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Association of Paraoxonse1 (PON1) Genotypes with the Activity of PON1 in Patients with Parkinson's Disease

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Abtract

Objective: Various numbers of factors such as oxidative stress, neurotoxins, and pesticides have been implicated in its pathophysiology of Parkinson's disease (PD). Paraoxonas1 (PON1) metabolizes xenobiotics, including pesticides. Therefore, we surveyed the relationship between PON1 polymorphisms with its activities in the pathogenesis of Parkinson's disease..

Methods: We investigated polymorphisms of the PON1 (L55M and Q192R) by PCR-RFLP assays; we also measure the levels of PON1, TAC (total antioxidant capacity) and TOS (total oxidant status) with ELISA (Enzyme-linked immunosorbent assay) and spectrophotometric method for their activities.

Results: Paraoxonase and arylesterase activity of PON1 as well as their concentrations were lower in patients with PD compared with control group, but from the view of the specific activity, it was not significant between two groups. In the compare of TAC, TOS, and OSI, the TOS and OSI were higher in the patients than controls, while patients had lower levels of TAC compared with controls. Serum PON1 concentrations and activities were higher in LL (comparison with LM and MM) and RR (comparison with QR and QQ) genotypes while we did not observe any significant differences in arylesterase levels among mentioned polymorphisms.

Conclusion: In the current study, we reported associations between PON1 polymorphisms (55, 192) and enzyme activities in Parkinson's disease as there was a significant reduction in PON1 levels in patients with Parkinson compared with healthy. Taken together, paraoxonase enzyme in subjects with different genotypes could be a potential biomarker for determining the severity and prognosis of Parkinson. However, more studies are needed to clarify its clinical values.

Key words: Parkinson's disease; paraoxonase1; Polymorphism.

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1. INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disease in the elderly, which characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra and characterized clinically by bradykinesia, rigidity, and resting tremor. The etiology of PD is still unclear, but gensetic factors are likely to environmental factors, oxidative stress and mitochondrial dysfunction involved in development PD [1].

One of the most important organs in the body, which is highly active in metabolism, is the brain that at rest consumes 20% of the body's intake oxygen. It is well known that high oxygen consumption leads to the production of free radicals and due to high consumption of oxygen in the brain, it produces more active oxygen species and nitrogen [2]. The free radicals are associated with oxidative stress as disruption of the balance between oxidants and antioxidants agents can lead to nervous cells damage and cause neurodegenerative diseases. The antioxidant system in the body is divided into two types of enzymatic and soluble; enzymatic such as PON1, glutathione peroxidase, catalase, and superoxide dismutase and soluble including the vitamin A. vitamin C, vitamin E, and bilirubin [3,4].

Paraoxonase1 (EC. 3. 1.8.1, aryldialkylphosphatase) (PON1) is a 43 KD glycoprotein with paraoxonase and arylesterase activity [5], and its gene is located at 7q21-22 on the long arm of chromosome 7 [6]. PON1 are synthesized in the liver and located on high-density lipoprotein (HDL) [7]. It has two types of activity: paraoxonase activity (breakdown of paraoxon) and arylesterase activity) decompose the phenylacetate) [8]. PON1 also appears to be a cyclohydrolase that cleaves the homocysteine-thiolactone ring and exhibits similar activity towards lipoxidation derivatives of low-density lipoprotein [9].

Studies have shown that PON1 have two important polymorphisms at position 55 and 192 generated variable susceptibility to different diseases. In position 55, change of leucine to methionine (L55M, rs854560) and replacement glutamine with arginine at position 192 (Q192R, rs662), may influence the PON1 activity and concentration [10-12], which are associated with disease such as diabetes, Alzheimer disease and other neurodegenerative disorders [13,14].

In this study, we investigated the relationship between PON1 genotypes with its activity and concentration, as well as TAC, TOS, and OSI (oxidant status index) levels in the studied groups.

2. MATERIALS AND METHODS

2.1 Materials

We purchased ELISA Kit for PON1 from Eastbiofarm Company, a kit for measurement of TAC and TOS from Zellbio Company, ethyl paraoxon, and phenylacetate from Sigma Company, primers and restriction endonuclease enzymes (Fermentas) from sinaclon.

