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A clinical study of restless leg syndrome from Northern India

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Abstract

Background: Restless leg syndrome (RLS) is an under-diagnosed and infrequently treated disease. Family history of RLS symptoms is considered a criteria for categorizing the type of RLS.

Methods: This study was a prospective study and included patients presenting with symptoms of RLS and fulfilling the RLS diagnostic criteria. These patients were divided into primary and secondary type according to age of onset, asymmetry in symptoms, presence of family history and comorbidities. Clinical features were studied and compared between both the groups. Predictors for response to drug therapy were assessed in both the groups. Data was analyzed using SPSS version 23. Categorical variables were compared using chi-square test and continuous variables were compared using student t-test. p value below 0.05 was considered significant.

Results: A total of forty-five RLS patients were included. Twenty patients were of primary RLS and twenty-five patients belonged to secondary RLS group. Clinical features varied in both the groups in term of age of onset of symptoms, asymmetry in symptoms, presence of co-morbidities. Family history of symptoms was present even in fifteen patients of secondary RLS. Female patients and family history of RLS irrespective of type of RLS shows better response to dopamine agonist.

Conclusion: The presence of family history in secondary RLS patients highlights the importance of detailed family history. This may also be an indicator that perhaps all the patients of RLS are genetically predisposed and presence of co-morbidities precipitates the symptoms making them secondary RLS. Therefore, family history may not be a clinical criteria in categorizing RLS as it is positive even in patients of secondary RLS.

Keywords: Restless leg syndrome, RLS, family history, drug response predictor

Introduction

Restless leg syndrome (RLS) is a common condition but often underdiagnosed because of varied symptoms. Prevalence of restless leg syndrome is 5% to 15 % in western [1, 2] and 0.1-2.3% in Asian population [3, 4]. Restless leg syndrome is defined as unpleasant sensation in limbs which gets aggravated by rest and relieved by walking, often being worse at night. The sensory symptoms varies from tingling, electric shock like sensation, insect crawling and pain which is difficult to differentiate from dysthesias [5]. Restless leg syndrome could be primary or secondary and latter is associated with pregnancy, diabetes mellitus, chronic kidney disease, iron deficiency and peripheral neuropathy and hemodialysis [6-8]. Clinical characteristics of both primary and secondary RLS differs. Primary RLS usually have family history, has slower progression, asymmetrical distribution of symptoms and earlier age of onset than secondary RLS.

In India, only few studies from cohort of sleep lab [9, 10], psychiatry department [11, 12] or movement disorder clinics [13]. Spectra of RLS differ according to settings like sleep lab, medicine clinics or movement disorder clinics depending on referral practices. There are few studies only regarding clinical spectrum, magnitude of problem, predictor of severity and disability because of RLS so this study was planned. We hereby describe clinical spectrum and response to treatment in two subgroups of RLS and tried to predict the severity and disability between both the groups. Primary and secondary RLS were categorized on the basis of three parameters that were age of onset, asymmetry in symptoms and positive family history for RLS [13]. Age less than 40 years, asymmetrical pattern of involvement and family history were primary RLS and presence of any comorbidities such as diabetes, chronic kidney disease, and peripheral neuropathy were categorized as secondary RLS.

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Material and Methods
Patient's selection: This study was done in a tertiary care teaching institute of North India.

Inclusion criteria
Patients fulfilling the criteria of restless leg syndrome according to modified IRLS [14] were enrolled from outpatient department from January 2015 to December 2015.

Exclusion criteria
Patients on neuroleptic medications, dementia, psychiatric disorders, vascular insufficiency in lower limbs were excluded.

Clinical spectrum
The demographic information like age, sex and family history were noted. Restless leg syndrome was classified as primary or secondary RLS.

The patients with positive family history, asymmetry in symptoms, younger age of onset and absence of other comorbidities were categorized as primary RLS.

The causes for secondary RLS like diabetes mellitus, chronic kidney disease (CKD), liver failure, pregnancy, peripheral neuropathy, iron deficiency anemia, intake of drugs likely to precipitate RLS were also noted. History of other chronic illness were recorded.

Details regarding age of onset, type of paraesthesia, distribution in various body part with pattern of involvement was documented using human body outline diagram.

Assessment of severity of RLS symptoms
The severity of RLS was graded on 0–10 rating scale as per the international restless leg syndrome rating scale (IRLS)/Wong Becker visual analogue scale was done (14) Sleep disturbance due to RLS was evaluated by the Epworth Sleepiness Scale (15) and Stanford sleepiness scale (16).

