Research Article / Araştırma Makalesi

Early Onset Parkinson's Disease and It's Genetic Consequences

Erken Başlangıçlı Parkinson Hastalığı ve Genetik Sonuçları

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Abstract: Genetic and environmental factors play an important role in the development and progression of Parkinson's Disease(PD). In this study, it was aimed to evaluate the genetic test results and clinical findings of early-onset Parkinson's Disease (EOPD) followed up in the movement disorders outpatient clinic of our hospital by comparing them with the literature. Patients who were followed up with the diagnosis of EOPD in the Movement Disorders Outpatient Clinic of Neurology Department, Marmara University Faculty of Medicine and whose genetic tests were performed; demographic characteristics, clinical findings and genetic test results were analyzed retrospectively. Forty-three EOPD patients (13 females, 30 males) who were genetically tested were enrolled in the study. The mean age was 52.3 (range; 31-64 years), and the mean age of disease onset was 42.8 (range; 25-49 years). Seven different mutations for PARK-2 and PINK-1 were detected in 93% of the patients for whom genetic testing was requested. Genetic mutation was not detected in 7% of the patients. While 57.5% of the patients with a positive genetic test had prodromal symptoms such as hyposmia, constipation and Rapid Eye Movement(REM) Sleep Behaviour Disorder (RBD), none of the patients with a negative genetic test had prodromal symptoms. It has been shown that some of the benign allelic mutations detected in EOPD patients may be genetic risk factors for EOPD. In our study, we wanted to draw attention to the need for multicenter studies with larger numbers of patients and healthy controls to determine the relationship between benign allelic mutations and EOPD.
Keywords: Parkinson's Disease, PARK-2, PINK-1

Özet: Genetik ve çevresel faktörler PH gelişmesinde ve ilerlemesinde önemli rol oynar. Bu çalışmada hastanemiz hareket bozuklukları polikliniğinde takipli EBPH'nın genetik test sonuçları ve klinik bulgularının literatür ile karşılaştırılarak değerlendirilmesi amaçlanmıştır. Üniversite hastanesi hareket bozuklukları polikliniğinde erken başlangıçlı Parkinson Hastalığı tanısı ile takip edilen ve genetik tetkikleri yapılmış olan hastaların; demografik özellikleri, klinik bulguları ve genetik test sonuçları retrospektif olarak incelendi. Hareket bozuklukları polikliniğinden takipli, genetik testi yapılmış 43 EBPH'sı çalışmaya alındı. Hastaların 13'ü kadın, 30'u erkekti. Yaş ortalaması 52, hastalık başlangıç yaşı ortalaması 42,8 (25-49) bulundu. Genetik test istenen hastaların %93 'ünde PARK-2 ve PINK-1 için 7 ayrı mutasyon saptandı. Hastaların % 7'sinde genetik mutasyon tespit edilmedi. Tremor başlangıç %65, akinetik-rijit başlangıç %35 hastada görüldü. Hiposmi, kabızlık, RUDB gibi prodromal semptomlar genetik testi pozitif saptanan hastaların %57,5'inde görülürken, genetik testi negatif gelen hastaların hiçbirinde mevcut değildi. EBPH'ında tespit edilen benign alel mutasyonların bazılarının EBPH için genetik risk faktörü olabileceği gösterilmiştir. Çalışmamızda benign alel mutasyonların hastalık ile ilişkisini tespit etmek için daha çok sayıda hastanın ve sağlıklı kontrolün katıldığı çok merkezli çalışmalara ihtiyaç olduğuna dikkat çekmek istedik.
Anahtar Kelimeler: Parkinson Hastalığı, PARK-2, PINK-1

