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RESEARCH

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Association of insertion/deletion (I/D) polymorphism of angiotensin-converting enzyme gene (*ACE*) with Parkinson's disease and factors risk in eastern Algeria: case–control study

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Abstract

Background This study aimed to explore the relationship between Parkinson's disease and insertion/deletion polymorphism (I/D) of the angiotensin-converting enzyme gene (*ACE*) and to highlight the related risk factors within Eastern Algerian population. A total of 262 individuals were recruited, including 100 PD patients and 162 controls. Polymerase chain reaction technique was employed to determine the *ACE* polymorphism genotype of each participant. Logistic regression analysis was conducted to examine factors potentially contributing to Parkinson's disease.

Results The mean age of onset of Parkinson's disease in the patient group was 56.18 ±12.99. The results revealed that the D allele of the angiotensin-converting enzyme gene and the DD genotype were most prevalent in both patients and controls. However, there were no significant differences in the genotype and allele frequencies of the I/D polymorphism of the angiotensin-converting enzyme gene between patients and healthy subjects. Cardiovascular disease, diabetes and profession were identified as potential risk factors for Parkinson's disease.

Conclusion The obtained data indicated no correlation between the angiotensin-converting enzyme I/D gene polymorphism and Parkinson's disease in our research cohort. Multiple logistic regression analysis revealed that cardiovascular disease, diabetes and profession were possible risk factors for Parkinson's disease.

Keywords Parkinson's disease, Risk factors, Angiotensin-converting enzyme gene, Insertion/deletion polymorphism

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Background

Parkinson's disease is a chronic, neurological, degenerative disorder, characterized by the progressive loss of dopamine neurons, located in a brain region known as the substantia nigra [1]. There is a potential link between this neurodegeneration and a chronic inflammatory process [2]. The clinical manifestations of PD encompass both motor signs (such as resting tremor, bradykinesia, muscle rigidity and postural instability) and non-motor signs (such as apathy, constipation, and sleep problems) [3]. While there is currently no definitive cure for PD, ongoing research explores novel therapeutic approaches, including neuron substitution, apomorphine, and α-synuclein interventions to alleviate or limit symptoms [4]. It is now well established that both genetic susceptibility and environmental factors significantly contribute to the development of PD [1]. Although the majority of PD cases are idiopathic, around 10% are attributed to inherited genetic mutations. Variations in susceptibility genes elevate the risk of developing PD [5]. Among these genes, *ACE* may play an essential role in PD development [6]. The Renin-Angiotensin System (RAS), a crucial regulator of blood pressure, is highly dependent on ACE. ACE primarily converts Angiotensin I (Ang I) into Angiotensin II (Ang II). The interaction of Ang II with its receptor induces potent vasoconstriction and triggers profibrotic, proapoptotic, and proinflammatory pathways in various organs [7]. Additionally, ACE plays a vital role in the degradation of bradykinin, a peptide controlling vascular tone [8]. Elevated ACE concentrations have been identified in the basal ganglia and nigrostriatal pathway. ACE also deactivates substance P, a neuropeptide prevalent in the basal ganglia, the loss of which has been linked to the etiology of several neurological disorders, including PD [9].

The *ACE* gene, located on chromosome 17q23, comprises 26 exons and 25 introns. The *ACE* I/D polymorphism results from the insertion or deletion of a 287-base pairs (bp) Alu repeated fragment in intron 16, leading to three genotypes: ID, DD, and II [10]. Previous studies on the association between the *ACE* I/D gene polymorphism and PD risk have yielded conflicting results. While one case–control analysis suggested a potential link [8], other studies found no evidence supporting an association [6, 11]. Consequently, the existing evidence on the association between *ACE* polymorphism and PD is inconclusive, necessitating further research for clarification of this relationship. Our case–control study aims to explore the correlation between I/D polymorphism of the *ACE* gene and PD within Eastern Algerian population. Additionally, the study seeks to identify potential risk factors associated with PD.