Response to drug therapy
Drug response was assessed using decreased severity in IRLS score and Clinical Global Impression. Patients having 50% improvement from baseline IRLS score were considered as responders to dopamine agonist. If patient fails to respond over a duration of 1 month then second line

drugs in form of pregabalin was added. Adverse effect if any were noted. Supplementation of iron, folate or vitamin B12 was done if required.

The RLS cohort was divided on the basis of age of onset of symptoms, family history and asymmetry of symptoms into primary and secondary RLS. These features were than compared in both the groups. Associated comorbidities were noted.

The statistical analysis was done using SPSS version 19. Continuous variables like age, duration of RLS were compared in both group using student t-test the categorical variables like family history, asymmetry were compared using chi-square test and two tailed p value of less than 0.05 was considered significant.

Results
Demographics
The results are based on 45 patients. Out of these forty-five patients, 20 (44.5%) were males and 25 (55.5%) were females. Mean age was 42.72+_12.9 years, (range 15-72) years. Family history of RLS symptoms was positive in 26 (57.8%). (Table-1)

Distribution of RLS symptoms
The RLS symptoms were symmetrical in 27(60%) and asymmetrical in 18 (40%) patients. Out of 45 patients the distribution of symptoms involving various body parts was as follows. (Table-1)
- Upper limb 12 (26.7%)
- Lower limb 26(57.8%)
- Trunk 7(15.6%)
- Back 3 (6.7%)

Age of onset and type of symptoms have been described in detail further in both the RLS group patients.

Comorbidities associated with RLS
Diabetes mellitus was present in 15 (33.3%) patients, chronic kidney disease in 6 (13.3%), peripheral neuropathy in 3 (6.6%), radiculopathy due to prolapsed intervertebral disc in one patient (2.2%). Migraine was present in 5 (11.1%) patients and Parkinson's disease in 1 (2.2%). Iron deficiency anemia was found in 10 (22.2%) patients and hypothyroidism in 8 patients (17.7%).

Table 1: Comparison of demographic profiles and symptomatology of primary and secondary RLS.

	Primary RLS (N =20)	Secondary RLS (N= 25)	*P* Value
Age	42.05+_11.58	51.67+_13.28	0.02
Asymmetry	14/20	5/25	0.001
Upper Limb Involvement	13/20	5/25	0.02
Trunk Involvement	6/20	1/25	0.001
Family History	11/20	15/25	0.49
Comorbidities	0/20	25/25	0.001

Clinical characteristics of primary and secondary RLS patients
Primary RLS
Out of 45 patients 20 (44.4%) were of primary RLS. Family history of RLS was present in 11 patients (53%). Age of the patients ranged between 18 and 55 years and age of onset of symptoms 15 and 55 years. Mean age was 42.05± 11.58 years. Out of 20 patients, 11 were females (55%) and 9 were males (45%).The RLS symptoms were distributed symmetrically in 14 patients (70%). Along with pain and

paraesthesia in lower limbs, 65% and 35% patients had paraesthesia in upper limb and trunk. Duration of symptoms ranged from less than 1 year in 1 patient, 1-5 years in 14 patients, 6-10years in 4 patients and more than 10 years in 1 patient.

Majority of these patients used methods like massaging their limbs, tying them with rope or bandage and walking around and avoiding sitting or lying still, in order to get some relief in RLS symptoms.

Examination did not reveal any abnormal findings and routine blood investigations were normal.

Sleep pattern was assessed using SSS and ESS. The disturbance in sleep pattern was delay in onset of sleep, sleep fragmentation, difficulty in falling asleep once awaken. Only one patient had difficulty in keeping wide awake and alert although no history of excessive day time sleepiness.

Secondary RLS
Secondary RLS patients were further divided into patients with positive family history and without positive family history. Number of patients with secondary RLS was 25(61%), out of which 15(60%) patients had family history of RLS.

Secondary RLS without family history
Total of 10 patients were registered under this category, out of which 4 were females and 6 were males. Mean age of patients in this group was 50±13.7 years with minimum age of 34 years and maximum of 76 years. Age of onset of RLS symptoms ranged from 30 to 52 years and mean age of symptoms onset was 43.6±6.94 years. Duration of symptoms ranged from less than 1 year in 6 patients (60%) to 1-5 years in 4 patients (40%).Pattern of symptoms were symmetrical in all the patients. Multiple symptoms were present in form of pain and paraesthesia involving feet most commonly, followed by thigh and back of legs. However, no truncal or upper limb involvement was noted.

