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The assessment of non-motor symptoms in idiopathic Parkinson's disease

Idiyopatik Parkinson hastalığında nonmotor bulguların değerlendirilmesi

Fatma GENÇ[1], Abidin ERDAL[1], Yasemin BİÇER GÖMCELİ[1], Aysun TİLTAK[1], Cenk ALTUNÇ[1], Levent RENDA[2], Gülnihal KUTLU[3]

ABSTRACT

Idiopathic Parkinson's Disease (IPD) is a progressive movement disorder, which is associated with nigro striatal dopaminergic neuron loss. Cardinal clinical symptoms of the disease are tremor at rest, bradykinesia, rigidity and postural instability. Although motor symptoms (NMSs) of IPD are well recognized, non motor symptoms of the disease are not known and hence are not treated adequately.

In our study, IPD patients diagnosed according to diagnostic criteria of United Kingdom Brain Bank and followed regularly in Antalya Research and Training Hospital Neurology Clinic Parkinson's disease and movement disorders outpatient clinic were evaluated retrospectively for clinical evaluation, United Parkinson's Disease Rating scale (UPDRS) was used. Constipation, anosmia, rapid eye movement (REM) sleep behavior disorder (SBD), history of depression diagnosed previously were inquired in order to investigate non motor symptoms.

There were 163 patients included in this study (61.3% was male and 38.7% female). Their mean age was 65.85±10.09 (min. 29-max. 87) and mean duration of disease 4.93±0.36 years. UPDRS score was 23.87±1.1 while 11 patients were on monotherapy, the remaining patients received combination treatment. Anosmia was present in 52 (31.9%), patients and constipation in 85 (52.1%). Rapid Eye Movement Behavior Disorder (RBD) in 84 (51.5%) and history of depression in 45 (27.6%) patients.

The diagnosis of non-motor symptoms, that can be encountered in large majority of Parkinson's disease patients at all stages of the disease and have a negative impact on quality of life is based on clinical characteristics. Early recognition and proper treatment of non-motor symptoms in IPD is important for quality of life of the patients. The first step for this is the inquiry of these symptoms.

Keywords: *Idiopathic Parkinson's disease, non-motor symptoms, early stage, quality of life*

ÖZ

Idiopatik Parkinson hastalığı (IPD) ilerleyici bir hareket bozukluğu olup, nigrostriyatal dopaminerjik nöron kaybı ile ilişkilidir. Hastalığın kardinal klinik belirtileri; istirahat tremoru, bradikinezi, rijidite ve postural instabilitedir. IPD motor semptomlarının iyi tanımlanmış olmasına karşılık, bu hastalığın motor olmayan semptomları yeterince tanınmamakta ve bunun sonucunda yeterince tedavi edilememektedir.

Çalışmamızda, Antalya Eğitim ve Araştırma Hastanesi Nöroloji Kliniği Parkinson Hastalığı ve Hareket Bozuklukları Polikliniğinde düzenli takip edilmekte olan United Kingdom Beyin Bankası Parkinson Hastalığı tanı kriterlerine göre Parkinson hastalığı tanısı almış IPD hastaları retrospektif olarak değerlendirildi. Klinik evreleme için Birleşik Parkinson Hastalığı Değerlendirme Ölçeği (UPDRS) kullanıldı. Hastaların konstipasyon, anosmia, rapid eye movement (REM) uyku davranış bozukluğu (UBD) ve daha önceden tanı almış depresyon öyküsü varlığı, non-motor semptomları incelemek amacıyla sorgulandı.

Çalışmaya alınan 163 hastanın 100 (%61,3)'ü erkek, 63 (%38,7)'ü kadındı ve yaş ortalamaları 65,85±10,09 (min. 29-maks. 87)'du. Ortalama hastalık süreleri ise 4,93±0,36 yıldı. UPDRS skoru 23,87±1,1 idi. Hastaların 11'i monoterapi alırken, diğer hastalar kombinasyon tedavisi almakta idi. Anosmi 52 (%31,9), konstipasyon 85 (%52,1) hastada mevcuttu. REM UDB 84 (%51,5) ve depresyon öyküsü ise 45 (%27,6) hastada mevcuttu.

