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Original Article

Association study of Angiotensin-Converting Enzyme Insertion/Deletion gene polymorphism with Neovascular Age-Related Macular Degeneration in a sample of Algerian population

Etude de l'association du polymorphisme Insertion/Délétion du gène de l'Enzyme de Conversion de l'Angiotensine avec la dégénérescence Maculaire néovasculaire liée à l'âge dans un échantillon de la population Algérienne

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Abstract

Introduction: Neovascular age-related macular degeneration (nAMD) is a progressive ocular disease and the major cause of central visual loss and blindness. Genetic factors play an important role in pathogenesis process of this disease. Findings on the presence of renin-angiotensin system (RAS) components including angiotensin-converting enzyme gene in the ocular tissues and its inflammatory response, suggest that deregulation of RAS may increase the risk of AMD. The aim of our study is to investigate the association of ACE I/D (rs1799752) polymorphism with Neovascular Age-related Macular Degeneration (nAMD) in a sample of Algerian patients. **Material and Methods:** This prospective study consisted of 72 patients with nAMD and 72 control subjects. DNA of 144 subjects was extracted using Salting Out method. Genotyping of I/D polymorphism of the ACE gene was carried out using multiplex polymerase chain reaction method. Statistical analysis was performed by SPSS.21.0 to evaluate the association of ACE I/D polymorphism with the risk of developing nAMD. **Results:** There was no difference of ACE I/D (rs1799752) genotypic (p=0.1, OR=0.5 [0.2-1.2]) and allelic (p=0.8, OR=0.8 [0.01-1.1]) distributions between patient and control groups. Stratification by age and by gender did not show any significant association between ACE I/D (rs1799752) polymorphism and nAMD. **Conclusion:** ACE I/D (rs1799752) polymorphism was not associated with nAMD in our sample of Algerian population. It would be interesting to study the impact of other genes involved in the renin angiotensin system.

KEYWORDS: Neovascular age-related macular degeneration, ACE gene, polymorphism, multiplex PCR, Algerian population

RESUME

Introduction: La Dégénérescence Maculaire néovasculaire liée à l'âge (DMLA) est une maladie oculaire évolutive et la principale cause de perte visuelle centrale et de cécité. Les facteurs génétiques jouent un rôle important dans le processus pathogénique de cette maladie. Les recherches sur la présence de composants du système rénine-angiotensine (SRA), y compris le gène de l'enzyme de conversion de l'angiotensine (ACE) dans les tissus oculaires et sa réponse inflammatoire, suggèrent que la dérégulation du SRA peut augmenter le risque de DMLA. Le but de notre étude a été d'étudier l'association du polymorphisme Insertion/Délétion du gène ACE (ACE I/D, rs1799752) avec la DMLA néovasculaire dans un échantillon de patients algériens. **Matériel et méthodes :** Cette étude prospective comprenait 72 patients atteints de DMLA néovasculaire et 72 sujets témoins. L'ADN de 144 sujets a été extrait à l'aide de la méthode Salting Out. Le génotypage du polymorphisme I/D du gène ACE a été réalisé en utilisant la méthode de réaction de polymérisation en chaîne (PCR) multiplexe. L'analyse statistique a été réalisée par SPSS.21.0 pour évaluer l'association du polymorphisme ACE I/D avec le risque de développer la DMLA néovasculaire. **Résultats :** Aucune différence significative de la distribution génotypique (p=0.1, OR=0.5 [0.2-1.2]) et allélique (p=0.8, OR=0.8 [0.01-1.1]) du polymorphisme ACE I/D (rs1799752) entre le groupe des cas et de témoins n'a été retrouvée. La stratification selon le sexe et l'âge n'a montré aucune association significative entre le polymorphisme ACE I/D (rs1799752) et la DMLA néovasculaire. **Conclusion :** Le polymorphisme ACE I/D (rs1799752) n'a montré aucune association avec la DMLA néovasculaire dans notre échantillon de la population Algérienne. Il serait intéressant d'étudier l'impact des autres gènes intervenant dans le système rénine angiotensine.

