ORIGINAL ARTICLE

Homocysteine and metabolic risk factors in individuals with family history of premature ischemic stroke

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KEY WORDS

atherosclerosis, homocysteine, stroke

ABSTRACT

INTRODUCTION Family history of stroke is an independent risk factor for cardiovascular disease (CVD).

OBJECTIVES The aim of this study was to evaluate selected metabolic risk factors and an association between the interaction of family history of premature ischemic stroke (PIS) and homocysteine (Hcy) levels with other risk factors in individuals with family history of PIS.

PATIENTS AND METHODS The study involved 344 healthy individuals, including 143 with family history of PIS and 201 without family history of PIS (control group).

RESULTS In the group with family history of PIS, a significantly higher mean body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), ApoB/ apolipoprotein A-I (ApoA-I), and glucose values were observed in women, while in men, significantly higher mean values of BMI, SBP and DBP, total cholesterol (TC), LDL-C, ApoB/ApoA-I, and lower ApoA-I. There was a significant interaction of family history of PIS × Hcy for TC/high-density lipoprotein cholesterol (HDL-C), HDL-C, and triglycerides (TG) in women, and for TC/HDL-C, TC, and TG in men. Higher Hcy levels were associated with significantly higher values of TC/HDL-C and TG both in men and women, and with lower HDL-C levels in women and higher TC and LDL-C levels in men.

CONCLUSIONS Men and women with family history of PIS are characterized by an unfavorable shift in the risk factor profile. This effect is additionally enhanced by higher Hcy levels, which might be an indication for primary prevention in these individuals.

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INTRODUCTION Stroke is one of the main causes of death in the adult population.[1] Family history of stroke is recognized as an independent risk factor for cardiovascular disease (CVD).[2] According to Framingham prospective studies, a family history of stroke before the age of 65 years increases the risk of this condition in progeny 2- to 3-fold. This correlation is independent of conventional risk factors for stroke such as age, sex, systolic blood pressure (SBP), arterial hypertension, diabetes, tobacco smoking, coronary events, or the presence of atrial fibrillation or left ventricular hypertrophy.[3] While not excluding the potential genetic factors, the underlying causes of family risk of stroke should be sought in the interaction of many environmental factors. One of such factors might be elevated homocysteine (Hcy) concentrations resulting from chronic B-group vitamin deficiency (folic acid, vitamins B_6 and B_{12}) in diet. Such an association has been indicated in the studies on the Japanese population, showing that low intake of B-group vitamins has an effect on the increase in the risk of stroke.[4] Moreover, it has been shown that the Hcy concentration in the Polish population is independently associated with all-cause mortality and

TABLE 1 Mean values of metabolic risk factors in women and men in the groups with and without family history of premature ischemic stroke

Parameters	Women			Men		
	(+) PIS	(–) PIS	P_{ANOVA}	(+) PIS	(–) PIS	P_{ANOVA}
	n = 71	n = 111		n = 72	n = 90	
age, y	30.4 ±7.6	32.1 ±12.7	0.320	30.4 ±9.0	28.8 ±11.6	0.336
BMI, kg/m^2	23.7 ±4.2	22.0 ±3.6	0.005	25.4 ±3.7	23.6 ±3.1	0.001
SBP, mmHg	124 ±20	119 ±13	0.039	131 ±15	126 ±13	0.020
DBP, mmHg	84 ±11	77 ±10	<0.001	87 ±12	81 ±8	<0.001
TC, mg/dl	190 ±45	180 ±43	0.112	204 ±60	181 ±51	0.011
LDL-C, mg/dl	108 ±26	92 ±23	<0.001	121 ±43	106 ±39	0.020
HDL-C, mg/dl	60 ±11	58 ±10	0.303	49 ±10	50 ±10	0.865
TG, mg/dl	92 ±35	91 ±48	0.850	131 ±107	106 ±48	0.053
ApoA-I, mg/dl	157 ±16	159 ±16	0.352	142 ±20	149 ±17	0.009
ApoB, mg/dl	94 ±17	89 ±17	0.045	97 ±22	94 ±22	0.401
TC / HDL-C	3.30 ±1.01	3.17 ±0.88	0.348	4.20 ±1.21	3.80 ±1.33	0.051
ApoB / ApoA-I	0.61 ±0.12	0.57 ±0.12	0.029	0.69 ±0.14	0.64 ±0.15	0.031
Lp(a), mg/dl	28 ±23	26 ±25	0.503	24 ±25	26 ±26	0.315
Hcy, µmol/l	10.5 ±3.7	10.5 ±3.5	0.901	11.8 ±4.3	12.4 ±3.8	0.117
fibrinogen, g/l	3.11 ±0.64	3.05 ±0.61	0.549	2.76 ±0.67	2.92 ±0.72	0.167
CRP, mg/l	1.8 ±2.6	1.4 ±2.4	0.074	2.0 ±3.4	1.7 ±3.5	0.125
glucose, mg/dl	94 ±8	91 ±10	0.022	97 ±11	94 ±12	0.096
uric acid, mg/dl	4.7 ±0.8	4.5 ±0.8	0.319	6.5 ±1.0	6.3 ±1.0	0.173
folic acid, g/ml	5.8 ±3.1	7.3 ±2.8	0.065	6.0 ±2.8	7.4 ±2.7	0.096

