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Restless legs syndrome in patients with chronic obstructive pulmonary disease

Suchita Pant[1], Sanjeev Kumar[1], Rakhee Khanduri[1]*, Rajat Ray[2]

[1]*Pulmonologist, Department of Pulmonary Medicine, Swami Rama Himalayan University, Jollygrant, Dehradun, Uttarakhand, 248140.*
[2] *Psychiatrist, Swami Rama Himalayan University, Jollygrant, Dehradun, Uttarakhand, 248140.*

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death. Restless Legs Syndrome (RLS) is associated with many systemic diseases. RLS is found in many patients with COPD. There is paucity of data on this topic from India. The aim is to find the prevalence of RLS in COPD patients and its distribution in study population with respect to various demographic and clinical characteristics. Correlation between severity of RLS and COPD severity was also aimed to be evaluated.

Materials and Methods: Prospective, observational study conducted in a tertiary care institute over a period of 12 months. After fulfilling the inclusion criteria the patients were categorized according to the severity of COPD using the GOLD guidelines. Diagnosis and severity of RLS was evaluated using IRLSSG criteria. Prevalence and association of RLS with COPD and its demographic and clinical characteristics was evaluated.

Results: A total of 294 patients were taken which included 229 (77.9%) males and 65 females (22.1%). Mean age was 62.05 ± 10.32 years. Smoking was a more common risk factor among the patients (85.7%). 110 patients were diagnosed with RLS. A statistical significant association was found between duration of COPD and RLS (p value =0.001) and also between severity of COPD and RLS (p value=0.001). A significant positive correlation (r=0.395, p value= 0.001) between severity of COPD and RLS. Forty two (87.5%) patients with definite RLS had stage D COPD. Degree of obstruction of airways showed a statistical significant association with prevalence of RLS (p value=0.001).

Conclusion: RLS showed increased prevalence in COPD patients making it crucial to screen all the COPD patients for symptoms of RLS and if required to treat the symptoms, thus improving the quality of life.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a disease of airways caused by inflammation as well as remodelling which leads to permanent destruction of the lung parenchyma. This causes limitation in airflow. Exacerbations and comorbidities have a bearing on overall severity of the disease in individual patients. Symptoms include dyspnoea, chronic cough and chronic sputum production (1). COPD is one of the leading causes of death around the world. Different reports suggest that prevalence of COPD ranges from 2% to 22 % in men and 1.2% to 19% in women (2). Urgency to move the legs during rest or periods of inactivity are characteristic features of a common neurological sensorimotor disorder which is named as RLS (3). The International

*Corresponding author: Rakhee Khanduri, Department of Pulmonary Medicine, Swami Rama Himalayan University, Jollygrant, Dehradun, Uttarakhand, 248140. Tel: +917579281136; Email: Rakhee.sodhi@gmail.com

Restless Legs Syndrome Study Group (IRLSSG) has described 5 mandatory clinical features to establish the diagnosis of RLS (4). Patients suffering from RLS have diurnal variation of symptoms i.e. the symptoms usually occur during night, which affects the sleep quality and the quality of life. Increased prevalence of poor sleep quality has been found in COPD patients. Hypoxemia is hypothesised to be a causative factor of RLS. There is an increase in severity of insomnia with increase in severity of RLS and COPD. Pathophysiology of RLS still has not been well understood but its association is seen with abnormalities in the metabolism of iron/transferrin and dopamine (5). RLS is found to be more prevalent in COPD (6). RLS is commonly seen in patients diagnosed with COPD (7). Severity of RLS increases with increased hypoxemia, thus it increases with increased severity of COPD (7). RLS is not present in all patients with COPD, hence genetic predisposition may have a role in the manifestation of RLS symptoms in these patients. There is also some ethnic predisposition as RLS has been found lesser in Asians (8). Prevalence of RLS is much lesser in Indian population as compared to the western population (9). Data suggests prevalence of 2.1% in the urban Indian population (8). RLS and COPD both greatly affect the quality of life of a patient (10). This impact needs to be studied. Due to the paucity of published data regarding the prevalence of RLS in COPD patients from India this study was planned.

