Original Paper

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Prevalence of Restless Legs Syndrome Among Psychiatric Patients Who are Under Antidepressant or Antipsychotic Monotherapy

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ABSTRACT:

Prevalence of restless legs syndrome among psychiatric patients who are under antidepressant or antipsychotic monotherapy

Objective: Several groups of medications, such as dopamine blockers, analgesics and antihistaminergics were associated with restless legs syndrome (RLS). Although case reports showed some significant relations, they have many methodological limitations such as co-medications or medical co-morbidities. The aim of this study was to investigate the prevalence and severity of RLS in patients on antidepressant (AD) or antipsychotic (AP) monotherapy.

Methods: One hundred and ninety-seven patients and 150 healthy controls were included in the study. RLS was diagnosed according to the International Restless Legs Syndrome Study Group (IRLSSG) criteria. The severity of RLS was evaluated according to IRLSSG rating scale. Participants diagnosed with RLS went under further neurological and psychiatric investigation for excluding secondary causes.

Results: One hundred and twenty patients (60.9%) were on AD therapy, while 77 patients (39.1%) were on AP monotherapy. Thirty-two patients (16.2%) and seven controls (4.7%) were diagnosed with RLS according to IRLSSG criteria. The most frequent cause of RLS was quetiapine (28.5%) in the antipsychotic group and paroxetine (22.2%) in the antidepressant group. There was no statistically significant correlation between drug usage duration and RLS severity.

Conclusion: AD or AP induced RLS is a common condition. ADs and APs should be considered as a cause for RLS when assesing RLS in psychiatric patients who are under treatment either of these medications.

Keywords: antidepressant, antipsychotic, restless legs syndrome, adverse effect

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INTRODUCTION

Restless legs syndrome (RLS) is a disabling disorder that is characterized by a sensation of discomfort, especially in the lower limbs. Paresthesia, defined as the urge to move, and formication are some common subjective complaints for RLS; however, it is frequently expressed as an inexpressible sensation. Motor activities, sometimes phenomenological, fulfill stereotyped behavior criteria, for example walking and shaking the legs can temporarily attenuate unrest. Symptoms also get worse at resting states. This, also, explains the circadian emergence of the symptoms especially at

evenings or nights[1]. Two to ten percent of the population suffer from RLS according to epidemiological studies[2].

The etiology of RLS still remains unclear, but there is much evidence that indicates the importance of the dopaminergic pathways in its pathophysiology. Improvements with pharmacological agents which tune dopaminergic pathways confirm this mechanism[3]. However, several medication groups, such as dopamine blockers, analgesics and antihistaminergics were also associated with RLS[4]. RLS has been reported with first or second generation neuroleptics such as haloperidol or olanzapine in previous studies[5-9]. Neuroleptic agents associated with RLS are not limited to the mentioned above[10-13]. Moreover, there is not enough data that indicates an increase in RLS frequency with some neuroleptics such as ziprasidone, paliperidone or zuclopenthixol. There is considerable evidence that indicates an increase in RLS prevalence with serotonergic agents such as sertraline, fluoxetine, paroxetine or citalopram known as selective serotonin reuptake inhibitors (SSRIs)[14-17] and serotonin noradrenaline reuptake inhibitors (SNRIs) such as duloxetine or venlafaxine[18,19].

There is limited study about RLS prevalence in patients on antidepressant (AD) or antipsychotic (AP) pharmacotherapy[20,21]. Data about RLS prevalence with psychopharmacotherapy were generally based on case reports or series. These studies, which had relatively small sample sizes, determined some correlation for RLS with only some of the ADs and APs. Other limitations of aforementioned studies were the comorbidities and additional medications. The aim of this study was to determine the prevalence and severity of RLS in patients taking AD or AP monotherapy and the relationship with psychiatric symptom severity.

MATERIALS AND METHODS

Samples

The study was conducted in the psychiatry outpatient clinic of Gaziosmanpasa University Faculty of Medicine, Tokat, Turkey between April 2013 and April 2014. One hundred and ninety seven patients on AD or AP monotherapy on the same dosage for at least one month were included in the study. One hundred and fifty drug naive healthy volunteers were included as the control group. Written informed consents were obtained from all participants. Patients who were on combined pharmacotherapy, had poor compliance with pharmacotherapy, or who had comorbid disorders were excluded. The study was approved by the local Ethics Committee of Gaziosmanpasa University.

Procedure

The diagnoses of patients who were on the same dosage of AD or AP monotherapy for the last one month were re-evaluated according to the DSM-IV[22]. The diagnosis of RLS and disease onset was evaluated according to the International Restless Legs Syndrome Study Group (IRLSG) RLS criteria[23]. Patients who met RLS criteria before the onset of ADs or APs were excluded (n=13). Patients who were diagnosed with RLS were referred to the department of neurology and physical therapy and rehabilitation for the exclusion of other causes. Fourteen patients with other secondary causes of RLS were excluded after consultation. After these initial steps the drug-induced RLS group was created. The RLS rating scale and the Hospital Anxiety and Depression (HAD) scale were applied to patients on AD monotherapy, while the Brief Psychiatric Rating Scale (BPRS) was applied to patients on AP monotherapy.

