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Cholesterol ester transfer protein (CETP) gene polymorphism and selected parameters of lipid metabolism in children from families with history of cardiovascular system diseases

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Background: Children from families with a history of cardiovascular system diseases are especially predisposed to early development of atherosclerosis. Therefore, the aim of this study was to examine the selected lipid parameters and polymorphisms of G279A located in the cholesterol ester transfer protein (CETP) gene.

Material/Methods: This longitudinal study was performed in 3 stages. During stage I the tests were carried out on 137 newborns after birth. Of these, we selected 30 children with a family history of cardiovascular system diseases. During stage II of the study the same children were evaluated at the age of 18–30 months, and during stage III at the age 5–6 years. Gestational age and the birth weight were evaluated in newborns. The older children were examined physically, and nutritional status was assessed. In all of the children examined, we determined the blood concentrations of triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, apolipoproteins (AI and B), lipoprotein(a) and polymorphisms, and the G279A locus of the CETP gene.

Results: In children with genotype B1B1 (after birth and aged 5–6 years), a significantly lower cholesterol concentration in the HDL fraction was found compared to those with genotype B1B2 and B2B2. Other biochemical parameters of lipid metabolism were not significantly different between these genetic polymorphisms.

Conclusions: A lower cholesterol concentration in the HDL fraction in children with a family history of cardiovascular system diseases was determined by polymorphism of the CETP gene. Homozygotes (genotype B1B1) show a tendency towards the phenotype favoring the development of atherosclerosis.

Key words: atherosclerosis • lipids • cholesterol ester transfer protein • polymorphism

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Background

Cardiovascular system diseases developing on the basis of atherosclerosis are a predominant factor responsible for deaths in highly industrialized countries. Atherosclerosis develops over many years, and although clinical symptoms are apparent in older age, the onset of atherosclerotic lesions may originate in early childhood [1–4]. Atherosclerosis is a chronic disease present in medium and large arteries. Atherosclerotic plaques in the membrane of the internal vascular wall result from many complex pathological processes [5]. The prevention of atherosclerosis requires an early diagnosis and control of risk factors [6].

It has been confirmed that during childhood and adolescence there occur many atherosclerosis risk factors, which may precede the manifestation of the disease in adulthood. The onset and development of atherosclerotic changes depend on the presence of genetic and environmental predisposing factors. The environmental, external factors (e.g., inadequate nutrition, low physical activity, cigarette smoking, or stress) lead to the development of internal risk factors (e.g., hyperlipidemia, obesity, diabetes, and arterial hypertension). Recently, family history of premature ischemic cardiac and brain ischemia has also been considered as an independent atherosclerosis risk factor. Moreover, it is suggested that vitamin D deficiency is attributed to development and progression of atherosclerotic cardiovascular disease [7,8]. A recent study among children with multiple modifiable atherosclerosis-promoting risk factors demonstrated an inverse correlation between vitamin D and cardiometabolic risk factors score. However, there was no association between vitamin D level and functional and structural vascular changes measured by vascular distensibility and carotid artery intima media thickness (CIMT). The authors presumed that vascular effect may be only seen in children with a history of chronic vitamin D deficiency [9]. Further studies are needed to explain this phenomenon.

Early detection and reduction of risk factors is important for prevention of atherosclerosis and its complications. However, it is not always possible to identify typical risk factors as being responsible for the occurrence of a cardiovascular disease. The detection of other risk factors is the subject of intensive research. For example, although atherosclerosis is the disease process underlying ischemic heart disease, at present it is possible to identify typical risk factors in only a half of the patients with symptoms of cardiac ischemia.

In consideration of the above, effective prevention of atherosclerosis requires early detection of risk factors, followed by their modification and treatment. For this purpose, lipid parameters, homocysteine, adhesion molecules, C-reactive protein (CRP), and homeostasis parameters are determined [10–12]. Also, disorders of lipid metabolism, particularly elevated cholesterol concentrations, are predisposing factors for atherosclerotic changes [10]. However, screening for lipids alone fails to identify all individuals at high risk; therefore, other markers that reflect different aspects of the disease process are needed to improve risk assessment for atherosclerosis development.