Parkinson hastalarının büyük çoğunluğunda rastlanabilen, hastalığın tüm evrelerinde görülebilen ve yaşam kalitesini olumsuz yönde etkileyen non-motor belirtilerin tanısı esas olarak klinik özelliklere dayanır. IPD'da non-motor belirtilerin erken tanınması ve onların uygun olarak tedavi edilmesi hastanın yaşam kalitesi açısından çok önemlidir. Bunun da ilk basamağı öyküde bu belirtilerin sorgulanmasıdır.

Anahtar kelimeler: *İdiopatik Parkinson hastalığı, non-motor semptomlar, erken evre, yaşam kalitesi*

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[1] Department of Neurology, Antalya Research and Training Hospital, Antalya, Turkey
[2] Department of Otorhinolaryngology, Antalya Research and Training Hospital, Antalya, Turkey
[3] Department of Neurology and Clinical Neurophysiology, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla, Turkey
Yazışma adresi: Fatma Genç, Antalya Research and Training Hospital, Department of Neurology, Antalya, Turkey
e-mail: sanivardr@yahoo.com

INTRODUCTION

Idiopathic Parkinson's disease (IPD) is a common neurodegenerative disease thought to affect 1% of the population over the age of 50[1]. Its prevalence is 31-201 per 100,000 population[2]. It is thought that IPD is a multisystemic disorder characterized by the combination of motor and non-motor symptoms (NMSs)[3]. In a large multicenter study, it was reported that NMSs were observed in 99% of 1072 IPD cases[4]. Non-motor symptoms of IPD occur not only in advanced stages of the disease but also in early stages and anosmia, constipation, Rapid Eye Movement Behavior Disorder (RBD) and depression may precede the emergence of motor symptoms by more than a decade[5]. In previous studies, it was demonstrated that IPD has prodromal or premotor stages before the onset of motor symptoms[3]. In a study carried out in England, it was reported that 21% of the patients presented to hospitals with NMS prior to onset of motor symptoms[6]. It was also stated that more than half of neurologists were usually inadequate in recognizing symptoms such as depression, sleep disturbances, anxiety and fatigue[7].

At present, medical advances increase the mean life span of humans, and will lead to an increase in the prevalence of diseases which are associated with advancing age such as IPD[8]. NMSs have become the most important prognostic factor in IPD determining overall disease burden and daily functions. NMS exerts a significant impact on quality of life of patients and their families. In addition, considering that many NMSs predate the appearance of motor symptoms by many years, NMSs can be a critical target in the early diagnosis and recognition of the disease in populations under risk of IPD. The aim of this study was to determine the prevalence of RBD, depression, anosmia and constipation, among NMSs, which occur frequently in IPD and have a negative impact on quality of life, before the onset of motor symptoms and to investigate the prevalence of NMSs in our patient population.

MATERIALS and METHODS

Ethical approval was obtained from the local ethics committee. A total of 163 patients diagnosed with IPD according to diagnostic criteria of United Kingdom Brain Bank and followed in Antalya Research and Training Hospital, Department of Neurology, Parkinson's disease and Movement Disorders outpatient clinic were included in the present study. For clinical staging, United Parkinson's disease rating scale (UPDRS) was used. At the first admission to outpatient clinic, patients and their relatives were asked about SBD, depression history, previous depression treatment, the presence of anosmia or hyposmia and constipation complaints prior to onset of motor symptoms for NMS evaluation. The exclusion criteria were as follows: the emergence of symptoms following the use of neuroleptic drugs, Parkinson's disease progressing with repeated stroke episodes, history of repeated head trauma or encephalitis, supranuclear palsies, cerebellar findings, autonomous findings in the early period and the presence of dementia, praxia, hydrocephaly at normal pressure and lack of response to levodopa.

Data obtained by the study were evaluated by, "SPSS (Statistical package for the social sciences) 20.0 for Windows" program. In the comparison of clinical and demographic characteristics among IPD patients, "Mann-Whitney U test" was used. Whether there was any difference between groups in terms of sex distribution was analyzed by chi-square test. Pearson Correlation analysis was used to test correlation of parameters. Statistical significance was defined as $p<0.05$.

