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The effects of simvastatin on the C-reactive protein level and lipid profile in the acute phase of ischaemic stroke in relation to -717A>G *CRP* gene polymorphism

Wpływ simwastatyny na stężenie białka C-reaktywnego i profil lipidowy u chorych w ostrej fazie niedokrwiennego udaru mózgu w zależności od polimorfizmu -717A>G genu *CRP*

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ABSTRACT

Introduction: The pathogenesis and risk of ischaemic stroke are associated with the inflammatory process that is involved in the development of atherosclerosis. The blood level of C-reactive protein (CRP) is a widely used predictor of inflammation. The level of this protein is used for the assessment of risk and prognosis in cardiovascular disorders and stroke. C-reactive protein level depends on genetic and environmental factors such as genetic polymorphism and statin use.

The aim of the study was to assess the potential effects of simvastatin on the CRP level and lipid profile in stroke in regard to the variant of -717A>G *CRP* gene polymorphism.

Materials and methods: There were 125 subjects enrolled in the study, hospitalized with a diagnosis of ischaemic stroke (95 patients in group 1 and 30 patients in group 2). Patients in group 1 were treated with a 40 mg dose of simvastatin from the 1st day; in group 2 simvastatin was not used. Blood CRP level and lipid profile were measured in all patients on day 1 and 10 after admission. The -717A>G *CRP* gene polymorphism status was genotyped in all patients.

Results: In both groups there was a significant increase in CRP level, despite simvastatin treatment. No association was found between genotype and levels of both CRP and lipids change from the 1st to the 10th day.

Conclusions: Simvastatin does not affect the CRP level in relation to any of the -717A>G *CRP* gene polymorphism variants in the acute phase of stroke. Simvastatin significantly changes lipid levels, but it does not depend on -717A>G *CRP* gene polymorphism.

Keywords: stroke; genetic polymorphism; C-reactive protein; lipids; atherosclerosis; statins.

ABSTRAKT

Wstęp: Patogeneza i ryzyko wystąpienia udaru niedokrwiennego mózgu związane są z obecnością zmian zapalnych biorących udział w rozwoju miażdżycy. Powszechnie stosowanym wykładnikiem procesu zapalnego jest stężenie białka C-reaktywnego (CRP) w surowicy. Poziom CRP wykorzystuje się w ocenie ryzyka wystąpienia i rokowania w chorobach sercowo-naczyniowych oraz w udarze. Stężenie CRP podlega wpływom czynników genetycznych, takich jak polimorfizm genetyczny, oraz środowiskowym, wśród których znajduje się stosowanie statyn.

Celem pracy było ustalenie potencjalnego wpływu simwastatyny na stężenie CRP i profil lipidowy w udarze z uwzględnieniem wariantu polimorfizmu -717A>G genu *CRP*.

Materiały i metody: Do badania włączono 125 chorych hospitalizowanych z powodu udaru niedokrwiennego mózgu. Na podstawie kryteriów włączenia i wyłączenia do I grupy zakwalifikowano 95, a do grupy II – 30 chorych. Pacjenci z grupy I otrzymywali simwastatynę w dawce 40 mg od 1. doby, natomiast w grupie II nie stosowano tego leczenia. U wszystkich chorych oznaczono stężenie CRP i profil lipidowy w 1. i 10. dobie hospitalizacji oraz oznaczono wariant polimorfizmu -717A>G genu *CRP*.

Wyniki: W grupie I i II odnotowano istotny wzrost stężenia CRP, pomimo leczenia simwastatyną. U osób w grupie I i II nie stwierdzono istotnego wpływu poszczególnych wariantów polimorfizmu -717A>G genu *CRP* na zmianę stężenia CRP i profilu lipidowego pomiędzy 1. a 10. dobą hospitalizacji.

Wnioski: Simwastatyna nie wpływa na stężenie CRP w ostrej fazie udaru mózgu w zależności od jakiegokolwiek wariantu polimorfizmu -717A>G genu *CRP*. Zastosowanie simwastatyny w ostrej fazie udaru niedokrwiennego mózgu wyraźnie wpływa na profil lipidowy, przy czym efekt nie jest zależny od wariantów polimorfizmu -717A>G genu *CRP*.

Słowa kluczowe: udar mózgu; polimorfizm; białko C-reaktywne; lipidy; miażdżyca; statyny.

