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Akathisia in Parkinson's Disease: A Comperative Cross-sectional Study

Parkinson Hastalığında Akatizi: Kesitsel-kontrollü Bir Çalışma

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Abstract

Objective: Akathisia is frequently seen as a drug side-effect. In Parkinson's disease (PD), it is relatively understudied. Moreover, few studies investigating akathisia differ concerning the assessment methods and prevalence rates, indicating a need for an objective approach. Our aim is to determine the prevalence of akathisia with an objective assessment tool and to investigate its relationship with neuropsychiatric symptoms and suicidal tendency.

Materials and Methods: One-hundred-one patients with PD and 75 age-and sex-matched control subjects were enrolled. Patients and controls were compared in terms of the presence of akathisia. Further, patients with and without akathisia were compared with regard to disease stage, severity, peak dose dyskinesia, suicide probability, presence of anxiety, and depression using validated tools.

Results: Akathisia was more frequent in patients with PD than in controls (6.9 vs. 0% p=0.02). Patients with akathisia scored worse in unified PD rating scale-part II (experiences of daily living) and reported anxiety and dyskinesia more frequently. The probability of suicidality was similar in patients with or without akathisia.

Conclusion: Our findings reveal that akathisia is more frequent in patients with PD than controls, and is associated with anxiety.

Keywords: Parkinson's disease, akathisia, anxiety, depression, dyskinesia, suicidality

Öz

Amaç: Akatizi sıklıkla bir ilaç yan etkisi olarak görülür. Parkinson hastalığında (PH) nispeten yetersiz çalışılmıştır. Akatizi araştıran az sayıda çalışma, değerlendirme yöntemleri ve yaygınlık oranları açısından farklılık göstermekte olup, objektif bir yaklaşıma ihtiyaç olduğunu göstermektedir. Amacımız, akatizi prevalansını objektif bir değerlendirme aracı ile belirlemek ve nöropsikiyatrik belirtiler ve intihar eğilimi ile ilişkisini araştırmaktır.

Gereç ve Yöntem: PH olan 101 hasta ve yaş ve cinsiyet açısından eşleşen 75 kontrol deneği kaydedildi. Hastalar ve kontroller akatizi varlığı açısından karşılaştırıldı. Ayrıca, akatizi olan ve olmayan hastalar, onaylanmış araçlar kullanılarak hastalık evresi, ciddiyeti, en yüksek doz diskinezi, intihar olasılığı, anksiyete varlığı ve depresyon açısından karşılaştırıldı.

Bulgular: Akatizi parkinson hastalarında kontrollere göre daha sıktı (%6,9 0 p=0,02). Akatizi hastaları, birleşik PH derecelendirme ölçeği-bölüm II'de (günlük yaşam deneyimleri) daha kötü puan aldı ve daha sık anksiyete ve diskinezi bildirdiler. Akatizi olan veya olmayan hastalarda intihar olasılığı benzerdi.

Sonuç: Bulgularımız, akatizinin parkinson hastalarında kontrol grubuna göre daha sık olduğunu ve anksiyete ile ilişkili olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Parkinson hastalığı, akatizi, anksiyete, depresyon, diskinezi, intihar eğilimi

Introduction

The term "akathisia" (in Greek, "not to sit") has two aspects: 1- A subjective restlessness or inner tension, referring particularly to the lower extremities described by the patient with a consequent inability to maintain a stable posture for several minutes, and 2- the objective manifestations of restlessness in the form of limb movements, a tendency to shift body position or rocking the feet around in the chair while sitting; or marching while standing (1).

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The subjective component can solely exist without any objective symptom, which can complicate the diagnosis. Akathisia has so far considered a side-effect of neuroleptics until recent studies have reported akathisia as a non-motor symptom of Parkinson's disease (PD). Akathisia in PD often emerges during the "off" periods or can be the initial symptom of PD (2). As it can be difficult for the patient to describe her/his subjective discomfort and can be easily overlooked by the clinician, akathisia seems to be an underdiagnosed problem in PD and, when diagnosed, may complicate the treatment process, impair patient's cooperation with the physician and caregiver, and even lead to suicide (2,3,4).