Due to progress in molecular biology, polymorphisms of the genes potentially associated with cardiovascular system diseases are being investigated. The group of genes regulating lipids metabolism has been studied [14]. Cholesterol ester transfer protein (CETP) is thought to regulate plasma HDL. Polymorphism in the CETP gene has a differential effect on the HDL cholesterol fraction (i.e, the cholesterol fraction showing a protective effect against the development of atherosclerosis) [15].

Plasma HDL cholesterol levels are associated with the CETP gene polymorphisms; therefore, the objective of our study was to assess the total cholesterol and its fractions (cholesterol HDL, LDL, VLDL) in blood plasma in different G279A polymorphisms of the CETP gene in children from families with history of cardiovascular diseases. In children from these families, we determined the levels of triglycerides, apolipoproteins (apo-AI and apo-B),and lipoprotein(a) in blood serum as early markers of atherosclerotic changes.

Material and Methods

The longitudinal study was performed in 3 stages. During stage I the tests were carried out on 137 newborns after birth. The study included newborns coming from normal, physiological pregnancy, spontaneously born, with general good condition. The evaluation of health condition of the newborns after birth was evaluated for 8–10 points on the Apgar scale. The gestational age of the studied newborns was evaluated on the basis of the date of the last menstruation of the mother and is presented in weeks of pregnancy. Physical development of the newborns after birth was defined on the basis of body weight and length. On the basis of the history of the mothers, the atherosclerosis risk factors were established in the families of the studied children (hypercholesterolemia, obesity, hypertension, diabetes, cardiac infarction, and stroke). In the final analysis there were included 30 children with a family history of cardiovascular system diseases. During stage II of the study the same children were evaluated at the age of 18–30 months, and during stage III we evaluated the children at the age 5–6 years. The children were examined physically and nutritional status assessed. All the children were examined and their physical development and nutritional status assessed. Evaluation of the nutritional condition of the children was made by defining the body mass index (BMI) and the sum of 3 skinfold tests. BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). Skinfold thickness was

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Table 1. The distribution of frequencies of genotypes and allele of G279A gene CETP in children from families with cardiovascular system diseases history.

Genotype frequency(n)			Allele frequency(n)	
B2B2	**B1B2**	**B1B1**	**B2**	**B1**
6.7% (n=2)	5.3% (n=16)	40.0% (n=12)	33.33% (n=20)	66.66% (n=40)

measured with skin-fold calipers to 0.1millimeter in 3 points (biceps, triceps, and subscapular triceps). The degree of obesity was assessed according to the sum of these 3 skin-fold tests in millimeters. In all of the children examined, the concentrations of triglycerides, total cholesterol, HDL-cholesterol, apolipoproteins (AI and B), and lipoprotein(a) were determined in blood serum. The concentration of triglycerides, total cholesterol, and HDL-cholesterol were assayed with the Cobas-Mira S analyser. The concentration of LDL-cholesterol (LDL-chol) and VLDL-cholesterol (VLDL-chol) was defined by using the formula by Friedewald [16]. Apolipoproteins apo-Al and apo-B were assayed by means of the immunoturbidimetric method using a Cobas-Mira S apparatus. The concentration of homocysteine was determined with ELISA method by use of an Axis-Shield AS (Germany) set. Lipoprotein(a) was determined by the immunoturbidimetric method using "Human" reagents.

The polymorphism G279A of the CETP gene was assessed by PCR-AFLP (Polymerase Chain Reaction – Amplified Fragment Length Polymorphism) method.

The statistical analysis was performed with the use of Statistica 5.1 software. Differences were assessed between the groups of children with genotype B1B1 and those with genotypes B1B2 + B2B2, with the consideration of the following the selected lipids parameters in blood plasma. The distribution of studied data sets was checked by use of the Kolmogorov-Smirnov test. For the analysis of the differences between the groups examined, the t test was used if the distribution of the parameter examined did not differ from normal distribution, and the Mann Whitney test was used when the distribution of the parameter examined was skewed. The p values <0.05 were considered statistically significant.

The study was approved by Medical University Bioethical Committee (number KE-0254/74/2009).

