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The Impact of Prodromal Stage Non-Motor Symptoms on Clinical Progression in Parkinson's Disease

Parkinson Hastalığında Prodromal Dönem Non-Motor Semptomların Hastalık Klinik Progresyonu Üzerine Etkisi

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Abstract

Objectives: Several non-motor symptoms (NMSs) were described in the prodromal Parkinson's disease (PD). The aim of this study is to investigate the impact of the presence of prodromal NMSs on clinical progression of PD.

Materials and Methods: We questioned the presence of NMSs in the prediagnostic stage in patients with PD. Group 1 reported at least one prodromal NMS and Group 2 reported no prodromal NMSs. As recommended by the Movement Disorder Society Task Force, the total likelihood ratios (LRs) of NMSs were calculated and correlated with disease progression. Clinical progression was determined by dividing the Unified Parkinson's Disease Rating Scale Part III total score by the duration of the disease. Generalized linear model (GzLM) was used to determine associations between clinical progression rate and the predictor variables.

Results: Group 1 had 48 patients (24 male, 24 female), and Group 2 had 46 patients (32 male, 14 female). Both groups were similar in terms of demographic and disease characteristics. Depression and constipation (for each symptom, 18 patients and 37.5%) were common in Group 1. The rate of clinical progression was higher in Group 1 than in Group 2 (p=0.037). There was no significant correlation between clinical progression rate and LRs of NMSs in Group 1 (rs=0.10, p=0.49). However, age of the diagnosis was the only significant factor associated with the clinical progression (p=0.69).

Conclusion: Prodromal NMSs do not seem to impact the rate of disease progression, which may be explained by the non-dopaminergic and extra nigro-striatal pathway that cause NMSs.

Key Words: Parkinson's Disease, Prodromal Stage, Constipation, Depression

Öz

Amaç: Parkinson hastalığı (PH) prodromal dönemi için birçok non-motor semptom tanımlanmıştır. Non-motor semptomlar PH riskini belirlemede yardımcı olabilir. Bu çalışmanın amacı prodromal dönemde non-motor semptom varlığının PH'nin klinik progresyonuna etkisini araştırmaktır.

Gereç ve Yöntem: Çalışma için Parkinson hastalarında hastalık tanısından önceki dönemde non-motor semptom varlığını sorguladık ve iki grup oluşturuldu. En az bir prodromal non-motor semptom varlığı bildirenler Grup 1, non-motor semptom varlığı olmayanlar ise Grup 2 olarak sınıflandırıldı. Her bir hasta için PH olabilirlik oranı, likelihood ratios (LRs), Uluslararası Hareket Bozuklukları komitesi önerisine göre hesaplandı ve hastalık progresyonu ile korelasyonu değerlendirildi. Klinik progresyon Birleşik PH Değerlendirme Ölçeği, bölüm 3 toplam puanı hastalık süresine bölünerek hesaplandı. Hastalık klinik progresyonu ve bunu etkileyen faktörler jeneralize lineer model ile analiz edildi.

Bulgular: Grup 1'de 48 hasta (24 erkek, 24 kadın), Grup 2'de 46 hasta (32 erkek, 14 kadın) vardı. Her iki grup demografik veriler ve hastalık özellikleri açısından benzerdi. Grup 1'de depresyon ve kabızlık (her bir semptom için oran ve sayı %37,5, n=18) yaygındı. Grup 1'in klinik progresyon oranı Grup

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2'den anlamlı olarak yüksekti (p=0,037). Grup 1'de hastalık progresyon oranı ile nonmotor semptomlara ait LRs arasında anlamlı korelasyon yoktu (rs=0,10, p=0,49). Bununla birlikte sadece hastalık tanı yaşının, klinik progresyonu etkileyen anlamlı bir faktör olduğu saptandı (p=0,69).

Sonuç: PH'de, prodromal dönemde non-motor semptom varlığının hastalık progresyonu üzerine etkisi görünmemektedir. Bu durum non-motor semptomların patogenezindeki dopaminerjik olmayan, ekstra nigrostriatal yolak varlığı nedeniyle de olabilir.

Anahtar Kelimeler: Parkinson Hastalığı, Prodromal Evre, Kabızlık, Depresyon

Introduction

Parkinson's disease (PD) is diagnosed on the basis of the cardinal motor findings according to the current criteria (1). However, it is known that the degenerative process leading to PD precedes the manifestation of motor symptoms by decades, indicating a long and relatively silent pre-diagnostic period. Within this period, two stages have been described: preclinical PD (PD-specific pathology without clinical signs or symptoms) and prodromal PD (emergence of PD-related symptoms insufficient for a clinical diagnosis) (2,3).