Previous studies reported a frequency between 26-44.6% for akathisia in PD (2,5,6). However, these studies differ regarding study design and non-validated assessment methods, which partly explain the wide range of the reported prevalence rates. Moreover, in the PD, no association of akathisia with psychiatric symptoms such as anxiety, depression, and suicidality has yet been thoroughly documented. Therefore, in this study, we aimed i) to investigate the prevalence of akathisia using an objective tool, and ii) its associations with depression, anxiety and suicidality in patients with PD.

Materials and Methods

One-hundred-and-one patients with PD admitted to the Movement Disorders Unit of Ankara University Faculty of Medicine were enrolled in the study. All patients were diagnosed as having PD according to the "United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria" by a movement disorders specialist (7). All patients were on optimum antiparkinsonian medication and assessed in the "off" state. Disease-related status was evaluated using the unified PD rating scale I-IV (UPDRS) and the Hoehn & Yahr scale (HYS). Levodopa equivalent daily doses were also recorded. The control group consisted of 75 volunteers admitted to our outpatient clinic without any neurodegenerative disorders, or medical conditions that could interfere with movement disorders. Participants with a mini-mental state exam (MMSE) score below 24 were excluded. Ankara University Faculty of Medicine, Local Ethics Committee approved the study (approval no: 133-3830, date: 23.06.2008), and all participants signed written consent. All procedures were in accordance with the Declaration of Helsinki.

Statistical Analysis

First, patients and controls were compared in terms of the presence of akathisia. Then, patients with and without akathisia were compared regarding disease stage, severity, peak-dose dyskinesia (DYSK), and the presence of anxiety, depression, or suicide probability. Group comparisons were made using Student's t-test, Mann-Whitney U, Pearson chi-square, or Fisher's Exact tests as appropriate. Further, logistic regression analysis was performed including potential covariates to determine the factors associated with the presence of akathisia. $P<0.05$ was considered statistically significant.

Results

Patients vs. Controls

Overall, 101 patients with PD and 75 controls were included. A comparison of the demographic and assessed data is shown in Table 1.

Akathisia was detected in 7 (6.9%) patients with PD. Akathisia severity scores of the patients, according to BARS were as follows; 1 (1.0%) patient had questionable, 4 (3.9%) had mild and 2 (2.0%) had marked akathisia. None of the patients had moderate or severe akathisia.

Patients with PD with vs. without Akathisia

Between the patients with and without akathisia, the severity of PD assessed by using the HYS significantly differed with higher scores in patients with akathisia (p=0.03). Moreover, scores of the UPDRS-II significantly differed between the groups of PD (Table 2). In the akathisia group, suicide probability scale (SPS) showed that none of the patients had a high risk for suicide. (0%), whereas in the patient group without akathisia, 83 (88.3%) scored low and 11 (11.7%) scored high for suicide probability, which was not significantly different (p=1.00). Disease features and test scores of patients with PD with and without akathisia are shown in Table 2.

To define if the neuropsychological symptoms were associated with akathisia, logistic regression analysis was used, including age, disease duration, UPDRS-III, AIMS score, the presence of anxiety and depression added as potential covariates. The model showed a good fit (Hosmer and Lemeshow test p=0.82) and explained 27% of the variance. Within the included variables, only anxiety was found to be the most likely variable to be significantly associated with the presence of akathisia [Odds ratio: 10.9 (95% confidence interval: 1.1-112.5, p=0.045) independent of the other confounders.