Data are presented as mean ± standard deviation.

Conversion factors to SI units are as follows: TC, LDL-C, and HDL-C: 0.02586; TG: 0.01143; ApoA-I, ApoB, and Lp(a): 0.01; glucose: 0.05551; uric acid: 0.05948; folic acid: 2.265.

Abbreviations: ApoA-I – apolipoprotein AI, ApoB – apolipoprotein B, BMI – body mass index, CRP – C-reactive protein, DBP – diastolic blood pressure, Hcy – homocysteine, HDL-C – high density lipoproteins cholesterol, LDL-C – low-density lipoproteins cholesterol, Lp(a) – lipoprotein(a), PIS – premature ischemic stroke, SBP – systolic blood pressure, TC – total cholesterol, TG – triglycerides

cardiovascular mortality in adults.[5] The results of numerous meta-analyses have demonstrated that, in individuals with elevated Hcy levels, the relative risk of ischemic heart disease and stroke was higher, and that the lowering of Hcy levels resulted in a reduction of this risk.[6,7] The NORVIT, HOPE 2, and VITATOPS studies on secondary prevention have not shown lower mortality due to CVD or stroke after the reduction of Hcy levels.[8-10] On the other hand, the meta-analyses of studies on primary stroke prevention conducted by Wang et al.[11] and by Lee et al.,[12] have indicated benefits from Hcy lowering with folic acid.

The aim of this study was to evaluate selected metabolic risk factors in a population of healthy women and men with family history of premature ischemic stroke (PIS), and, in particular,to analyze potential associations between the interaction of 2 factors: family history of PIS (nonmodifiable factor) and Hcy levels (modifiable factor) with the other analysed risk factors. We hypothesized that the interaction of these 2 factors allows to distinguish individuals with higher risk associated with the presence of conventional risk factors and thus apply primary prevention in this population.

PATIENTS AND METHODS The study involved 344 healthy individuals, including 143 with family history of PIS (71 women and 72 men), constituting the study group, and 201 individuals without family history of PIS (111 women and 90 men), constituting the control group. The age of the subjects was between 18 and 55 years. The inclusion criteria for the study group were as follows: age ≥18 years, written informed consent to participate in the study, at least 1 parent who had suffered from PIS (fathers at the age of up to 55 and mothers of up to 65 years), absence of concurrent inflammation, no hypolipidemic or metabolism-modulating agents, and no administration of B-group vitamins or vitamin preparations within the 6 previous months. The exclusion criteria were as follows: age <18 years, lack of consent to participate in the study, administration of hypolipidemic, metabolism-modulating agents, supplements, and vitamin preparations, chronic inflammation, CVD diagnosed prior to or during the study, diabetes, chronic kidney disease, and gout. Clinical characteristics of the study group were as follows: 49.7% of participants were women, low physical activity was reported in 65% and hypertension in 30% of the individuals, almost 31% of the subjects were overweight, 7% were obese, and 35% were smokers. The control group

TABLE 2 Two-way interaction analysis: family history of premature ischemic stroke and homocysteine levels in the upper compared with the lower quartiles with metabolic risk factors in women