Methods

ACE I/D genotyping

A volume of 5 millilitres to 8 millilitres of venous blood was collected in vacutainer tubes containing Ethylene DiaminoTetraacetic Acid (EDTA). This blood was intended for Deoxyribonucleic acid (DNA) extraction from blood leukocytes using the sodium chloride (NaCl) method as referred to by Miller et al. [12]. A polymerase chain reaction (PCR) assay was applied to identify *ACE* polymorphism genotypes. The primers for the *ACE* gene were as follows: forward 5′CTGGAGACCACTCCC ATCCTTTCT3′ and reverse 5′GATGTGGCCATCACA TTCGTCAGAT3. The PCR technique was performed in a 10 µL volume of the mix containing template DNA, MgCl2 (50 mM), deoxynucleotide triphosphate (dNTPs) mix (final concentration 0.2 mmol/L), and oligonucleotide primers (100 ng/µL). Amplification of DNA samples was performed as follows: predenaturation at 94 °C for 5 min, followed by 35 cycles. Each cycle contained a denaturation at 94 °C for 30 s, annealing at 56 °C for 45 s and primer extension at 72 °C for 30 s. At the end of the cycles a final extension occurred at 72 °C for 7 min. PCR products of size 490 bp (allele I) and 190 bp (allele D) were separated using 2% agarose gel electrophoresis with ethidium bromide and viewed under ultraviolet light.

Statistical analysis

Statistical analyses were performed using IBM SPSS software (version 25.0; Spss Inc., Chicago, IL., U.S.A). Descriptive statistics and frequency analyses were used for the initial characterization Mean ± standard deviation (SD) was used for continuous data, while frequencies and percentages were used for categorical data. To investigate variations in the frequency of *ACE* gene alleles and genotypes between individuals with PD and control groups, the chi-square X2 test was utilized. The chi-square test for goodness of fit was used to assess the validity of the genotype distributions within the two groups matching the predictions of Hardy–Weinberg equilibrium (HWE). Multiple logistic regression analysis was also performed to investigate the association between the homozygote DD genotype and potential risk factors related to PD. A significance level of $P < 0.05$ was used in all statistical analyses.

Results

The ethnic origin of Parkinson's cases and controls was consistent. The mean age of onset for PD was 56.18 ± 12.99 years, while healthy subjects had a mean age of 59.40 ± 11.47 years. Additionally, the sex ratio in patients with PD was 1.17, and in controls, it was 1.10. Examination of the characteristics of patients and controls revealed associations between PD and

hypertension, as well as diabetes ($p=0.004$, $p<0.001$), respectively. Moreover, profession was also correlated to PD ($p=0.021$). Manual labor (33.8%), particularly in masonry and cement, administration (20%) and education (10.8%) were the most prevalent professions in our patient group (Table 1).

No significant variations were observed in the distribution of II, DD, and ID genotypes across all members of the study cohort. However, the homozygote DD genotype was the most prevalent among both patients (81%) and controls (84%). Additionally, the D allele was more common in both groups; nevertheless, there was no statistically significant result (OR = 0.82, 95% CI = 0.46–1.47, $p=0.133$). The population analyzed in this study was in Hardy–Weinberg equilibrium. Furthermore, a comparison was conducted between carriers of PD with and without the homozygous DD genotype. Among those with the DD genotype, 81% were PD patients and 84% were healthy cases, while the remaining 19% of PD patients and 16% of healthy cases did not possess the DD genotype (DI and II genotypes) (Table 2).

Additionally, the logistic regression analysis with various possible confounding factors indicated that the DD genotype was not significantly associated to PD (OR = 1.34, 95% CI = 0.65–2.76).

According to the results of this regression analysis, cardiovascular disease (OR = 7.52, 95% CI = 1.27–44.53), diabetes (OR = 3.80, 95% CI = 1.32–10.88) and profession (OR = 2.97, 95% CI = 1.53–5.74) were potential risk factors for PD. Nevertheless, no statistically significant correlations were found with the other factors (Table 3).

To conduct a further analysis, the distribution of the DD genotype among patients and controls was compared by classifying them by age range (< 50, 50–59, 60–69, and ≥ 70 years). According to our results, the DD genotype was more common in the 60–69 age group in PD

Table 1 Characteristics of patients and controls

Variable	Patients ($n=100$)	Controls ($n=162$)	*p*-value
Sex (male/female)	54/46	85/77	0.809
Hypertension	16.3	32.8	0.004
Stroke (%)	2.0	7.3	0.071
Cardiovasculardisease (%)	7.1	2.2	0.064
Diabetes (%)	5.1	23.4	0.000
Profession (%)	34.8	61.4	0.021
Manual labor	33.8	13	
Transport	7.7	4.3	
Security	6.2	2.2	
Education	10.8	23.9	
Health	1.5	17.4	
Business	7.7	4.3	
Agriculture	3.1	2.2	
Administration	20.0	23.9	
Authors	9.2	9.0	

n, Number

Table 3 The odds ratio and confidence interval of multiple potential risk factors of PD

Variable	OR	95% CI
Hypertension (%)	1.76	0.85–3.66
Stroke (%)	5.03	0.64–39.28
Cardiovasculardisease (%)	7.52	1.27–44.53*
Diabetes	3.80	1.32–10.88*
Somoking	0.92	0.45–1.91
Profession	2.97	1.53–5.74*
DD genotype	1.34	0.65–2.76

