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RETINAL DISORDERS

Association of monocyte chemoattractant protein-1 (MCP-1) 2518A/G polymorphism with proliferative diabetic retinopathy in northern Chinese type 2 diabetes

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Abstract
Background The pathogenesis of proliferative diabetic retinopathy (PDR) remains poorly understood. Recent studies have implicated that monocyte chemoattractant protein-1 (MCP-1) is associated with diabetic microvascular or macrovascular complications. However, the relationship between single nucleotide polymorphism(SNP)c.2518A/G - rs1024611 in the MCP-1 gene with diabetic retinopathy remains controversial. In the present study, we evaluated the association of SNP in the MCP-1 gene with diabetic retinopathy (DR) and diabetic macular edema (DME) in a Chinese population from Northern China with type 2 diabetes.
Methods We conducted a case–control study, which enrolled 1,043 subjects with type 2 diabetes (528 with DR, including 277PDR; 515 without DR), and SNP genotyping of c.2518A/G in the MCP-1 gene was performed using the polymerase chain reaction. Genomic DNA was isolated from 3 ml samples of whole blood using a modified conventional DNA extraction method. The genotype and allele frequencies of 2518A/G were studied by using an automated DNA sequencer (ABI PRISM 3730 DNA Sequencer).
Results The demographic and clinical characteristics did not differ among genotype subgroups. The MCP-1(−2518) GG genotype was significantly associated with DR susceptibility with OR of 1.481 (95 % CI, 1.019-2.153) (P=0.046). There were no significant differences in the MCP-1(−2518) G allele frequencies in DR compared to non-diabetic retinopathy (DNR) (P>0.05, OR=0.841, 95 % CI, 0.705–1.002). The MCP-1(−2518) GG genotype was significantly associated with high-risk PDR susceptibility with OR of 2.656 (95 % CI, 1.222–5.775) (P=0.014). The MCP-1(−2518) G allele was significantly increased in high-risk PDR patients (P= 0.020, OR=1.481, 95 % CI, 1.070–2.051) compared with A allele. Genotype and allele frequencies of various DME of the DR patients were compared, but there were no significant associations established (P>0.05).
Conclusions It is likely that the MCP-1 c.2518G/G genotype is a susceptibility gene for DR in Chinese type 2 diabetic patients, especially the high-risk PDR. There is no association with DME and c.2518G/G .

Keywords Monocyte chemoattractant protein-1 (MCP-1) · Proliferative diabetic retinopathy (PDR) · Diabetic macular edema (DME) · Single nucleotide polymorphism (SNP) · Type 2 diabetic retinopathy

Introduction

Diabetic retinopathy (DR) remains the leading cause of blindness among working-age individuals in developed countries [1, 2]. Visual loss develops primarily from either increased DME or proliferation of new retinal vessels [3]. Although the pathogenesis of DR has not been fully elucidated, inflammation may play an important role in DR and several cytokines and chemokines have been suggested in the etiology of DR.

Recently, a potent cytokine, monocyte chemoattractant protein-1 (MCP-1), was shown to have the ability to activate monocytes, macrophages, and lymphocytes [4]. Activation of it has been demonstrated for hyperglycemia accelerates MCP-1 production in vascular endothelial cells and retinal pigmented epithelial cells [5]. Moreover, the levels of MCP-1 in aqueous and vitreous conditions were significantly increased in patients with diabetic retinopathy [6–8]. MCP-1

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production may lead to neovascularization and permeability of retinal vessels, which is the cause of proliferative diabetic retinopaty (PDR) and DME.

MCP-1 gene located at positions −2518 (G or A) has been reported to affect MCP-1 transcription activity [9], and this polymorphism has been associated with type 2 diabetes, insulin resistance [10], type 1 diabetes [11], and cardiovascular disease [12]. The association between polymorphism of MCP-1 (ID: 6347) c.2518A/G – rs1024611 and DR had been reported in Japan and Korea [13, 14], but their opinion was inconsistent. However, there is no report in China so far. This study was designed to clarify the relationship of polymorphism of MCP-1 c.2518A/G with type 2 diabetes with or without DR. The relationship between MCP-1 c.2518A/G and a different stage of DR has also been studied.