The study was primarily aimed to find the prevalence of RLS in patients with COPD. The secondary outcome of this study was to see whether there is a difference in prevalence of RLS with respect to demographic and clinical characteristics of COPD and to correlate severity of RLS with severity of COPD.

Materials and Methods

Study design:

This is an Observational-Cross sectional study, performed in the department of pulmonary medicine at a tertiary care teaching institution of northern India, over a period of 12 months (January 2017 - December 2017).

Study population:

350 consecutive patients with COPD presenting in out-patient department, emergency or admitted in wards of the department of pulmonary medicine, during the study period were screened for inclusion and exclusion criteria. Written informed consent was taken.

Inclusion Criteria :

Patients diagnosed with COPD using the GOLD guidelines, age more than 40 years with no other long standing pulmonary disease and no pulmonary or extra-pulmonary malignancy.

Exclusion Criteria:

Immunocompromised patients, intubated patients, patients with active tuberculosis, history of myocardial ischemia within the last 3 months, patients with Parkinson's disease, neurological deficit on clinical examination or those under treatment for neurological condition, patients taking RLS causing drugs (dopamine antagonists, antidepressants, caffeine, cocaine, alcohol or amphetamines) for more than 1 month and opioid use disorder during past 3 months (>10 days/months), patients with diabetes, chronic renal disease and iron deficiency anemia.

Study Protocol:

Demographic data, habits, and comorbidities were recorded. Smoking habits of the patient was recorded using the smoking index (cigarettes smoked per day x years of smoking). Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines were used to diagnose the patients with COPD(11). Which included COPD assessment test (CAT) score(12). mMRC dyspnoea scale was used to grade the patient's breathlessness. The number of exacerbations per year was recorded. These recordings were then used to categorise the patients according to GOLD guidelines. Hyp' Air compact spirometer was used to confirm the diagnosis of COPD and to calculate the degree of obstruction in COPD patients by finding FEV1, FVC and FEV1/FVC predictable percentage standardized according to age and BMI. According to GOLD guidelines these patients were graded into GOLD 1(FEV1≥ 80), GOLD 2(FEV1 50-79), GOLD 3(FEV1 30-49) AND GOLD 4(FEV1 < 30). The symptomatic assessment with the patient's

spirometric classification and/or risks of exacerbations were used to categorise the patient into 4 categories i.e. A, B, C and D. Treatment profile for COPD was also recorded and categorized as one drug, two drugs and three drugs combinations and add on therapy.

Patients with COPD were diagnosed with RLS by using the IRLSSG criteria (13). CHRLS questionnaire was used to categorise the patients of COPD with RLS(14). Validated scoring system was used for the questionnaire(14). According to the answered questions the patient was divided into the RLS diagnostic classification: definite RLS (clinically typical), probable RLS (not typical of clinical cases but meets the diagnostic criteria) and not RLS. These patients with RLS were then evaluated for severity using the IRLSSG severity scale which is comprised of five questions (4).

The total score was calculated. According to this the severity of RLS symptoms were categorized as: mild (1-10), moderate (11-20), severe (21-30) and very severe (31-40). To find correlates of RLS and other comorbidities we performed laboratory investigations like arterial blood gas analysis , complete hemogram , Serum Ferritin levels blood sugar , HbA1c, serum creatinine and blood urea.

Data Management & Statistical Analysis:

The data thus obtained was analysed with Statistical Package for Social Sciences (SPSS) version 22.0, manufactured in the USA. Interpretation and analysis of obtained results was carried out using descriptive statistics. The prevalence of RLS in COPD and prevalence of poor sleep quality in COPD was assessed using descriptive statistics. Mean and standard deviation of quantitative variables for example age, spirometry recordings and ABG results were compared with RLS using ANOVA. To compare variables such as sex, smoking habit, pack years of cigarettes between subjects with and without RLS Chi-square test was used. P value was calculated and value < 0.05 was considered to be significant. Effect of severity of COPD and comorbidities on the occurrence of RLS was tested using Chi-square test. Correlation (Pearson's correlation coefficient r) was applied to find the contribution of different pharmacological methods used for COPD in the occurrence of RLS and to find the correlation of COPD severity with severity of RLS.