Parameters	(+) PIS		(–) PIS		P_{ANOVA}
	Hcy Q4	Hcy Q1–3	Hcy Q4	Hcy Q1–3	
BMI, kg/m^2	24.1 ±3.9	23.6 ±4.3	22.3 ±4.2	22.0 ±3.4	0.960
SBP, mmHg	124 ±11	123 ±22	119 ±13	118 ±13	0.957
DBP, mmHg	81 ±10	84 ±11	76 ±10	78 ±10	0.753
TC, mg/dl	199 ±46	188 ±44	175 ±43	181 ±44	0.246
LDL-C, mg/dl	109 ±31	107 ±25	95 ±26	92 ±23	0.836
TG, mg/dl	114 ±52	85 ±25	91 ±16	91 ±50	0.042[a]
ApoA-I, mg/dl	150 ±17	159 ±15	160 ±16	159 ±16	0.103
ApoB, mg/dl	96 ±18	94 ±17	91 ±16	89 ±17	0.925
ApoB / ApoA-I	0.65 ±0.13	0.59 ±0.12	0.57 ±0.11	0.56 ±0.12	0.239
Lp(a), mg/dl	35 ±26	26 ±22	33 ±29	24 ±23	0.846
fibrinogen, g/l	3.12 ±0.67	3.10 ±0.63	2.78 ±0.61	3.13 ±0.59	0.103
CRP, mg/l	2.7 ±1.4	2.0 ±2.9	1.5 ±2.3	1.4 ±2.5	0.782
glucose, mg/dl	95 ±7	94 ±9	92 ±11	90 ±10	0.811
uric acid, mg/dl	5.0 ±0.8	4.6 ±0.8	4.3 ±0.6	4.6 ±0.8	0.098
folic acid, ng/ml	5.9 ±2.5	6.9 ±3.2	7.2 ±2.9	6.7 ±3.2	0.376

Data are presented as mean ± standard deviation.

Tukey's post-hoc test:
a (+) PIS × Hcy Q4 vs. (–) PIS × Hcy Q4, $P = 0.057$; (+) PIS × Hcy Q4 vs. (+) PIS × Hcy Q1–3, $P = 0.007$

For conversion factors: see TABLE 1

Abbreviations: see TABLE 1

were sex- and age-matched individuals whose parents did not have a history of PIS or myocardial infarction or other cardiovascular disorders with comparable distribution of smoking and low physical activity among individuals. All subjects had their medical history taken, underwent physical examination, had blood samples collected for laboratory testing, and had their systolic and diastolic blood pressure (DBP), pulse, height, and body weight measured and the body mass index (BMI) calculated. Laboratory testing involved the measurement of glucose, creatinine, uric acid, lipids and apolipoproteins, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoproteins A-I and B (ApoA-I, ApoB), lipoprotein (a) [Lp(a)], as well as other biochemical cardiovascular risk factors such as Hcy, C-reactive protein (CRP), fibrinogen, and folic acid. The study was approved by the Bioethics Committee of the Pomeranian Medical University in Szczecin, Poland, and a written consent was obtained from all participants.

The statistical analysis was performed with the use of STATISTICA PL, v. 9.0 package (StatSoft Polska, StatSoft Tulsa, Oklahoma, United States). The analysed parameters were evaluated using the Shapiro–Wilk test for normal distribution. Logarithmic transformation was performed for CRP, Lp(a), Hcy, and TC/HDL-C. The analysis of variance (ANOVA) for single-factor and two-factor classification was used to compare the mean values of evaluated parameters between the studied groups. In the former, the classifying factor was family history of PIS with age as a covariate. Two-way ANOVA was used in the assessment of the effect of family history of PIS × Hcy interaction on the analysed parameters. The level of the second grouping factor, Hcy, was defined based on the value of its upper quartile (Q4) in relation to the rest of the values (Q1–3). The significance of the effects of interaction of both factors on the analyzed variables was determined, and the Tukey's post-hoc multiple comparison test was used for the evaluation of the significance of differences between the means in individual groups depending on the level of the classifying factor. In all analyses, the adopted significance threshold was P-value of less than 0.05.

RESULTS

TABLE 1 presents the comparison of the arithmetic mean values for the studied parameters in women and men, including the family history of PIS. Both in women and men with family history of PIS, the mean values of BMI, SBP, DBP, LDL-C, and ApoB/ApoA-I were higher compared with subjects without family history of PIS. In women with family history of PIS, the mean values of ApoB and glucose were higher, while in men ApoA-I values were lower. Mean Hcy levels did not differ depending on the family history. TABLE 2 presents the results of the analysis of a two-factor interaction: family history of PIS × Hcy for the analysed parameters in women, while TABLE 3 – in men. For Hcy, we adopted 2 levels, opposing the levels from the upper

TABLE 3 Two-way interaction analysis: family history of early ischemic stroke and homocysteine levels in the upper compared with the lower quartiles on metabolic risk factors in men