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease in which motor symptoms such as bradykinesia, rigidity, tremor, and postural instability develop gradually, along with nonmotor symptoms consisting of cognitive changes, hallucinations, depression, sleep disorders, behavioral changes, constipation and sensory abnormalities(1). Early-onset Parkinson's Disease (EOPD) can be defined as PD with onset of symptoms before the age of 40 or diagnosed before the age of 40. In some studies, the age of onset has been reported as before the age of 50 and constitutes 4% of Parkinson's patients(1-4). PD prevalence is reported to be 1.5-2% in the population aged 60 and over. Although the etiology is not fully known, genetic and environmental factors play an important role in the development and progression of PD (5, 6). It has been shown in previous studies that mutations in some genes (SNCA, UCHL1, GIGYF2, GBA, LRRK2, PRKN, PINK1, ATP13A2, PLA2G6 and FBXO7) may be the cause of PD (7). It is known that PRKN and PINK1 genes, which are involved in the metabolic pathway, are associated with EOPD. PRKN gene mutation, which is the most common cause of autosomal recessive PH; It constitutes 49% of familial EOPD and 20% of sporadic EOPD (8). Clinically, patients with PRKN mutations respond well to anticholinergics and levodopa, but can cause dyskinesia and, rarely, psychosis, even at low doses of levodopa. Patients with these mutations show slow disease progression, but atypical fluctuations and dyskinesias may occur early (9).

Genetic and environmental factors play an important role in the development and progression of PD (6). It is known that PRKN and PINK1 genes, which are involved in the metabolic pathway, are associated with EOPD. The aim of the study was to evaluate the genetic test results and clinical findings of EOPD patients who were followed up in the outpatient movement disorders clinic of xxx University Hospital by comparing them with the literature.

2. Materials and Method

This study is a retrospective observational study to designed to investigate the of the genetic test results and clinical findings of EOPD patients.The study protocol received ethical approval from the Marmara University Ethics Committee (Protocol Code: 03.03.2023.351) and the research was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

2.1. Patient Selection

Inclusion criteria to participate in the study; participants in the patient group meet the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's Disease(10), be over 18 years old, PD symptoms began before the age of 50, medical genetic test has been performed. Exclusion criteria is the EOPD patients without genetic testing.

2.2. Clinical Assessment and Molecular Analysis

Demographic characteristics, clinical findings, and genetic test results of patients who were followed up at the Movement Disorders Clinic of Marmara University Hospital and met the inclusion criteria for the study were retrospectively analyzed. Peripheral blood samples were analyzed in the Neurogenetics Laboratory of the Department of Medical Biology using PCR and DNA sequencing methods. Exon 2-12 region of the coding sequence was examined.

2.3. Statistics

All statistical analyses in this study were implemented using SPSS Statistics version 26. Descriptive statistic methods applied in the data analysis.

3. Results

3.1. Demographic Features

Forty-three EOPD patients (13 females, 30 males) who were genetically tested were enrolled in the study. The mean age was 52.3

(range; 31-64 years), and the mean age of disease onset was 42.8 (range; 25-49 years).

3.2. Molecular Analysis

Seven different mutations for PARK-2 and PINK-1 were detected in 93% of the genetically tested patients. Genetic mutation was not detected in 7 % of the patients. The most common mutation (85%) was rs4709583 homozygous/heterozygous PARK-2 mutation. Other mutations detected respectively; rs1043424 (PINK-1), rs1801582 (PARK-2), rs56092260 (PARK-2), rs1801334 (PARK-2), p.C441C (PARK-2) rs55830907 (PARK-2). All of the detected mutations are registered as benign in the ClinVar database. Mutation detected patients; 62.5% had a single mutation, 32.2% had 2 mutations, and 5% had 3 mutations together (Table-1). While 20% of patients with genetic mutations had a family history, none of the patients without mutations had a family history. Among patients with a positive genetic mutation, 12.5% had a history of consanguineous marriage, while none of the patients with a negative genetic mutation had a history of consanguineous marriage.

