Research Article / Araştırma Makalesi

Evaluation of the Effect of Age-Related Macular Degeneration Type And Stage on the Risk of Parkinson's Disease

Yaşa Bağlı Makula Dejenerasyonu Tipi Ve Evresinin Parkinson Hastalığı Riskine Etkisinin Değerlendirilmesi

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Abstract: The aim of the study was to investigate the distance between Parkinson's Disease (PD) and Age-Related Macular Degeneration (AMD) type and stage.. Our prospective study, the dry-type AMD group consisted of 296 patients with early and 284 patients with late-stage. The neovascular AMD group included 285 early and 277 late-stage patients. The control group consisted of 300 patients. AMD patients were grouped as dry and neovascular type and early and late stage. The patients were questioned about the use of drugs for PD, and the use was recorded as having the disease. If any of the complaints seen in the PD were present, the patient was referred to a neurologist. PD was detected in 1% of the control group and 4.6% in the neovascular type AMD group, and this difference was significant (p:0.04). This difference was present in both the early (%4.5) and late-stage (%4.6) (p:0.04, p:0.04). PD was determined 3.78 times greater among neovascular AMD patients(p:0.03), and significant association was present in both early (3.72 times) and late-stage (3.82 times) (p:0.03, p:0.03). In the dry-type AMD group 2.7% PD was detected and there was no statistical difference (p>0.05). This difference was not significant in the early stage (%2.3) or late-stage (%2.8) and also there was no association with dry-type AMD (p>0.05). Also, unilateral and bilateral involvement in AMD was not associated with PD (p>0.05). Our study revealed the association between both early and late neovascular AMD and PD. However, any significant relationship was not detected in terms of both unilateral and bilateral involvement.
Keywords: Age-related Macular Degeneration, Parkinson's disease, prevalence, stage, type

Özet: Çalışmamızın amacı Parkinson Hastalığı (PD) ile Yaşa Bağlı Makula Dejenerasyonu (YBMD) tipi ve evresi arasındaki ilişkiyi araştırmak idi.. Prospektif çalışmamızda kuru tip YBMD grubu 296 erken evre ve 284 geç evre hastadan oluşuyordu. Neovasküler AMD grubu 285 erken ve 277 geç evre hastayı içeriyordu. Kontrol grubu 300 hastadan oluşuyordu. YBMD hastaları kuru ve neovasküler tip ile erken ve geç evre olarak gruplandırıldı. Hastalara PH için ilaç kullanımı sorgulandı ve kullananların hastalıklı olduğu kaydedildi. PH'de görülen şikayetlerden herhangi birinin mevcut olması durumunda hasta nöroloji uzmanına yönlendirildi. Kontrol grubunun %1'inde, neovasküler tip YBMD grubunda ise %4,6 oranında PH saptandı ve bu fark anlamlıydı (p:0,04). Bu fark hem erken (%4,5) hem de geç dönemde (%4,6) mevcuttu (p:0,04, p:0,04). Neovasküler YBMD hastalarında PD 3,78 kat daha fazla saptandı (p:0,03), hem erken (3,72 kat) hem de geç dönemde (3,82 kat) anlamlı ilişki mevcuttu (p:0,03, p:0,03). Kuru tip YBMD grubunda %2,7 PD tespit edildi ve istatistiksel olarak fark saptanmadı (p>0,05). Bu fark erken dönemde (%2,3) ve geç dönemde (%2,8) anlamlı bulunmazken, kuru tip YBMD ile de ilişki saptanmadı (p>0,05). Ayrıca YBMD'nin tek taraflı ve iki taraflı tutulumu PH ile ilişkili değildi (p>0,05). Çalışmamız hem erken hem de geç neovasküler YBMD ile PD arasındaki ilişkiyi ortaya çıkardı. Ancak hem tek taraflı hem de iki taraflı tutulum açısından anlamlı bir ilişki saptanmadı.
Anahtar Kelimeler: Yaşa Bağlı Makula Dejenerasyonu, Parkinson hastalığı, prevalans, evre, tip

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1. Introduction

Age-related macular degeneration(AMD) is one of the leading causes of visual impairment and blindness in the elderly (1). The pathogenesis of AMD is still not fully understood and is attributed to a complicated interplay of aging, genetic, oxidative stres, and environmental factors (2). Currently, AMD is described as a macular neurodegenerative disease (3). It occurs as a complex degeneration in the macula that affects the photoreceptor, retinal pigment epithelium [RPE), Bruch's membrane and choriocapillaris, and is characterized by the presence of abnormal extracellular materials such as drusen (4). There are two types of AMD. One of which is Dry-type AMD, which can start with drusen, pigment epithelial changes and, or drusenoid pigment epithelial detachments in the early stage and result in geographic atrophy in the late-stage (5-6). On the other hand, neovascular type AMD starts with macular neovascularization in addition to dry-type AMD findings and may result in a disciform scar in the last stage (7-8).