Parameters	(+) PIS		(–) PIS		P_{ANOVA}
	Hcy Q4	Hcy Q1–3	Hcy Q4	Hcy Q1–3	
BMI, kg/m^2	25.8 ±3.6	23.4 ±3.2	25.3 ±3.8	23.7 ±3.1	0.535
SBP, mmHg	132 ±15	128 ±11	130 ±16	125 ±13	0.772
DBP, mmHg	89 ±14	81 ±8	87 ±12	81 ±9	0.740
TC, mg/dl	243 ±64	193 ±54	174 ±48	185 ±52	0.003[a]
LDL-C, mg/dl	48 ±8	50 ±10	49 ±9	50 ±11	0.910
TG, mg/dl	208 ±206	110 ±45	105 ±46	106 ±49	0.001[b]
ApoA-I, mg/dl	142 ±17	141 ±17	152 ±19	148 ±18	0.762
ApoB, mg/dl	104 ±24	95 ±21	95 ±23	94 ±21	0.299
ApoB / ApoA-I	0.75 ±0.18	0.67 ±0.13	0.63 ±0.17	0.64 ±0.14	0.126
Lp(a), mg/dl	17 ±16	25 ±26	20 ±20	28 ±27	0.958
fibrinogen, g/l	2.82 ±0.81	2.74 ±0.64	3.09 ±0.86	2.85 ±0.65	0.589
CRP, mg/l	3.1 ±4.1	1.6 ±3.1	2.7 ±5.1	1.2 ±2.1	0.851
glucose, mg/dl	98 ±13	97 ±10	93 ±9	94 ±12	0.555
uric acid, mg/dl	7.0 ±1.0	6.4 ±0.9	6.0 ±1.0	6.3 ±1.0	0.079
folic acid, ng/ml	5.5 ±2.1	7.4 ±2.8	6.4 ±2.6	9.2 ±2.9	0.794

Data are presented as mean ± standard deviation.

Tukey's post-hoc test:
a (+) PIS × Hcy Q4 vs. (–) PIS × Hcy Q4, P <0.001; (+) PIS × Hcy Q4 vs. (+) PIS × Hcy Q1–3, P <0.001
b (+) PIS × Hcy Q4 vs. (–) PIS × Hcy Q4, P <0.001; (+) PIS × Hcy Q4 vs. (+) PIS × Hcy Q1–3, P <0.001

For conversion factors: see **TABLE 1**

Abbreviations: see **TABLE 1**

quartile (Hcy Q4) to the remaining values (Hcy Q1–3); the Hcy Q4 levels were 11.8 µmol/l for women and 13.3 µmol/l for men. We observed a significant interaction between family history of PIS × Hcy and TC/HDL-C (P = 0.007), HDL-C (P = 0.011), and TG (P = 0.042) in women, and for TC/HDL-C (P = 0.015), TC (P = 0.003), and TG (P = 0.001) in men. In women with family history of PIS and higher Hcy (Q4), as compared with those with family history of PIS and low Hcy (Q1–3) and those without family history of PIS and Hcy Q4, the mean HDL-C levels were lower, while those of TG and TC/HDL-C were higher. The above parameters did not differ in women without family history of PIS depending on Hcy levels. The higher TC/HDL-C level in women with family history of PIS and Hcy Q4 was most likely associated with lower HDL-C levels in this subgroup of women, while TC levels did not differ between the analyzed subgroups of women. In men with family history of PIS and higher Hcy (Q4), as compared with those with family history of PIS and lower Hcy (Q1–3) and those without family history of PIS and Hcy q4, TC, TG, and TC/HDL-C levels were significantly higher. The higher TC/HDL-C level could be explained by higher TC levels in the subgroup of men with family history of PIS and Hcy Q4 as compared with the other men. No differences in HDL-C levels were observed (**TABLE 3**). In men, the interaction between family history of PIS and Hcy for LDL-C was not significant, yet the mean LDL-C level was significantly higher in men with family history of PIS and higher Hcy (Q4) as compared with men with family history of PIS and lower Hcy (Q1–3) and those without family history of PIS and Hcy Q4 (**FIGURE 1D**). Higher TC levels in men with family history of PIS and higher Hcy (Q4) were associated with higher LDL-C levels.

