Araştırma Makalesi / Research Article

The association between blood homocystein-paraoxonase levels and the polymorphisms of methylenetetrahydrofolate reductase and paraoxonase 1 genes in Alzheimer's disease patients

Alzheimer hastalarında serum homosistein ve paraoksonaz seviyeleri ile mthfr ve pon 1 gen polimorfizminin klinik ile korelasyonu

Hasan BAYINDIR[1], Gülay GÜLEÇ CEYLAN[2], Salim NEŞELİOĞLU[3]

[1] Harran University, Faculty of Medicine, Department of Neurology, Şanlıurfa, Turkey
[2] Yildirim Beyazit University, Faculty of Medicine, Department of Medical Genetics, Ankara, Turkey
[3] Yildirim Beyazit University, Faculty of Medicine, Department of Biochemistry, Ankara

Abstract

Background: The aim of this study is to detect serum homocysteine increase (Hcy) and paraoxonase decrease together with methylenetetrahydrofolate reductase (MTHFR) and paraoxonase 1 (PON1) gene polymorphisms in Alzheimer's patients and to evaluate the correlation with clinic in these patients.
Material and Methods: In our study; total 103 individuals were included and 51 of them had Alzheimer's disease (AD) diagnosis clinically according to DSM-IV criteria and 52 of them did not have AD. In patient and control group; Hcy levels and paraoxonase activity, MTHFR C677T – A1298C and PON1 L55M - Q192R gene polymorphisms were investigated.
Results: Average age of the patients in our study was found as 73.67±7.91 years. In patient group; Hcy level was significantly high (p:0,024) and paraoxonase activity was found low in patient group (p:0,047). In patients with MTHFR C677T and A1298C polymorphism, Hcy levels were high but there was no significant difference between groups (p>0,05). In PON1 L55M polymorphism PON levels were low (p<0,009). In patients with Q192R polymorphism PON levels were significantly high especially in heterozygote group (p:0,024).
Conclusion: It was seen that Hcy levels were high and PON activity was low in Alzheimer's disease. MTHFR C677T and A1298C polymorphism could not be associated with AD but it was observed that the polymorphism could increase Hcy levels. As a result; PON 1 L55M polymorphism was thought to be a risk factor in AD and on the other hand Q192R polymorphism was thought to be a protective factor.

Keywords: Alzheimer's disease, Homocysteine, Methylenetetrahydrofolate reductase, Paraoxonase gene polymorphism.

Öz.

Amaç: Bu çalışmanın amacı Alzheimer hastalarında, serum homosistein (Hcy) yüksekliği ve paraoksonaz düşüklüğü ile metilentetrahidrofolat redüktaz (MTHFR) ve paraoksonaz 1 (PON1) gen polimorfizmlerinin tespit edilmesi, bu hastalarda klinik ile korelasyonunun değerlendirilmesidir.
Materyal ve Metod: Çalışmaya klinik olarak Alzheimer hastalığı (AH) tanısı DSM-IV kriterlerine göre konulan 51 hasta ve AH olmayan 52 kişi olmak üzere toplam 103 olgu alındı. Hasta ve kontrol grubunda, Hcy düzeyleri ve paraoksonaz aktiviteleri, MTHFR C677T – A1298C ve PON1 L55M - Q192R gen polimorfizmleri incelendi.
Bulgular: Çalışmamızda hastaların yaş ortalaması 73.67±7.91 yıl olarak bulundu. Hasta grupta Hcy düzeyi anlamlı olarak yüksek iken (p:0,024), paraoksonaz aktivitesi hasta grupta düşük olarak bulundu (p:0,047). MTHFR C677T ve A1298C polimorfizmi olanlarda Hcy seviyeleri yüksekti ancak gruplar arasında anlamlı bir fark yoktu (p>0,05). PON1 L55M polimorfizminde PON düzeyleri düşüktü (p<0,009). Q192R polimorfizmi olanlarda PON düzeyi heterezigot grupta daha belirgin olmak üzere yüksekti (p:0,024).
Sonuç: Alzheimer hastalığında Hcy düzeylerinde yükseklik ve PON aktivitesinde düşüklük olduğu görüldü. MTHFR C677T ve A1298C polimorfizmi AH ile ilişkili bulunmadı, ancak Hcy düzeylerini arttırdığı gözlendi. PON 1 L55M polimorfizmi AH da risk faktörü, Q192R polimorfizminin ise koruyucu faktör olabileceği sonucuna varıldı.