Materials and methods

Sample collection

A total of 1043 type 2 diabetic patients (with and without retinopathy) were recruited for this study, all patients belonged to the same ethnic group, and they were unrelated Han Chinese. This study was approved by Harbin Medical University Institutional review Board. All patients provided written informed consent for participation in the study and donation of samples. Inclusion criteria were age at diagnosis of diabetes ≥30 years and a known duration of diabetes of ≥5 years. Diabetes was diagnosed according to WHO criteria. All patients underwent biochemical tests and medical history. Diabetic retinopathy was assessed through dilated pupils by trained ophthalmologists. All the patients underwent a complete eye examination, which included a dilated retinal examination and a fundus color photogram. Patients with pathological changes of retina were examined by fundus fluorescein angiography (FFA). FFA was graded for DR severity in a masked fashion by ophthalmologists at the Ophthalmology Department in the First Affiliated Hospital of Harbin Medical University. The modified Early Treatment of Diabetic Retinopathy Study Airlie House classification of DR was used to grade the retinopathy into the following categories: mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, Severe NPDR and proliferative diabetic retinopathy (PDR) (including high-risk PDR). High-risk PDR: New vessels within 1 disc diameter of the optic nerve head that are larger than 1/3 disc area; vitreous or preretinal hemorrhage associated with less extensive neovascularization of the optic disk (NVD) or with neovascularization elsewhere (NVE) 1/2 disc area or more in size [15]. All the patients with DR were checked for foveal thickness of macula by optical coherence tomography (OCT), according to the thickness of the macular centre divided into three parts (Mild ≤ 250 um; 250 um < Moderate < 350 um; Severe ≥350um). The severity of DR or DME between the two eyes of the same patient was compared, excluding one left eye because of atrophy of the eyeball. Macular thickness was checked by using OCT, and patients with previous laser treatment, eyeball atrophy, epimacular membrane, age-related macular degeneration (ARMD), previous intravitreal injection medicine and vitreous hemorrhage were excluded.

Genotyping

Peripheral leukocytes were isolated from EDTA-treated whole blood obtained from each patient, and genomic DNA was extracted with QIAamp DNA Mini Blood Kit (Qiagen, Hilden, Germany) for polymerase chain reaction (PCR) amplification of MCP-1. DNA samples were collected in a 1.5 ml Eppendorf tubes and stored at −20 °C until use.

This SNP was detected by using an automated DNA sequencer (ABI PRISM 3730 DNA Sequencer). PCR was used to amplify the primer. In the MCP-1(−2518A/G), the forward primer 5′CTGTGGCATGACCACTTGTT 3′ and reverse primer 5′ACTTCT CTCACGCCAGCACT 3′ were used to amplify in a final PCR mixture of 20 μl containing 100 ng of genomic DNA and 12.5 pmol of each primer. The DNA was then subjected to initial denaturation at 95 °C for 2 min, followed by annealing 57 °C for 30 s and elongation at 72 °C for 40 s. After 30 cycles, the reaction was extended for an additional 5 min at 72 °C.

Statistical analysis

All statistical tests were performed with SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Age, sex, blood pressure, duration of diabetes, body mass index, glycosylated hemoglobin, smoking and alcohol use were compared between the study groups (DR and non-DR) using the two-tailed Student *t* test. The genotype phenotype association was done using a $\chi 2$ test, and to test for deviation of genotype distribution from the Hardy-Weinberg equilibrium using Haploview (version 3.32). The odds ratio (OR) and the 95 % confidence interval (95 % CI) were calculated, and *p* values were evaluated using the same method. The level of statistical significance was set at $p<0.05$.

Results

Among the 1,043 recruited type 2 diabetic patients, 515 patients were DNR, and 528 with DR. Among the DR patients, we graded DR and DME according to the right eyes. There were 76 Mild NPDR patients, 79 Moderate NPDR patients, 96 Severe NPDR patients and 277 PDR patients (including 169 high-risk PDR).