After screening 350 patients who attended respiratory medicine OPD during the study period, 10 were excluded for age less than 40 years, 15 patients had other associated pulmonary disease, 7 patients had pulmonary and extra-pulmonary malignancies, 6 had active tuberculosis and 11 patients did not give consent for the study. Remaining 294 patients were included in the study.

Mean age was 62.05 ± 10.32 years. There was a male predominance in our study with 229 (77.9%) males and 65 (22.1%) females. Most of the patients in the study population were > 60 years of age (64.3%). Smoking as a risk factor was more common than biomass fuel exposure which was found in 85.7% and 13.3% of the patients respectively. Out of the smokers 146 (57.9%) had history of 16-30 pack years. Majority of the smokers (86.4%) had smoking index of >200 (Table 1). Most of the patients had been diagnosed with COPD for a duration of 1-5 years (67%). Majority of the patients were in the stage D of COPD according to the GOLD guidelines (47.6%) followed by stage C (38.8%), stage B (13.3%) and stage A (0.3%) (Table 2)

Most of the patients were on three drug combination (39.1%) as per the GOLD guidelines for the treatment of COPD (Table 2).

Out of the 294 COPD patients 110 patients were diagnosed with RLS. Among these 62 (21.1%) patients were diagnosed as probable RLS and 48 (16.3%) had definite RLS. The patients diagnosed with RLS were categorized according to severity using the IRLSSG severity criteria into mild, moderate, severe and very severe i.e. 18, 35, 40 and 17 (16.36%, 31.81%, 36.3% and 15.4%) respectively (Table 3) Out of the 294 COPD patients 110 patients were diagnosed with RLS. Among these 62 (21.1%) patients were diagnosed as probable RLS and 48 (16.3%) had definite RLS. The patients diagnosed with RLS were categorized according to severity using the IRLSSG severity criteria into mild, moderate, severe and very severe i.e. 18, 35, 40 and 17 (16.36%, 31.81%,

36.3% and 15.4%) respectively (Table 3).

Table 1: Distribution of pack years and smoking index among the smokers (n=252)

		Frequency	Percentage
Pack Years	<15 years	36	14.3
	16-30 years	146	57.9
	>30 years	70	27.8
Smoking Index	<200	33	13.1
	>200	219	86.4

Table 2: Distribution of clinical profile of COPD (n=294)

		Frequency	Percentage
Duration of COPD	0-1 years	17	5.8
	1-5 years	197	67
	>5 years	80	27.2
Exacerbation per Year	0	20	6.8
	1	122	41.5
	2	104	35.4
	3	43	14.6
	4	5	1.7
Combined Assessment of COPD	A	1	0.3
	B	39	13.3
	C	114	38.8
	D	140	47.6
Treatment status	No treatment	21	7.1
	One Drug Combination	65	22.1
	Two Drugs Combination	93	31.6
	Three Drugs Combination	115	39.1
	With Add-on Therapy	19	6.5

Table 3: Prevalence of RLS in COPD patients and distribution of these patients according to the severity of RLS (n=294)

		Frequency(n=294)	Percentage (%)
RLS	No RLS	184`	62.6
	Probable RLS	62	21.1
	Definite RLS	48	16.3
Total		294	100.0
	Mild	18	16.36
	Moderate	35	31.81
Severity of RLS	Severe	40	36.3
	Very Severe	17	15.4
Total		110	100.0

Table 4: Association between RLS and various demographic and clinical parameters of COPD

