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RESEARCH ARTICLE

The prevalence of 4G/5G polymorphism of plasminogen activator inhibitor-1 (*PAI*-1) gene in central serous chorioretinopathy and its association with plasma PAI-1 levels

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Abstract

Context: Central serous chorioretinopathy (CSCR) is a poorly understood disease and the choroidal circulation abnormality induced by the plasminogen activator inhibitor type 1 (PAI-1) seems to be associated with the pathogenesis. There are many reports indicating that 4G/5G polymorphism of the *PAI*-1 gene is a risk factor for several diseases related to the elevated serum levels of PAI-1.

Objective: To evaluate the 4G/5G polymorphism of the *PAI*-1 gene and its association with serum levels of PAI-1 in acute CSCR patients.

Materials and methods: Sixty CSCR patients and 50 healthy control patients were included. The PAI-1 4G/5G was genotyped using the polymerase chain reaction–restriction technique. Serum PAI-1 level was measured using enzyme-linked immunosorbent assay. Demographic data consisting of age, sex, body mass index (BMI) as well as genotype disturbances and serum PAI-1 levels were compared between the groups. Statistical significance for differences in the serum PAI-1 levels of each group with different genotypes was also analyzed.

Results: The CSCR group consisted of 40 male (66.7%) and 20 female (33.3%) patients with a mean age of 46.7 ± 8.39 years. The control group consisted of 32 male (64%) and 18 female (36%) healthy subjects with a mean age of 45.8 ± 8.39 years. There was no statistically significant difference between the groups in terms of age, sex and BMI. In the CSCR group the genotype frequencies were 4G/4G: 30% ($n = 18$), 4G/5G: 50% ($n = 30$), 5G/5G: 20% ($n = 12$) and in the control group genotype frequencies were 34% ($n = 17$), 42% ($n = 21$) and 24% ($n = 12$), respectively. There was no statistically significant difference in the distribution of genotypes among the groups (chi-squared, $p = 0.70$). The CSCR group had a significantly higher serum PAI-1 concentration than the control group ($p = 0.001$). In both groups the mean plasma PAI-1 concentration did not vary significantly among the different genotypes ($p > 0.05$).

Discussion and conclusion: Although our results demonstrated that the patients with acute CSCR have higher serum *PAI*-1 concentrations than the controls, no significant difference was found in the genotype disturbances of the *PAI*-1 gene between the groups. The current study indicates that 4G/5G polymorphism in the promoter of the *PAI*-1 gene cannot be considered a risk factor for the elevated serum PAI-1 levels and consequent development of CSCR.

Keywords

4G/5G polymorphism of PAI-1 gene, central serous chorioretinopathy, serum PAI-1 level

History

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Introduction

Central serous chorioretinopathy (CSCR) is characterized by focal serous detachment of the neurosensory retina in the macular area with or without retinal pigment epithelial (RPE) detachment. Although different theories have been speculated, the pathogenesis of the disease still remains unclear. Numerous recent reports have claimed a transient or persistent occlusion of choriocapillaris for the RPE decomposition and neurosensory detachment of the retina[1,2]. It has previously been reported that platelet aggregation induced by elevated plasminogen activator inhibitor type-1 (PAI-1) level promotes microthrombus formation, resulting in delayed arterial filling with capillary and venous dilation[3]. Iijima et al. have noticed increased levels of PAI-1 which is the major inhibitor in physiological fibrinolysis in patients with CSCR[4]. Accordingly, a recent study demonstrated that lowering serum PAI-1 levels with low-dosage acetyl salicylic acid in CSCR patients had resulted in accelerated visual rehabilitation with fewer recurrences when compared with the untreated controls[5,6].

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The expression of the *PAI*-1 gene is regulated at the transcriptional level through the action of many hormones such as glucocorticoids and the renin angiotensin-aldosterone system[7]. However, previous studies reported that a single-base-pair guanine (G) insertion/deletion polymorphism (4G/5G) in the promoter region of the *PAI*-1 gene was also associated with increased plasma PAI-1 levels in several diseases like osteonecrosis, pre-eclampsia, pulmonary thromboembolism, diabetes type II, myocardial infarction and septic shock[8–13]. It was also demonstrated that the serum levels of PAI-1 in homozygous 4G/4G patients are approximately 25% higher than homozygous 5G/5G subjects[14]. In order to evaluate the potential involvement of high serum PAI-1 levels and insertion/deletion polymorphism of *PAI*-1 gene in the development of CSCR, we first evaluated the 4G/5G polymorphism of the *PAI*-1 gene in patients with an active form of the disease and its association with serum levels of PAI-1. We also compared the levels in our control patients.