Measures

RLS diagnostic criteria include: a) a diagnostic questionnaire, developed by the IRLSG, b) a diagnostic questionnaire, developed by the research team, according to IRLSG criteria to meet the diagnosis of four basic criteria that must be fulfilled; 1) a desire to move limbs associated with discomfort; 2) motor restlessness the relieves the discomfort; 3) symptoms get worse at rest and temporary activity weakens the discomfort; 4) symptoms are worse later in the day or at night[23].

International RLS study group rating scale (IRLSSG-RS): RLS were evaluated by using a brief self-rating scale which assesses the severity and impact on daily function[24].

Brief Psychiatric Rating Scale (BPRS): BPRS, developed by Overall and Gorham[25], is a scale to assess the severity of psychotic and depressive symptoms. The validity and reliability of the Turkish version was conducted by Soykan[26].

Hospital Anxiety and Depression Scale (HAD): HAD was developed by Zigmond and Snaith[27]. It measures the severity of anxiety and depression symptoms especially in patients with physical illnesses. The validity and reliability of the Turkish version was conducted by Aydemir et al.[28].

Statistical Analysis

Statistical Package for Social Sciences Software (SPSS 14, Chicago, IL, USA) was used for analysis. The distributions of continuous variables were tested by Kolmogorov Smirnov test. Student-t test and Mann-Whitney U test were used for comparisons of normally and abnormally distributed variables, respectively. Pearson's chi-square test was used to compare the proportions between the RLS group and controls. Pearson's and Spearman's correlation coefficients were used to evaluate the relationship between the parameters. $p<0.05$ was accepted as significance level for all statistical analysis.

RESULTS

One hundred and twenty-five male (63.5%) and 72 female (36.5%) patients taking monotherapy were included (n=197). Ninety-one male (60.7%) and 59 female (30.3%) participants were included as control group (n=150). Mean ages for patient and control groups were 38.1±12.4 and 35.7±10.8, respectively. There were no statistically significant age and sex differences between groups ($p>0.05$). Sociodemographic characteristics of participants is shown in Table 1.

One hundred and twenty patients (60.9%) were taking AD, 77 patients (39.1%) were taking AP monotherapy. Forty-two patients on AP monotherapy were diagnosed with schizophrenia and 24 patients on AP monotherapy were diagnosed with bipolar disorder according to the DSM-IV diagnostic criteria. Seventy-three patients were diagnosed with unipolar depression and 16

Table 1: Socio-demographic characteristics of the participants

	Patients n (%)	Controls n (%)	Statistics (χ^2)	p value
Gender				
Female	125 (63.5)	91 (60.7)	0.281	0.596
Male	72 (36.5)	59 (39.3)		
Educational status				
Primary school	61 (31.0)	44 (29.3)	0.482	0.874
Secondary school	35 (17.8)	32 (21.3)		
High school	74 (37.6)	52 (34.7)		
University	27 (13.7)	22 (14.7)		
Marital status				
Married	123 (62.4)	77 (51.3)	4.300	0.038*
Single	74 (37.6)	73 (48.7)		
Income status				
Low-income	51 (25.9)	35 (23.3)	0.306	0.858
Middle-income	125 (63.5)	98 (65.3)		
High-income	21 (10.6)	17 (11.4)		
Smoking				
No	148 (75.1)	121 (80.7)	1.500	0.221
Yes	49 (24.9)	29 (19.3)		

*p<0.05

Table 2: Diagnoses of the patients in antidepressant and antipsychotic groups

	N (%)
Antidepressant group (n=120)	
Depressive disorder	73 (60.9)
Dysthymic disorder	16 (13.3)
Anxiety Disorders	31 (25.8)
Schizophrenia	42 (54.5)
Antipsychotic group (n=77)	
Bipolar Disorders	24 (31.2)
Other PD	11 (14.3)