Variable		No RLS (184)	Probable RLS (62)	Definite RLS (48)	Total (294)	p Value
Sex	Female	35 (19.9%)	17 (27.4%)	13 (27.1%)	65 (22.1%)	0.26
	Male	149 (81.8%)	45 (72.6%)	35 (72.9%)	229 (77.9%)	
Age Group	<60yrs	65 (35.7%)	25 (40.3%)	15 (31.3%)	129 (35.7%)	0.50
	>60yrs	119 (64.7%)	37 (59.7%)	33 (68.8%)	165 (64.3%)	
Smoking	Yes	160 (87%)	49 (79%)	43 (89.6%)	252 (85.7%)	0.21
	No	24 (13.01%)	13 (21%)	5 (10.4%)	42 (14.3%)	
Biomass fuel exposure	No	161 (87.5%)	51 (82.3%)	43 (89.6%)	255 (86.7%)	0.433
	Yes	23 (12.5%)	110 (17.7%)	5 (10.4%)	39 (13.2%)	
COPD duration	<5 years	149 (81%)	39 (62.9%)	27 (56.3%)	215 (73.1%)	0.001*
	>5 years	35 (19%)	23 (37.1%)	21 (43.8%)	79 (26.9%)	
Severity of COPD	A	1 (.5%)	0 (0.0)	0(0.0)	1(.3%)	0.001*
	B	33 (17.9%)	4 (6.5%)	2 (4.2%)	39 (13.3%)	
	C	92 (50.5%)	18 (29%)	4 (8.3%)	114 (38.8%)	
	D	58 (31.5%)	40 (64.5%)	42 (87.5%)	140 (47.6%)	

*Chi- square test (p value <0.05

Table 5: Treatment profile of COPD and its association with RLS

Variable		No RLS (184)	Probable RLS (62)	Definite RLS (48)	Total (294)	p Value
Treatment	Yes	167 (90.8%)	61 (98.4%)	45 (93.8%)	273 (92.9%)	0.13
	No	17 (9.2%)	1 (1.6%)	3 (6.3%)	21 (7.1%)	
One Drug	Yes	42 (64.6%)	14 (21.5%)	9 (13.8%)	65 (22.1%)	0.83
	No	142 (62.0%)	48 (21.0%)	39 (17.0%)	229 (77.9%)	
Two Drug	Yes	61 (33.2%)	16 (25.8%)	16 (33.3%)	93 (31.6%)	0.54
	No	123 (66.8%)	46 (74.2%)	32 (66.7%)	201 (68.4%)	
Three Drug	Yes	64 (34.8%)	31 (50%)	20 (41.7%)	115 (39.1%)	0.097
	No	120 (65.2%)	31 (50%)	28 (58.3%)	179 (60.9%)	
Add-on Therapy	Yes	7 (3.8%)	7 (11.3%)	5 (10.4%)	19 (6.5%)	0.05
	No	177 (96.2%)	55 (88.7%)	43 (89.6%)	275 (93.5%)	

*Chi- square test (p value <0.05)

Table 6: Comparison of mean of laboratory studies, spirometry and arterial blood gas readings between patients with and without RLS.

Variable	No RLS		Probable RLS		Definite RLS	
	Mean	SD	Mean	SD	Mean	SD
Hb (g/dL)	13.36±2.01		12.82 ± 2.27		12.80 ± 2.57	
PCV(%)	40.86 ±6.62		39.93±7.83		39.46±8.18	
MCV(fL)	86.24±7.71		84.75±7.65		84.32±12.81	
MCHC(%)	31.93±2.16		31.52±2.71		31.45±1.85	
S.Ferritin(ng/mL)	133.20±106.26		98.72±109.57		53.65±71.87	
Blood Glucose(mg/dL)	111.34±26.34		114.14±21.51		116.22±47.74	
HbA1C(%)	6.17±0.97		6.51±1.38		6.27±1.44	
S. Urea(mg/dl)	14.34±6.14		14.31±6.65		14.28±5.48	
S. Creat(mg/dL)	0.91±0.29		0.89±0.32		0.83±0.25	
FVC	75.59±18.63		65.96±16.85		62.65±17.49	
FEV1	52.65±18.98		42.76±14.358		32.85±14.87	
FEV1/FVC	66.89±13.95		63.04±12.33		63.04±12.33	
PaO2(mmHg)	74.27±21.28		81.95±44.97		73.34±29.61	
PaCO2(mmHg)	50.54±12.61		53.69±13.82		50.59±12.03	
HCO3(mmol/L)	26.14±4.37		26.16±4.94		26.73±5.14	

*Significant difference in mean (<0.05) by ANOVA

Out of the 294 COPD patients 110 patients were diagnosed with RLS. Among these 62 (21.1%) patients were diagnosed as probable RLS and 48 (16.3%) had definite RLS. The patients diagnosed with RLS were categorized according to severity using the IRLSSG severity criteria into mild, moderate, severe and very severe i.e. 18, 35, 40 and 17 (16.36%, 31.81%, 36.3% and 15.4%) respectively (Table 3).