Parkinson's Disease(PD) is a progressive neurodegenerative disorder that results in the loss of dopaminergic neurons in the substantia nigra and manifestations of Parkinsonian motor abnormalities include bradykinesia, resting tremor, and postural imbalance (9). Risk factors include drug, substance, ortoxin exposure, infections, and vascular insults (10-11). The prevalence of PD in the population over 65 years is approximately 1% (12-13). Several molecular studies suggested that oxidative stress, chronic inflammation, impairment of the processing and degradation of dysfunctional cellular components, and alterations of neuronal homeostasis are common biological pathways of PD (14-15). An increased risk of PD in neovascular type AMD patients has been shown in several studies (16-18). Pathomechanisms that contribute to AMD may be associated with the development of Parkinson's disease because both seem to share similar pathogenesis pathways and common risk factors.

To the best of our knowledge, there are no studies that have investigated the association between AMD types, stages, and eye involvement PD at the same time. Therefore, this study aimed to investigate the prevalence of PD in early and late-stage dry and neovascular AMD.

2. Materials and Methods

Patients diagnosed with Age-Related Macular Degeneration by fundus examination in the Ophthalmology outpatient clinic between March 1, 2022 and September 1, 2022 were included in this prospective study. In our study, the dry-type AMD group consisted of 300 patients with early stage and 284 patients with late stage. The neovascular AMD group included 295 early stage and 286 late stage patients. The control group consisted of 300 patients who were similar in terms of age and gender.

AMD patients will be grouped as dry and neovascular type, as well as the early and late stages. The control group was formed from patients of similar age groups without AMD. The control group was selected from patients who applied to the ophthalmology clinic for routine examination and who were sure that they did not have age-related macular degeneration. Additionally, patients with corneal, lens, and vitreous disease who could not performed retinal examination were also excluded from the control group. Drusen and pigment epithelial changes were accepted as early stage dry-type and those with geographic atrophy as late stage dry-type AMD(5-6). In addition to drusen and pigment epithelial changes, neovascular membranes, pigment epithelial detachment and intra-subretinal fluid were accepted as early stage neovascular type AMD and those with disciform scar as late stage neovascular type AMD (7-8). Optical coherence tomography was used when diagnosing AMD, and optical coherence tomography angiography and or fundus fluorescein angiography were also performed when necessary.If a patient had early stage AMD in one eye and late stage AMD in the other eye, the late stage eye was included in the study. In addition, patients with one eye dry-type and the other neovascular type AMD were not included in the study. Pachychoroid Neovasculopathy,

Retinal Angiomatosis Proliferation, Central Serous Retinopathy, Vitelliform Dystrophy and Macular Telangiectasia diseases were included in the differential diagnosis and these diseases were excluded. In addition, those with corneal, lens, and vitreous diseases that could affect retinal examination in one of their eyes were not included in the study.

Patients were questioned whether they were using Parkinson's medication for PD, and if they were using medication for Parkinson's disease, their previous records were checked for this disease in the system and the disease was recorded as present.. However, if there is no drug use, patients will be questioned about slowness in speech, slowness in walking, and tremors in the hands for Parkinson's. If any of these complaints were present, the presence or absence of these diseases was confirmed by referring the patient to a neurologist.

The patient was evaluated by the neurologist as follows. The diagnosis of Parkinson's was made according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria. Bradykinesia (slowness in initiating voluntary movement, in which the speed and amplitude of movement gradually decrease with repetitive activity) was determined as the main criterion in the diagnosis of the disease. The diagnosis was made by the presence of at least one of accompanying muscle rigidity, 4-6 Hz rest tremor, and postural instability (not due to primary visual, vestibular, cerebellar, or deep sensory dysfunction).

Exclusion criteria for PD are recurrent stroke history and cascading progression of Parkinsonian features, history of recurrent head trauma, definitive encephalitis, history of neuroleptic use at the onset of symptoms, affected in more than one relative, persistent remission, the unilateral continuation of symptoms after 3 years, supranuclear gaze paralysis, cerebellar symptoms, early severe autonomic involvement, early severe dementia (with memory, language and praxis disorders), babinski sign, history of cerebral tumor or communicating hydrocephalus, MPTP(It was determined as exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Also, patients with a regular smoking and alcohol history were excluded from the study.