Table 1 Clinical characteristics of the study groups

Parameters	Diabetic retinopathy (DR) (n=528)	Non-diabetic retinopathy (DNR) (n=515)	P value
Age	55±13.0	54±12.0	0.42
Male	275 (52.08 %)	261 (50.68 %)	0.06
Body mass index (kg/m2)	25.2±3.8	24.8±3.7	0.28
Smoking (N, %)	195 (36.9)	175 (34.0)	0.32
Alcohol use (N, %)	213 (40.34)	198 (38.45)	0.38
HbA_1c (%)	7.7±1.2	7.6±1.3	0.09
Blood urea (mgs%) (Mean ± SD)	31±11	28±8	0.06
Duration of diabetes (years)	14±9	13±8	0.45
Blood pressure (mmHg)			
Systolic	138±9	139±8	0.36
Diastolic	82±5	82±6	0.36

HbA1C means glycosylated hemoglobin. Data are means ± SD or, for categorical variables, n or ratio. Comparisons between retinopathy groups are by unpaired Student's t test or x^2 test. P values _0.05 are considered significant

The demographics of the study population are summarized in Table 1. There was no significant difference in age, sex, smoking, alcohol use, blood urea, blood pressure, glycemic, and nutritional status among the two study groups.

Three genotypes (AA, AG and GG) of MCP-1-2518 A/G polymorphisms were found in Han people in Helongjiang Province. Genotype and allele frequencies are shown in Table 2. The MCP-1(−2518) GG genotype was significantly associated with DR; the odds ratio (OR) for the G/G genotype of MCP-1(−2518) to DR was 1.481 (95 % CI, 1.019–2.153, P<0.05) (Table 2), while the association of A/G genotype and DR was not so significant with DR with OR of 1.326 (95 % CI, 0.926–1.899, P>0.05). The MCP-1(−2518) G allele was not related with DR compared with A allele (P>0.05, OR= 0.841, 95 % CI, 0.705–1.002).

Genotype and allele distribution of MCP-1 gene polymorphisms in different stages of type 2 diabetic patients with retinopathy were also analyzed (Table 3). The MCP-1 (−2518) GG genotype was significantly associated with high-risk PDR susceptibility with OR of 2.656 (95 % CI, 1.222–5.775, P=0.014). While the A/G genotype was not associated with DR susceptibility with OR of 1.993 (95 % CI, 0.926–4.290, P>0.05). The MCP-1(−2518) G allele was significantly increased in high-risk PDR patients (OR=1.481, 95 % CI, 0.070–2.051 P<0.05) compared with the A allele. Genotype and allele frequencies of various DME of the DR patients were compared. No significant associations have been found (P>0.05) (Table 4).

There was no significant difference (P>0.05) in the severity of DR or DME between the two eyes of the same patient (Tables 5 and 6). In the multiple logistic regression model, HbA1c was significantly associated with DR after adjustment for conventional risk factors (OR=1.21, 95% CI, 1.06–1.37, P=0.025) (Table 7).

Discussion

The present study investigated the association of the MCP-1 c.2518 polymorphism with DR and DNR in a northern Chinese Han population. We found that the MCP-1 c.2518G/G genotype was associated with the increased risk of DR. When comparing NPDR with PDR, severe NPDR and non-high-risk PDR were excluded in order to clarify the relationship between mild and severe DR. The results showed that the G allele was associated with increased risk of high-risk PDR. All DR patients were checked with FFA, so that the diagnose of DR could be accurate and reliable. There was no association between the MCP-1 c.2518 polymorphism and DME.

Table 2 Genotype and allele distribution of MCP-1 gene polymorphisms in type 2 diabetic patients with and without retinopathy

SNP	Genotype	DR		DNR		OR(95 % CI)	P
		N=528	%	N=515	%		
rs1024611	A/A	69	13.1 %	89	17.3 %	Reference	
	A/G	258	48.9 %	251	48.8 %	1.326 (0.926–1.899)	0.145
	G/G	201	38.0 %	175	33.9 %	1.481 (1.019–2.153)	0.046
Allele							
	A	396	37.5 %	429	41.7 %	0.841 (0.705–1.002)	0.053
	G	660	62.5 %	601	58.3 %		