Prodromal PD is characterized by mainly non-motor symptoms (NMSs), also referred to as markers. NMSs such as olfactory dysfunction, mood disorders, gastrointestinal and urogenital disorders, rapid eye movement (REM) sleep behavior disorder (RBD) may observed in prodromal period. These NMSs are expected to be more in motor stage of PD. When patients with PD diagnosis were followed up, it was observed that patients with motor progression reported more NMS as symptom specific. Furthermore, NMSs can affect quality of life of patients and treatment of disease like motor symptoms in PD (4-7).

Prodromal PD is a period that has attracted attention with regard to the potential use of neuroprotective/disease-modifying therapies. Studies on prodromal PD have been shown that the presence or absence of prodromal markers is contributed to future probability of disease (8,9). Presence of marker/markers in prodromal period may also affect clinical progression Therefore, the aim of this study was to investigate the impact of prodromal NMSs on disease progression.

Materials and Methods

Patients

Ninety-six consecutive patients with idiopathic PD diagnosed according to the Movement Disorder Society (MDS) clinical diagnostic criteria for PD were selected from Movement Disorders Unit of the Department Neurology in Ankara University for this study (10). Patients with hydrocephalus, brain tumors, repetitive head trauma, prolonged use of neuroleptics that may be the cause of secondary parkinsonism, abrupt onset or gradual progression of disease symptoms, unresponsiveness to levodopa were excluded from the study. Cognitive impairment was also excluded with Mini-mental Status Examination (MMSE ≤26) to examine self-reported prodromal NMSs (11). Ten patients did not accept to participate the study. Patients were questioned about the prodromal NMSs in a face-to-face interview. The clinical progression rate was compared between the patients with at least one prodromal NMS and those without any prodromal NMS.

Clinical Assessments

The disease severity was rated by Hoehn and Yahr staging (HYS) and MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (12,13). The hospital anxiety and depression scale (HADS) and MMSE were used to evaluate the current symptoms of depression and anxiety, and the cognitive status, respectively. The rate of clinical progression was determined by dividing the UPDRS Part III (off period) score by the disease duration (14).

Demographic characteristics, education (year), age of diagnosis, disease duration since the diagnosis, treatment and comorbidities of patients, HYS, scores of UPDRS, MMSE and HADS were recorded.

Detection of Prodromal NMSs

Patients were evaluated by a movement disorder specialist. Symptoms of the disease, such as constipation (difficulty in bowel emptying and/or less than three bowel movements per week), olfactory dysfunction (anosmia/hyposmia), urinary dysfunction (using the MDS-UPDRS Part I, Item 1.10), symptomatic hypotension (orthostatic dizziness), depression (according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), RBD (by REM Sleep Behavior Disorder Screening Questionnaire), and excessive daytime sleepiness (using the MDS-UPDRS Part I, Item 1.8) were questioned in face-to-face interview for the time period before the diagnosis of PD (3,15-18). The presence of stress incontinence for more than 10 years in women was not included as a positive sign. Symptomatic hypotension resulting from intensive antihypertensive therapy was not taken into consideration (8).

Two groups were created and compared based on the reported prodromal NMSs; Group 1 consisted of patients who reported at least one prodromal NMS, and Group 2 included patients with no reported prodromal NMSs. For the prodromal NMSs that the patients reported, they were asked to report the time between the initial diagnosis of PD and the first recognition of the prodromal NMS. Clinical progression was further re-evaluated between patients with one prodromal symptom

(Group A) and two prodromal symptoms (Group B) and more than two prodromal symptoms (Group C) to demonstrate any additive effect of multiple symptoms.

Calculation of Likelihood Ratio (LR) of Prodromal NMSs

NMSs were determined. Each symptom has two LR values as LR+ and LR-. The meaning of LR+ is that prodromal NMS exists and the likelihood for PD increases. LR-, on the other hand, has the opposite meaning. The LR of each symptom were multiplied as stated in the published criteria for risk of PD in prodromal stage (19). For example, in the presence of constipation (LR=2.5) and depression (LR=1.6), absence of olfactory dysfunction (LR=0.40), symptomatic hypotension (LR=0.80), urinary dysfunction (LR=0.90), RBD (LR=0.89), and excessive daytime sleepiness (LR=0.86) in a patient, total LR of NMSs is 2.5 x 1.6 x 0.40 x 0.80 x 0.90 x 0.89 x 0.86=0.88.