Anahtar Kelimeler: Alzheimer hastalığı, Homosistein, Metilentetrahidrofolat redüktaz, Paraoksonaz gen polimorfizmi.

Sorumlu Yazar / Corresponding Author

Dr. Hasan BAYINDIR

Harran Üniversitesi, Tıp Fakültesi Nöroloji Anabilim Dalı, Şanlıurfa, Türkiye

Tel: +90 505 430 91 47

E-mail: hsnbayindir12@gmail.com

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia that constitutes 50-70% of all dementias (1). AD is a progressive neurodegenerative disease that can cause intellectual decline together with various neuropsychiatric disorders and impairments in daily living activities. In AD; short-term memory impairment can occur due to central limbic system degeneration, neocortical involvement occur with an insidious, slow pace and other cognitive functions also impair. Despite the strict criteria of AD, diagnosis is made by exclusion of secondary causes and other disease with dementia. Golden standard in diagnosis is to observe typical neuropathological changes in brain in people who had AD diagnosis clinically. In histological examination of AD; reduction in brain volume, together with ventricular dilation; cortical neuronal atrophy; extracellular amyloid plaques and neurofibrillary tangles in neuronal cytoplasm can be seen (2).

In AD; senile plaques, neurofibrillary tangles, and synapse loss can be seen pathologically. The principal component of the senile plaques is amyloid beta peptide and this is related with increased oxidative stress. The most important known risk factor for Alzheimer type dementia is age and the incidence of this disease increases by two fold for each 5 years passed between the ages of 65 to 85. Elevated plasma Hcy levels are shown as a vascular risk factor and vascular risk factors are important in AD pathogenesis and because of this elevated plasma Hcy levels are thought to be a risk factor for AD. Hcy increase in AD is not only responsible for vascular risk increase but also it is responsible for degeneration and excitotoxicity by effecting via NMDA receptors (3). Although many causes were blamed in etiology; oxidative stress is assumed to be in pathogenetic mechanisms of AD. In AD, neurons in the specific structures of the central nervous system undergo apoptosis (4).

Hcy, is a non-essential amino acid which includes sulfur and is formed by the demethylation of methionine. Hcy elevation is associated with cardiovascular, neurodegenerative, neurovascular and kidney diseases. Several genetic mutations were defined in enzymes involved in Hcy metabolism such as; methionine synthase (MTR), methylenetetrahydrofolate reductase (MTHFR) and cystathionine beta-synthase (5). The most common mutation in the MTHFR gene is C677T and this can cause a decrease a decrease in enzyme activity, thermolability and folate metabolism disorders as well as medium or higher plasma Hcy level. Another mutation in MTHFR gene is A1298C point mutation. As in other types of mutations, this mutation can cause a decrease of MTHFR activity. In such a situation that A1298C and C677T mutations are together as heterozygote; MTHFR enzyme activity is for about 50-60% of enzyme activity in which both alleles are normal homozygotes. The frequency of the A1298C and C677T mutation varies according to the population (6).

PON enzyme group; is a hydrolase that have both arylesterase and paraoxonase activity. In Mammals; paraoxonase gene family have three members as PON1, PON2, PON3 and they are on 7.chromosome. PON1 is an enzyme that has three activities and associated with HDL which includes paraoxonase, arylesterase and diyazoksanaz. It is the first shown and most studied member of the family of PON (7). Paraoxonase activity is genetically determined. Today PON1 shows two common codon polymorphisms. These polymorphisms are; methionine change to leucine at 55.codon (M/L55) polymorphism and glutamine change to arginine at 192. codon (Q/R192) polymorphism. Generally; PON1 has a protective role against cell-mediated oxidation of LDL (8).

In this study; it was aimed to detect the genotype and allele frequencies of MTHFR gene C677T and A1298C polymorphism, methionine change to leucine at 55.codon (M/L55) polymorphism in PON 1 gene, glutamine change to arginine at 192. codon (Q/R192) polymorphism in PON 1 gene and to investigate the relation between these genotypes and plasma total Hcy and paraoxonase levels in Alzheimer's disease patients.