Material and methods

Consecutive patients diagnosed with CSCR at the Ophthalmology Department of Balikesir University Medical Faculty between January 2012 and August 2013 were enrolled. The study was approved by the ethics committee of our institution and an Institutional Review Board was obtained. Sixty CSCR patients and 50 healthy individuals were included in the study. BMI was calculated according to the World Health Organisation guidelines[15]. Inclusion criteria for patients were acute manifestation of CSCR characterized by serous retinal detachment, RPE detachment or dysfunction without evidence of any other possible cause of fluid exudation, such as choroidal neovascularization, inflammation or infiltration. All subjects underwent a complete ophthalmic examination including best-corrected visual acuity, slit-lamp biomicroscopy and dilated fundus examination. CSCR was confirmed by fluorescein angiography and neurosensory or RPE detachment was also evaluated by optical coherence tomography imaging (Cirrus HD-OCT Model 4000, Carl Zeiss Meditec Inc, Dublin, CA).

Exclusion criteria for both patients and controls were: concurrent ocular and retinal disease, history of coagulation abnormalities such as thromboembolism, pregnancy, congestive heart failure, diabetes mellitus, coronary artery disease, uncontrolled arterial hypertension, smoking, hyperlipidemia, cancer, autoimmune inflammatory diseases, renal and hepatic abnormalities, endocrine pathology and concomitant treatment affecting fibrinolysis metabolism (such as glucocorticoids and oral contraceptives), drug and/or alcohol intake.

4G/5G polymorphism genotype and serum PAI-1 analyses

Genomic DNA was extracted from a 200-μL peripheral venous blood sample according to the standard protocol by using GeneJet DNA Purification Kit (Thermo Fisher Scientific Inc., Waltham, MA). DNA samples were stored at −20 °C until the end of the study, which was completed in 5 months. Applied Biosystems 7500 Real-Time PCR Systems (Life Technologies, Carlsbad, CA) were used for analyzing the 4G/5G polymorphism in the *PAI*-1 gene. This polymorphism is amplified with specific primers and detected with Taqman probes. Cycling conditions for PAI-1 were initial denaturation at 95 °C for 10 min, followed by 32 cycles at 95 °C for 15 s and at 60 °C for 1 min.

Serum PAI-1 level was measured with enzyme-linked immunosorbent assay by using Boster Human PAI-1 ELISA kit (Boster Biological Technology Co., Inc., Fremont, CA, kit sensitivity <10 pg/ml). The assays were performed according to the manufacturer's recommendations. Plasma samples were obtained from the patients within one week after the diagnosis was confirmed with fluorescein angiography and optical coherence tomography. Peripheral venous blood was collected in the morning and was centrifuged at 1000 rpm for 15 min at 4 °C. After centrifugation, serum was separated from the sediment and stored frozen (−80 °C) until use.

Data analyses

Quantitative data was described as mean ± standard deviation (SD) and range and qualitative data was described as a percentage. SPSS for Windows software (version 11.0, SPSS, Inc., Chicago, IL) was used for statistical analysis. Statistical analyses of the differences in sex and genotype frequencies between groups were analyzed with chi-square test. Normality of the quantitative data sets were first checked using the Shapiro–Wilk test. When parametric analysis was possible, the Student's *t* test was used for evaluating differences between the groups and when parametric analysis was not possible, the Mann–Whitney *U* test was performed. Statistically significant differences in the serum PAI-1 levels of each group with different PAI-1 genotypes was tested by univariate analysis of variance (ANOVA). A p value less than 0.05 was considered statistically significant.

Results

The CSCR group consisted of 40 male (66.7%) and 20 female (33.3%) patients with a mean age of 46.72 ± 8.39 years (range, 29–62 years). The control group consisted of 32 male (64%) and 18 female (36%) healthy subjects with a mean age of 45.82 ± 8.13 years (range, 36–59 years). There was no statistically significant difference between the groups in terms of age, sex and BMI (Table 1). The mean duration of disease was 2.80 ± 1.77 weeks (range, 1–8 weeks).

Distributions in the genotypes of *PAI*-1 gene are shown in Table 2. In CSCR group, the genotype frequencies were 4G/4G: 30% ($n = 18$, 13 male [32%] and 5 female [25%]), 4G/5G: 50% ($n = 30$, 21 male [53%] and 9 female [45%]), 5G/5G: 20% ($n = 12$, 6 male [15%] and 6 female [30%]) and in the

Table 1. Demographic characteristic of CSCR patients and healthy controls group.