2.2 Population

This study included 70 idiopathic Parkinson's disease (54 men and 16 women, aged mean 63.7 years) from Golghasht Clinic, St. Golghasht, Tabriz, Iran (Ethical code: IR.TBZMED.REC.1394.899). Control group included 75 (55 men and 20 women, aged mean 61.4 years) healthy individuals, that were free from nervous and metabolic illness, individuals in control group randomly recruited during a detailed check-up examination. We selected patients, who were in the primary stage of PD and they did not begin any treatment, because such antidepressant drugs like haloperidol and flouxetine used for PD patients could inhibit PON1 activity [15], and oxidant – antioxidant ratio changes overtime [16].

2.3 Clinical and Biological Data

Blood samples were collected in two tubes, one tube was free anticoagulant and the plasma of these samples were separated then stored at -70 Ċ for measurement of PON1 activity. The second tubes containing EDTA, these samples were used for DNA extraction.

2.4 DNA extraction and genotyping of PON1

Genomic DNA was extracted from the whole blood by the phenol-chloroform method as described elsewhere [17].

Genotyping procedures for the detection of the PON1 wild-type (wt) gene and the two mutated alleles; M55L in exon 3 and Q192R in exon 6. These primers were used in this study; the forward primer for M55L (5-GAAGAGTGATGTATAGCCCCAG-3), reverse primer

for M55L (5-TTTAATCCAGAGCTAATGAAAGCC-3), and forward primer for Q192R (5-TATTGTTGCTGTG GGACCTGAG-3), reverse primer for Q192R (5-CCT GAG AAT CTG AGT AAA TCC ACT-3). After PCR amplification, the DNA fragments (170bp) of exon3 were digested with Nla111 (Fermentas), the Allele L (leucine) was not cut by Nla111 whereas M (methionine) was cut by Nla111 and gave 126 and 44 bp products. Genotyping procedures for exon 6 were digested with AlwI (Fermentas), the wild-type allele did not have a site for the cut by AlwI (99bp) and mutant alleles (R) were digested with endonuclease and gave 63 and 36 bp fragments. Digested PCR products were analyzed on 3% agarose gels and stained with ethidium bromide.

2.5 Paraoxonase1 activity assay

Serum paraoxonase activity of PON1 was determined using paraoxon as a substrate and liberation of p-nitrophenol (diethyl-p-nitrophenol phosphate) measured at 405nm. Enzyme activity was measured in 0.1M Tris/HCl buffer at pH 8.5, containing 1.32 Mm CaCl2. Primarily 535 μL buffers were poured in the tubes then 25 μL of serum and 140 μL paraoxon were added. The amount of generated p-nitrophenol was calculated from the molar extinction coefficients, which was 18,050M-1 cm-1 and the activity was expressed as the number of nmol of p-nitrophenol/min/ml of serum. In the end, results were presented as U/L. Arylesterase activity of PON1 was measured by using phenylacetate as a substrate, measuring the increase in the absorbance at 270nm by a continuous recording spectrophotometer due to the formation of phenol product. Primarily 3 ml of the reaction mixture (1 mmol/L phenylacetate, 1 mmol/L CaCl2 and 20 mmol/L Tris-HCl buffer pH 8) was poured into the tubes, then 5 μL of the plasma sample was added. The absorbance at 270 nm and 37°C was measured per min and arylesterase activity was calculated using the molar absorption coefficient 1310 mol-1 Lcm-1. In the end, results were presented as U/mL [5,18,19].

PON1 specific activity was calculated as an activity of enzyme per its concentration:

Specific activity of PON1 (U/μg) = PON1 (U/L)/ PON1 (ng/mL)

PON1 concentration was determined by using competitive ELISA kit as described previously [20].

2.6 Measurement of TOS and TAC

Serum TOS (total oxidant status) and TAC (total antioxidant capacity) were determined by colorimetric method with ELISA KIT in 490 and 560nm (from ZellBio GmbH) assay kits.

2.7 Calculation of the OSI

OSI is equal to TOC divided by TAC.

OSI = (TOS, mmol) / (TAC, μmol).

2.8 Statistical analysis

SPSS (version16) used for data analyses of the normality of the quantitative variables are done by kolmogorov- smirnov test. Chi-square test for qualitative

Table 1. Demographic characteristics of patients and healthy groups.