Material and Methods

Total 52 patients, 60 years old and older, who had Alzheimer's Disease dementia diagnosis clinically were applied to Neurology clinic were included to the study. As a control group total 51 individuals with compatible ages were included into this study and both of these groups were evaluated prospectively. Dementia diagnosis was clinically made according to Diagnostic and Statistic Manuel of Mental Disorders, Fourth Edition (DSM- IV) criteria. Standardized Mini Mental State Examination Test (SMMT) was applied to both patient and control groups, mini mental scores that are 24 and below were evaluated as cognitive disorder AD and these individuals were included in to the study. The patients underwent a detailed neurological examination. In Cognitive status assessment; Standardized Mini Mental State Examination Test (SMMT), Clinical Dementia Rating Scale (CDRS) were used. Routine biochemical examination of patients was performed. Patients with severe systemic disease, vitamin and mineral use, psychiatric and neurological disorders apart from dementia, vascular pathology in cranial imaging (CT, MR), hydrocephalus and mass lesion were excluded. The ones with MMSE score of 24 and lowere were accepted as impaired cognitive function. For this study; ethical approval was taken from Yıldırım Beyazıt University Ankara Ataturk Training and Research Hospital Ethics Committee. Before inclusion in to the study; patient and if needed a relative was informed about the study and approval was taken from them by filling a informed consent form.

Venous blood samples were taken from people who were included in the study with an empty stomach. Vitamin B12 levels were measured with electro-chemiluminescence immunoassay (ECLİA) method in a COBAS-E601 (Roche) autoanalyser, Hcy measurement was made with chemiluminescence immunoassay (CLİA) method in a İMMU-LİTE 2000 (Siemens) autoanalyser, paraoxonase enzyme activity was measured spectrophotometrically in a COBAS-C501 (Roche) autoanalyser. DNA isolation was made from the peripheral blood of patients (QIAamp DNA mini kit, Qiagen, Hilden, Germany). Samples, in which PON 1 and MTHFR gene mutations will be examined, were stored at -80ºC until analysis time. The subjects were genotyped for C677T and A1298C of MTHFR mutations by PCR with Rotor Gene 6000 Light Cycler (Corbett Life ScienceScience, Concorde, NSW) according to the guidelines of the manufacturer.
Statistical analyzes were performed using SPSS 20.0 for Windows software package. ANOVA test was used for comparison of all groups. Chi-square test was used for gender distribution of the groups, Kruskal-Wallis ANOVA was used for age distribution and Mann-Whitney U test was used to understand which groups have a significant difference from each other and Pearson correlation test was used for correlation analysis. Results were given as mean ± SD. Statistical significance was defined as P< 0.05.

Results

In total 103 individuals who were included in to this study; 48 of them were male and 55 of them were female and their age interval was between 61-89 years. In patient group; there was total 51 individual with average age of 77.45 ± 6.97 years and 23 of them were fenale and 28 of them were male. On the other hand the average age of control group was 69.98±7,02 years. In control group there was 20 males and 32 females. There was no significant difference between females and males (p:0,649).
In total 103 individuals in both control and patient groups; vitamin B 12 levels were measured between 101 pg/mL as the lowest value and 650 pg/mL as the highest value. Homocysteine values were measured between 2-44 µmol/L in both groups and the values were higher than normal values (Hcy<15 µmol/L) for about 17,41 µmol/L. Paraoxonase enzyme activity was measured, lowest values was 41,0 and the highest value was 439,8 (Table 1).
MTHFR C677T polymorphism was checked in total 103 individuals. In patient group consisting of 51 individuals; normal CC genotype was detected in 22 people with a ratio of 43,1%, homozygote TT genotype was detected in 4 people with a ratio of 7,8% and heterozygote CT genotype was detected in 25 people with a ratio of 49,0%. In control group consisting of 52 individuals; normal CC genotype was detected in 25 people with a ratio of 48,1%, homozygote TT genotype was detected in 4 people with a ratio of 7,8% and heterozygote CT genotype was detected in 48 people with a ratio of 46,6%. MTHFR A1298C polymorphism was also checked in all groups.