Data Analysis

Quantitative data were expressed as mean and standard deviation for parametric variables and median (minimum-maximum) for nonparametric variables. Data were evaluated according to its distribution; independent t-test was used for the data showing normal distribution, and Mann-Whitney U test was used for abnormally distributed data for the comparison of the two groups. For comparing data of more than two groups, ANOVA or Kruskal-Wallis test was used. Chi-squared test and Fisher's exact test were used to compare categorical data. The Spearman correlation test was applied to measure the direction and magnitude of the relationship between two continuous variables when the data were not normally distributed.

Generalized linear model (GzLM) was used to determine associations between clinical progression rate in the sampled population and the predictor variables group, LR of NMSs and age of diagnosis, sex. In our model fitting, we included the group as a fixed effect and LR of NMSs and age of diagnosis as covariates in GzLM. SPSS 21 (SPSS Inc., Chicago, IL, USA) program was used for data analysis. $P<0.05$ was regarded as significant. Power analyses were performed by G Power 3 to sample size.

Results

The demographic and disease characteristics of the patients are presented in Table 1. Both groups were similar ($p>0.05$).

Prodromal NMSs, their duration before PD diagnosis, and total LR of groups

Depression (18 patients, 37.5%) and constipation (18 patients, 37.5%) were the most common prodromal NMSs. The duration of constipation (median: 9, minimum-maximum: 2-50) and olfactory dysfunction (median: 10, minimum-maximum: 1-30) was longer than the other prodromal NMSs. The detailed information regarding prodromal NMSs are presented in Table 2.

In Group 1, LR of NMSs was median=0.09 (minimum-maximum: 0.2892-44.3843) and in Group 2 (no non-motor prodromal symptom), LR of NMSs of each patient was same (median=0.16) for each patient.

Clinical progression rate of groups and correlation analysis between LRS and disease progression

The rate of clinical progression was significantly higher in Group 1 [6.63±5.14 (median: 5, minimum-maximum: 11.1-23)] than Group 2 [5.23±5.52 (median: 3.5, minimum-maximum: 0-24)] ($p=0.037$).

The clinical progression rate was further evaluated according to the number of prodromal symptoms. Group A had 27 patients (56.3%), Group B had 17 patients (35.4%), and Group C had 4 patients (8.3%).

There was no significant correlation between clinical progression rate and LR of NMSs in Group 1 ($rs=0.10$, $p=0.49$).

The GzLM showed that the reason for the significant difference in clinical progression rate between the groups was not due to LRs of NMSs ($p=0.69$). The effect of the age of diagnosis on clinical progression rate was statistically significant ($p<0.001$), which explained 20.9% of the total variance (Table 3). Correlations between clinical progression (rate) and age of diagnosis are showed in Figure 1.

Discussion

Although the reliability of this study based on the retrospective information of the patients was low, it was observed that the clinical progression of PD was higher in patients who reported

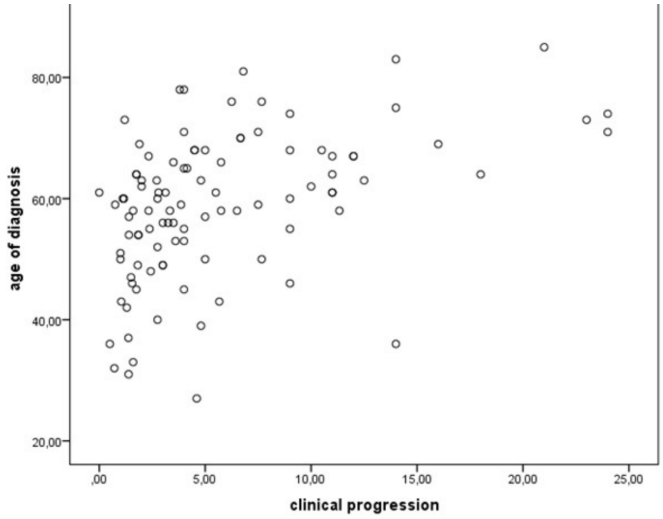

Figure 1: Scatter diagram of correlations between clinical progression (rate) and age of diagnosis

NMSs in the prodromal period than those who did not report symptoms. When the factors affecting clinical progression were examined, it was found that prodromal NMS is not a factor and the age of disease diagnosis is a factor. The mean age at diagnosis was greater in patients with prodromal symptoms than the other patients. According to the literature, the rate of progression and the age at time of the diagnosis are in a known positive correlation in clinical trials, and it is also described that elder patients are at higher risk for nonmotor symptoms (5,20).

