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Original Research Article

Prevalence and risk factors of restless legs syndrome in patients of migraine without aura

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ABSTRACT

Background: An association between migraine and Restless Legs Syndrome (RLS) has been proposed due to shared dopaminergic dysfunction. Both have substantial effects on the quality of life. Identifying co morbidities of migraine helps in optimizing patient management. Objectives To study the prevalence of RLS in patients of migraine without aura, and associated co morbidities of RLS.
Methods: This was a hospital based prospective observational study. All patients diagnosed as Migraine without aura as per ICHD-3 criteria completed the questions regarding migraine headache, Migraine Disability Assessment (MIDAS) questionnaire, Hospital Anxiety and Depression Scale (HADS), Pittsburgh Sleep Quality Index (PSQI) and International RLS Study Group (IRLSSG) Rating Scale. RLS was diagnosed using the IRLSSG criteria. Serological investigations were done to look for secondary causes of RLS.
Results: Out of 200 consecutive patients of migraine without aura were included in the study over a period of 18 months. Frequency of RLS was 13.5% (n=27). All patients had primary RLS. Mean PSQI score was higher in the patients of migraine without aura with RLS than in non RLS patients of migraine without aura (3.30±2.66 vs 2.24±2.03 p≤0.0168). Poor sleep quality, anxiety, depression was found in 9%, 8% and 2.5% respectively in patients of migraine without aura.
Conclusions: An association between migraine without aura and RLS was demonstrated. Migraine without aura was associated with increased frequency of poor sleep quality, anxiety and depression.

Keywords: Hospital anxiety and depression scale, International restless legs syndrome study group rating scale, Migraine without aura, Migraine disability questionnaire, Pittsburgh sleep quality index, Restless legs syndrome

INTRODUCTION

Migraine is the most common headache related neurological cause of disability in the world. It affects approximately 25.2% of the general population in India over the period of one year.[1] The sensory sensitivities that are characteristic of migraine are probably due to dysfunction of monoaminergic sensory control systems located in the brainstem and hypothalamus. Restless Legs Syndrome (RLS) is a sensorimotor disorder. The prevalence of RLS is 2.1% in Indian general population.[2] It has substantial impact on sleep as well as on health-related quality of life. Recently, RLS has been found to be a risk factor for cardiovascular diseases.[3]

Migraine and RLS both have impact on quality of life. Migraine is disorder of dopamine hypersensitivity; dopamine antagonists are used in treatment of migraine whereas dopamine agonists are used in the treatment of RLS. There are very few studies about co morbidities associated with migraine. In this study authors are studying prevalence of RLS in migraine patients without

aura and looking for risk factors for RLS and other co morbidities associated with it. Only patients of migraine without aura were included to make study population homogenous.

METHODS

This study was a hospital based prospective observational study carried out at hospitals attached to the Bangalore Medical College and Research Institute, Bangalore between the periods January 2016 to July 2017. After obtaining clearance and approval from the institutional ethics committee and written informed consent of the patients, 200 patients of migraine without aura diagnosed according to ICHD - 3 criteria 4 attending the OPD were screened for RLS over a period of eighteen months from January 2016 to July 2017.

Inclusion criteria

- Migraine without aura according to the ICHD-3 criteria.
- Age ≥18 years at the time of the study

Exclusion criteria

- Patients who were less than 18 years of age
- Patients with subtypes of migraine other than migraine without aura
- Patients with non migrainous headache

Patients of RLS were diagnosed according to International Restless Legs Syndrome Study Group (IRLSSG) criteria. Patients demographic data, characteristics of migraine associated co-morbidities (sleep impairment, affective symptoms), prophylactic medications, and systemic illness were enquired and entered in the proforma.

Migraine severity and frequency were assessed by the migraine disability assessment scale (MIDAS). Severity of RLS was assessed by the IRLSSG rating scale. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) and those with PSQI score ≥6 were considered as poor sleepers. Presence of co-morbid depression and anxiety were assessed using hospital anxiety and depression scale (HADS). HADS A or HADS-D ≥11 was takes as significant to increase the specificity of the diagnosis of anxiety or depression. Patients, who were found to have RLS, were investigated for secondary causes of RLS like anemia, hypothyroidism and azotemia. Patient was considered to have anemia if hemoglobin is <13 among males, <12 among females. Among thyroid hormonal profile TSH: 0.4-5 mu/L; Free T4:10-23; Free T3:5.4-12.3 was considered normal. Creatinine >1.6 was taken as significant for azotemia.