Results

The distribution of frequencies of genotypes and allele of G279A gene CETP in children from families with history of cardiovascular system diseases are presented in Table 1. In assessing the distribution of polymorphisms Taq1B gene CETP in the 30 studied children, the following were found: 12 (40.0%) homozygote (genotype B1B1), 16 (53.3%) heterozygote (genotype B1B2), and 2 (6.7%) with wild type genotype (B2B2). In the group examined, the incidence of allele B2 constituted 33.33% (n=20) and allele B1 was 66.67% (n=40). Due to the low frequency of the incidence of genotype B2B2 (n=2) in the research material, comparison was carried out between the features studied and the biochemical parameters in blood serum of children with B1B1 genotype, in relation to the sum of the 2 genotypes (B1B2 + B2B2).

The characteristics of 30 children after birth with a family history of cardiovascular system diseases according to the genotype G279A are presented in Table 2, characteristics of children aged 18–30 months in are shown in Table 3, and those of children aged 5–6 years are shown in Table 4.

In newborns and children aged 5–6 years with genotype B1B1, we found a lower percentage of cholesterol concentration in the HDL fraction compared to children with genotypes B1B2 and B2B2 ($p<0.05$). We also noted that children with genotype B1B1 weighed less at ages 18–30 months) and were shorter at ages 5–6 years) than children with genotypes B1B2 and B2B2. This difference was statistically significant ($p<0.05$). We found no statistically significant differences in analyzing the changeability of the remaining biochemical parameters (total cholesterol, LDL-cholesterol, VLDL-cholesterol, apo-AI, apo-B and lipoprotein(a)) according to the polymorphism of CETP.

Discussion

Mutation of gene CETP G279A is the significant regulator of cholesterol concentration within the HDL fraction. The presence of allele G279 (allele B1) of the CETP gene is responsible for higher CETP activity and lower cholesterol concentration within the HDL fraction; therefore, it may be responsible for the development of cardiovascular system diseases [15–19]. However, the presence of allele A279 (allele B2) is associated with lower CETP activity and higher HDL cholesterol value, which are connected with antiatherogenic activity.

The prevalence of allele B1, the so-called risk allele, has been assessed in many studies on adults; however, studies on Caucasian children are lacking [20–23].

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Table 2. Characteristics of the studied features and biochemical parameters in cord blood serum in children according to the genotype G279A.

Parameters	B1B1 (n=12)	B1B2+B2B2 (n=16)+(n=2)=18	p
	M ±SD	M ±SD	
Gestational age (weeks)	39.67±1.50	39.39±1.54	ns
Weight at birth (g)	3508.33±297.59	3493.89±478.39	ns
Height at birth (cm)	53.42±5.38	55.78±1.93	ns
Triglycerides (mg/dl)	90.92±161.01	39.83±10.98	ns
Total-Cholesterol (mg/dl)	66.25±26.19	63.17±19.05	ns
HDL-cholesterol (mg/dl)	17.77±6.20	21.06±7.43	ns
%HDL- cholesterol	27.98±7.29	33.49±4.48	p<0.05
LDL-cholesterol (mg/dl)	36.96±13.75	34.42±12.47	ns
VLDL-cholesterol(mg/dl)	11.52±9.61	8.19±2.25	ns
Apolipoprotein-AI(mg/dl)	87.92±19.51	93.11±17.49	ns
Apolipoprotein-B (mg/dl)	37.58±15.63	36.50±13.03	ns

Table 3. Characteristics of the studied features and biochemical parameters in blood serum in children according to the genotype G279A (II stage).