Table 1. Age, SMMT, Vit B12, Hcy and PON values

	N	Lowest	Highest	Average	Standard deviation
Age	103	61	89	73,67	7,91
SMMT	103	3	30	22,44	7,01
B12 level	103	101	650	324,47	138,88
Hcy level	103	2	44	17,41	7,15
PON level	103	41	439,8	202,06	104,39

For patient group; AA genotype was detected in 15 people with a ratio of 29,4%, homozygote CC was detected in 6 people with a ratio of 11,8% and heterozygote CT genotype was detected in 30 people with a ratio of 58,8%. In control group; AA genotype was detected in 19 people with a ratio of 36,5%, homozygote CC was detected in 8 people with a ratio of 15,4% and heterozygote CT genotype was detected in 25 people with a ratio of 48,1% (Table 2).
PON 1 L55M polymorphism was checked in study group and in patient group; 25 people with normal LL allel with a ratio of 49%; 6 people with homozygote MM allel with a ratio of 11,8%, 20 people with heterozygote LM allel with a ratio of 39,2% were detected. In control group; 30 people with normal LL allel with a ratio of 57,7%; 3 people with homozygote MM allel with a ratio of 5,8% and 19 people with heterozygote LM allel with a ratio of 36,5% were found. There was no significant relation between groups (p: 0,479). PON 1 Q192R polymorphism was checked in total 103 individuals who were included in to the study. In patient group; normal QQ was detected in 35 people with a ratio of 68,6%, homozygote RR was detecte in 3 people with a ratio of 5,9% and heterozygote allel was detected in 13 people with a ratio of 25,5%. In control group; normal QQ was detected in 29 people with a ratio of 55,8%, homozygote RR was detecte in 6 people with a ratio of 11,5% and heterozygote allel was detected in 17 people with a ratio of 32,7% (Table 3). There was no significant relation between groups (P:0,352).

Table 2. MTHFR C677T and MTHFR A1298C polymorphism ratios in patient and control groups

p: 0,876	C677T			Total
	Normal CC	Homozygote TT	Heterozygote CT	
Patient	22 (43.1%)	4(7.8%)	25(49.0%)	51
Control	25 (48.1%)	4 (7.7%)	23 (44.2%)	52
Total	47 (45.6%)	8 (7.8%)	48 (46.6%)	103

p: 0,548	A1298C			Total
	Normal AA	Homozygote CC	Heterozygote AC	
Patient	15 (29.4%)	6 (11.8%)	30 (58.8%)	51
Control	19 (36.5%)	8 (15.4%)	25 (48.1%)	52
Total	34 (33.0%)	14 (13.6%)	55 (53.4%)	103

Hcy level was detected as lower than 12 µmol/L in 23,3% of whole group, between 12-15 µmol/L in 20,4% of whole group and higher than 15 µmol/L in 56,3% of whole group. Hcy level was found as 19.01±7.95 µmol/L in patient group and 15.84±5.94 µmol/L in control group. Average hyc levels were found to be high in both groups and Hyc levels in two patients in both groups were found to be significantly high when compared with normal distribution. When groups were compared; Hyc level in patient group was significantly high (p:0.024, p<0.05). Measured Pon level in patient group was found as average 181,50±97,16. In control group PON level was found as 222,21±108,19. When patient and control groups were compared according to PON levels; a significant difference was found between them (p:0,047) (Table 4).

When MTHFR C677T polymorphism was compared with Hcy levels; a significant relation could not be detected. Hcy levels were higher than normal in all three groups. A significant relation between MTHFR A1298C polymorphism and Hcy levels was not found. Hcy levels were higher than normal in all three groups (Table 5).