DISCUSSION Our results showed that among young healthy women and men with family history of PIS, the values of conventional cardiovascular risk factors (SBP, DBP, BMI, LDL-C, and ApoB/ApoA-I) were significantly higher compared with individuals without family history of PIS. The available studies on risk factors of premature stroke analyzed men and women aged from 35 to 64 years. According to their authors, the episodes of stroke in young individuals could be explained by risk factors that were present in this population.[13] A case study involving a young adult revealed that hyperhomocysteinemia, which contributes to premature atherosclerosis, can cause premature stroke.[14] A recent PRESARIO study on the risk of premature stroke was a population-based matched retrospective cohort study. It defined premature stroke as stroke that occurs before 65 years of age.[15] According to American guidelines from the '"National Cholesterol Education Program", cardiovascular events occurring due to premature atherosclerosis are diagnosed in men younger than 55 and women younger than 65 years.[16] Therefore, based on the earlier studies, to determine the term of premature stroke in parents of our subjects we adopted the same age criteria as

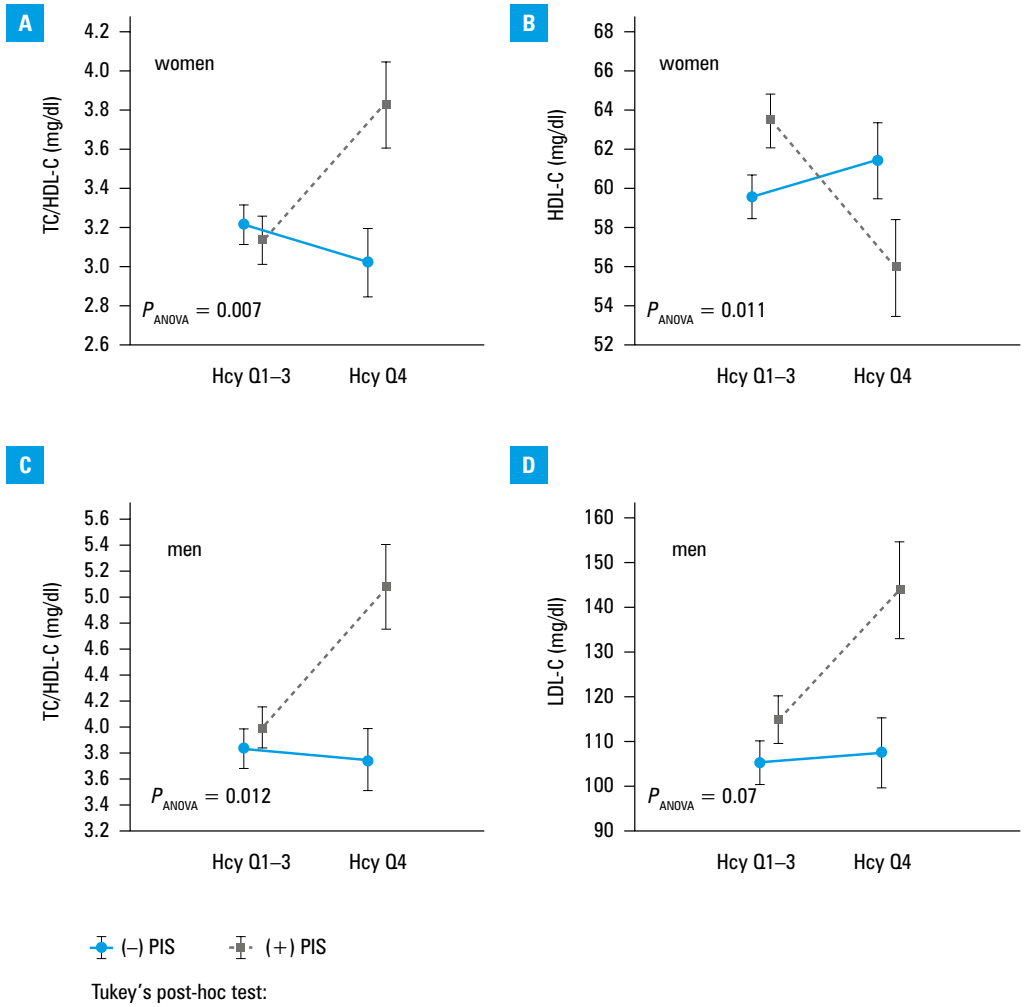

FIGURE 1 Two-way interaction analysis: family history of early ischemic stroke (PIS) and homocysteine levels in the upper compared with the lower quartiles on:
A – TC/HDL-C in women;
B – HDL-C in women;
C – TC/HDL-C in men;
D – LDL-C in men
Abbreviations: see **TABLE 1**