Table 3 Genotype and allele distribution of MCP-1 gene polymorphisms in different stages of type 2 diabetic patients with retinopathy

SNP	Genotype	High-risk PDR		Mild and moderate NPDR		OR(95 % CI)	P
		N=169	%	*N*=155	%		
rs1024611	A/A	12	7.1 %	23	15.1 %	Reference	
	A/G	78	46.2 %	75	48.5 %	1.993 (0.926–4.290)	0.092
	G/G	79	46.7 %	57	36.4 %	2.656 (1.222–5.775)	0.014
Allele							
	A	102	30.2 %	121	39.0 %	1.481 (1.070–2.051)	0.020
	G	236	69.8 %	189	61.0 %		

MCP-1 is widely known as a pro-inflammatory cytokine due to its chemotactic activity. It has been implicated that the pathogenesis of many diseases are characterized by monocytic infiltration, such as psoriasis, rheumatoid arthritis and atherosclerosis. Elevated MCP-1 serum levels have been reported in many diseases including coronary artery disease (CAD), hepatitis, obesity, acute myeloid leukemia and autoimmune diseases (such as rheumatoid arthritis, chronic autoimmune thyroiditis) [16–21]. Recently, it was demonstrated that chemokines play a pivotal role in mediating angiogenesis and fibrosis [22–24]. More important, MCP-1 has been shown to play a possible role as a modulator of PDR due to its ability to regulate arterial smooth muscle cell proliferation and induce retinal neovascularization [25–27]. It has been reported that MCP-1-induced angiogenesis was as potent as that induced by vascular endothelial growth factor (VEGF) in vivo [28, 29], which is implicated strongly in the development of retinal and iris neovascularization in PDR [30]. However, there is no report so far about the relationship of MCP-1 and DME.

A polymorphism at position −2518 in the 5′-flanking region of the MCP-1 gene was identified and the G allele of this polymorphism was associated with increased MCP-1 expression [31, 32]. Katakami, et al. [13] reported that the G allele in the 2518A/G polymorphism was a susceptibility allele for diabetic retinopathy in a Japanese population of diabetic patients. Hyun Jeong, et al. [14] reported that the 2518A/A genotype in MCP-1 could be used as a susceptibility gene to predispose Koreans exhibiting type 2 diabetes for the development of PDR. Their conclusions were not consistent. Our conclusion was similar with Katakami's but different from Hyun Jeong's. We found that MCP-1 c.2518G/G was a susceptibility gene to predict DR, especially high-risk PDR in type 2 diabetes patients in the northern Han population of China. G allele in the 2518A/G polymorphism was associatied with the severity of DR . There was no significant relation for G allele and DR, and further study is necessary. There are several reasons for the difference of our findings compared with previous reports: First, ethnic differences might play a role. Gene SNPs have a different influence in type 2 diabetes for ethnic variation. Palmer proved several candidate loci have been identified, which are nominally associated with insulin resistance in Hispanic Americans. So we speculate ethnic variation may play an important role in DR [33]. Second, there were different sample sizes (there were 3,802 subjects in the Japanese paper, 590 in the Korean paper, and 1,043 in our paper). Different examiners can also cause bias. Laslyt and the mostly, when we compared NPDR with PDR, we used different methods from theirs. We excluded severe NPDR and non-high-risk PDR, because their disease stages were similar [34]. In order to eliminate interference with the difference of the left and right eye, the severity of DR and DME of both eyes of the same patient were compared, and there was no statistical difference ($p>0.05$). Thus right eyes were selected to analyze the severity of DR and DME.