Table 3. PON 1 L55M and Q192R polymorphism ratios in patient and control groups

p: 0,479	L55M			Total
	normal LL	homozygote MM	heterozygote LM	
Patient	25(49.0%)	6(11.8%)	20(39.2%)	51
Control	30(57,7%)	3(5.8%)	19(36.5%)	52
Total	55(53.4%)	9(8.7%)	39(37.9%)	103

p: 0,352	Q192R			Total
	normal QQ	homozygote RR	heterozygote QR	
Patient	35(68.6%)	3(5.9%)	13(25.5%)	51
Control	29(55.8%)	6(11.5%)	17(32.7%)	52
Total	64(62.1%)	9(8.7%)	30(29.1%)	103

Table 4. Hyc and PON levels average values in patient and control groups

	Patient control	N	Average µmol/L	Standard deviation	P value
Hcy level	Patient	51	19,01	7,95	**0.024**
	Control	52	15,84	5,94	**(p<0.05)**
Pon level	Patient	51	181,5	97,16	**0,047**
	Control	52	222,21	108,19	**(P<0,05)**

Table 5. Relation between MTHFR C677T and A1298C polymorphisms and Hcy levels

MTHFR C677T		N	Average µmol/L	Standard deviation	P
Hcy level	normal CC	47	18,41	7,83	0,972
	homozygote TT	8	18,31	8,96	
Hcy level	normal CC	47	18,41	7,83	0,140
	heterozygote CT	48	16,28	6,05	
Hcy level	homozygote TT	8	18,31	8,96	0,418
	heterozygote CT	48	16,28	6,05	
MTHFR A1298C					
Hcy level	normal AA	34	17,65	6,97	0,599
	homozygote CC	14	18,90	8,46	
Hcy level	normal AA	34	17,65	6,97	0,620
	heterozygote AC	55	16,89	6,98	
Hcy level	homozygote CC	14	18,90	8,46	0,361
	heterozygote AC	55	16,89	6,98	

Hcy level in individuals with PON 1 L55M homozygote MM polymorphism was higher than normal LL genotype but there was no statistically significant relation (p:0,311). In heterozygote group; Hcy levels were significantly low when compared with normal and homozygote groups (p:0,037 - p:0,04). A significant relation between PON 1 Q192R polymorphism and Hcy level was not found. Average Hcy level in normal QQ genotype was lower than that of homozygote RR genotype but p>0,05 value was not significant (Table 6).

A significant positive relation was found between PON 1 L55M polymorphism and PON level. 55 individuals had normal LL genotype, 9 individuals had homozygote MM and 39 individuals had heterozygote genotype. PON levels were significantly high in normal group when compared with homozygote and heterozygote groups (p:0,009- p:0,010). For PON values statistical significance between homozygote and heterozygote groups was p>0,05 and there was no signficant difference (p:0,181). Between PON 1 Q192R polymorphism and PON level; a significant negative correlation was found between heterozygote QR and normal QQ groups (p:0,024). In 64 patients normal QQ, in 9 individuals homozygote RR polymorphism and in 30 individuals heterozygote QR polymorphism was detected (Table 7).

Table 7. Relation between PON1 L55M and Q192R polymorphisms and PON levels

PON 1	L55M	N	Average	Standard deviation	P
Pon level	normal LL	55	231,66	105,72	0,009
	homozygote MM	9	130,63	94,14	
Pon level	normal LL	55	231,66	105,72	0,010
	heterozygote LM	39	176,79	91,51	
Pon level	homozygote MM	9	130,63	94,14	0,181
	heterozygote LM	39	176,79	91,51	
PON 1	**Q192R**	**N**	**Average**	**Standard deviation**	**P**
Pon level	normal QQ	64	182,61	100,60	0,164
	homozygote RR	9	233,48	109,67	
Pon level	normal QQ	64	182,61	100,60	0,024
	heterozygote QR	30	234,11	104,03	
Pon level	homozygote RR	9	233,48	109,67	0,988
	heterozygote QR	30	234,11	104,03	

Discussion

AD is a complex neurodegenerative disease which affects central nervous system in elder population. Lately, it has been thought that the disease can occur due to interaction of genetic and environmental factors all together (9).

Hcy is effective for amyloid plaques formation in AD (10). Metabolism of Hcy is mainly regulated by vit B6, vit B12, folic acid and as well as MTHFR. In C677T mutation, which is a genetic variation in MTHFR, replacement of cytosine (C) to thymine (T) makes a decline in enzyme activity for about 60% and this increases serum Hyc level for about 20% (11). Another important polymorphism is replacement of adenosine (A) to cytosine (C) at A1298C. In this case enzyme activity decreases for about 35-40%. Both of these polymorphisms cause an increase of plasma Hcy levels (12). In our study; there was no statistically significant difference between groups for MTHFR C677T and A1298C polymorphisms.