Characteristic		PD (n=70)	Controls (n=75)	p values
Gender	Male, n (0/0)	54 (77.2)	55 (73.3)	> 0.05*
	Female, n (0/0)	16 (22.8)	20 (26.6)	
Age		63.7 ± 9.37	61.4 ± 8.49	> 0.05**
BMI		24.4 ± 3.82	25.1 ± 2.69	> 0.05**
Weight		68.3 ± 9.24	70.2 ± 10.56	> 0.05**
Smoking n (0/0)		6 (8.5)	5 (6.6)	> 0.05*
DD (years)		3.56 ±2.1	0	-
Hypertension n (0/0)		12 (0.17)	11 (0.14.5)	> 0.05*

PD: Parkinson disease, BMI: body mass index, DD: disease duration

Values are as mean ± SD

*p value is based on chi-square test. **p value is based on independent samples t-test.

data and independent sample t-test for quantitative data analysis were used, one way ANOVA test was used to compare the means of quantitative parameters in different genotypes. Also, binary regression was used for calculation of odd ratios. Data variable were presented as mean ± SD and pvalue < 0.05 was significant.

3. RESULTS

3.1 Demographic information of study population

Out of 145 studied subjects, 70 cases with Parkinson's disease and 75 controls were enrolled in this study as they did not have any other nervous and metabolic disease. Our results indicated that the two groups did not show any significant relationships in gender, BMI, and age ($p > 0.05$). Table 1 shows the demographic data from two groups.

3.2 Paraoxonase and arylesterase levels in two studied groups

The mean paraoxonase activity and concentration of PON1 were significantly decreased in the PD population compared to the control subjects. In addition, the arylesterase activity of PON1 in Parkinson's subjects was statistically lower than healthy ones ($p<0.05$) (Table 2). The specific activity of paraoxonase and arylesterase were not significant between the two groups ($p>0/05$). In the terms of TAC, TOS, and OSI among our groups, TOS and OSI were higher in the patients than controls ($p<0.05$), while patients had lower levels of TAC compared with controls ($p<0.05$)(Table 2).

3.3 The frequencies of PON1 genotypes among studied groups

PON1 genotype and allele distribution have been shown in the table 3. The frequencies of PON1 genotypes were in Hardy–Weinberg equilibrium except the Q192R polymorphism in the control group was not consistent with equilibrium. This departure may reflect the small sample size, genotyping errors, or biological selection. In L55M genotypes, the amount of the LL and LM polymorphisms were lower in patients than healthy subjects, but the amount of the MM polymorphism in PD was more than controls ($p < 0.05$). But in Q192R genotype, the frequency of the QQ, QR, and RR was not significantly different. In our study, allele's frequencies were different between two groups. There were lower (PON1 L55) and higher (55M) frequencies of mentioned alleles in patients compared with healthy cases ($p < 0.05$), although the difference between Q192 and 192R alleles were not significant.

3.4 PON1 genotypes, serum PON1, and arylesterase values

Regarding the combined polymorphisms and activity of PON1, the L55Mpolymorphism had a major effect on PON1 activity and concentration. In both populations, serum PON1 activity and concentration were significantly higher in the LL genotype than LM and MM polymorphisms. However, we did not observe any significant difference in arylesterase activity between these polymorphisms in the two groups (Table 5). Our results regarding the 192 polymorphism showed that the activity and concentration of PON1 enzyme in subjects with RR

Table 2. Comparison of studied factors between patients and healthy groups.

Groups / Factors	Patient	control	* P value
PON1 concentration (ng/ml)	302.96 ± 61	329.49 ± 75	0.013
PON1 activity(U/L)	161.29 ± 16	175.53 ± 18	< .001
Aryl esterase activity(U/mL)	48.21 ± 9.11	50.12 ± 8.13	0.017
PON1specific activity(U/μg)	0.54 ± 0.14	0.56 ± 0.23	0.88
Arylesterase specific activity(U/ng)	0.16 ± 0.05	0.15 ± 0.06	0.309
TAC (mmol/L)	0.206 ± 0.048	0.236 ± 0.047	< .001
TOS (μmol/L)	6.86 ± 1.05	6.30 ± 1.21	0.001
OSI (arbitrary unit)	35.91 ± 13.3	28.14 ± 8.40	< .001

*p value was reported based on independent sample t- test

Table 3. PON1 55 and 192 genotypes distribution in PD and control populations.

genotype	PON1 55				PON1 192			
		PD n (%)	CO n (%)	p value		PD n (%)	CO n (%)	*p value
	LL	24(34%)	36(48%)		QQ	33(47.3%)	35(46.5%)	
	LM	21(30%)	31(41%)	0.013	QR	32(45.3%)	32(42.5%)	0.715
	MM	25(36%)	8(10%)		RR	5(0.7%)	8(10.5%)	
Alleles	L	73(52%)	103(69%)	0.004	Q	97(69%)	102(68%)	0.814
	M	67(48%)	47(31%)		R	43(31%)	48(32%)	

*p value was reported based on independent chi-square test.