INTRODUCTION

Ischaemic stroke is the leading cause of death and permanent disability, especially after 60 years of age [1]. The main cause of stroke is atherosclerosis, which develops as a result of arterial endothelium dysfunction caused by many factors, such as hypertension, diabetes, lipids deposition (especially low density lipoproteins – LDL), inflammation, free radicals, infections, increased blood homocysteine level, and tobacco smoking [2]. Inflammatory factors play a crucial role in the process of atherogenesis. The inflammatory process is reflected in the level of acute phase proteins, such as C-reactive protein (CRP). C-reactive protein plays a role in mediating complement activation, adhesion molecules synthesis and regulation of blood rheologic properties. The level of this protein is associated with the process of forming atherosclerotic plaque in carotid arteries. It positively correlates with the risk of vascular episodes, including cardioembolic stroke connected with atrial fibrillation [3, 4, 5, 6, 7]. High CRP levels were observed 1 and 3 months after stroke [4, 8]. Measurement of CRP level may be helpful in the assessment of recurrent stroke risk [9, 10]. C-reactive protein is a marker of increased 1-year risk in ischaemic stroke. C-reactive protein at discharge is related to later outcomes, and could be of greater utility for risk stratification [11]. Levels of CRP increase with stroke severity and are associated with higher mortality at the beginning and 3 months after the stroke [12, 13].

Expression of CRP is conditioned by genetic background. The *CRP* gene is located on chromosome 1 (1q21 to 1q23) and is characterized by genetic variation. There have been 30 *CRP* gene single nucleotide polymorphisms (SNP) described [14]. There is an association between particular alleles of the *CRP* gene and diverse expression of CRP [3, 15, 16, 17, 18, 19, 20, 21]. Variants that change the risk of ischaemic stroke, acute coronary syndrome, recurrent stroke, cardioembolic stroke and development of atherosclerosis in intracranial arteries were identified [4, 13, 15, 22].

The results of the association between CRP level and -717A>G *CRP* gene polymorphism are inconclusive. Significant increments in CRP concentrations in individuals carrying the -717G allele in the acute phase of stroke were found when compared with the baseline state [23]. Other authors did not observe any effect of the above-mentioned SNP on CRP level [19, 20, 24, 25]. The association of this SNP with myocardial infarct and coronary heart disease (CHD) supports the belief that carriers of the -717A allele of the *CRP* gene are genetically predisposed to CHD [26]. On the other hand, other authors demonstrated that -717A>G *CRP* gene polymorphism is associated with a decreased risk of myocardial infarct and CHD [20, 27]. The G to A exchange at the site of -717A>G *CRP* gene polymorphism resulted in an increased transcriptional activity of the *CRP* gene promoter [28].

C-reactive protein level also depends on environmental factors, such as statin use [18, 29]. Statins inhibit 3-hydroxy-3-methyl-glutaryl-CoA reduction to mevalonian, which results in decreased cholesterol synthesis. Rosuvastatin and atorvastatin exert the strongest effect on LDL, decreasing its level by up to 63% [30]. Statins demonstrate an anti-inflammatory effect by decreasing the number of inflammatory cells and by stabilizing atherosclerotic plaque [31, 32]. The multidirectional activity of statins refers to a pleiotropic effect and is connected with the influence on coagulation, the complement system, and change in the activity of inflammatory cells [33]. Statins are widely used in primary and secondary prevention of cardiovascular episodes, including stroke and CHD. The use of statins decreases the relative risk of stroke by 21–28%, and mortality by 9% [31, 34, 35]. Atorvastatin treatment decreases the risk of recurrent stroke by 16% [36, 37].

Pathogenesis and risk of ischaemic stroke are associated with the presence of the inflammatory process that is involved in atherosclerosis and non-valvular atrial fibrillation development. Blood CRP level reflects inflammation and may be used as a prognostic factor in stroke. Changes in the CRP level depend on genetic and environmental factors.

The aim of the study was to analyse the relationship between CRP level, lipid profile and simvastatin in the acute phase of stroke, including the potential effect of a variant of -717A>G *CRP* gene polymorphism.

MATERIALS AND METHODS

125 Caucasian patients that were hospitalized between January 2008 and June 2010 in the Neurology Department of Pomeranian Medical University in Szczecin (in Poland) were enrolled in the study. Subjects were divided into two groups depending on the following criteria.

The main inclusion criterion was the diagnosis of ischaemic stroke, confirmed by the results of examination and brain computed tomography. Patients were older than 18 years, stroke was both of embolic and thrombotic types. Two groups were formed based on the lipid profile on the 1st day after stroke. Group 1 consisted of patients with LDL ≥130 mg/dL or total cholesterol (CH) ≥200 mg/dL. In group 2 patients had LDL <130 mg/dL and CH <200 mg/dL. The exclusion criteria were body temperature of more than 37.4°C, clinical or biochemical symptoms of infection, chronic inflammatory disorders, and cancers. Patients taking statins or other lipid-lowering drugs in the preceding year were also excluded from the study.