Statistical analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements were presented as Mean±SD (Min-Max) and results on categorical measurements were presented in Number and percentage. All statistical analyses were performed using Epi-Info 7.2 software for windows. Parametric data were compared using independent t-test and ANOVA. All the categorical data were compared by using chi-square test. A value of $p<0.05$ was considered statistically significant.

RESULTS

Out of 200 persons with migraine, 27(13.5%) had symptoms of RLS; most of the patients were females 20(74.1%); mean age of the RLS patients was 32.41± 8.78 years. Characteristics of the study population with and without RLS. (Table 1)

Tables 1: Comparison of patients of migraine without aura with and without RLS.

No.	Study parameters		RLS	No RLS	p value
1	Number of patients		27	173	
2	Mean age (years)		32.41±8.78	31.91±10.0	0.8064
3	Female patients, n (%)		20(74.07)	124(71.68)	0.7963
4	Headache, N (%)	Unilateral	16(59.26)	112(64.74)	0.5811
		Bilateral	11(40.74)	61(35.26)	
5	Triggers n%		23(85.19)	136(78.61)	0.4314
6	Mean duration of each attack in hrs.		7.52±5.06	11.64±13.71	0.1246
7	Midas mean score		14.04±11.36	11.54±9.63	0.2226
8	PSQI (mean score)		3.30±2.66	2.24±2.03	0.0168*
9	PSQI ≥6, N (%)		04(14.81)	14(8.09)	0.2572
10	HADS A ≥11		2(7.4)	14(8.1)	0.9029
11	HADS mean score		4.33±3.68	4.04±3.56	0.6955
12	HADS D ≥11		1(3.7)	4(2.31)	0.6667
13	HADS D mean score		4.14±3.24	3.07±2.91	0.0817
14	Family history of migraine		04(14.81)	20(11.56)	0.6284
15	Medication		03(11.11)	27(15.61)	0.5429

Mean IRLSSG rating scale is 10.85±3.43 and median is 11. 48.15% of patients had mild RLS and 51.85% had moderate severity. All 27 patients had primary RLS. On comparing the migraine patients who had RLS with those who were not having RLS, mean PSQI score was significantly higher among patients of RLS (3.30±2.66 versus 2.24±2.03, p=0.0168).

Family history of migraine, presence of triggers, number of attacks per month, prophylactic drugs, MIDAS score, presence of anxiety and depression were not found to be significant for the occurrence of RLS in migraine patients without aura.

Among 27 RLS patients 3 were taking prophylactic medications (11.11%, all 3 were taking Flunarizine) and among 173 without RLS patients 27 were taking prophylactic drugs (15.61%, amitriptyline- 14 patients; flunarizine- 9 patients; propranolol, topiramate, divalproex sodium each in 2 patients). p value is not significant for prophylactic medication for occurrence of RLS among patients of migraine without aura (p=0.5429) in this study. On comparing patients with mild RLS to those with moderate RLS, there was no significant difference in the mean MIDAS score, PSQI Scores, HADS-A and HADS-D scores.

Number of patients with Poor sleep (PSQI score >6), anxiety (HADS A ≥11), depression (HADS D ≥11) were higher in RLS group but it was statistically not significant.

Among patients of migraine without aura, 18(9%) were poor sleepers. Among them 4 patients (22.2%) had RLS. Patients who were poor sleepers (PSQI score ≥ 6) were of higher age (38.33±8.49 vs. 31.35±9.75 p=0.0038), had higher incidence of anxiety (4, 22.22% vs. 12, 6.59% p=0.0197) and depression (2, 11.11% vs. 3, 1.65% p=0.0142). The characteristics of patients with poor sleep quality. (Table 2)

Table 2: Characteristics of patients with poor sleep quality (PSQI ≥6).

No		PSQI ≥6 (N=18)	PSQI <6 (N=182)	p Value
1	RLS, N (%)	4(22.22)	23(12.64)	0.2572
2	Age (years)	38.33±8.49	31.35±9.75	0.0038*
3	Female patients, N (%)	13(72.22)	131(71.98)	0.9824
4	Midas mean score	15.22±10.17	11.55±9.83	0.1335
5	Unilateral, N (%)	12(66.67)	116(63.74)	0.8048
6	HADS-A ≥11, N (%)	4(22.22)	12(6.59)	0.0197*
7	HADS-D ≥11, N (%)	2(11.11)	3(1.65)	0.0142*

About 16(8%) patients had anxiety (HADS A ≥11). Poor sleep quality (p=0.0197) and higher mean MIDAS score (3.38±2.80 vs. 2.3±2.07 p=0.0286) were associated with anxiety. The characteristics of patients with anxiety. (Table 3)

Depression was found in 5(2.5%) of migraine patients. It was associated with poor sleep quality (2(40%) vs. 16 (8.2%) p=0.0142). The characteristics of patients with depression. (Table 4)

DISCUSSION

Frequency of RLS is higher in patients of migraine without aura in this study (13.5%) as compared to 2.9% in the general population.[2] Previous studies found frequency of RLS of 13.7-16.1% in patients with migraine with pooled prevalence being 18.8% among individuals with migraine with aura and 18.5% among individuals with migraine without aura.[5,6] All the patients had primary RLS. This finding explains association between RLS and migraine and shared central dopaminergic dysfunction.