MOTS CLES: Dégénérescence maculaire liée à l'âge néovasculaire, gène ACE, polymorphisme, PCR multiplexe, Population Algérienne

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Received on: 29/06/2021
Accepted on: 02/12/2021

DOI : 10.5281/zenodo.6024614

Introduction

Neovascular age-related macular degeneration form (nAMD) is one of the two types of Age-related macular degeneration (AMD), a progressive ocular disease and the major cause of central visual loss and blindness [1]. nAMD affects the macular, central region of the retina and it is characterized by choroidal neovascularization (CNV) and degeneration of the retinal pigment epithelium (RPE) [1]. The incidence of this disease is increasing in developed countries and in aging people who are over 65 years old. The World Health Organization (WHO) reported that AMD is responsible for 8.7% of blindness worldwide [2]. In Algeria, blinding eye pathologies are a real public health problem, AMD comes in the 4th position after cataract, glaucoma, and diabetic retinopathy with a prevalence of 2.1%, according to a study conducted by the Algerian Ministry of Health in 2008 [3].

AMD is a complex disease, in which both genetic and environmental factors are implicated and have an important impact in its pathogenesis [1]. One of important genetic factor is the renin-angiotensin system (RAS), which is a hormone system known as a blood pressure regulator [4]. Recently, it was demonstrated to be an important mediator of inflammation involved in the various age-related ocular disorders through exacerbation of the inflammatory molecules [5]. The key enzyme in the RAS is Angiotensin Converting Enzyme (ACE) which plays an important role; it catalyzes the conversion of angiotensin I (Ang-I) into a physiologically active peptide angiotensin II (Ang-II), that regulates through the activation of Angiotensin II type I receptors various biological effects including vasoconstriction, electrolyte homeostasis, fibrosis, inflammation, and proliferation [5]. ACE also metabolizes bradykinin, a powerful vasodilator involved in mediation of the inflammatory response [2]. The presence and expression of transcript and protein of the RAS components including ACE in the retinal tissues of human eye propose that it plays an important functional role in the regulation of the ocular physiology [2]. Also, it was reported to promote nAMD development through various mechanisms, such as inducing inflammation, oxidative stress, and endothelial dysfunctions [6].

Angiotensin Converting Enzyme gene encoding the ACE enzyme was located on chromosome 17 (17q23.3) of the human genome, and composed of 26 exons and 25 introns [7]. The most studied polymorphism

consists of an insertion / deletion (I / D) polymorphism (rs1799752), linked to the presence (insertion, I) or absence (deletion, D) of 287-base pair Alu repeat sequence in the 16th intron of the gene [8], therefore, we have three genotypes in this polymorphism: homozygotes for D allele (DD), homozygotes for I allele (II) and heterozygotes (ID). The DD genotype encodes a high level of the circulating enzyme; however II and ID are associated with lower and intermediate ACE levels respectively [9,10]. The I/D genetic polymorphism of ACE gene was extensively investigated in various populations with a variety of cardiovascular disorders [11], spondylarthropathies [12], and diabetic retinopathy [13]. However, findings on the presence of RAS components in the ocular tissues and its inflammatory response, suggest that deregulation of RAS may enhance the risk of AMD [5]. Therefore, angiotensin-converting enzyme gene has been an obvious candidate gene in developing nAMD.

The objective of our study was to investigate the association of angiotensin-converting enzyme I/D gene polymorphism (ACE I/D, rs1799752) with the risk of developing nAMD in a sample of Algerian population.

Material and Methods

Study's Population

Our case-control study evaluates the association of ACE I/D (rs1799752) polymorphism with nAMD in a sample of Algerian population. A total of seventy-two patients with Neovascular AMD and seventy-two age- and sex-matched healthy controls subjects were recruited in Oran and Sidi Bel Abbes, two different cities Western Algeria, with latitude and longitude [35.6° N, 0.6°W] and [35.2°N, 0.6°W] respectively. All patients and control subjects enrolled provided informed consent, and the study was carried out in accordance with The Code of Ethics of The World Medical Association (Declaration of Helsinki) for experiments in humans.

nAMD patients were recruited from Hassani Abdelkader Hospital, department of ophthalmology, (SBA) and the Nour ophthalmology clinic (Oran) in Algeria. nAMD was diagnosed by ophthalmic examinations included best-corrected visual acuity measurements (BCVA), fundus examinations, fluorescein angiography, and optical coherence tomography (OCT). All patients were free of diabetic retinopathies, degenerative myopathy or any other AMD related complications. Whereas control, were recruited from people visiting the AHMED SEGHIR Public Medical Center in (Sidi Belabess-Algeria) for regular medical checkup. All control subjects included in our study were a healthy volunteer's people free of retinal disorder, history of nAMD or any other ocular pathology.