All subjects from group 1 received simvastatin 40 mg daily starting from the 1st day after stroke onset. Patients from group 2 were not treated with simvastatin. In all subjects -717A>G *CRP* gene polymorphism was detected. Besides standard laboratory tests, lipid profile and blood CRP level were measured on admission and on the 10th day of hospitalization.

The NIHSS scale (National Institutes of Health Stroke Scale) [29] was used for the evaluation of neurological deficit (0–42 points). Patients were evaluated immediately upon admission and before discharge from the hospital.

Blood serum CRP was measured on the 1st and 10th days of hospitalisation, using the immunoturbimetric method, strengthened with latex particles with a bottom detectability

line amounting to 1 mg/L, using the standard manufacturer's protocol (Fast Digest Bsh1236I, Fermentas UAB, Lithuania).

Venous blood was collected into EDTA tubes for DNA isolation. Detection of *CRP* gene promoter polymorphism 717A>G (rs 2794521) was made using the PCR-RFLP method with *Bsh12*361 enzyme [26, 37].

The normal distribution of continuous variables was evaluated by the Shapiro–Wilk test. For asymmetric distribution of CRP, logarithmic transformation was applied. The examined groups were compared with the use of the non-parametric Mann–Whitney U-test. For fraction analysis of discrete variables the χ^2 test was used. The one-way ANOVA test with LSD as a *post hoc* test or the non-parametric Kruskal–Wallis test were applied to analyse the interaction of the examined factors. Statistical significance was adopted as $p < 0.05$ for all tests.

RESULTS

According to the presented criteria, group 1 consisted of 95 patients with LDL level of 158.3 mg/dL (100–255), CH of 238.8 mg/dL (65 – 396). Group 2 consisted of 30 patients with mean LDL level 108.9 mg/dL (55–142) and CH of 180.4 mg/dL (121–205).

As presented in Table 1, systolic blood pressure and diastolic blood pressure values on admission were higher in group 1.

There were also differences between groups in previous hypertension treatment and history of CHD. Significantly, more patients had not been taking hypotensives (48% in group 1 vs. 73%, Pearson's χ^2 test, $p = 0.017$). Coronary heart disease was more common in group 1 (40% vs. 17%, $p = 0.017$). There were no differences between groups in relation to other tested parameters.

Lipid level changes presented in Table 2 were not dependent on any of the -717A>G *CRP* gene variants.

In both groups there was a significant increase in serum CRP level between the 1st and the 10th day (group 1: 5.8 mg/L, SD 8.4 mg/L, $p < 0.004$; group 2: 5.6 mg/L, SD 6.5 mg/L, $p = 0.047$), but it was not dependent on the CRP genotype (Tables 3 and 4). The intensification of the increase did not differ significantly between groups.

The distribution of gene variants in the groups was as follows: AA – 51 (54%), AG – 38 (40%), GG – 6 (6%), in group 2: AA – 16 (54%), AG – 12 (40%), GG – 2 (7%).

There were no statistical differences in the distribution of alleles between groups.

DISCUSSION

Considering the effect of statins on inflammation modification (pleiotropic effect), the inclusion of atrial fibrillation patients is reasonable. It has been shown that inflammation plays a role in the pathogenesis of atrial fibrillation, and CRP level is an independent risk factor of atrial fibrillation incidence [38, 39, 40].

TABLE 1. Comparison of selected parameters in groups 1 and 2

Parameter	Group 1			Group 2			p
	mean	SD	n	mean	SD	n	
Age (years)	64.7	10.3	95	63	13.8	30	NS
BMI (kg/m^2)	27.6	4.4	64	27.8	3.6	22	NS
SBP on admission (mmHg)	164.1	30.2	95	148.3	30.5	30	0.01
DBP on admission (mmHg)	95	18.6	95	84	16.3	30	0.004
Glycaemia on admission (mg/dL)	134.5	58.7	95	129.5	52	30	NS
IMT L (mm)	0.09	0.02	92	0.09	0.02	28	NS
IMT R (mm)	0.08	0.02	92	0.08	0.02	28	NS
NIHSS on admission	6.2	5	95	6.6	5.1	30	NS
NIHSS on discharge	3.4	4.6	95	2.9	3.8	30	NS