PD=Psychotic Disorders

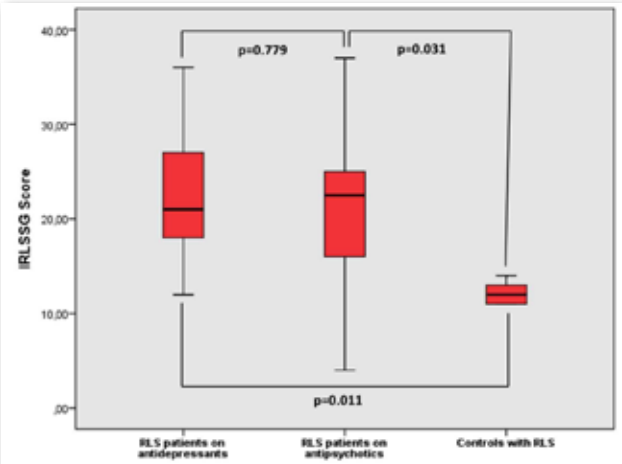

Figure 1: International restless leg syndrome study group rating scale (IRLSSG-RS) scores of the participants with RLS

patients were diagnosed with dysthymia. The diagnoses of patients are shown in Table 2. The AP group was taking medication for 101.4±63.7 days and AD group for 64.3±41.1 days. The mean BPRS score of AP group was 20.2±7.1 and mean depression score of AD group was 11.4±7.7.

Thirty-two patients (16.2%) and seven controls (4.7%) were diagnosed as RLS according to the IRLSSG criteria. The difference between two groups was statistically significant (p=0.001). Median IRLSSG-RS scores of patient and control groups were 2 (min 0-max 37) and 0 (min 0-max:23), respectively. The difference between symptom severity of the groups was also statistically significant (p=0.001). The relations between groups with RLS according to IRLSSG-RS are shown in Figure 1. There were no statistically significant differences for socio-demographic characteristics such as age, gender, years of education, marital status and income between RLS (n=32) and non-RLS (n=165) patients. There was not a significant correlation between medication duration and IRLSSG-RS scores in the patient group (r=0.032, p=0.65).

The most commonly used AP and AD were quetiapine (n=21, 27.2%) and escitalopram (n=23, 19.2%), respectively. Pharmacological agents used by the patient group are shown in Table 3. Mean medication durations for quetiapine and escitalopram were 93.9±59.2 and 75.8±32.4 days, respectively. The most frequent cause of RLS was quetiapine (28.5%) in the antipsychotic group, while paroxetine (22.2%) was most frequently implicated in the antidepressant group. There

Table 3: RLS frequencies and drug duration of the patients in antidepressant and antipsychotic groups

	N n (%)	Duration of drug (day)	RLS (+) n (%)	p value
AD				
Paroxetine	18 (15.0)	69.9±36.2	4 (22.2)	0.84
Essitalopram	23 (19.2)	75.8±32.4	2 (8.7)	
Sertralin	26 (21.7)	75.1±37.2	3 (11.1)	
Fluoksetine	21 (17.5)	60.1±23.4	3 (14.2)	
Duloksetine	11 (9.2)	70.2±50.7	2 (18.1)	
Venlafaksine	21 (17.5)	77.6±23.1	4 (19.0)	
AP				
Quetiapine	21 (27.2)	93.9±59.2	6 (28.5)	0.52
Olanzapine	20 (25.9)	101.2±64.9	3 (15.0)	
Risperidone	13 (16.8)	123.5±77.4	2 (15.4)	
Paliperidone	11 (14.2)	75.7±22.2	1 (9.1)	
Aripiprazole	12 (15.6)	79.9±36.6	1 (8.3)	

AD= antidepressants, AP= antipsychotics, RLS= restless leg syndrome

were no statistically significant differences within the antidepressant or antipsychotic drugs in terms of RLS adverse effect (p values are shown in Table 3). In the paroxetine and quetiapine group, there was not a significant correlation between IRLSSG-RS scores and medication duration. RLS frequency according to agent is shown in Table 3.

DISCUSSION

In this study, we aimed to examine RLS prevalence and severity in patients taking AD or AP monotherapy. Previous studies on RLS prevalence had some limitations such as comorbid psychiatric disorders and combined pharmacotherapies. RLS prevalence in patients on AD or AP were 16.2%. There was no significant difference between medication duration and RLS severity.

In the present study, the prevalence of AP induced RLS was 18.2%. Population studies showed a prevalence of 5-10%[1]. The literature lacks population studies on AP induced RLS. Most of studies on AP induced RLS were a case report or series[7-12]. Thus, according to our study, it would be reasonable to propose that APs increase RLS. Contrary to our results, Jagota et al.[20], reported the prevalence of typical or atypical AP induced RLS was 1%. However, the study of the Jagota et al.[20] had significant methodological limitations. For example, most of the participants were also on benzodiazepine therapy, additionally, this study was conducted in patients of Asian ethnicity. Other studies have demonstrated a low prevalence of RLS in Asians when compared with Caucasians. Also, the mean age was 20 which indicates a statistically significant demographic difference with most of the studies[29]. Thus, the geriatric population may have an increased incidence of RLS.