DNA extraction and Genotyping

Eight ml of venous blood were collected from each subject and DNA of 144 subjects was extracted using the Salting Out method, DNA samples were after that stored at -20°C. Genotyping was performed by applying the multiplex polymerase chain reaction (PCR) method. Multiplex PCR was applied in a final volume of 25µl consisted of: 1X of buffer with MgCl2 (10X), 0.2µM of dNTP mix (2.5 mM), 0.4 µM of forward and reverse primer (10µM), 0.12 µM of internal primer (10µM), 1 unit of Taqpolymerase (5U/µl) 1 µl of DNA (50-100ng/µl) and water. Primer sequences used are: forward Primer: 5'-CATCCTTTCTCCCATTTCTC-3' - reverse primer: 5' AATTTTATTCCAGCTCTGAAAT-3'and internal primer 5'-TGGGATTACAGGCGTGATACAG-3'. PCR conditions were as follows: hot lid 105ºC for 5 min, denaturation 95ºC for 5 min, 35 cycles consisting of denaturation at 94ºC for 45 seconds, annealing for 45 seconds at 50.7ºC and extension at 72 ºC for 1.5 minutes, followed by final extension at 72ºC for 5 minutes and hold at 15ºC forever. Amplified products were resolved by electrophoresis in 2% agarose gels and visualized under UV illuminator. Three bands were observed, 370pb + 63pb bp for (I allele) and 83pb for (D allele) [17].

Statistical analysis

Statistical analysis was performed by SPSS.21.0. Hardy-Weinberg equilibrium (HWE) was performed to compare the observed and expected frequencies of ACE I/D (rs1799752) genotypes and alleles using the Chi-square test in the control groups. The distribution of genotype and allele frequencies of ACE I/D genetic polymorphism between patients and controls group was also analyzed by the use of the Chi-square test and regression logistic. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the association of this polymorphism with the risk of developing nAMD. For statistical analyses, we did a correction for multiplicity according to Bonferroni correction due to the number of tests (four tests were performed, 0.05/4 = 0.01). Therefore, statistical significance was defined as $P < 0.01$.

Results

Demographic characteristics of the study population are given in **Table 1**. A total of 144 subjects were recruited (72 cases and 72 controls). From the subjects who were recruited, cases reported a higher mean age (72±9 years). However, it was not significantly different compared to controls (65±7.8 years, p=0.08). Gender did not reveal any significant difference between cases and controls (p=0.74).

Table 1: Distribution of Demographic characteristics among nAMD patients and controls

	Patients (72) **n (%)**	**Controls (72)** **n (%)**	**P** **Value**	**OR** **95% [CI]**
Age (mean and range)	72±9 [50-90]	65±7.8 [46-89]	0.08	0.5 [0.1-1.1]
Gender				
Male	37 (51.4)	39 (54.2)	0.74	0.9[0.5-1.7]
Female	35 (48.6)	33 (45.8)		
Smoking				
-Never	30	39	0.2	1(Ref)
-Ex-smoker	22	23		0.3[0.1-1.1]
-Current smoker	09	05		0.4[0.1-1.4]
-Passive smoker	11	05		0.8[0.1-3.7]
BMI	26.6±5.2	25.4±4.5	0.79	1[0.9-1.1]
Comorbidities				
- Arterial hypertension	42	28	0.02	2.2[1.1-4.1]
-Diabetes	19	30	0.5	0.5[0.2-1.1]
-Thyroid disease	15	05	0.01	3.5[1.2-10]

Hardy–Weinberg equilibrium

The observed frequencies of ACE I/D (rs1799752) genotypes were in Hardy–Weinberg equilibrium in the control group (Khi2=2.7) as shown in Table 2 (A). ACE II, ID and DD genotype frequencies were 0.0%, 22.2% and 77.8%, respectively. The frequency of the ACE I minor allele was 0.11.