Tukey's post-hoc test:
A: (+) PIS × Hcy Q4 vs. (–) PIS × Hcy Q4, $P = 0.023$; (+) PIS × Hcy Q4 vs. (+) PIS × Hcy Q1–3, $P = 0.033$
B: (+) PIS × Hcy Q4 vs. (–) PIS × Hcy Q4, $P = 0.018$; (+) PIS × Hcy Q4 vs. (+) PIS × Hcy Q1–3, $P = 0.009$
C: (+) PIS × Hcy Q4 vs. (–) PIS × Hcy Q4, $P = 0.005$; (+) PIS × Hcy Q4 vs. (+) PIS × Hcy Q1–3, $P = 0.014$
D: (+) PIS × Hcy Q4 vs. (–) PIS × Hcy Q4, $P = 0.022$; (+) PIS × Hcy Q4 vs. (+) PIS × Hcy Q1–3, $P = 0.046$

in the case of positive family history of premature atherosclerosis resulting in cardiovascular events.

The multicenter INTERHEART[17] and INTERSTROKE[18] studies have indicated that cardiovascular risk factors are similar in men and women. Conventional risk factors, such as HDL-C level and tobacco smoking, could have explained the differences in the risk of coronary heart disease between men and women.[19] In our study, the parameters differentiating between men and women were ApoA-I and ApoB as well as glucose. In addition, in individuals with family history of PIS, higher Hcy levels coexisted with other risk factors: TC/HDL-C and TG, both in men and women, as well as HDL-C in women and TC and LDL-C in men.

Based on the results of Kuopio Ischemic Heart Disease Risk Factors (KIHD) Study, Virtanen et al.[20,21] concluded that an increase in the Hcy level by 2 μmol/l, within the accepted normal range of up to 12 μmol/l, results in an approximately twice higher risk of death due to cardiovascular causes in men in the presence of other risk factors such as tobacco smoking or elevated TC, LDL-C, ApoB, or fibrinogen levels. In addition, in that study, higher Hcy levels were associated with 2.6-fold higher risk of ischemic stroke. The coexistence of elevated LDL-C and Hcy in men with family history of PIS, observed in our study, might increase the probability of LDL modification by Hcy. In an experimental model, it has been demonstrated that homocysteinylated LDL intensifies the cytotoxic effect associated with increased lipid peroxidation and oxidative vascular endothelial cell damage.[22,23] The vascular endothelium damaged by hyperhomocysteinemia initiates inflammation and development of atherosclerotic lesions.[24] In women, we observed an association between lower HDL-C and elevated Hcy levels, which might increase the probability of HDL modification by Hcy. It has been shown that modified HDL molecules exhibit lower antioxidant and anti-inflammatory action.[25] Incubation of HDL molecules with homocysteine thiolactone resulted in the formation of Hcy-HDL and an increase in the sulfhydryl -SH groups on lipoprotein surface. A negative correlation has been demonstrated between the activity of paraoxonase bound with HDL and an increase in Hcy–HDL complexes.[26] High-density lipoproteins isolated from individuals with hyperhomocysteinemia inhibited the interleukin-6 release to a lower extent than in control individuals. An inverse correlation has been demonstrated between the paraoxonase activity and homocysteine and triglyceride levels, as well as direct proportionality with folic acid

levels and cholesterol efflux.[27] In our study, the higher Hcy levels were associated with higher TG levels in women and men with family history of PIS. In men, the mean ApoA-I level was significantly higher. In a study by Mikael et al.[28] and by Liao et al.,[29] a negative correlation was observed between homocysteine levels and ApoA-I and HDL-C in men with coronary heart disease. The authors suggested that low HDL-C and ApoA-I levels in individuals with elevated Hcy might explain the higher risk of CVD. A prospective study of the population from north-eastern Italy confirmed that in long-term follow-up, Hcy and vitamin B_6 are the best prognostic markers of coronary and cerebral events in healthy individuals.[30] It has been shown that supplementation with folic acid not only lowered the Hcy level but also effectively reduced the risk of stroke by 18% in individuals with no history of stroke.[11] The results of a meta-analysis conducted by Lee et al.[12] indicated that folic acid supplementation did not have a major effect on averting stroke. However, mild benefits in primary stroke prevention, especially when folate is combined with B vitamins and in male patients, merit further investigation.

