.0 mmol/l, respectively. 2. The Lp(a) risk levels as a concentration of >20 and >30 mg/dl, respectively. 3. The risk index (RI) as the proportion of apo-B:apo-A-I. Comparisons between cases and controls were made using Student's t-test, the Mann-Whitney U-test and the chi-square test. Discriminant analysis was used for testing the power of

the examined parameters to discriminate between the cases and controls (SAS, Statgraphics). A p value = 0.05 was considered as significant. Table 1 demonstrates characteristics of children and parents from two different family groups. A comparison between the children showed interesting results in the CH-MI whose cholesterol and apo-A-I levels were significantly lower than in the CH-C and the RI values were significantly higher. The prevalence of HLP according to Fredrickson's classification revealed a higher frequency of type IIA HLP in control children than in the children from MI families (Table 2). No statistical difference in the occurrence in their parents was found.

Table 1
Characteristics of children and parents

	Children		Parents	
	CH - MI n = 51	CH - C n = 90	P - MI n = 34	P - C n = 62
Age (year)	14.8±2.7	14.6±2.6	46.4±6.7	45.4±6.7
Cholesterol mmol/l	4.38±0.70	4.65±0.79*	7.10± 1.33	6.15±1.31***
Triglycerides mmol/l	0.86±0.40	0.78±0.38	2.55±1.86	1.35±1.23***
apo-AI g/l	1.22±0.22	1.34±0.13***	1.33±0.16	1.42±0.17**
apo-B g/l	0.60±0.12	0.61±0.14	1.07±0.22	0.87±0.25***
Risk index (RI)	0.58±0.66	0.46±0.11*	0.82±0.18	0.62±0.20***
Lp(a) (mg/dl)	19.6±25.7	12.3±15.8	41.7±40.2	16.0±19.0**

*Statistical significance of differences between children (CH-MI compared with CH-C) and between parents (P-MI compared with P-C) is indicated: * p=0.05, ** p=0.01, *** p=0.001*

Table 2
Prevalence of hyperlipoproteinaemia in children and parents

	Children		Parents	
	CH-MI n (%)	CH-C n (%)	P-MI n (%)	P-C n (%)
HLP type IIA	8 (15.7)	24 (26.7)*	10 (29.4)	21 (33.8)
HLP type IIB	1 (2)	0	12(35.3)	4 (6.4)***
HLP type IV, V	0	0	5 (14.7)	3 (4.8)
Total HLP	9 (17.6)	24 (26.7)*	27 (79.4)	28 (45.1)**

*The statistical significance of differences between children (CH-MI compared with CH-C) and between parents (P-MI compared with P-C) is indicated: * p=0.05, ** p=0.01, *** p=0.001*

Since the frequency of hypercholesterolaemia in the CH-C was significantly higher than in the CH-MI, we evaluated the measured parameters in 43 of CH-MI and 66 of CH-C cases with normal cholesterol levels (< 5.2 mmol/l). In this normocholesterolaemic group of CH-MI, apo-A-I levels were significantly lower (1.20 ± 0.24, 1.32 ± 0.12, $p < 0.005$) and RI values (0.58 ± 0.72, 0.43 ± 0.1, $p < 0.05$) were significantly higher than in the normocholesterolaemic group of CH-C, respectively. Lp(a) concentrations were higher in the CH-MI with borderline statistical significance ($p = 0.08$) (Table 3). A distribution of Lp(a) levels did not exhibit a typically skewed distribution in the CH-MI as it was found in CH-C. Lp(a) risk levels were found in 17 CH-MI (33%) while in 13 of the CH-C (14%) ($p < 0.01$). Discriminant analysis showed that the appliance of the presented biochemical criteria was satisfactory to distinguish the CH-MI in 64.7 %.

Table 3
Characteristics of children with normocholesterolaemia

	Children-MI (n = 43)	Children-control (n = 66)
Cholesterol mmol/l	4.17 ± 0.48	4.28 ± 0.54
Triglycerides mmol/l	0.84 ± 0.39	0.80 ± 0.38
apo-B g/l	0.57 ± 0.10	0.57 ± 0.12
apo-A-I g/l	1.20 ± 0.24	1.32 ± 0.12**
apo-B:apo-A-I	0.58 ± 0.72	0.43 ± 0.10*
Lp(a) mg/dl	16.55 ± 21.01	12.21 ± 16.65

*Normocholesterolaemia: cholesterol less than 5.2 mmol/l. The statistical significance of differences between children (CH-MI compared with CH-C): * $p = 0.05$, ** $p = 0.005$*

Evaluation of the prevalence of HLP among both groups of children showed an unexpected result that significantly higher levels of total cholesterol and a higher incidence of hypercholesterolaemia were found in the control children. This corresponds with the high prevalence of type IIA HLP in healthy parents which did not differ from that of MI ones (Rašlová *et al.* 1993). This might be explained by the high cholesterol diet in the Slovak population and/or genetic factors which influence cholesterol levels, such as common apo-E and LDL receptor polymorphisms (Hallman *et al.* 1991, Poledne *et al.* 1993).

In our study, reverse cholesterol transport is reflected in two parameters, the concentration of apo-A-I, and the risk index (25% higher in CH-MI mainly as a result of significantly lower apo-A-I concentration, because apo-B levels did not differ between the two groups of children). The significantly lower apo-A-I and higher risk index seen in the offsprings of MI-parents point to the possibility that the children from affected families have a disturbance of reverse cholesterol transport which might account for their dyslipoproteinemia (Fruchart *et al.* 1992). In an Austrian study, lower total cholesterol and HDL-cholesterol levels in the children with positive parental MI-history were found when compared with the controls (Yang *et al.* 1993). Since HDL-cholesterol levels correlate highly with apo-A-I, these findings are very close to those presented in our study. Widhalm *et al.* (1992) found that the proportion of apo-A-I:apo-B presented the best discriminator in children aged less than 20 years, which seems to be very comparable with the results found in our group of offsprings of MI-parents.

Furthermore, the synthesis of small dense cholesterol ester depleted LDL particles (Austin *et al.* 1992) in normolipaemic children from the affected families may also be related to their lower cholesterol concentrations. As the concentrations of apo-B did not differ among the risk and non-risk children, the speculation that this defect is present in CH-MI is less likely.

Since the most frequent primary HLP in adult members from MI families was familial combined hyperlipoproteinaemia (Rašlová *et al.* 1993), which is rarely manifested in childhood and adolescence, we assume that this condition is presented at the level of an unfavourable proportion of apolipoproteins in the lipoprotein classes in the affected children. Hence, the apo-A-I and RI values represent useful methods for identifying children at higher risk with respect to premature atherosclerosis.

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