*$p<0.05$; OR, odds ratio; CI, confidence interval

Table 2 Genotype and allele frequencies of *ACEI*/D polymorphism in patients and controls

	Patients (n = 100)	Controls (n = 162)	X^2	OR	95% CI	*p-value*
Genotype						
DD	81 (0.81)	136 (0.84)	0.38	–	–	0.827
DI	16 (0.16)	22 (0.14)	–	–	–	–
II	3 (0.03)	4 (0.02)	–	–	–	–
Genotype						
DD	81 (0.81)	136 (0.84)	0.37	0.81	0.42–1.56	0.538
DI and II	19 (0.19)	26 (0.16)	–	–	–	–
Allele						
D	178 (0.89)	294 (0.91)	0.42	0.82	0.46–1.47	0.133
I	22 (0.11)	30 (0.09)	–	–	–	–

I allele (reference allele); *ACE,* angiotensin-converting enzyme; I/D, insertion/deletion; n, number; X^2, chi-square test; OR, odds ratio, CI, confidence interval.

patients, while it was more frequent in the 50–59 age group among control subjects. Additionally, we divided the population into two age ranges (< 60 and ≥ 60) and indicated the increased frequency of the DD genotype in both patient and control groups among those less than 60 years old. However, overall, our findings indicated that the differences in genotype distribution, in each age group, did not demonstrate statistical significance (Table 4).

ACE, angiotensin-converting enzyme; I/D, insertion/deletion; PD, Parkinson's disease; n, number; X^2, chi-square test.

Discussion

Our objective in this study was to explore the potential correlation between the *ACE* I/D gene polymorphism and PD within the Eastern Algerian population, involving 100 PD patients and 162 controls. Additionally, we aimed to evaluate various risk factors associated with PD development and determine if any associations existed among them.

Literature research revealed a correlation between hypertension and PD, consistent with our results. A meta-analysis of various cohort studies suggested that hypertension may contribute as a risk factor for the motor stage of PD diagnosis [13]. Another systematic review reported altered blood pressure patterns in individuals with PD, associated with an unfavorable prognosis [14]. However, findings from a case–control study indicated that hypertension reduces the risk of PD by 0.2 times in the general population but elevates the risk by 1.9 times in the Asian population [15]. Additionally, a meta-analysis of analytical studies suggested that hypertension might augment the likelihood of developing PD [16]. Further research is necessary for a comprehensive understanding of the intricate relationship between hypertension and PD.

Regarding cardiovascular disease, it has been reported that people with PD have a high risk of developing cardiovascular disease during the follow-up period [17]. Furthermore, PD treatments, including levodopa, anticholinergic agents, and dopamine agonists, are also responsible for cardiovascular adverse effects. However, more studies need to be conducted to clarify the underlying mechanisms [18]. Our findings also revealed a significant correlation between the development of PD and cardiovascular disease.

According to a review study, PD and diabetes are related. Both conditions are becoming more common worldwide and are particularly linked to aging. In addition to increasing the risk of PD, diabetes and insulin resistance may impact the progression of PD symptoms. Importantly, antidiabetic treatments have shown a neuroprotective effect in diabetic and non-diabetic parkinsonian patients [19]. A meta-analysis highlighted diabetes' impact on PD clinical progression and pathophysiological mechanisms, including protein misfolding, oxidative stress, neuroinflammation, and mitochondrial dysfunction [20]. A nationwide cohort study indicated that the severe form of diabetes may be a risk factor for PD [21]. In our study, we observed a significant correlation between PD and diabetes, aligning with the findings of the previously mentioned investigations.

The current analysis revealed that profession was a significant risk factor for PD (OR = 2.97). The most prevalent occupations in our patient group included manual labor (particularly in masonry and cement), administration and education. Tanner et al. [22] found that engaging in occupations, such as agriculture, education, healthcare, or welding, did not increase the risk of Parkinsonism. Conversely, the use of pesticides in one's occupation was associated with an almost 80% higher risk of developing PD. Additionally, a case–control study identified associations between PD and professions, such as teaching and healthcare services [23], Torti et al. [24] suggested that professions like pilots and physicians might have an etiological role in PD. Nevertheless, the choice of profession has been linked to the risk of PD. According to Darweech et al. [25] study, the risk of PD seems to vary based on the chosen profession, with artistic occupations

Table 4 Comparison of DD genotype of *ACE* I/D polymorphism in patients and controls classified by age range