The UPDRS is a widely accepted scale for the monitoring of disease progression and identification of disease severity in PD with a chronic and progressive disease course (14). Along with the disease course, the scale also allows the monitoring of additional NMSs, mental involvement, mood changes, and existing motor findings. In the follow-up of the patients, it was seen that the disease-related disability causes an approximately 8-10-point increase in the UPDRS score per year on average. Part III of MDS-UPDRS score increases average 2.4 points per-year but annual increase of MDS-UPDRS-Part III is 1.77 points for patients who are taking dopaminergic medications. Early dopaminergic therapy has a significant effect on motor findings and progression (21). However, *in vitro*, levodopa can induce degeneration of dopaminergic neurons, but it is not clear *in vivo* (22). The change in MDS-UPDRS is longitidunal in the first 5 years and it can be used in clinical monitoring (23-25). However, score of MDS-UPDRS-Part III may be quite low in patient with early PD because of substantial percentage of patients may rate as normal their motor signs (26). The present study, accordingly, displays the clinical disease progression as a ratio of the UPDRS-Part III total score to disease duration in years, and thus evaluates the relationship between disease progression and prodromal NMSs. Comparisons were made

Table 1: Demographic and clinic characteristics of patients

	Group 1 n=48	Group 2 n=46	p-value
Age, mean ± SD	64.01±11.08	63.00±9.6	0.481
Gender, n (%)			0.053
Male	24 (50)	32 (69.6)	
Female	24 (50)	14 (30.4)	
Education, year, median (min-max)	7.5 (1-18)	6 (1-16)	0.429
Age of diagnosis, year, mean ± SD	59.79±12.10	57.34±11.52	0.493
Disease duration, year, median (min-max)	3 (1-18)	5 (1-25)	0.429
HYS, mean ± SD	1.71±0.67	1.66±0.53	0.827
UPDRS score, median (min-max)			
Part I	6 (1-16)	6 (0-22)	0.360
Part II	8 (0-22)	9 (0-26)	0.603
Part III	16 (7-28)	21.5 (10-34)	0.829
Part IV	0 (0-10)	0 (0-9)	0.175
Total	35 (10-71)	32.5 (8-69)	0.531
Treatment, n (%)			
Levodopa	35 (72.9)	30 (65.2)	0.419
Dopamine agonist	23 (47.9)	27 (58.7)	0.295
Rasagiline	23 (47.9)	18 (39.1)	0.391
Amantadine	11 (22.9)	6 (13)	0.214
DBS	2 (4.2)	2 (4.3)	1
MMSE score, mean ± SD	28.3±1.9	29±1.41	0.394
HADS score, median (min-max)			
Anxiety	1.5 (0-14)	1 (0-8)	0.079
Depression	2.5 (0-15)	2 (0-16)	0.109
Co-morbidities, n (%)			
HT	15 (31.2)	12 (26.1)	0.580
DM	11 (22.9)	6 (13)	0.214
CVD	6 (12.5)	4 (8.7)	0.550

p<0.05 significant
SD: Standard deviation, min: Minimum, max: Maximum, HYS: Hoehn and Yahr Stage, UPDRS: Unified Parkinson disease scale, MMSE: Mini-mental status examination, HADS: Hospital anxiety and depression scale, HT: Hypertension, DM: Diabetes mellitus, CVD: Cardiovascular disease, DBS: Dried blood spot

between two similar groups in terms of dopaminergic treatment that may affect UPDRS-Part III and comorbid conditions that may contribute to clinical progression of the disease. It has been previously reported that cardiovascular risk factors, including hypertension, and diabetes affect motor feature severity in PD (23,27,28). However, baseline UPDRS scores of patients were not known. Furthermore UPDRS-Part III scores may be seen low because of early-stage patients with PD.