ACE I/D (rs1799752) genotype distribution in exudative age-related macular degeneration and control groups

Frequencies of ACE I/D (rs1799752) genotype and allele distribution in exudative age-related macular degeneration and control groups are presented in (**Table 2B)**. Statistical analysis did not show significant differences comparing the three genotypes (II, ID, and DD) of ACE I/D polymorphism (p=0.12). The distribution of the frequency of alleles between cases and control group was not significantly different either (p = 0.89) (**Table 2B).**

ACE I/D (rs1799752) genotype distribution in exudative age-related macular degeneration and control groups by gender and age

ACE I/D (rs1799752) analysis was made in neovascular AMD and the control groups by gender and age (**Table 3**). Our results show no difference in the distribution of ACE I/D genotype and allele frequencies between males and females (p=0.06 for genotype frequency and p=0.82 for allele frequency) (**Table 3A)**. The distribution of ACE I/D genotype frequencies did not show any significant association of

nAMD with ACE I/D polymorphism between the group of cases and controls aged more or less than 65 years old (p=0.02, OR=3.1 [1.1-8.9]) **(Table 3B)**.

ACE I/D (rs1799752) genotype distribution in exudative age-related macular degeneration and control groups in females and males by age

ACE I/D (rs1799752) genotype and allele distribution analysis in male and female groups by age was performed **(Table 4)**. Analysis of ACE I/D genotype and allele distribution in younger and older females (**Table 4A)** and males (**Table 4B)** did not reveal any statistically significant results. We only observed a difference distribution of genotypes to be linked with nAMD development when compared males in nAMD and control group aged less than 65 years, albeit the differences did not reach statistical significance (p=0.05; OR=0.08 [0-2.4]) (**Table 4B)**.

Table 2: Analysis of Hardy-Weinberg equilibrium in control group (A) and distribution of genotype and allele frequencies for ACE (I/D) among nAMD patient's vs controls (B)

(A): Analysis of Hardy-Weinberg equilibrium in control group

SNP	**Allele frequencies**	**Genotype Distribution**	**Khi2**	**P value**	**OR 95% [CI]**
ACE I/D	D 0.89 I 0.11	DD 56 ID 16 II 00	1.03	0.59	-

(B): Genotype and allele frequencies for ACE (I/D) genetic polymorphism among nAMD patients vs controls.

	Cases **N (%)**	**Controls** **N (%)**	***P-value***	**OR 95% [CI]**
Genotypes				
II	00 (0.0)	00 (0.0)	0.12	0.5[0.2-1.2]
ID	09 (12.5)	16 (22.2)		
DD	63 (87.5)	56 (77.8)		
Alleles				
Allele I	0.06	0.11	0.89	0.8[0.01-1.1]
Allele D	0.94	0.89		

Table 3: Frequency of ACE I/D genotypes and alleles in nAMD patients and control groups by gender (A), and by age (B)

(A): Frequency of ACE I/D genotypes and alleles in neovascular age-related macular Degeneration and control groups by gender								
ACE I/D	**Females**		**P value**	**OR 95% [CI]**	**Males**		**P value**	**OR 95% [CI]**
	Patients (35)	**Controls** (33)			**Patients** (37)	**Control** (39)		
Genotype								
DD	30	22	0.06	2.8 [0.9-8.9]	33	35	0.9	0.9 [0.2-3.7]
ID	05	11			04	04		
Allele								
D	0.93	0.83		1.2 [0.1-88]	0.95	0.95	1.0	1 [0.1-80]
I	0.07	0.17	0.82		0.05	0.05		
(B): Frequency of ACE I/D genotypes and alleles in neovascular age-related macular Degeneration and control groups by Age								
ACE I/D	**<65**		**P value**	**OR 95% [CI]**	**≥65**		**P value**	**OR 95% [CI]**
	Patients (13)	**Controls** (28)			**Patients** (59)	**Controls** (44)		
Genotype								0.5
DD	10	24	0.4	0.5 [0.1-2.6]	53	32	0.02	[0.2-1.2]
ID	03	04			06	12		
Allele								
D	0.88	0.93	0.9	0.9 [0.01-64]	0.95	0.86	0.82	1.2 [0.01-91]
I	0.12	0.07			0.05	0.14		