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; IMT L – left intima-media thickness; IMT R – right intima-media thickness; NIHSS – National Institutes of Health Stroke Scale

TABLE 2. Comparison of simvastatin effect on lipids between groups

Parameter (mg/dL)	Group 1			Group 2		
	mean	SD	p	mean	SD	p
CH	238.8	40.9	<0.001	180.4	20.1	NS
CH on 10th day	164.6	29.8		178.5	28.9	
HDL	50.5	12.3	<0.001	47.3	11.8	<0.001
HDL on 10th day	40.0	9.7		41	9.9	
LDL	158.3	32.1	<0.001	108.9	19.2	NS
LDL on 10th day	97.8	25.4		109.8	23.9	
TG	167.3	101.1	0.01	111.7	43.8	0.017
TG on 10th day	144.9	67.4		155.4	96.3	

CH – total cholesterol; HDL – high density lipoproteins; LDL – low density lipoproteins; TG – triglycerides

TABLE 3. Comparison of C-reactive protein level change in group 1 in relation to -717A>G *CRP* genotype

Genotype	n	Mean (mg/dL)	SD	p (ANOVA test)
AA	51	6	13.7	
AG	38	1.7	13.7	NS
GG	6	3.9	15.4	

TABLE 4. Comparison of C-reactive protein level change in group 2 in relation to -717A>G *CRP* genotype

Genotype	n	Mean (mg/dL)	SD	p (ANOVA test)
AA	16	2.7	9.7	
AG	12	16.6	32.6	NS
GG	2	5.7	1.7	

There were differences found between subjects assigned to groups 1 and 2. The differences in lipid profile resulted from the study design. In group 1 CHD was more frequent and there were higher values of blood pressure measured on admission. Patients in group 2 had been using hypotensives more often. Such differences may be connected with the fact that dyslipidaemia is associated with higher risk of hypertension and CHD, and this may also be connected with the study design.

C-reactive protein level between the 1st and the 10th day was higher in both groups. The increase in CRP despite simvastatin use may be due to stroke evolution and activation of the inflammatory process [41]. It was shown that the CRP level changes or remains at a stable, but higher level after stroke [8]. Such an effect was not noticed in our study, but the patients were only followed up for 10 days. The question emerges of when the pleiotropic effect of statins can be observed after stroke. The first effect of statin use is evident after 2 days in reduced CRP level, but this observation was made in stroke-free patients [42]. A longer time may be necessary to observe a more pronounced effect.

The effect of simvastatin on lipid profile was evident and diverse in the study groups. This is consistent with other studies that showed hypolipemic effect after 14 days [43].

In both groups there was high density lipoproteins (HDL) decrease, which plays a protective role. According to other studies, simvastatin should exert no effect or elevate the HDL level [44]. Our observation may result from the short period of the study. On the other hand, the strong effect on other lipids may be proof of the different metabolism and effect of simvastatin on HDL. Decreased level of LDL may be connected with inflammation activation in the acute phase of ischaemic stroke. Such inflammatory factors may be more strongly associated with HDL compared to other lipids metabolism. This presumption is supported by the fact that HDL is involved in the transport of antioxidative enzymes, such as paraoxonase and platelet-activating factor acetylhydrolase [45].

The results of our study suggest that rapid statin introduction in stroke patients may have beneficial effects due to the pleiotropic effect initiation as the evident effect on the lipid profile was observed.

Another aim of our study was to analyse the effect of simvastatin on the CRP level in relation to -717A>G *CRP* gene polymorphism as more results appear [46]. We did not reveal such an effect, so none of the genotypes can be used as prognostic factors in the acute phase of stroke. There was also no effect of simvastatin use on the lipid profile in relation to any of the genotypes. Such a relationships has not been investigated in other studies so far.

As we examined patients in the acute phase of stroke, this could have had an influence on the results. The potential pleiotropic effect of simvastatin reflected in CRP change could be dimmed by the active inflammatory process. We also cannot exclude that clinically silent infection biased our results, although we included only patients without symptoms of infection. On the other hand, it was interesting for us to elucidate this acute-phase period, as interactions between statins, polymorphism and CRP are still not fully known.

CONCLUSIONS

In the current study we found that simvastatin use in the acute phase of stroke does not prevent CRP increase. Simvastatin effect on CRP in the acute phase of stroke is not associated with -717A>G *CRP* gene polymorphism. Simvastatin use in the acute phase of stroke significantly changes lipid profile, but it does not depend on -717A>G *CRP* gene polymorphism.

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