Comorbidities associated with these patients were diabetes mellitus in 7(70%), hypothyroidism in 5 patients (50%), CKD in 3 patients (30%),iron deficiency anemia in 4 patients(40%) and multiple comorbidities like diabetes, CKD, iron deficiency anemia in 5 patients (50%).

Secondary RLS with positive family history
This consisted of total 15 patients out of which 10 (66.7%) were female and 5 were males (33.4%). Mean age in this group was 51.6 ±13.48, maximum age was 82 and minimum was 37 years respectively. However, the age of onset was 48.6±16.1 years and minimum age was 26 years and maximum was 74 years. Family history was positive in all the patients. Duration of symptoms less than 1 year in 2 patients that is 13.3%,1-5 years in four patients (26.6%), 6-10 years in 6 patients (40%),11-15 years in 2 patients (13.3%) and only one patient had symptoms duration of more than 15 years. Distribution of pain and paraesthesia involved feet, front and back of legs and thighs in 6(60%) patients also had involvement of upper limbs in 5 patients (33.3%) and one patient had truncal involvement. Pattern of involvement was symmetrical in 10 patients (66.6%) and 5 patients (33.4%) had asymmetrical involvement. Comorbidities were noted majority being diabetes (60%), followed by iron deficiency anemia in (33.3%) followed by CKD. Further analysis between two groups i.e. primary and secondary RLS did not show any significant difference in term of investigations and various scales used to determine the severity of RLS symptoms. (Table 2).

Table 2: Comparison of various scales/score between two RLS groups by using independent t test

Variables (scales/scores)	P value using independent t test
Wong becker	0.40
IRLS	0.82
SSS	0.44
EPS	0.25

Analysis of the factors affecting symptoms relief and response to drug
Drug response assessment showed significant correlation with sex, symptoms, family history, presence or absence of sleep disturbance, distribution of symptoms, severity of symptoms using various scales, comorbidity and type of RLS (p value less than 0.001).

Discussion
In this study of forty-five RLS patients, we tried to emphasise on demographic profile of RLS patients overall, as well as further categorization into two groups of primary and secondary RLS. On comparing both the groups, significant difference was seen in terms of age of onset of disease (younger age of onset was seen in primary compared to secondary RLS), which is in accordance with past studies showing younger age of onset in primary RLS because of hereditary causes. Various cut-off age has been considered like 45 years, 40 years as well as 36 years in previous studies [13-17]. Similarly, significant difference was seen in clinical symptoms which showed asymmetry of symptoms, was again common in primary RLS patients with predominant upper limb and truncal symptoms. The reason for this asymmetry and upper limb involvement is because of involvement of upper levels of neuronal system and not only the lumbar spinal cord [18].

RLS pattern of inheritance described is mainly autosomal dominant along with phenomena of anticipation and high penetrance, intra-familial as well as interfamilial variation is present [13-17]. Although positive family history is considered as a feature of primary RLS, we had many patients of secondary RLS who had positive family history. In majority of patients there was inheritance suggestive of vertical transmission and variability of symptoms in same family. Thus the concept of family history in classification of RLS seems ambiguous. Presence of family history even in patients with presence of comorbidities may favour the concept that if a genetically predisposed perso who otherwise would have classified as primary becomes secondary RLS if he develop peripheral neuropathy, diabetes, iron deficiency anaemia or any other causes of secondary RLS.

Through this study we would like to highlight that the features of primary and secondary RLS overlaps and only the presence of co-morbidities differentiates both of them. In our patients with diabetes the duration was not long enough to cause peripheral neuropathy and hence it can be said that a person is usually genetically predisposed to RLS and its gets precipitated in presence of diseases mentioned above.

We also studied the factors affecting response to therapy. Female sex, presence of family history, asymmetry of

symptoms, absence of sleep disturbances and lower disease score showed better treatment response to first line drugs like dopamine agonist. However secondary RLS patients did required second line add on drugs. The reason for better response in presence of family history is not well understood. It may be possible that genetic predisposition is more likely associated with impaired dopaminergic pathway thus response to dopamine agonist is better.

Conclusion

This study shows the importance of detailed family history even if secondary RLS is suspected. The presence of co-morbidities is the only difference between the type of RLS. Response to treatment is better in females and patients with presence of family history.

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