Table 4: Frequency of ACE I/D genotypes and alleles in females (A) and males (B) by age

(A): Frequency of ACE I/D genotypes in females by age								
ACE I/D	**<65**		**P value**	**OR 95% [CI]**	**≥65**		**P value**	**OR 95% [CI]**
	Patients (8)	**Controls** (11)			**Patients** (27)	**Controls** (22)		
Genotype				1.5				3.3
DD	06	07	0.59	[0.2-10]	24	15	0.07	[0.8-14]
ID	02	04			3	07		
Allele								
D	0.88	0.82	0.9	1.1	0.94	0.84	0.8	1.2
I	0.12	0.18		[0.02-75]	0.06	0.16		[0.02-90]
(B): Frequency of ACE I/D genotypes in males by age								
ACE I/D	**<65**		**P value**	**OR 95% [CI]**	**≥65**		**P value**	**OR 95% [CI]**
	Patients (5)	**Controls** (11)			**Patients** (32)	**Controls** (22)		
Genotype							0.17	0.3
DD	04	17	**0.05**	0.08	29	17		[0.1-1.6]
ID	01	00		[0-2.4]	03	05		
Allele								
D	0.9	01	0.74	0.8	0.95	0.89	0.89	1.1
I	0.1	00		[0.01-63]	0.05	0.11		[0.01-87]

Discussion

Choroidal neovascularization (CNV) is a critical pathogenesis in age related macular degeneration. Molecular and cellular mechanisms for promoting CNV are not fully elucidated. CNV seen in AMD develops with chronic inflammation including macrophage infiltration and the cytokine network adjacent to the retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaris [14]. The presence of RAS components in the ocular tissues including RPE, choroid, and photoreceptor cells and its inflammatory response, suggesting that deregulation of RAS may enhance the risk of AMD [15]. Angiotensin II, the final product of the RAS generated by angiotensin-converting enzyme (ACE) from angiotensin I, has two cognate receptors, angiotensin II type 1 receptor (AT1-R) and AT2-R, the activation of AT1R and (pro)renin receptor (PRR) promotes choroidal neovascularization by activating signal transduction ERK1/2, VEGF, ICAM-1, and monocyte chemoattractant protein in the ocular tissues leading to nAMD [16]. Therefore, AT1R blockers, ACE inhibitors, and PRR blockers prevent progression of CNV through suppression of such inflammatory molecules [14–16].

These findings suggested that deregulation of RAS may enhance the risk of AMD and encourage more investigation in genetic factors of this system. For this purpose, our study has investigated the impact of ACE I/D (rs1799752) polymorphism on neovascular AMD's development in a representative sample of the Algerian population. To our knowledge, this is the first study on the association of ACE I/D polymorphism with nAMD in a population originating from Algeria.

According to our results, the frequency of the ACE I allele in the present population was estimated at 11%. These results are in agreement (MAF, for minor allele frequency < 50%) with those characterizing the North African populations such as Algeria [11, 17], Morocco [18], Tunisia [19], and Europeans [20]. In addition, similar results were also found in Euro-Asian countries such as Turkey [21]. However, Asian control subjects had very high frequencies of the I allele (MAF> 50%) such as a frequency of 61% in Chinese population [22]. Finding's divergence in these studies may be due to the ethnic of studied populations, methods of genotyping, and to the simple size of the studies.

Our results revealed also that stratification by gender did not show any significant association concerning the genotypic and allelic distribution of the studied polymorphism; it appears that the gender factor may have no impact on the risk of occurrence of AMD. The results of studies associating sex with the development of AMD are divergent. The Beaver Dam study reported a higher prevalence of AMD in women than in men [23]. In contrast, a meta-analysis, included a large number of patients, gender does not seem to be involved in the pathology [24]. These contradictory results do not allow concluding the role of sex in the development of the disease. In addition, this contradiction may be due to the different life expectancy between women and men [24].