In Dufoil et al., study in 2003; it was reported that in patients older than 60 years with Hcy levels of 15 µmol/L or more, there was a 3 fold increase for cognitive disorder risk (13). In MTHFR A1298C homozygote CC genotype, a significant increase in Hcy level was detected. It was shown that there was no positive relation with Hyc levels in C677T homozygote TT genotype (14). Recently, in Mansoori et al., study; it was reported that A1298C homozygote CC genotype polymorphism significantly increased Hyc levels when compared with AA normal genotype but C677T heterozygote and homozygote polymorphisms had no relation with development of AD (15). In another study of Mansoori et al.; they worked with 38 patient and 100 normal people in their control group. They did not find any relation between MTHFR C677T mutation and AD but MTHFR A1298C mutation was significantly different between patient and control groups and a relation between this mutation and AD was shown (16). In our study; Hcy elevation (p:0,045) and PON decline (p:0,006) togetherness was observed. This association between Hyc elevation and PON decline was thought to be predisposing for AD occurrence.

Relation between serum PON activity and AH was investigated in two studies and first of these studies was Paragh et al., study. In this study; serum PON activity in AD group was significantly lower than PON activity in control and vascular dementia group. Other study was conducted by Dantoine et al., and in that study PON activity was lower in vascular dementia group when compared with control group and there was no significant relation with AD group (17, 18). According to these studies; relation of PON polymorphism with PON serum activity and AD is not clear. This shows the importance of investigating whatever PON is a

risk factor in AD or not. In a autopsy-based study in Canada; it was reported that PON 1 polymorphism was related with AD and also L55M and Q192R mutations had a significant relation with β- amyloid levels (p <0.001) the accumulation of senile plaques (p <0.001) and choline acetyl transferase activity (p <0.05) in brain autopsy series (19).

In our study; no significant relation was found between patient and control groups according to PON 1 L55M and Q192R polymorphisms (p:0,479, p:0,352) but it was observed that PON level was lower in patient group and when we compared patient group with control group, this decrease seemed to be statistically significant (p:0,047). Besides Hyc level in heterozygote individuals (LM genotype) for PON 1 L55M polymorphism was normal and significantly lower than that of individuals with homozygote genotype (p:0,037 - p:0,04). According to this finding, as homozygote L55M mutation increases Hcy level, it can be evaluated as risk factor in AD.

In a study which was conducted in The Chinese population; relation between PON 1 polymorphism and Q192R mutation in Alzheimer's patients was inverstigated. When Q/R or R/R alleles were compared with control group; they were reported to be lower than individuals with AD. Additionally it was advocated that PON 1 genotype did not have an impact on Alzheimer's disease and it can be interpreted as a protective factor from AD in The Chinese population (20).

In conclusion; Hyc elevation and paraoxonase decline are thought to be risk factors for occurance of AD according to our study's findings. No relation was found for MTHFR C677T and A1298C polymorphisms with Hcy levels and AD. It was observed that PON 1 L55M homozygote mutation causes a decrease in paraoxonase level and elevates Hyc levels. But against long odds PON 1 Q192R mutation caused an elevation in paraoxonase levels. Similar to the study in literature which was conducted in The Chinese population; our study also showed that Q192R polymorphism can have a protective effect against AD. Our study was conducted in 103 patients which is a limited number of patients and this reason reduced the power of our study. At the same time, high average of age and higher average level of Hyc in both groups when compared with normal values might also prevent the occurance of significant difference between groups.

We think that this study is the first one in literature which investigates Alzheimer disease with MTHFR and PON 1 polymorphisms in Turkey. There are limited studies in literature which investigates the different effects of ethnic differences and genetic factors on PON 1 activity. Our study is important for being a guideline for further studies. Besides our study is on the same side in discussions about PON polymorphism in literature which accepts L55M mutation as a risk factor for AD and Q192R mutation as a protective factor for AD.

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