Although the most severe vision loss is a consequence of tractional retinal detachment,vitreous hemorrhage or

Table 4 Genotype and allele distribution of MCP-1 gene polymorphisms in type 2 diabetic patients with DME

SNP	Genotype	Mild DME		Moderate DME		Severe DME		OR	P
		N=207	%	*N*=173	%	*N*=66	%		
rs1024611	A/A	26	12.6 %	26	15.0 %	3	4.5 %	Reference	
	A/G	96	46.4 %	92	53.2 %	41	62.1 %	1.477 (0.842,2.592)	0.174
	G/G	85	41.1 %	55	31.8 %	22	33.3 %	0.978(0.544,1.758)	0.942
Allele									
	A	148	35.7 %	144	41.6 %	47	35.6 %	1.139 (0.314,4.128)	0.418
	G	266	64.3 %	202	58.4 %	85	64.4 %		

Table 5 Comparison of severity of DME in the right and left eyes

Grade of DME	Right (%) (n=446)	Left (%) (n=444)	P value
Mild edema(≤250 um)	207 (46.4 %)	210 (47.3 %)	>0.05
Moderate edema(250–350 um)	173 (38.8 %)	166 (38.4 %)	>0.05
Severe edema(≥350 um)	66 (14.8 %)	68 (15.3 %)	>0.05

Exclude after PRP, atrophy of eyeball, epimacular membrane, ARMD, intravitreal injection medicine and vitreous hemorrhage

Categorical data were analyzed with the x^2 -test, p values over 0.05 were not significant

neovascular glaucoma, the major cause of moderate vision loss is DME, which is a complication of DR that can occur at any stage of the disease [35]. For the first time, we showed that there was no association between the MCP-1-(2518) polymorphism and the severity of DME (p>0.05). In this study, we excluded eyes after laser treatment, atrophy of eyeball, epimacular membrane, ARMD, intravitreal injection medicine and vitreous hemorrhage, as these conditions could either cause macula thickness change or affect the measurement.

Our study also indicates that the MCP-1 c.2518G/G genotype may increase the risk to the development of proliferative diabetic retinopathy in patients with long-standing diabetes. The MCP-1 c.2518G/G genotype was related to neovascularization, but not to the blood vessel leakaging. We do not know the underlying mechanisms. The patients enrolled in this study were recruited from north Chinese Han individuals, and the results presented here need to be confirmed by using different ethnic populations, larger groups and other related genes. A long-term follow-up study would be necessary to confirm the association between this polymorphism and DR. We expect to learn of more reports about the MCP-1 A-2518G polymorphism from other countries, which can help to prevent and cure DR patients.

In conclusion, it is likely that the MCP-1 c.2518G/G genotype is a susceptibility for DR in Chinese type 2 diabetic patients, and it is related to the high-risk PDR as well, but it has no association with DME.

Table 6 Comparison of severity of DR in the right and left eyes

The grade of DR	Right (%) (n=528)	Left (%) (n=527)	P value
Mild NPDR	76 (14.4 %)	73 (13.8 %)	>0.05
Moderate NPDR	79 (14.9 %)	84 (16.0 %)	>0.05
Severe NPDR	96 (18.2 %)	98 (18.6 %)	>0.05
Mild PDR	108 (20.5 %)	104 (19.7 %)	>0.05
High-risk PDR	169 (32.0 %)	168 (31.9 %)	>0.05

One eye has been excluded because of eyeball atrophy

Categorical data were analyzed with the x^2 -test, p values over 0.05 were not significant

Table 7 Multivariate logistic regression analysis to identify independent determinants for diabetic retinopathy

Parameters	Odds ratio (95%CI)	P value
Age(years)	0.91 (0.81–1.13)	NS
Gender(male)	0.95 (0.76–1.15)	NS
Smoking (N, %)	1.08 (0.86–1.21)	NS
Alcohol use (N, %)	0.93 (0.80–1.20)	NS
HbA_1c(%)	1.21 (1.06–1.37)	0.025
Blood urea (mgs%) (Mean ± SD)	0.94 (0.82–1.11)	NS
Duration of diabetes (years)	1.01 (0.82–1.04)	NS
Systolic	1.08 (0.90–1.30)	NS
Diastolic	0.91 (0.77– 1.09)	NS
The number of -2518G allele	1.11 (0.97–1.26)	NS

Multivariate logistic regression analysis was done by 1,043 type 2 diabetic patients to select variables significantly associated with an increase in the risk of diabetic retinopathy. The threshold of statistical significance was defined as P<0.05

Abbreviations: *NS* not significant, *B.I.* Brinkman's Index

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Competing interests None.

Patient consent Obtained.

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