Parameters	B1B1 (n=12)	B1B2+B2B2 (n=16)+(n=2)=18	p
	M ± SD	M ± SD	
Age (years)	1.90±0.32	2.00±0.35	ns
Weight (kg)	11.94±1.05	13.28±2.04	p<0.05
Height (cm)	85.50±6.50	87.00±6.01	ns
Adipose tissue thickness (mm)	19.00±4.45	18.77±3.77	ns
Duration of breastfeeding (months)	8.40±5.08	5.92±5.84	ns
Triglycerides (mg/dl)	118.90±83.74	89.85±36.84	ns
Total-Cholesterol (mg/dl)	169.50±37.20	162.54±25.54	ns
HDL-cholesterol (mg/dl)	46.01±13.99	49.31±10.52	ns
%HDL- cholesterol	28.73±13.76	31.05±9.10	ns
LDL-cholesterol (mg/dl)	99.71±44.02	95.26±28.24	ns
VLDL-cholesterol (mg/dl)	23.78±16.75	17.97±7.37	ns
Apolipoprotein-AI (mg/dl)	143.90±18.83	145.77±17.62	ns
Apolipoprotein -B (mg/dl)	82.00±20.04	76.31±12.30	ns
Lipoprotein(a) (mg/dl)	6.83±6.23	6.09±4.22	ns

In the present study, the distribution of the mutation of G279A CETP gene was assessed in children from families with history of cardiovascular system diseases: 66.67% had allele B1, 40.0% (12) had genotype B1B1, 53.3% (16) had genotype B1B2, and 6.7% (2) had B2B2.

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Table 4. Characteristics of the studied features and biochemical parameters in blood serum in children according to the genotype G279A (III stage).

Parameters	B1B1 (n=12)	B1B2+B2B2 (n=16)+(n=2)=18	p
	M ±SD	M ±SD	
Age (years)	5.33±0.33	5.44±0.42	ns
Weight (kg)	19.56±3.27	21.58±4.07	ns
Height (cm)	111.29±5.00	114.41±5.88	p<0.05
BMI (kg/m^2)	15.71±1.73	16.42±2.29	ns
Adipose tissue thickness (mm)	23.42±7.67	25.72±6.30	ns
Triglycerides (mg/dl)	66.17±32.16	64.17±41.74	ns
Total-Cholesterol (mg/dl)	154.25±26.67	147.39±26.32	ns
HDL-cholesterol (mg/dl)	39.77±14.63	46.24±12.28	ns
%HDL- cholesterol	25.11±7.46	31.49±7.80	p<0.05
LDL-cholesterol (mg/dl)	102.08±24.20	88.31±25.14	ns
VLDL-cholesterol (mg/dl)	13.23±6.43	12.83±8.35	ns
Apolipoprotein-AI (mg/dl)	126.44±35.12	129.07±27.72	ns
Apolipoprotein -B (mg/dl)	68.75±14.55	62.78±11.57	ns
Lipoprotein(a) (mg/dl)	12.63±15.27	10.04±11.13	ns

Among Greek children recruited into the Gene-Diet Attica Investigation on childhood obesity (GENDAI), genotype B1B1 was present in 35.44%, B1B2 in 49.37%, and B2B2 in 15.15% of children [24].

In Polish adults with overweight and obesity, 45.2% were B1B2 heterozygotes, B1B1 genotype was present in 34.2%, and B2B2 was present in only 20.6% of adults [25].

In population studies conducted among Chinese adults, genotype B1B1 was present in 35.6% of the adults examined [22], and genotype B1B1 was present in 30.4% of Chinese with hyperlipidemia [26]. Studies conducted among Americans with confirmed coronary disease showed genotype B1B1 in 32.9% of the adults examined [18]. In studies conducted among Americans according to race, Cuchel et al. reported that genotype B1B1 was present in 56.0% of African-Americans and in 33.0% of Caucasians [27].

In the present study, we assessed the effect of polymorphism Tag1B of gene CETP on the concentration of total cholesterol and its fractions, triglycerides, lipoprotein(a), apolipoprotein (AI and B), homocysteine, and adhesive molecules in blood serum of children from families with history of cardiovascular system diseases. We compared the studied features and biochemical parameters in blood serum in children with B1B1 genotype (n=12), and with genotype B1B2 (n=16) and B2B2 (n=2). In children with genotype B1B1, a lower percentage of cholesterol concentration was noted in the HDL fraction than in children with genotype B1B2 and B2B2. Analysis of the changeability of the remaining features and biochemical parameters in children according to polymorphism of the CETP gene showed no significant differences. In children with the B1B1 genotype, we found a higher concentration of total cholesterol and cholesterol in the LDL fraction and a lower concentration of cholesterol in the HDL fraction, compared to children with genotypes B1B2 and B2B2.