Discussion

In this study, we set out to measure the frequency of akathisia and its association with neuropsychiatric symptoms. Our results

Table 1. Demographics and disease-related data of the participants

	PD n=101	Controls n=75	p value
Age, years, median (IQR)*	65 (16)	67 (11)	0.13
Female sex, n (%)	46 (45.5%)	42 (56.0%)	0.17
Depression, n (%)	42 (40.6%)	22 (29.3%)	0.12
Anxiety, n (%)	33 (32.7%)	22 (29.3%)	0.74
Akathisia, n (%)‡	7 (6.9%)	0 (0%)	0.02
Median PD duration, months (min-max)	36 (0-300)	-	-
Median LEDD, mg (min-max)	500 (0-851)	-	-

*Mann Whitney-U test, ‡Fisher's Exact test, LEDD: Levodopa equivalent daily dose, IQR: Interquartile range, min: Minimum, max: Maximum, PD: Parkinson's disease

Table 2. Disease features and test scores of PD patients with and without akathisia

	Patients without akathisia (n=94)	Patients with akathisia (n=7)	p value
UPDRS part I, median (IQR)*	2.5 (3.0)	2.5 (3.8)	0.88
UPDRS part II, median (IQR)*	10 (5.0)	19.5 (15.5)	**0.01**
UPDRS part III, median (IQR)*	29 (8.8)	39.5 (33.3)	0.16
UPDRS part IV, median (IQR)*	2.0 (2.0)	1.5 (6.8)	0.94
UPDRS total, median (IQR)*	43.5 (16)	58.5 (56.5)	0.15
Hoehn & Yahr, median (IQR)*	3.0 (2.0)	5.0 (1.8)	**0.03**
Peak dose dyskinesia, n (%)	4 (4.2%)	2 (28.6%)	0.06
High suicide probability, n (%)	11 (11.7%)	0 (0%)	1.00
Anxiety, n (%)‡	27 (28.7%)	5 (71.4%)	0.03
Depression, n (%)	38 (40.4%)	3 (42.9%)	0.90

*Mann Whitney-U test, ‡Fisher's Exact test, UPDRS: Unified Parkinson's disease rating scale, IQR: Interquartile range, PD: Parkinson's disease

Table 3. Studies reporting akathisia and Parkinson's disease

	Lang and Johnson/1987 (6)	Comella and Goetz/1994 (5)	Witjas et al./2002 (2)	Present study
Number of patients	100	56	50	102
Age (years)	Not available (age of PD onset + disease duration: 62,6)	55	66.2	64.5
Female sex (%)	38%	30.4%	40%	46.1%
Disease duration	9.5 years	-	12.7 years	36 months
Diagnosis of akathisia	Non-specific and no validated assessment tools were used	Akathisia questionnaire and examination	Patient history	Barnes akathisia rating scale
Hoehn-Yahr stage	N/A	3.0	3.8	3.5
Akathisia (%)	26 (26%)-(a total of 43% patients clinically had mild to severe restless feelings or symptoms), 26% unequivocal akathisia	25 (44.6%)	22 (54%)	7 (6.9%)
Control group	No	No	No	Yes
Relationship of akathisia to PD on-off state	On 92%, off 80%	- Related to the timing of antiparkinsonian medications dosage 52% - Associated with dyskinesias 16%	Off 63% Pre off 11% On 11% Pre on 11% Dyskinesia None	Off
More frequent in patients with akathisia	- Earliest symptom slowness/ stiffness (akinetic-rigid form) - Dominant current symptom not tremor - Crawling sensations	- An earlier age of PD onset - A more severe disease (higher H&Y stage) - Treatment with carbidopa/ levodopa and a direct dopamine agonist (either pergolide or bromocriptine)	Correlated with severity of the disease (higher H&Y score) and handicap-UPDRS part II-"off" state	- Higher H&Y stage - Worse UPDRS II scores - Anxiety - Higher dyskinesia scores
Association with psychiatric symptoms	No difference between groups with or without akathisia, not detailed. 2 of 26 patients with akathisia reported anxiety, depression or nervousness as their non-akathisia related cause for their need to move	N/A	N/A	Anxiety was higher in the with akathisia group than in the without akathisia group

N/A: Not applicable, H&Y: Hoehn-Yahr, PD: Parkinson's disease, UPDRS: Unified Parkinson's disease rating scale

showed that akathisia was significantly higher in patients with PD than in controls. To the best of our knowledge, this study is the first comparative study investigating the frequency of akathisia in PD. Furthermore, akathisia in PD was associated with anxiety but (contrary to tardive akathisia) not with suicidality.