Furthermore, stratification by age did not show any significant association concerning the genotypic and allelic distribution of ACE I/D (rs1799752) polymorphism. It seems that the age factor have no impact on the risk of occurrence of nAMD in our sample. Uncontroversial results were observed firstly in two previously published studies [25, 26]; to our knowledge, currently, these two studies are the only ones analyzing ACE I/D (rs1799752) gene polymorphism association on nAMD development in Caucasian and Turkish population. The first one conducted on 364 unrelated Caucasian patients with advanced AMD and 261 control subjects; distribution of the ACE genotypes and alleles in cases was not significantly different from controls (p=0.41) [25]. The second one, consisted of 78 Turkish patients with AMD and 68 control subjects, findings of this study did not support the idea that ACE I/D polymorphism were risk factors for AMD (p = 0.218) [26]. Controversial results was reported in case-control studies exploring the impact of ACE I/D polymorphism on the occurrence of inflammatory rheumatic diseases, as ACE gene is an important regulator in inflammatory signal transduction pathways. The study of Bayram et al (2011), revealed that the DD genotype is significantly associated with osteoarthritis and osteoarthritis in a sample of Turkish population (P <0.001) [27]. DD genotype was also been reported to be associated with proliferative diabetic retinopathy [28]. Also, it has been shown to be associated with ocular involvement in a sample of Turkish patients having ankylosing spondylitis [29].

Genetic factors play a key role in nAMD development. ACE is a key regulator in inflammatory signal transduction pathways. Insertion-deletion (I/D) polymorphism of ACE determines the plasma and tissue levels of ACE. This genetic determinism was confirmed when it was shown that the ACE I/D (rs1799752) polymorphism can take three forms: The short form (DD) codes for a high level of the enzyme circulating, the long form (II) for a lower rate and the heterozygous form (ID) for an intermediate rate [30].

The hypothesis of a functional role that this polymorphism could play was validated in a quantitative study in which subjects carrying the ID and DD genotypes were associated with higher plasma and tissue levels of ACE compared to genotype II [9]. All of this work confirmed that the elevated levels of ACE in plasma as well that in the walls of the vessels promote the formation of Ang II molecules which activate the NF-κB factor and the production of pro-inflammatory cytokines and chemokines witch play an important role in inflammation [31]. Therefore, Angiotensin-converting enzyme (ACE) inhibitors reduce the production of angiotensin II and could act as anti-inflammatory agents [31]. These findings are in favor with the involvement of inflammation in the pathogenesis of neovascular age related macular degeneration.

Despite the findings reported in this study, there are some limitations such as the small sample size, which could be larger in future studies by recruiting patients from multiple centres around Algeria to confirm these findings. Another limitation is that this study only focused on one variant of ACE gene (ACE I/D) which do not exclude the possibility of other variants in genes of renin angiotensin system including polymorphisms in angiotensin II and AT1R genes that might play an important role in the pathogenesis process of nAMD.

Conclusion

In conclusion, our results suggest that ACE I/D (rs1799752) polymorphism may have no impact on the risk of neovascular AMD in our sample. Nevertheless, this finding may need to be tested in a larger Algerian independent study. Further investigations in other genetic factors of renin angiotensin system including polymorphisms in angiotensin II and AT1R genes are required in future studies; to clarify the involvement of this system in the pathogenesis of neovascular age related macular degeneration, in order to help the understanding of this pathology and to facilitate nAMD's patient care and prevention. Also, to approve the socioeconomic impact of this type of study in the prevention and management of this disease in our society.

Conflicts of interest

Authors do not declare any conflict of interest.

Acknowledgments

The authors are grateful to the Algerian Thematic Agency for Research in Health Sciences (ATRSS), and to individuals with nAMD and the control subjects for their participation in this study

Funding

This research was supported by Thematic Agency for Research in Health Sciences (ATRSS).

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