Prodromal NMSs have recently become the focus of attention. The studies, to investigate the presence of prodromal NMSs in patients with PD are limited in the literature and the reported symptom rate varies due to the variety and differences in symptoms. The rates were 88.4% in a study by Swallow et al. (29) that evaluated RBD, hyposmia, depression, and constipation; 69% in a study by Walter et al. (30) that evaluated hyposmia, parosmia, depression, anxiety, dysphoria/personality change, vivid dreams, RBD, constipation, bowel incontinence, bladder urgency, sexual dysfunction, and excessive sweating; 98% in a study by Gaenslen et al. (31) that evaluated 19 NMSs, including color vision disorders, sleep disturbances, anosmia, or hyposmia, autonomic dysfunction, psychiatric complaints, and cognitive changes; and 90.3% in a study by Durcan et al. (32) that made use of NMS Questionnaire. The present study investigated NMSs, and identified a higher number of patients who reported no such symptoms. This condition may be attributed subjective assessing method (retrospective clinical interview to detect of NMSs, even after a long disease history) In another study, in a large study population, prodromal features were questioned retrospectively by survey, and the rate of symptom reporting was low and the patients reported more cardinal motor features in the diagnosis of the disease (33). In the present study, constipation was the most common prodromal NMS with the longest duration, and olfactory dysfunction was another long-standing symptom, consistent with the literature (23). However, it has been previously reported that hyposmia is the most common NMS among PD patients both before and after diagnosis followed by constipation in a meta-analyses study (34). Constipation is an early non-motor manifestation of PD to occur years ago (more than 20 years) before major cardinal motor findings (35). Depression is also a common symptom before and after diagnosis in patients with PD, and the second most common symptom in the present study (36). Patients reporting with a single symptom were recorded at a higher rate. According to published data, the co-occurrence of multiple symptoms in the prodromal period is more frequently encountered in individual patients rather than the occurrence of a single symptom (31).

Table 2: Prevalence of prodromal NMSs and median duration before the diagnosis of disease

Symptom	Total n (%)	Symptom duration*, year, median (min-max)
Constipation	18 (37.5)	9 (2-50)
Olfactory dysfunction	13 (27.1)	10 (1-30)
Urinary dysfunction	1 (2.1)	2 (1-7.8)
Symptomatic hypotension	9 (18.8)	2 (1-10)
Depression	18 (37.5)	4.5 (1-17)
RBD	12 (25)	2 (1-7.8)
Excessive daytime sleepiness	3 (6.2)	2 (1-2)

RBD: Rapid eye movement sleep behavior disorder, PD: Parkinson's disease
*in the prodromal period

Table 3: Generalized linear model results

Parameter	b	SE	p-value
Intercept	-6.744	2.4622	0.006
Group 1	1.373	1.0121	0.319
LR non-motor	1.009	0.0941	0.694
Age of diagnosis	0.209	0.0412	<0.001*
Sex	-0.274	0.997	0.784

*p<0.05
LR: Likehood ratio, b: Regression coefficient, SE: Standard errors, Group 1; reported prodromal NMS

Risk factors and prodromal markers have an important role in the diagnosis of PD in the prodromal period. Over time, there was an increase in the number of defined risk and prodromal markers for the prodromal period. Finally, the markers included diabetes mellitus (Type II), global cognitive deficit, physical activity and, low plasma urate level in men was added and predictive value (LR) for each was determined (19). However, in our knowledge and literature research, the effect of non-motor features, which many patients do not recognize, on the clinical progression is a subject that has not been studied sufficiently. Therefore, although there is no significant relationship, this study is thought to create a different perspective on prodromal NMSs. The reason for the lack of a relationship between NMSs and disease progression may be the presence of non-dopaminergic and extra nigrostriatal pathway pathology in the pathogenesis of NMS (37,38).

Study Limitations

The main limitation of this study was the retrospective questioning and reporting of frequently observed, but limited number of prodromal NMSs. However, we aimed to provide objective data by giving the LR value determined by MDS to each prodromal marker reported by the patients. We also evaluated the disease progression rate with the last UPDRS part III score and disease duration.

Conclusion

Prodromal NMSs do not seem to impact the rate of disease progression, which may be explained by the non-dopaminergic and extra nigro-striatal pathway that cause NMSs. However, age of the diagnosis may a significant factor associated with the clinical progression. Future studies with more robust and

longitudinal assessment methods should further clarify the effect of prodromal NMSs on the disease progression.

Ethics

Ethics Committee Approval: The study was approved by the Ankara University Ethics Committee (03-160-18/2018).

Informed Consent: All participants provided a written informed consent.

Authorship Contributions

Concept and Design: M.C.A., Y.Ü., B.S., R.Y., Data Collection; B.S., Z.Ö.A., Analysis of Data: R.Y., M.C.A., B.S., Literature Research: B.S., Z.Ö.A., Y.Ü., Writing: B.S., R.Y., Editing: M.C.A., Y.Ü.

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