Ethics Committee

The study was approved by the Ethics Committee of University Hospital with the number 2022/04-05

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS)version 23.0 for Windows software (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to evaluate the normality of the distribution of numerical data. In the comparisons of mean values between groups, the Independent Samples t-test was used for numerical variables and the Chi-square test for categorical variables. Binary logistic regression analyses were applied to compute the odds ratios of the association between the explanatory variables. A value of $p<0.05$ was accepted as statistically significant.

3. Results

The control group comprised 159(53%) females and 141 (47%) males with a mean age of 67.3 ± 5.4 years. The dry-type AMD group comprised 315(54.3%) females and 265(45.7%) males with a mean age of 66.4 ± 7.1 years. The neovascular type AMD group comprised 303(53.9%) males and 259(46.1%) females with a mean age of 68.2±6.4 years. No statistically significant difference was determined between the groups in terms of age and gender ($p>0.05$).

PD was detected in 1% (n: 3) of the control group and in 3.6% (n:41) of the AMD group. No statistically significant difference was determined between the groups in terms of PD (p:0.18). In the dry-type AMD group, 2.7% (n:15) PD was detected and there was no statistically significant differences compared to the control group (p:0.23). In addition, 4.6% (n:26) PD was found in the neovascular-type AMD group, and this difference was significantly higher than in the control group (p:0.04). The prevalence of PD in early-late type dry and neovascular-type AMD groups is shown in Table 1.

The effect of age, gender, disease stage and involvement in AMD varieties on the prevalence of PD is presented in Table 2. A significant association was determined between age and the prevalence of PD in both types of AMD (0.02, p:0.03).AMD stage and eye involvement were not associated with PD (p>0.05) and there were no significant association with other factors (p>0.05).

The association between the prevalence of PD and both of the presence and types of AMD is shown in Table 3. A significant association was found between PD and neovascular-type AMD (p:0.03, Odds ratio:3.78, 95% CI). PD was not associated with dry-type AMD.

Table 1. Prevalence of Parkinson's Disease according to AMD type and stage

	Control Group (n:300)	**Early DryAMD (n:296)**	**p**	**Late DryAMD (n:284)**	**p**	**Early NeovascularAMD (n:285)**	**p**	**Late Neovascular AMD (n:277)**	**p**
PD	n:3(%1)	n:7(%2.3)	0.46	n:8(%2.8)	0.39	**n:13(%4.5)**	**0.04**	**n:13(%4.6)**	**0.04**

AMD: Age-related macular degeneration,PD:Parkinson'sDisease

Table 2. Factors affecting the prevalence of Parkinson's Disease

	PD in Dry-type AMD	**PD in Neovascular-type AMD**
Age	**p:0.02 OR:1.22**	**p.0.03 OR:1.22**
Gender	p:0.92 OR:0.78	p:0.54 OR:1.32
Stage(Early/Late)	p:0.91 OR:0.87	p:0.85 OR:1.23
Involvement (Unilateral/bilateral**)**	p:0.72 OR:0.97	p:0.79 OR:0.98

PD:Parkinson'sDisease, OR:OddsRatio

Table 3. The relationship between the prevalence of PD and AMD

Type	**Parkinson's Disease**
AMD	p:0.17 OR:3.13
Dry-type AMD	p:0.27 OR:2.54
-Early-stage	p:0.32 OR:2.28
-Late-stage	p:0.26 OR:2.61
Neovascular-type AMD	**p:0.03 OR:3.78**
-Early-stage	**p:0.03 OR:3.72**
-Late-stage	**p:0.03 OR:3.82**

AMD: Age-related macular degeneration, OR:OddsRatio

4. Discussion

This study showed that Neovascular AMD is more common in Parkinson's patients, and this prevalence is significantly higher in both the early and late stages (p:0.04, p:0.04). As a result of the study, it was determined that PD was seen 3.72 times more in the early-stage

and 3.82 times more in the late stage in Parkinson's patients(p:0.03, p:0.03). However, although the prevalence of dry-type AMD was high in Parkinson's patients, it was not statistically significant, and this rate did not change in both the early and late stages (p>0.05). In addition, at the end of the study, no significant relationship was found in the early and late stages of Parkinson's patients(p>0.05).