RESULTS

Of 163 patients included in the study, 100 (61.3%) was male and, 63 (38.7%) were female with an overall mean age of 65,85±10,09 (min:29-max:87). Mean duration of disease was 4,93±0.36 years (4.5 years in males and 5.5 years in females). UPDRS score was 23,87±1.1. One hundred and nine (66.8%) patients were receiving levodopa, 126 (77.3%) patients dop-

amin antagonists, 142 (87.1%) patients MAO-B inhibitors, 2 patients anticholinergic drugs and 3 patients amantadin. Eleven patients were on monotherapy while other patients were on combination treatment. Anosmia was present in 52 (31.9%) patients. Constipation occurred in 85 (52.1%) and RBD in 84 (51.5%) patients. In neuropsychiatric evaluation, 45 cases were found to have (27.6%) depression (Table 1). There was no statistical differences in anosmia, constipation, RBD and depression between the sexes (p values: 0.469, 0.311, 0.637, 0.194, respectively). Constipation was more frequent in patients with RBD ($p<0.05$). While there was no relation was found between UPDRS values and anosmia and depression, in Pearson correlation analysis there was positive correlation between RBD and constipation ($p<0.05$). No statistically significant difference was found between men and women with regard to non-motor symptoms ($p>0.05$). Since the onset of NMS was not remembered clearly by the patients, we had not any data on its onset.

DISCUSSION

Although IPD is traditionally considered as degeneration of dopaminergic neurons in substantia nigra pars compacta (SNc), it has been proven that it is a much more prevalent disease with multiple system involvement[9]. The emergence of NMS before motor symptoms is associated with Lewy pathology in IPD. It is known that Lewy substance accumulation and neuron dysfunction starts at lower part of bulbus and medulla, but motor symptoms of IPD do not become marked until dopaminergic neuron loss takes place in pars compacta of substantia nigra[10,11]. Investigations on the presence of premotor symptoms in IPD patients have potential significance for early detection of disease and better understanding of its etiology. However, the fact that these symptoms are not specific to IPD render them less beneficial. In addition, the development of more than one symptom in the same person may reflect a more fulminant disease process. Therefore, presence of more than one symptom may be more specific in predicting the development of IPD[12]. In our study, RBD was more frequently associated with constipation was and also correlated with the UPDRS score.

Shulman et al reported that NMSs are not recognized adequately by physicians and frequently neglected. This may be due to lack of awareness of or more familiarity with motor symptoms on the part of physicians[1,7]. Or else, these patients may not have reported their symptoms as they did not know their relation with IPD or they were ashamed[13]. Hence, since patient loses the chance of adequate treatment, care costs increase and the duration of hospitalization is prolonged. Some studies have demonstrated that in NMS, distress, impairment in quality of life and economic burden are more significant than motor symptoms[14-16]. NMSs have major negative effects on the lives of patients and their families and contribute to impairment of quality of life and severe disability. They may even shorten their lives[15]. In our center, these patients are being followed by physicians who are particularly concerned with movement disorders and questioning the patients in terms of NMS, so we have obtained findings consistent with the literature.

RBD is a common comorbidity of IPD. A study demonstrated that in IPD patients with RBD, other NMSs also occur more commonly[17]. Similarly, in the present study, constipation occurred at a significantly higher rate in patients with RBD. RBD is motor activity disorder during REM sleep. Motor activity is associated with excessive muscular activity arising due to loss of muscular atonia in relation to REM sleep[18].

RBD has been reportedly present in 42-58% of all IPD patients. Patients with RBD have a 65% risk of development of IPD in the next ten years, making RBD specific clinical marker for premotor IPD[8,19]. In the present study, consistent with the literature, the rate of RBD was found to be 51.5%, which is compatible with the literature. There was also a positive correlation between UPDRS and RBD ($r:0.183$, $p<0.05$).