Our study was limited by the place of residence of analyzed individuals. Both, the study and control groups consisted of urban area inhabitants. It has been shown that distribution of atherosclerotic risk factors differs between urban and rural residents. Lack of funds and modern imaging tests made it impossible to enroll adult progeny of patients who had suffered PIS and were hospitalized in smaller units in rural areas. Therefore, we focused on the group of individuals that was homogenous with regard to the place of residence. Another limitation was the fact that we did not assess family history of PIS and higher Hcy levels as a covariant in regard to nonmetabolic risk factors of atherosclerosis. Such an analysis exceeds the scope of this paper. As the frequency of smoking and low physical activity was comparable between the study and control groups, we focused on metabolic risk factors, which differed between the groups in this study.

Men and women with family history of PIS are characterized by an unfavorable shift in the risk factor profile. This effect is additionally intensified by higher Hcy levels, which might be an indication for primary prevention in these individuals.

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REFERENCES

1 Mancia G. Prevention and treatment of stroke in patients with hypertension. Clin Ther. 2004; 26: 631-648.

2 Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association. Stroke. 2006; 37: 1538-1633.

3 Seshadri S, Beiser A, Pikula A, et al. Parental occurrence of stroke and risk of stroke in their children: the Framingham study. Circulation. 2010; 121: 1304-1312.

4 Cui R, Moriyama Y, Koike KA, et al.; JACC Study group. Serum total homocysteine concentrations and risk of mortality from stroke and coronary heart disease in Japanese: the JACC study. Atherosclerosis. 2008; 198: 412-418.

5 Waśkiewicz A, Sygnowska E, Broda G. Homocysteine concentration and the risk of death in the adult Polish population. Kardiol Pol. 2012; 70: 897-902.

6 Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ. 2002; 325: 1202-1206.

7 Homocysteine Studies Collaboration: Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA. 2002; 288: 2015-2022.

8 Bønaa KH, Njølstad I, Ueland PM, et al.; the NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med. 2006; 354: 1578-1588.

9 Lonn E, Yusuf S, Arnold MJ, et al.; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med. 2006; 354: 1567-1577.

10 VITATOPS Trial Study Group. B vitamins in patients with recent transient ischemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial. Lancet Neurol. 2010; 9: 855-865.

11 Wang X, Qin X, Demirtas H, et al. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. Lancet. 2007; 369: 1876-1882.

12 Lee M, Hong KS, Chang SC, Saver JL. Efficacy of homocysteine-lowering therapy with folic acid in stroke prevention: a meta-analysis. Stroke. 2010; 41: 1205-1212.

13 Bonita R, Scragg R, Stewart A, et al. Cigarette smoking and risk of premature stroke in men and women. Br Med J. 1986; 293: 6-8.

14 Ray JG, Harvey DT. Hyperhomocysteinemia as a cause of premature stroke in a young patient. Arch Phys Med Rehabil. 1998; 79: 343-345.

15 Saposnik G, Redelmeier DA, Lu H, et al. Risk of premature stroke in recent immigrants (PRESARIO): population-based matched cohort study. Neurology. 2010; 74: 451-457.

16 Stone NJ, Bilek S, Rosenbaum S. Recent National Cholesterol Education Program Adult Treatment Panel III update: adjustments and options. Am J Cardiol. 2005; 96: 53E-59E.

17 Yusuf S, Hawken S, Ounpuu S, et al.; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART Study): case-control study. Lancet. 2004; 364: 937-952.

18 O'Donnell MJ, Xavier D, Liu L, et al.; INTERSTROKE investigators: Risk factors for ischemic and intracerebral hemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010; 376: 112-123.

19 Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. Circulation. 1999; 99: 1165-1172.

20 Virtanen JK, Voutilainen S, Alfthan G, et al. Homocysteine as a risk factor for CVD mortality in men with other CVD risk factors: the Kuopio Ischemic Heart Disease Risk Factor (KIHD) Study. J Intern Med. 2005; 257: 255-262.

21 Virtanen JK, Voutilainen S, Happonen P, et al. Serum homocysteine, folate and risk of stroke: Kuopio Ischemic Heart Disease Risk Factor (KIHD) Study. Eur J Cardiovasc Prev Rehabil. 2005; 12: 369-375.

22 Ferretti G, Bacchetti T, Moroni C, et al. Effect of homocysteinylation of low density lipoproteins on lipid peroxidation of human endothelial cells. J Cell Biochem. 2004; 92: 351-360.