Group by age at onset of PD	Patients (n = 100)			Controls(n = 162)			x^2	*p-value*
	N	DD	DI + II	N	DD	DI + II		
< 50	24	(0.79)	(0.21)	18	(0.72)	(0.28)	0.27	0.601
50–59	30	(0.86)	(0.14)	69	(0.84)	(0.16)	0.11	0.739
60–69	31	(0.77)	(0.23)	47	(0.91)	(0.09)	3.05	0.081
≥ 70	11	(0.73)	(0.27)	28	(0.78)	(0.22)	0.15	0.697
< 60	54	(0.83)	(0.17)	87	(0.81)	(0.19)	0.07	0.794
≥ 60	42	(0.76)	(0.24)	75	(0.87)	(0.13)	2.08	0.149

associated with a lower risk and conventional occupations potentially linked to a higher risk. The study suggests that dopaminergic degeneration might influence occupational choices, possibly beginning in the pre-diagnostic phase of PD.

The allele frequencies and genotypes of patients compared to controls did not show any significant differences in the genetic study. Mellick et al. [26] proposed the potential significance of the *ACE* gene in PD development within the Caucasian population. Their findings indicated that ID was the most frequent genotype (52% in patients and 56% in control), but the distribution of genotypes did not differ between both groups. The D and I allele frequencies were also identical among parkin[2]sonian patients and healthy subjects. Our results align with Mellick et al., indicating that the *ACE* I/D variant does not correlate with PD pathogenesis. However, in our study, the most frequent genotype was DD (81% in patients and 84% in control), and the D allele represented the highest frequency (D 89% and I 11%) in the patient group.

Lin et al. [27] also evaluated the impact of *ACE* I/D polymorphism on PD in a Chinese population. They revealed that the DD genotype was more frequent in patients (22% versus 12% in control), with a statistically significant difference ($p=0.048$). Although the D allele was more frequent in PD patients, significance was not reached ($p=0.133$). In Chinese and Caucasians controls, the frequencies of the D allele are 35–39% and 50–58%, respectively, but in normal Italians, there is 67% [27, 28]. Our findings were different from previous results (D 91%). Greek and Italian populations similarly showed that the distribution of genotypes was not statistically significant between patients and healthy subjects [8]. In their studies, the most frequent genotype was ID. A Colombian study also revealed no association, consistent with our results. However, their findings demonstrated the ID genotype as the most common [29]. The difference in significance between our study and others could be explained by various factors, including our African ethnicity, lifestyle, exposure to environmental agents, or a mix of these factors.

Conclusion

This case–control study aimed to assess the association between the *ACE* I/D gene polymorphism and PD within the Eastern Algerian population, alongside the identification of associated risk factors. The finding of this investigation revealed no significant association between PD and the *ACE* I/D gene polymorphism. The application of multiple logistic regression analysis identified cardiovascular disease, diabetes, and profession as potential risk factors for PD. Importantly, this study represents the initial exploration of this relationship within the Eastern Algerian population. It is crucial to acknowledge that further investigations with larger sample sizes, diverse Algerian populations, and various ethnic groups are imperative to validate our findings and gain a deeper understanding of the potential implications of this polymorphism in PD.

Abbreviations

ACE	Angiotensin converting enzyme
Ang I	Angiotensin I
Ang II	Angiotensin II
Bp	Base pairs
CI	Confidence interval
DNA	Deoxyribonucleic acid
dNTPs	Deoxynucleotide triphosphate
EDTA	Ethylene diamino tetraacetic Acid
I/D	Insertion/deletion
HWE	Hardy Weinberg equilibrium
NaCl	Sodium chloride
n	Number
OR	Odds ratios
PCR	Polymerase chain reaction
PD	Parkinson's disease
RAS	Renin Angiotensin system
SD	Standard deviation

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Author contributions

H-M.M collected and analyzed the data, realized the PCR method and wrote the manuscript. A.R participated in data collection and realization of PCR. D.I carried out statistical analysis. LR participated in data collection and helped in the revision of the manuscript. G.R participated in the revision of the work. TN, AN provided detailed clinical and examined patients. SD helped in making this study, revised and approved the manuscript.

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Availability of data and material

The data utilized and/or examined during the current study are available the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the ethical Scientific Committee of the Faculty of Sciences of Nature and Life of the University of the Mentouri Constantine 1, Algeria. The work has been carried out in accordance with the usual accepted protocol, the ethical principles of the Declaration of Helsinki and the Algerian legislation on the protection of privacy and experimentation on the human person. A Consent form was obtained from all study cohort.

Consent for publication

Consent form was obtained from the participants for publication.

Competing interests

The authors declare that they have no competing interests.

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