Parameters	CSCR	Control	p Value
Age (years)	46.72 ± 8.39	45.82 ± 8.13	0.731*
Sex (male/female)	40/20	32/18	0.463**
BMI	24.93 ± 2.04	25.36 ± 1.30	0.282*

BMI: body mass index.
*t Test.
**Chi-square test.

control group genotype frequencies were 4G/4G: 34% ($n = 17$, 12 male [37%] and 5 female [28%]), 4G/5G: 42% ($n = 21$, 13 male [41%] and 8 female [44%]), 5G/5G: 24% ($n = 12$, 7 male [22%] and 5 female [28%]). There was no statistically significant difference in the distribution of genotypes among the groups (chi-squared, $p = 0.70$). The calculated allele frequencies were 0.55 for 4G and 0.45 for 5G, as well as 0.55 for 4G and 0.45 for 5G in CSCR group and the controls, respectively ($p > 0.05$).

The CSCR group had a significantly higher serum PAI-1 concentration than the control group (89.55 ± 9.81 ng/ml and 76.85 ± 14.62 ng/ml, respectively, $p = 0.001$). In both groups, the mean plasma PAI-1 concentration did not vary significantly among the different genotypes (ANOVA test, $F = 0.22$ and $p = 0.802$ for CSCR group; $F = 1.19$ and $p = 0.112$ for control group, Table 3).

Discussion

Despite numerous studies on CSCR over the years as well as advances in imaging techniques, the pathophysiology of the disease still remains unclear. Several reports have been demonstrated by the indocyanine green angiography that the choroidal circulating abnormalities seems to be a main pathogenic factor[1,16]. Impaired choroidal fibrinolysis could predispose to ischemia and lead to delayed choroidal filling with associated areas of venous dilation and increased hyperpermeability[17]. Previous studies implied a thrombotic pathomechanism related to the elevated serum levels of PAI-1[3,4]. Also, factors such as systemic glucocorticoid use, pregnancy and organ transplantation which are reported to be associated with higher incidence of subretinal fibrin formation in CSCR are also found to be characterized by high serum PAI-1 levels[18]. Although, there are many reports indicating that 4G/5G polymorphism of the *PAI*-1 gene is a risk factor for several diseases related to the elevated serum levels of PAI-1 and thrombosis, to date there has been no report on the role of PAI-1 promoter polymorphism for the development of CSCR.

Table 2. *PAI*-1 4G/5G gene distribution of CSCR patients and healthy controls.

	CSCR	Control	*p* Value*
Genotypes *n* (%)			0.700
4G/4G	18(30%)	17(34%)	
4G/5G	30(50%)	21(42%)	
5G/5G	12(20%)	12(24%)	

*Chi-squared test.

In the current study, we observed that CSCR patients in the acute phase had a significantly higher serum PAI-1 concentration than the healthy controls. Similarly, Iijima et al. demonstrated the increased PAI-1 concentrations in patients with CSCR and hypothesized that the choroidal hyperpermeability was a result of impaired fibrinolysis and the associated thrombotic occlusion of choroidal vessels[4]. Accordingly, Caccavale et al. investigated the low-dose aspirin treatment in order to reduce antifibrinolytic activity in 109 CSCR patients and this regimen appeared to reduce the rate of recurrences together with slightly better visual outcomes[5,6]. In the literature, there have been several reports that focused on the thrombotic mechanism in the pathogenesis of CSCR[3,19–22]. The study published by Iijima et al. noticed that the abnormality of the choroidal circulation in CSCR seems to be analogous to the angiographic abnormality in the retinal circulation of branch retinal vein occlusion[4]. This was also supported by the case report of a patient with coexistent branch retinal vein occlusion and CSCR, both probably due to antiphospholipid antibody syndrome (APAS)[23]. More recently, Singh et al. reported elevated serum PAI-1 levels as a contributing factor in pathogenesis of hypercoagulable state in APAS. This data is applicable to CSCR, since we know that CSCR has also been reported as an ocular manifestation of APAS[24,25]. The exact cause of choroidal microthrombosis in CSCR remains unknown, but genetic predisposition to dysregulation of the coagulation and fibrinolytic pathway may be one possible mechanism. From this point of view to investigate the possible genetic contribution of the development of the disease, we evaluated 4G/5G polymorphism of *PA1*-1 gene in CSCR patients and its association with the high plasma PAI-1 levels.