It should be mentioned, however, that the differences were not statistically significant. Perhaps because CETP activity in children is lower than in adults, the stated differences of lipid economy were therefore not statistically significant. However, this was probably due to the underpowered, small study sample.

The current study shows that children with genotype B1B1 (therefore with the risk genotype) have a proatherogenic lipid profile, and therefore are at higher risk of early development of cardiovascular system diseases.

Based on the available literature, it appears that most of the studies assessing the effect of polymorphism of the CETP gene on the concentration and activity of CETP and the metabolism

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of lipids and lipoproteins in blood serum were conducted in adult patients and that studies on children are lacking.

In a Greek study among children, the association of the B2 allele with higher HDL-C levels was observed. Homozygotes for the B2 allele had approximately 10% higher mean HDL-C levels compared to the B1/B1 individuals [24].

In a recent study among 50 Polish children with nephritic syndrome in remission, CETP polymorphism was detected in 31 (62%) patients. Within this group, dyslipidemia was found in 71% (22/31) of children *versus* 78.9% (15/19) in the remaining cases [28]. It should be noted that this study did not confirm the essential influence of other specific polymorphisms of genes coding selected proteins involved in lipoprotein metabolism on persistent lipid profile abnormalities during remission of nephrotic syndrome [28].

Among Polish obese men, the B2 allele was associated with an increased HDL-C levels. Thus, the highest HDL-C level was observed in B2B2 homozygotes and the lowest in B1B1 homozygotes. However there was no such correlation in obese women [25].

Zheng et al. assessed the relationship between 3 polymorphisms of the CETP gene and the concentration of lipids and lipoproteins in blood serum of patients with diagnosed cardiovascular disease, as well as in a control group [17], confirming that the distribution of allele and the occurrence of genotype Taq1B was similar in patients with a cardiovascular disease and in healthy individuals. Among patients with a cardiovascular disease and with genotype B1B1, a higher concentration of total cholesterol and LDL cholesterol was observed compared to patients with genotype B2B2. Among healthy individuals with genotype B1B1, there was a higher concentration of LDL cholesterol in blood serum compared to healthy individuals with genotype B2B2. Based on the results of the study, the authors suggest that in the studied population the genotype B1B1 may possibly be a genetic risk factor for cardiovascular system diseases. Liu et al. conducted a prospective study concerning the definition of the polymorphism of Taq1B of the CETP gene and the assessment of risk of heart attack in males [20]. The polymorphism Taq1B of the CETP gene in males who had a heart attack in middle age was investigated. Genotype B2B2 was present in 17% of the studied group, among whom there was a higher concentration of HDL cholesterol than in males with genotypes B1B1 and B2B2. While evaluating the risk of heart attack according to the particular genotype, no significant differences were noted in the 3 groups studied. However, on the basis of the conducted analysis, it was confirmed that the vectors of allele B2 Taq1B of the CETP gene have a higher concentration of HDL cholesterol. This fact, however, does not mean that there is a lower risk of heart attack. Comprehensive population studies examined the effect of changeability of the CETP gene on the total cholesterol concentration and its fractions and on the risk of cardiovascular system diseases.

Wu et al, studying patients with cardiac ischemia, showed that in patients with this coronary disease in which allele A C629A of the CETP gene was present, there is a lower risk of future cardiovascular system diseases and mortality due to those diseases [29]. Based on their study, the authors suggest that the CETP genotype has an important influence on the CETP and on the concentration of HDL cholesterol.