Prevalence of Akathisia in Parkinson's Disease

Studies about akathisia in PD are scarce. In the literature, we could identify only 3 studies, 2 of which primarily reporting about akathisia, and one investigating non-motor fluctuations in general including akathisia data (Table 3). Amongst our 101 patients, 6.9% (n=7) had akathisia; a rate less frequent than previous reports with a range of 26-54% (2,5,6). This discrepancy is probably be due to the different assessment methods of the studies. For instance, Comella and Goetz (5) evaluated akathisia with their own "Akathisia Questionnaire", which included 18 patient-reported questions. Their results could not be repeated by other studies (5). By patient report, the presence of restless feelings and an inner urge to move occurred at least once daily. After the questionnaire, patients were evaluated by two blinded examiners for the presence or absence of akathisia. Akathisia was considered when the patient felt restlessness and an urge to move, which was not directly related to other causes. The specific presence of motor manifestations was not required to diagnose akathisia. The sensitivity and specificity of the questionnaire were found 1.00 and 0.81, respectively. It could not be repeated in other studies.

Despite the small sample size, we investigated patients' neuropsychological profile with akathisia, given that no previous study we were aware of reported such data. The association between akathisia and suicide in patients with tardive syndromes entailed such analysis, which was crucial in the clinical routine but was also not investigated previously (2). The present study results revealed no relation between akathisia and suicidality in PD evaluated by using the SPS. Furthermore, patients with akathisia had anxiety more frequently compared to anxiety-free patients.

Depression scores and frequency of psychosis, and DYSK did not significantly differentiate between patient groups, which might, of course, be due to the small number of patients with akathisia. Usually, both DYSK and akathisia are the features of relatively advanced parkinsonism. Thus, it may be expected that patients with DYSK may have a greater probability to have repeated "off" periods, in which akathisia also frequently occurs (2). Several shortcomings of this study should be mentioned. Our study's primary limitation was having a relatively limited number of patients, especially to investigate akathisia's association with psychiatric symptoms. Therefore, these findings should be interpreted with the utmost caution.

Moreover, we did not evaluate the effect of akathisia on cognition. As all patients were tested during "off" periods, the results of some tests, such as Beck depression inventory, body adiposity index, and MMSE, might be artifactually skewed, but this was to keep the data uniform in terms of avoiding dopaminergic drug effects. However, it may be essential to keep this in mind while interpreting our findings. The more decisive aspects of this study was that it had a control group and used a standardized test which provided the comparability of studies that allowed for a better understanding of akathisia and related features.

Conclusion

In conclusion, our findings reveal that akathisia in PD is not as frequent as previously reported when assessed by using an objective scale. It may also be associated with anxiety but not with suicidality in contrast to patients with tardive akathisia. While these findings may provide a basis for future research, more studies with bigger sample sizes are needed to define akathisia's prevalence and its association with neuropsychological symptoms.

Ethics

Ethics Committee Approval: Ankara University Faculty of Medicine, Local Ethics Committee approved the study (approval no: 133-3830, date: 23.06.2008).

Informed Consent: All participants signed written consent.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.A., Ş.O.K., Concept: Ö.A., E.B., M.C.A., Ş.O.K., Design: Ö.A., F.N.D.Ç., M.C.A., Ş.O.K., Data Collection or Processing: Ö.A., F.N.D.Ç., R.Y., E.B., M.C.A., Analysis or Interpretation: Ö.A., R.Y., E.B., M.C.A., Literature Search: Ö.A., F.N.D.Ç., M.C.A., Writing: Ö.A., M.C.A.

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