Table 4. The frequency of PON1 55 and PON1 192 genotypes, alleles and odds ratios in PD and controlsusing 2 test and regression logistics analysis.

Genotypes		PD n(%)	Controls n(%)	p value (df)	Odds ratio, 0/095 CI (Lower-Upper)
PON1 55	LL	24(34%)	36(48%)	0.016 (df=2)	Reference group
	LM	21(30%)	31(41%)	0.005 (df=1)	4.16 (1.54-11.2)
	MM	25(36%)	8(10%)	0.016 (df=1)	3.32 (1.24-8.8)
	L	73(52%)	103(69%)	0.003 (df=1)	Reference group
Alleles	M	67(48%)	47(31%)		2.06 (1.26-3.34)
PON1 192	QQ	33(47.3%)	35(46.5%)	0.636 (df=2)	Reference group
	QR	32(45.3%)	32(42.5%)	0.861 (df=1)	0.89 (0.25-3.1)
	RR	5(0.7%)	8(10.5%)	0.507 (df=1)	0.65 (0.19-2.27)
Alleles	Q	97(69%)	102(68%)	0.520 (df=1)	Reference group
	R	43(31%)	48(32%)		0.843 (0.506-1.40)

df: degree of freedom; CI: confidence interval

Table 5. PON1 activity in PD and Control populations according to the PON1 55 and 192 genotypes.

Genotype	PON1 Concentration		PONase activity		Arylesterase activity		TAC		TOS		OSI	
PON155	CO	PD	CO	PD	CO	PD	CO	PD	CO	PD	CO	PD
LL	356.23	355.12	177.23	165.71	50.44	48.62	0.25	0.23	5.90	6.53	24.24	29.38
LM	326.42	[a]280.80	175.55	156.88	49.32	48.24	[a]0.22	[a]0.19	6.41	6.09	[a]29.68	[a]40.01
MM	[a,b]247.35	[a,b]269.05	[a,b]167.50	161.48	51.75	47.71	[a,b]0.18	[a]0.19	[a]7.30	7.00	[a,b]39.61	[a]38.47
PON1 192												
QQ	337.11	290.31	171.81	159.59	49.63	47.81	0.23	0.18	6.33	6.47	29.31	39.49
QR	311.31	307.36	[α]177.38	161.21	50.28	48.21	0.23	[α]0.22	6.28	6.27	28.19	32.63
RR	[β]390.00	352.00	[α,β]184.01	172.60	51.62	50.80	0.24	0.21	6.29	6.11	27.12	38.32

Values are median (range)

1. Significant different (p<0.05) in comparison with aLL and bLM genotype.

2.Significant different (p<0.05) in comparison with αQQ and βQR genotype

polymorphism were higher than other polymorphisms(QR, QQ).

3.5 PON1 genotypes, serum TAC, TOS and OSI values

Investigation of the relationship between PON155 genotype with studied factors demonstrated that the levels of TAC were increased in the LL polymorphism in comparison with the LM and MM. In contrast to TAC, TOS and OSI values were high in MM polymorphism. The genetic polymorphism at 192 had no significant effect on the plasma TAC, TOS, and OSI in either group except in the patient with QR genotype where the TAC level was significantly higher than QQ and RR genotypes ($p<0.05$).

4. DISCUSSION

PD is considered to be influenced by environmental and genetic factors [21]. Epidemiological studies have found associations between pesticide exposure and Parkinson disease [22]. PON1 have a protective role in organophosphate toxicity and it has an antioxidant capacity that is important in the prevention of some disorders like cardiovascular disease, PD, and AD [23]. Certain histidine and cysteine amino acid in the active site of PON1 are important for paraoxonase and arylesterase activity. It is possible that some substances and metals modify these amino acids and inhibit the PON1 activity [24,25]. In the current study we found that serum paraoxonase concentrations and activities were higher in LL (comparison with LM and MM) and RR (comparison with QR and QQ) genotypes while we did not observe any significant differences in arylesterase levels among mentioned polymorphisms.