There was statistical significant association between duration of COPD and RLS (p value =0.001) which means that longer the duration of COPD more are the chances of developing RLS. These patients also showed a statistical significant association with severity of COPD (p value=0.001). Out of all the patients diagnosed with definite RLS 42(87.5%) had stage D COPD, similarly majority of the patients who were categorized in the probable RLS group also had stage D COPD. Out of other demographic and clinical parameters no significant association of RLS with age, gender and smoking habit was found (Table 4).

No significant association was found between the treatment profile of COPD patients and RLS. However, the patients who were on COPD treatment along with an add-on therapy had borderline significant association (p value 0.05) with RLS (Table 5).

Among all the laboratory investigations performed the difference in the mean and SD of serum ferritin levels in patients with and without RLS were statistically significant (p value<0.001 by ANOVA). The mean levels of serum ferritin in probable and definite RLS were found to be 98.72±109.57 ng/mL and 53.65±71.87 ng/mL respectively (Table 6).

Spirometry findings in these COPD patients were evaluated and the association of degree of obstruction in the airways with RLS was calculated. It showed a statistical significant association with prevalence of RLS (p value=0.001). No significant difference in the mean and SD values of PaO2 and PaCO2 in patients with and without RLS was found (Table 6).

Among all the laboratory investigations we found a negative correlation between serum ferritin levels and RLS (r=-0.278) which was statistically significant (p value <0.001) (Table 7).

Table 7: Correlation of RLS with laboratory studies, spirometry and arterial blood gas readings of COPD patients

Variable	Correlation coefficient (r)	P value
Hb(gm/dL)	-0.114	0.05
PCV(%)	-0.079	0.178
MCH(pg)	-0.059	0.317
MCV(fL)	-0.092	0.117
MCHC(%)	-0.092	0.117
S.Ferritin(ng/mL)	-0.278**	<0.001*
Blood Glucose(mg/dL)	0.063	0.278
HbA1C(%)	0.069	0.236
S. Urea(mg/dL)	-0.003	0.953
S. Creat(mg/dL)	-0.089	0.127
FEV1/FVC	-0.412**	0.001*
PaO2(mmHg)	0.024	0.685
PaCO2(mmHg)	0.033	0.574
HCO3(mmol/L)	0.041	0.481

*p value < 0.05 – statistically significant
**Correlation is significant at the 0.01 level

Discussion

General baseline demographic characteristics included in our study were age, gender and smoking habits. A total of 294 patients were taken which included 229 (77.9%) males and 65 females (22.1%). Our study suggests that COPD is more common in males as compared to females. This may be

294 COPD because all these studies were done in India where smoking is more common among males than females. Most of the females with COPD in our study had biomass fuel exposure (13.3%) as the risk factor. As our hospital is situated in a hill state, many patients are still using biomass fuel as a cooking medium which is the major risk factor for COPD among the females. We could also not establish a significant difference in the prevalence of RLS based on gender (p =0.26).

Most of the patients in the study population were > 60 years of age (64.3%). Mean age 62.05 ± 10.32 years with ages ranging from 40 to 90 years. The prevalence of RLS did not vary in a statistically significant manner in the different age groups in our study (p=0.50).

Out of all the patients with COPD 252 (85.7%) were smokers which was similar to observations of Mahesh et al (15). We found no significant association of RLS with smoking (p value=0.21). Smoking was present in 49 (79%) with probable RLS and 43 (89.6%) patients diagnosed with definite RLS. Similar results were also reported by Lavigne et al (16). They surveyed 2,019 Canadians and did not find any difference in RLS prevalence between smokers and non-smokers.

We found that the prevalence of RLS in patients was 37.4% (among which 21.1% had probable RLS and 16.3 % had definite RLS). This is in stark contrast to a prevalence rate of 2.1% in general population(8) . We suggest that the prevalence rate in our study has better accuracy as we had a comprehensive exclusion criteria but due to not using the nerve conduction velocity study peripheral neuropathy could not be excluded, which is a limitation of our study. A prevalence study done by LoCoco et al (17) reported similar prevalence of RLS in COPD (36.8%) (p < 0.001) (7).