23 Jawień J. Atherosclerosis in 2012: what is new? Pol Arch Med Wewn. 2012; 122: 170-173.

24 Adamczyk T, Mizia-Stec K, Mizia M, et al. Biomarkers of calcification and atherosclerosis in patients with degenerative aortic stenosis in relation to concomitant coronary artery disease. Pol Arch Med Wewn. 2012; 122: 14-21.

25 Ferretti G, Bacchetti T, Masciangelo S, Bicchiega V. Effect of homocysteinylation on high density lipoprotein physico-chemical properties. Chem Phys Lipids. 2010; 163: 228-235.

26 Ferreti G, Bacchetti T, Marotti E, Curatola G. Effect of homocysteinylation on human high-density lipoproteins: a correlation with paraoxonase activity. Metabolism. 2003; 52: 146-151.

27 Holven KB, Aukrust P, Retterstøl K, et al. The antiatherogenic function of HDL is impaired in hyperhomocysteinemic subjects. J Nutr. 2008; 138: 2070-2075.

28 Mikael LG, Genest J Jr, Rozen R. Elevated homocysteine reduces apolipoprotein A-I expression in hyperhomocysteinemic mice and in males with coronary artery disease. Circ Res. 2006; 98: 564-571.

29 Liao D, Tan H, Hui R, et al. Hyperhomocysteinemia decreases circulating high-density lipoprotein by inhibiting apolipoprotein A-I protein synthesis and enhancing HDL cholesterol clearance. Circ Res. 2006; 99: 598-606.

30 Vanuzzo D, Pilotto L, Lombardi R, et al. Both vitamin B6 and total homocysteine plasma levels predict long-term atherothrombotic events in healthy subjects. Eur Heart J. 2007; 28: 484-491.

ARTYKUŁ ORYGINALNY

Homocysteina i metaboliczne czynniki ryzyka u osób z dodatnim wywiadem rodzinnym w kierunku przedwczesnego niedokrwiennego udaru mózgu

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SŁOWA KLUCZOWE

homocysteina, miażdżyca, udar

STRESZCZENIE

WPROWADZENIE Dodatni wywiad rodzinny w kierunku udaru mózgu jest niezależnym czynnikiem ryzyka choroby sercowo-naczyniowej.

CELE Celem badania była ocena wybranych metabolicznych czynników ryzyka i związku interakcji dodatniego wywiadu rodzinnego w kierunku przedwczesnego niedokrwiennego udaru mózgu (*premature ischemic stroke* – PIS) i homocysteiny (Hcy) z innymi czynnikami ryzyka u osób z wywiadem rodzinnym w kierunku PIS.

PACJENCI I METODY Badanie przeprowadzono na 344 osobach zdrowych, w tym 143 z dodatnim i 201 z ujemnym wywiadem rodzinnym w kierunku PIS (grupa kontrolna).

WYNIKI W grupie z dodatnim wywiadem rodzinnym w kierunku PIS stwierdzono istotnie wyższe średnie wartości wskaźnika masy ciała (*body mass index* – BMI), skurczowego i rozkurczowego ciśnienia krwi (*systolic and diastolic blood pressure* – SBP i DBP), cholesterolu LDL (LDL-C), apolipoproteiny B (ApoB), ApoB/apolipoproteiny A-I (ApoA-I) i glukozy u kobiet, a wśród mężczyzn – istotnie wyższe średnie wartości BMI, SBP i DBP, całkowitego cholesterolu (*total cholesterol* – TC), LDL-C, ApoB/ApoA-I i ApoA-I. Zaobserwowano istotną interakcję wywiadu rodzinnego w kierunku PIS × Hcy z TC/cholesterolem HDL (HDL-C), HDL-C i triglicerydami (TG) u kobiet i TC/HDL-C, TC i TG u mężczyzn. Wiekse stężenie Hcy wiązało się z istotnie większymi wartościami TC/HDL-C i TG zarówno u kobiet jak i mężczyzn oraz z niższym poziomem HDL-C u kobiet i wyższym stężeniem TC i LDL-C u mężczyzn.

WNIOSKI Mężczyźni i kobiety z dodatnim wywiadem rodzinnym w kierunku PIS charakteryzują się niekorzystnymi zmianami w profilu czynników ryzyka. Efekt ten jest dodatkowo wzmocniony większym stężeniem Hcy, co może być wskazaniem do stosowania prewencji pierwotnej u takich osób.

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