In our study, with regard to activity and concentration of PON1, we found that these factors were lower in the patients with Parkinson than healthy subjects, but the amounts of the TOS and OSI unlike the TAC in the PD were higher than controls. Some studies showed that the activity of PON1 in PD was less than the control group [26,27]. One study by Kirbas et al. reported that paraoxonase and arylesterase activities of PON1 enzyme were decreased in the patient group in contrast to controls. Moreover, they found higher TOS and OSI levels in the patient compared to controls [28]. The low PON1 activity could have a significant effect on the ability of the enzyme to metabolize TOS in PD. Therefore, it would be a reason for the increased TOS often reported in PD. In fact, because TOS in PD is higher than the healthy people and it may bind with cysteine and histidine of the active site of PON1, in which it can lead to decrease the activity of this enzyme.

In human population, PON1 have two important polymorphisms that may lead to change the PON1 activity and level [12,29]. Regarding the L55M genotypes, in this study, we found higher (MM genotype) and lower (LL genotype) frequency

in patients compared with controls. Almost other studies in this area are in agreement with our observation. Carmine A. and his colleagues found that the prevalence of 55MM genotype was significantly higher in PD compared with controls [30], and some studies also confirm these findings [31,33] ; however, a few researches could not found significant difference in MM and LL polymorphisms frequency between PD and controls [13,34].

In the present study, there were no significant differences in frequency of the Q192R polymorphisms and alleles between the two studied populations. Like our study, Clarimon et al. and Akhmedova et al. did not observe significant differences in the frequency of 192 genotype [31,34]. Kondo et al. described a significant increase in the RR192 polymorphism in PD patients in comparison to healthy cases [32]. Ethnic populations are known a reason for differences among PON1 genotypes, which may be a possible explanation for controversies between these studies.

In the current study, we evaluated PON1activity with each genotype (Q192R and L55M). The Q192R polymorphism has shown different activity for the substrate. We found that the activity of paraoxonase1 in 192RR was more than the QQ192. Studies demonstrate that the 192QQ polymorphism hydrolyzes diazoxon, soman and sarin more rapidly than the PON1 192RR. On the other hand, PON1 192RR polymorphism has a dominant role in hydrolizationof paraoxon in contrast to 192QQ polymorphism [35]. A growing body of evidence reports the same results regarding the Q192R polymorphism [36-39].

Studies show that different polymorphism at the position of 55 like 192 has diverse impacts on enzyme activity [30,40]. The results of our study indicated that L55

isoform has higher PON1 enzyme concentration and activity than individuals with 55M isoform. Although the concentration of this enzyme related to L55M polymorphism, some of the studies reported that the M55 isoform has the lower PON1 activity and levels. The exchange of the amino acids could lead to lower PON1 levels in the HDL, and it would be a logical reason for lower levels of the enzyme in MM genotype in comparison with LL[12,29,36,41].

The polymorphisms of enzymes can alter drug and organophosphate metabolisms [42]. It is important that PON1 polymorphisms have a major effect on the metabolism of organophosphates as its polymorphisms are different depending on the region of the geographical world [42].

Individuals with different polymorphisms of PON1 could be more or less sensitive to the toxicity of organophosphate, suggesting that pesticide exposure is a potential high risk for the agriculture workers as their DNA damage has been reported in high levels especially during the spraying/using seasons [43].

The investigation of the relationship between the genotype of this enzyme with TAC, TOS, and OSI, indicated that L55M polymorphism had a better effect than Q192R on these factors and the LL polymorphism is superior to MM in the metabolizing the oxidative stress agents. Therefore, the MM polymorphism and M alleles may be a possible risk factor for PD. With these findings, people with Parkinson's disease can be screened with PON1 enzyme polymorphism, which has a different effect on metabolizing the drugs and toxins.

Our findings demonstrate different results from some previous studies [13,32] as this may be due to a many factors such as impacts of other enzymes (glutathione peroxidase, superoxide dismutase, catalase and etc), gender, age, condition living, affect the metabolizing of the xenobiotics as well as organophosphate and also sensitivity to disease.

In conclusion, our study for the first time shows that the PON1 polymorphisms are correlated with activity and concentration of this enzyme in PD. Our results also show that the amounts of the TAC, TOS, and OSI are different between two groups and these factors are affected by genotypes, which may be effective in preventing or progressing of PD.

Conflict of interest

The authors announce that there are no conflicts of interest.

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