We categorized RLS into not RLS, probable RLS and definite RLS and we found that out of all the patients diagnosed with RLS, majority of the patients fall under the category of probable RLS which was 21.1% and 16.3% patients were diagnosed with definite RLS. Mandal et al (18) took a small number of patients (n=76) , out of which 20 (26.5%) patients with COPD were diagnosed with RLS. Their mean age group was similar to our study. They also did not find any significant association between RLS and treatment of COPD with add on therapy (theophylline).

We found a positive correlation between RLS and severity of COPD (r=0.395) which was statistical significant (p=0.001) which was also seen in a study done by Aras et al , who found a higher frequency of RLS symptoms in COPD patients (54.5%) in a retrospective study comprising 22 male patients with exacerbation of COPD (19). In contrast we took 294 patients prospectively irrespective of gender and COPD severity and duration. Their study population was small and also they took all the male patients. Moreover, their study was a retrospective study and there is chance of selection and recall bias, which was excluded in our study. There is an increased hypoxia and hypercapnia in patients with exacerbation of COPD which has been found to increase the symptoms of RLS. We also found a statistically significant positive correlation between degree of airflow limitation in the first second of forceful expiration and the presence of RLS (r=0.411, p=0.001) i.e. greater is the degree of airflow limitation greater is the prevalence of RLS. This can be explained by the association of COPD severity and RLS which was explained earlier, as degree of airflow limitation is directly related to COPD severity as described in the GOLD guidelines. Hypoxia and hypercapnia were found to have no significant association with RLS and its severity. However the effect on RLS symptoms by improvement in hypoxia and hypercapnia could not be assessed as this was a cross sectional study.

Another major finding was a statistical significant association between COPD duration and RLS (p=0.001). Similar findings were seen in a cross sectional study done by Kaplan et al (20). They studied 134 patients of COPD and compared with a control group. They found a statistical significant association of COPD duration with duration of RLS (r=0.817; p= 0.001). We suggest that early diagnosis of RLS and its early management along with COPD would improve the quality of life of these patients.

There was no significant association between COPD treatment and RLS prevalence, symptoms and severity (p value=0.13). Aras et al (19) also did not find any association of RLS symptoms with COPD treatment. They discussed the increased prevalence of RLS in COPD exacerbation which has been related to the effects of theophylline in the form of irritability and anxiety. We also found a borderline association of RLS in the patients who were started on add-on therapy which included theophylline, but we included all other add-on therapies in a single group, so the specific association of theophylline with RLS symptoms could not be evaluated.

We found that serum ferritin levels were significantly lower in patients with RLS and had a significant negative correlation with RLS (r=-0.278; p value <0.001) which was also found by Bryndis et al(21). They found borderline significance of RLS prevalence with low serum ferritin levels (p value= 0.07). Similarly, Cavalcante et al(22) also found a positive association between RLS and low serum ferritin levels. This suggests that serum ferritin levels should be measured in all the patients with RLS and iron stores play a role in the pathogenesis of RLS which has to be further evaluated. We did not find significant correlation of RLS with haemoglobin levels of the patients. In our study we could not perform detailed iron studies due to resource limited setting.

After a thorough available literature search we could only find a very few studies which had been done in Indian population for RLS and associated diseases. We could find a prevalence which was comparable to that of the western data, but a study in a larger number of patients needs to be done. This study would throw some light into the importance of screening of RLS in COPD patients which would improve the quality of life of the patients.

Conclusion

COPD is a common disease affecting more number of males compared to females in India where smoking is more common among males. There is an increased prevalence of RLS in COPD patients. The prevalence of RLS in COPD was 37.4 % in our study. Chances of developing RLS was found to be increasing with increased duration and severity of COPD. This helps to understand the importance of screening all the COPD patients for symptoms of RLS and if required to treat the symptoms. It is needed to study a larger population for finding more accurate prevalence of RLS in COPD in Indian population.

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Conflicts of interest

The authors declare that they have no competing interest regarding the publication of this study.

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