Polymorphism Taq1B of CETP in patients with normolipidemia is connected with higher activity and a higher concentration of CETP, as well as with higher HDL cholesterol in blood serum. Studies have also been carried out to evaluate the connection between polymorphism Taq1B of the CETP gene in patients with family history of hypercholesterolemia. The researchers defined the frequency of occurrence of allele B2 in heterozygotes among the Spanish population with family history of hypercholesterolemia, and observed the occurrence of allele B2 with the frequency 0.43 among this group. A similar situation appears in other populations. While analyzing the results of the study, a correlation was noted between the occurrence of allele B2 and higher concentrations of HDL and apolipoprotein A-I. Simultaneously, the researchers observed that patients with genotype B2B2 had a lower concentration of LDL cholesterol and apolipoprotein-B than those with genotype B1B1 and B2B2. It was also shown that polymorphism Taq1 of the CETP gene in heterozygotes with a family history of hypercholesterolemia influences the decrease of atherogenic lipid profile due to a lower LDL concentration, a higher HDL concentration, and a lower index value for LDL cholesterol/HDL cholesterol. It was additionally observed that in these patients, to a lesser extent, allele B2 was a predisposing factor for the occurrence of arcus cornealis, xanthomata, and clinical arteriosclerotic disease [30].

In other studies, the value and activity of the CETP gene in 30 patients with primary hypercholesterolemia has been noted. A higher activity of CETP was observed in patients with genotype B1B1 compared to patients with genotype B2B2. But in patients with genotype B1B2, the value of CETP was mid-way between the values in the groups with genotypes B1B1 and B2B2. A positive correlation was also noted between the activity and concentration of CETP and the concentration of LDL cholesterol in blood serum [31].

Zhao et al. assessed the relationship between polymorphism of the CETP gene and hyperlipidemia in the Chinese population group aged 35–81 years [26]. Among patients with hyperlipidemia, the frequencies of genotype Taq1B of the CETP

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gene were as follows: B1B1 – 30.4%, B1B2 – 52.0%, B2B2 – 17.6%, allele B1 – 56.4%, and allele B2 – 43.6%. However, the researchers did not observe any relationship between polymorphism of the CETP gene and hyperlipidemia in middle-aged and elderly Chinese patients.

In contrast, other researchers have shown that genotype B2B2 is connected with a higher HDL cholesterol concentration as a result of lower CETP activity, consequently lowering the risk of cardiac ischemia [24,32].

On the basis of several studies, it is possible to state that polymorphism Taq1B of the CETP gene is the determinant responsible for the concentration of CEPT. This constitutes the key element of cholesterol reverse transfer – the protective system against the development of atherosclerosis. Many researchers, however, stress the fact that environmental factors (eg, cigarette smoking, alcohol consumption, stress, inadequate nutrition, or low physical activity), apart from genetic factors, play a major role in the regulation of CETP concentration [22,33].

At present, in the assessment of atherosclerosis risk, much attention is being paid to genetic studies. Many polymorphic forms of genes and mutations connected with a higher risk of atherosclerosis development have been identified. It is believed that in the future genetic markers will enable the detection of people belonging to the group at high risk, and it will be possible to undertake efficient preventive actions.

Subsequent preventive actions would require the identification of children at particular risk of early development of atherosclerosis changes and cardiovascular system diseases. Children at high risk of premature atherosclerosis, from the moment of birth, require study not only of the hereditary, but also environmental risk factors. Therefore, selective screening and early detection of risk factors of cardiovascular system diseases in children and adolescents, as well as their modification and treatment, constitute the biggest challenge for pediatricians and general practitioners.

The limitation of our study is that it had a quite small, underpowered study group and lacked healthy controls without positive family history of cardiovascular system diseases. It should be noted that obtaining an informed consent for genetic tests in perfectly healthy newborns and children without positive family history of cardiovascular system diseases is an extremely difficult process and it may raise ethical controversy. Test results may cause stigmatization and discrimination, family discord, or psychological distress [34].

However, it should be highlighted that there is a need for a study comparing lipid profiles of an adequate number of children with and without positive history of cardiovascular system diseases according to their genotypes.

Conclusions

A lower cholesterol concentration in the HDL fraction in blood serum in children from families with cardiovascular system disease history was determined by polymorphism of the CETP gene. Homozygotes (genotype B1B1) show a tendency towards the phenotype favoring the development of atherosclerosis. In the future, proper early prevention based on the modification of risk factors, periodic lipid profile control, and the assay of markers of early atherosclerosis changes can reduce morbidity and mortality due to cardiovascular system diseases among children.

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