3.3. Clinical Features

Twenty-seven (62,7 %) patients had tremor onset PD, 16 (37,2%) patients had akinetic-rigid onset PD. The genetic positivity rate was 92.5% in patients with tremor dominant onset, and 93.7% in those with akinetic-rigid onset. While 57.5% of the patients with a positive genetic test had prodromal symptoms such as hyposmia, constipation and RBD, none of the patients with a negative genetic test had prodromal symptoms. It was observed that 40% of EOPD patients with a positive genetic test developed dyskinesia within the first 5 years. The incidence of dyskinesia was 33.3% in EOPD patients with a negative genetic test. The incidence of impulse control disorders was 35% in EOPD patients with a positive genetic test, while it was 0% in those with a negative test.

Table 1. Concomitant Genetic Mutations

Single mutation (25 patients)		**Two mutations (13 patients)**		**Three mutations (2 patients)**	
rs4709583 (PARK-2)	22	rs4709583 (PARK-2) rs1801582(PARK-2)	10	rs4709583 (PARK-2) rs1801582(PARK-2) rs55830907(PARK-2)	2
rs1043424 (PINK-1)	3	rs4709583 (PARK-2) rs56092260(PARK-2)	1		
		rs4709583 (PARK-2) rs1801334 (PARK-2)	1		
		rs4709583 (PARK-2) p.C441C (PARK-2)	1		

4. Discussion

Seven distinct mutations were detected for PARK-2 and PINK-1 mutations in our study. PARK-2 and PINK-1 mutations detected in EOPD patients; It is registered as benign allele with rs numbers specified in NCBI and ClinVar databases. Although the detected mutations are defined as benign in databases, there are studies that show they could be risk factors for EOPD. In our study; the most common mutation (85%) was rs4709583 homozygous/heterozygous PARK-2 mutation. This rs4709583(PARK-2) mutation frequency was found to be statistically significant for EOPD patients compared to healthy controls (11). Similarly, in the study of Zau et al. with 312 PD (99 EOPD-213 late-onset PD) and 236 healthy controls, it was stated that PARK2 variant IVS3 20T>C (c.413-20T>C, rs4709583) mutation may be a genetic risk factor for EOPD (12). In the study of Nguyen et al., genetic analysis was performed in 112 EOPD patients and 112 healthy controls There

was no statistically significant difference between EOPD patients and healthy controls in the frequency of rs1801582 (PARK-2) and rs1043424 (PINK-1) mutations that we detected in our patients.. While the study by Lucking et al. found a statistically significant difference in rs1801334 (PARK-2) mutation frequency between PD and healthy controls, another study reported no such difference (13, 14).

In PD patients treated with levodopa, levodopa-induced dyskinesia develops within 5-10 years. There are studies demonstrated that levodopa-induced dyskinesia occurs earlier in EOPD patients with genetic muations.(15, 16). Similarly to the literature, our study found that 40% of EOPD patients with a positive genetic mutation developed dyskinesia within the first 5 years. In the study by Flores et al., when evaluated by the severity of levodopa-induced dyskinesia (LID), the frequency of rs1801582(PARK-2) mutation, which was detected in 28% of EOPD patients in our study, was twice as high in patients with no or mild LID (20%) as in those with severe LID (10%)(15). EOPD patients with genetic mutations also is a risk factor for impulse control disorder (17, 18). Our study found that the rate of impulse control disorder was 35% in EOPD patients with a positive genetic test, compared to 0% in those with a negative genetic test. This finding is similar to other studies. Previous studies have shown that PRKN and PINK1 gene mutations are risk factors for EOPD(2, 19-21). Genetic testing in EOPD patients may be important for the predictability and management of LID and impulse control disorder, even if benign allelic mutations are detected in these genes.

5. Conclusion

This study is important in that it shows that some of the benign allelic mutations detected in EOPD patients may be genetic risk factors for EOPD, and that their detection may improve the predictability of complications such as LID and impulse control disorder. In our study, we wanted to draw attention to the need for multicenter studies with larger numbers of EOPD patients and healthy controls to determine the relationship between benign allelic mutations and EOPD.

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Ethic

Ethics Committee Approval: The study was approved by Ethics Committee of Marmara University Faculty of Medicine (Protocol Code: 03.03.2023.351)

Informed Consent: The authors declare that consent was get from the patients.

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