In IPD, depression occurs commonly and it is a major predictor of low quality of life. Depression is associ-

Table 1. Demographic and clinical characteristics of Parkinson's disease patients.

	N (%)
Sex	
Male	100 (61.3%
Female	63 (38.7%)
Age (years)	65.85±10,09 (min:29-max:87)
Duration of disease (years)	4,93±0,36
UPDRS	23,87±1,1
Medication	
Levodopa	109 (66,8%)
Dopamine agoinst	126 (77,3%)
MAO-B inhibitor	142 (87,1%)
Non-motor features	
Olfactory dysfunction	52 (31,9%)
Constipation	85 (52,1%)
RBD	84 (51,5%)
Depression	45 (27,6%)

UPDRS, Unified Parkinson Disease Rating Scale; MAO-B, monoamine oxidase B; RBD, Rapid Eye Movement Behavior Disorder

ated with physical and cognitive decline, increased risk of dementia and high mortality. Due to differences in the evaluation of depression, the prevalance and incidence of depression in IPD varies widely between 2.7-90% and 4-75%, respectively. Clinical studies have demonstrated the significance of adverse impact of even subclinical depression on quality of life. In the present study, the frequency of depression was found to be 27.6%[20-22]. Fluctuating course of depressive symptoms as in motor symptoms, especially more severely in off-periods, is of great significance for the optimization of treatment. Although it is sometimes difficult to detect depressive symptoms in patients, some risk factors have been determined. i.e.; female sex, the onset of Parkinson symptoms before the age of and history of depression before IPD[23-25]. There was no statistically significant difference between sexes in terms of depressive symptoms (p=0.19).

In IPD, olfactory dysfunction is the most common finding following bradykinesia and rigidity. Olfactory deficits occur at a similar frequency with resting tremor and occur in early stage of disease in around 70-90% of IPD cases. They may occur years before the onset of motor symptoms[26-29].

There is an association between increase in the number of dopaminergic neurons and smell performance. According to The Braak hypothesis, olfactory bulb is one of the regions influenced in early stages of IPD[30]. Recent neuropathologic advances suggest that olfactory system is one of the earliest involved regions of brain in IPD. In postmortem examination, in patients who have olfacory deficit without parkinsonism or dementia, Lewy bodies have been observed incidentally. In other postmortem investigations, it has been demonstrated that Lewy bodies in olfactory bulb as well as other brain regions such as the piriform cortex, the amygdaloid complex, the entorhinal cortex, and the hippocampal formation are associated with smell[29]. In a new study, atrophia has been detected in regions associated with smell in limbic and paralimbic cortices[31]. Olfactory loss is proportional to the degree of structural and functional changes in olfactory bulb[10,32-34].

In this study, smell test was not used and decrease or loss of smell sensation was questioned in patients only by a questionnaire, which may have led to lower rates of anosmia than in those reported in the literature. This may be owing to the fact that patients may not notice the decrease in the sensation of smell.

Constipation occurs in over 50% of IPD patients[35]. The mechanism of constipation is slow transit through colon. It has been established that colon transit time is up to two fold longer in IPD patients than the control group[36-39]. This finding may be explained by impaired reflex relaxation of distal smooth muscles due to inhibitor neuron loss resulting from the accumulation of Lewy bodies in enteric neurons[40]. Constipation usually arises in early periods of disease course and may occur a few years before the onset of motor symptoms. In a study carried out with more than six thousand males without IPD, it was demonstrated that in subjects with less than one bowel movement per day, the risk of PD in the future has increased four fold compared to subjects with more than one bowel movement a day[41]. In our study, the incidence of constipation is similar to the literature ie >50%. There was no significant difference between sexes (p=0.31)

and there was a positive correlation between UPDRS and constipation (r:0.176, p<0.05).

CONCLUSIONS

NMSs in IPD are closely associated with motor symptoms and considered an integral component of a multisystem disorder. The recognition and treatment of NMSs carries great importance in that they are present in a large spectrum starting from the early stages of IPD and cause a pronounced decrease in quality of life. Elucidation of the relation between IPD and its prodromal conditions has critical importance for investigations aiming to prevent and modify disease course in these patients.

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