The PAI-1 promoter insertion/deletion (4G/5G) polymorphism has been associated with variable PAI-1 plasma activity and serum concentrations[26]. Studies reported that the 4G/4G genotype has a higher affinity for the transcription factor stimulators (such as glucocorticoids, tumor necrosis factor alpha, and interleukin-1) and individuals carrying these genotypes have an increased PAI-1 gene expression as well as increased PAI-1 levels[14,27]. Although many studies reported the polymorphism of the *PAI*-1 gene as a risk factor for some diseases associated with hypercoagulopathy, the exact role of this functional polymorphism in the development of the related disorders still remains unclear. In the current study, no significant differences were found in the genotype disturbances and the allele frequencies of the *PAI*-1 gene between group of CSCR patients and healthy controls. Moreover, no association was seen between the serum PAI-1 levels and 4G/5G genotypes in both groups. These data indicate that the

Table 3. Serum PAI-1 concentration (ng/ml) of different genotypes in CSCR patients and controls.

Mean ± SD (range)	CSCR	Control	*p* Value*
4G/4G	88.43 ± 3.45 (82.85–93.25)	78.55 ± 12.91 (45.19–98.78)	0.034
4G/5G	90.37 ± 9.01 (81.04–125.48)	77.91 ± 15.44 (65.05–105.12)	0.029
5G/5G	89.55 ± 16.75 (80.47–138.66)	72.61 ± 15.81 (45.39–98.30)	0.022
Total	89.55 ± 9.81 (80.47–138.66)	76.85 ± 14.62 (45.19–105.12)	0.001
p Value**	0.802	0.112	

*Mann–Whitney *U*-test.
**ANOVA test.

4G/5G polymorphism in the promoter of the *PAI*-1 gene is not a pathogenetic risk factor for high-serum PAI-1 levels and consequently development of acute CSCR. However, since the number of subjects was relatively small, further studies are needed to confirm our results.

It is difficult to speculate which mechanism increased PAI-1 levels in CSCR patients. It is very well known that glucocorticoids as well as mineralocorticoids may also participate in regulation of proteolysis and fibrinolysis[28]. Subsequently, it was reported that medications with local or systemic steroids can cause the CSCR and the conditions with hypercorticolism such as Cushing's disease, bone marrow and solid organ transplantations, vasculitis, lupus, inflammatory bowel disease and pregnancy have also been associated with the disease[29,30]. Even CSCR patients without concomitant endocrine abnormalities also have approximately 50% higher levels of serum cortisol with increased rate of urinary cortical extraction[29]. Therefore, glucocorticoids were identified as the main risk factor for the onset of CSCR with their known effect of increasing PAI-1 levels. Studies demonstrated that dexamethasone stimulates *PAI*-1 gene expression and secretion in a dose- and time-dependent manner[28]. It was also shown that the subjects carrying the 4G/4G genotype of *PAI*-1 gene have a higher affinity for the transcription stimulators[14]. The 4G allele specific increase in plasma PAI-1 activity is related to a differential binding of transcription factors to the polymorphic site[27]. However, the present study demonstrated that the patients with CSCR were not associated with the higher carriage rate of 4G allele when compared to the healthy controls and 4G allele could not be considered as a risk factor for the development of CSCR. Additionally, both serum cortisol and serum PAI-1 levels are shown to be associated with the disease and correlation analyses between these two would be important in determining the causative role of glucocorticoids on PAI-1-induced choroidal hypercoagulopathy and hyperpermeability. This hypothesis may provide the ground for future studies.

It is widely known that PAI-1 is an endothelial product that behaves as an acute phase reactant. Therefore, it is considered to be an indicator of endothelial activation[31]. Underlying mechanisms for increased PAI-1 activity and impaired fibrinolysis in CSCR can be explained by inflammatory endothelial dysfunction. Following release from the endothelium due to choroidal vascular inflammation, PAI-1 inhibits the fibrinolytic system causing focal fibrin deposition in the choroidal circulation that promotes further endothelial injury and subsequent inflammatory cell infiltration[32]. This process seems to create a vicious cycle which may be involved in the development of the CSCR.

Conclusion

Although our results demonstrated that the patients with acute CSCR have higher serum PAI-1 concentrations than the controls, no significant difference was found in the genotype disturbances and the 4G/5G allele frequencies of the *PAI*-1 gene among groups. The current study indicates that 4G/5G polymorphism in the promoter region of the *PAI*-1 gene could not be considered as a risk factor for the elevated serum PAI-1 levels and consequent development of acute CSCR. However, a similar analysis in another group of patients with chronic and/or recurrent form of the disease would add strength to our hypothesis. Further cohort studies with the larger sample size are needed to make a definitive conclusion.

Declaration of interest

The authors report no declaration of interests.

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