Akathisia, another obstacle in RLS diagnosis, can be often misdiagnosed as RLS and vice versa[3]. The differences between RLS and akathisia are, for the former, an aggravation of symptoms predominantly at nights and concomitant paresthesia in the lower limbs, whereas for the latter inner restlessness is a salient characteristic. Temporary relief by moving the legs is also more typical for RLS[30]. Unfortunately, RLS is underdiagnosed because RLS symptoms are reluctant to present during a daytime interview and can be overlooked if not considered. Although patients may complain of RLS symptoms, it may not be diagnosed because of its phenomenological vagueness and non-specificity. If diagnostic stigmas were considered, RLS symptoms can be attributed to agitation or positive symptoms. The last mentioned is another similarity with akathisia as expected.

The most common cause of RLS was quetiapine (28.5%) in the antipsychotics group. But it would be reasonable to expect a high prevalence of RLS with risperidone, olanzapine or paliperidone because of their well-known antidopaminergic potencies compared to quetiapine. The lower extrapyramidal side effect profile is an important pharmacodynamic aspects of quetiapine, with its low D2 receptor binding and limbic selectivity[31]. Also, the akathisia risk with quetiapine is comparable to placebo[32]. Quetiapine has an initial transient binding profile to D2 receptors which may explain the emergence of RLS symptoms after medication administration[31]. Quetiapine's antihistaminergic properties might be another explanation since antihistaminergic drugs were associated with RLS[33]. Pharmacodynamics characteristics of quetiapine lies behind its hypnotic properties which makes quetiapine "the drug of bed time". In our study, the most commonly used AP was quetiapine which could have influenced the results. However, compatible with our results, quetiapine becomes the first candidate of AP induced RLS[34,35].

Kang et al.[36] suggested that AP induced RLS is a manifestation, otherwise latent form, of idiopathic RLS. But, the question remains, why do all patients taking APs not develop RLS? Perhaps, genetic predispositions may explain these effects. The BTBD9 gene was found to be associated with AP induced RLS in schizophrenia patients[36]. Such susceptibility differences might be attributable to biological factors, including the pharmacokinetic factors and genetic vulnerability[37]. In another study by Kang et al.[38], no correlations were found

between symptom severity of RLS and AP dosages. These findings are consistent with our findings. In our study, there were no significant correlations between symptom severity and IRLSSG-RS scores. Briefly, there is not enough data that indicate any correlation between RLS and psychiatric symptom severity.

Depressive symptoms were frequently reported in patients with RLS. Sleep disturbances, altered by RLS, also interfere with depression course[39]. Several case reports suggest the possibility of antidepressant-induced RLS[17,40]. Contrary to mentioned studies, Dimmit and Relay[41] revealed no associations between AD and RLS, in contrast, they even demonstrated some improvements on pre-existing RLS with SSRIs. In our study, similar to these results, RLS prevalence in patients taking SSRIs was 16.2% and 4.7% in controls. In another study, 9% of patients were diagnosed with drug-induced RLS[42]. Brown et al.[43] showed that 45% of patients taking AD met RLS criteria. Methodological limitations of previous studies can explain these results. The retrospective nature of the latter, concomitant medications, and comorbidities of the former may be related with these controversial results. Our strict inclusion criteria might provide more accurate results than previous studies.

Pathophysiology of RLS is still a matter of debate, however, dopaminergic hypofunction and serotonergic and noradrenergic hyperfunction was proposed as one of the possible etiologies[44]. In our study, paroxetine (22%) was the most commonly used AD in patients with RLS. Indirect dopaminergic antagonism due to serotonergic alterations by paroxetine has been proposed in the pathogenesis of RLS[10]. Serotonin (5-HT) elevation due to preexisting paroxetine, it was likely quetiapine induced 5-HT1A hyper activation under its 5-HT2A antagonism[45]. Thus, this mechanism can explain our results on paroxetine and the other ADs.

Our study had some limitations. Conducting a cross-sectional study and small sample size are two limiting factors. We applied strict inclusion criteria for eliminating the confounders. For example, most of psychiatric patients are on combined therapy and we excluded other comorbidities. Another limitation was the absence of polysomnography measurements. There was a limitation about the gender characteristics because there was a female predominance in patients with RLS in this study. Results about gender issues on RLS are also controversial[46]. Studies show a female predominance, but equal distribution for gender is not an exception[46]. Thus, female predominance in our study may be either a sampling bias or just a consistent finding as seen with previous studies. Another limitation was the range of AD classes. In our study, ADs were limited as, proper to the methods of psychiatric prescription routine, SSRIs or SNRIs. TCAs or mirtazapine were not reported in our study, although these were found to be potent enhancers of RLS. But, unfortunately, nowadays these groups of drugs are rarely used as monotherapy. This limitation also must be considered when assessing the results of our study.

In conclusion, AD- or AP-induced RLS is a common condition. Unfortunately, it is often under and misdiagnosed. ADs and APs should be considered as a cause for RLS when assesing RLS in psychiatric patients who are under treatment with either of these class of medications.

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