Chung et al showed that in their retrospective cohort study, neovascular-type AMD patients had a higher risk of PD compared to a control group with non-AMD (16). Etminan et al. suggested that neovascular AMD may predict the onset of PD in their retrospective study (19). They used the Canadian British Columbia Retinal Disease Database and Neovascular AMD patients undergoing intravitreal injections (Bevacizumab or Ranibizumab) were included in this study. Choi et al. determined that AMD was associated with higher PD risk in their retrospective study (18). Dry-type AMD patients were not included in these 3 studies and also AMD was not classified as early and late. In the retrospective cohort study of Chen et al., AMD patients were divided into 3 groups as neovascular, non-neovascular and unspecified (17). During the analysis of AMD subtypes, there was no significant difference in the risk of PD. However, since this study screened AMD types through diagnostic codes, it was reported that at the end of the study, it could be insufficient to differentiate AMD types. Also, in this study, the relationship of AMD types with PD in the early and late stages was not evaluated. In our study, PD was determined 3.78 times greater among neovascular AMD patients. (p:0.03). These rates were 3.72 and 3.82 times in early-stage and late-stage neovascular-type AMD, respectively, and a significant relationship was found in both(p:0.03, p.0.03). There was no statistically significant relationship between the early or late dry AMD group and the control group (p<0.05).

A previous study has suggested a potential genetic association between retinal pigmented epithelial degeneration and PD (20). There are some common factors in the etiopathogenesis of AMD and Parkinson's diseases. Inflammation and related neurodegeneration are one of the common factors in studies with high complement factors (21-22). The other common factor is the accumulation of some misfolded proteins in the form of lipofuscin deposition in retinal pigment cells of AMD patients and alpha-synuclein deposition in neurons of PD patients due to autophagy dysfunction (23-24). As another common factor, this inflammation and autophagy dysfunction will induce oxidative stress with high oxygen consumption of both retinal cells and brain cells, and as a result of mitochondrial dysfunction that decreases with aging, oxidative damage occurs with an increase in reactive oxygen products (25-26). Studies with optic coherence tomography have reported thinning of the RNFL of both AMD and PD patients, and this thinning process was also associated with the duration of PH (27).

It was determined that the reason was the loss of dopaminergic amacrine cells in the retina and the deterioration of ganglion cell axons (27). The underlying pathological mechanism between PD and dry-type AMD is still unclear, but it is commonly accepted that decreased dopamine levels in the basal ganglia and retina result in clinical signs of motor and visual symptoms.28 Another finding showing the similarity between both diseases is that L-Dopa treatment given for PD has a role in preventing AMD.29 In this study, it was emphasized that under normal conditions, RPE cells expressed GPR143, a G protein-linked receptor, through dopamine, and reduced the release of VEGF responsible for neovascular-AMD. In this study, it was determined that the risk of AMD development was lower by providing an anti-VEGF effect with the L-Dopa treatment given. We thought that the decrease in anti-VEGF activity was a result of decreased dopamine in the retina in neovascular-AMD, which is similar to decreased dopamine in PD, and the resultant increase in VEGF, increased the incidence of neovascular-AMD.

To the best of our knowledge, there is no prospective study in the literature investigating the types and stages of AMD, and the relationship between ocular involvement and PD at the same time. In

previous retrospective cohort studies, retrospective cohort scans were performed with very high patient numbers, and the relationship between PD and neovascular AMD was investigated. Dry-type and neovascular-type AMD were not evaluated separately, except for only one study. In the study in which the dry-type and neovascular-type were evaluated simultaneously, the condition of some patients could not be specified. Again, in none of these studies, neovascular-type and dry-type AMD were classified as early-stage and late stage, and the prevelance of PD in unilateral and bilateral eye involvement was not evaluated. Our study is the first prospective study in which AMD type, stage and mode of involvement were evaluated simultaneously with the prevelance and relationship of PD, and with this aspect, it will make a valuable contribution to the literature.

Limitations of this study were the relatively low number of patients. Among the limitations of our study, it can be said that the drusen varieties were not specified in the patients. Among other limitations, it can be said that the patients were not questioned whether they took antioxidant and not being questioned for the presence of DM and HT.

5. Conclusion

In conclusion, the results of this study showed that the prevalence of Parkinson's was significantly higher in both the early and late stages of neovascular-type AMD.However, any significant relationship was not detected in terms of both unilateral and bilateral involvement. It was concluded that the relationship between neovascular-AMD and PH may be related to decreased dopamine in both the brain and retina, and accordingly increased VEGF through various pathways. Further studies with a larger number of patients and in detail are needed.

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Ethics

Ethics Committee Approval: The study was approved by Aksaray University Clinical Research Ethical Committee (Decision no: 2022/04-05, Date: 24.02.2022

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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