On comparing factors influencing RLS among patients of migraine without aura only mean PSQI score was statistically significant (3.30±2.66 versus 2.24±2.03, p=0.0168). In the studies conducted by Chen et al, and Suzuki et al, who has included all types of migraine patients, risk factors for development of RLS found was higher mean MIDAS score and higher mean PSQI global score.[7,8] Valente et al, showed that PSQI score was higher in migraine patients with RLS as compared to migraine patients without RLS.[5] They also showed that family history and serotonergic overload were significantly associated with RLS occurrence. In this study mean PSQI score was the only parameter among patients of migraine without aura, which was statistically associated with development of RLS.

Family history of migraine and prophylactic drugs were not found to be associated with the occurrence of RLS in patients of migraine without aura. This study included only patients of migraine without aura in order to investigate a homogenous patient population.

As compared to another study by Karthik N which also revealed an increased occurrence of RLS in migraine

without aura (32.2%) as compared to age and gender matched healthy controls (5.6%), the present study used the IRLSSG criteria to identify cases of RLS.[9] Table 5 shows comparison of this study with that of Chen et al, and Suzuki et al.[7,8]

Table 3: Characteristics of the patients with anxiety (HADS-A score ≥11).

No			HADS -a score ≥11 (n=16)	HADS -a score <11 (n=184)	p value
1	Mean age (years)		31.06±8.64	32.06±9.94	0.6972
2	Gender, N (%)	Female	13(81.25)	131(71.20)	0.3903
		Male	03(18.75)	53(28.80)	
3	Laterality, N (%)	Unilateral	12(75)	116(63.04)	0.3392
		Bilateral	04(25)	68(36.96)	
4	RLS, N (%)		02(12.5)	25(13.59)	0.9029
5	MIDAS mean score		17.06±10.42	11.43±9.74	0.0286*
6	PSQI ≥6, N (%)		04(25)	14(7.61)	0.0197*
7	PSQI mean score		3.38±2.80	2.3±2.07	0.0536
8	Migraine attacks per month		8.06±5.12	6.21±4.47	0.1181
9	Family history of migraine		02(12.5)	22(11.96)	0.9488

Table 4: Characteristics of the patients with depression (HADS-D score ≥11).

No			HADS-D score ≥11 (n=05)	HADS-D score <11 (n=195)	p value
1	Mean age (years)		32.40±14.08	31.97±9.75	0.9234
2	Gender, N (%)	Female	04(80)	140(71.79)	0.6866
		Male	01(20)	55(28.21)	
3	Laterality, N (%)	Unilateral	03(60)	125(64.10)	
		Bilateral	02(40)	70(35.90)	
4	RLS, N (%)		01(20)	26(13.33)	0.6667
5	MIDAS mean score		14.20±5.85	11.82±9.97	0.5963
6	PSQI ≥6, N (%)		02(40)	16(8.20)	0.0142*
7	PSQI mean score		3.40±3.36	2.36±2.11	0.2851
8	Migraine attacks per month		5.2±2.68	6.39±4.58	0.5642
9	Family history of migraine		01(20)	23(11.79)	0.5772

Table 5: Comparison with other studies.

Patient characteristics	Chen et al[6](n-772)			Suzuki et al[10] (n-262)			This study (n-200)		
	RLS N-88	No RLS N-684	P value	RLS N-36	No RLS N-226	P value	RLS N-27	No RLS N-173	p value
Mean age (years)	40.1±12.7	42.4613.4	0.14	37.0±12.7	38.4±13.0	0.544	32.41±8.78	31.91±10.0	0.8064
Female gender n (%)	76 (86.4%)	568(83%)	0.43	32(8.9)	183(81.0)	0.350	20(74.7)	124 (71.68%)	0.7963
Unilateral	69 (78.4%)	495 (72.4%)	0.23				16(59.6)	112(64.7%)	0.5811
Mean MIDAS score	42.9±52.2	30.86±39.6	0.04	30.0±37	17.1±24.8	0.016	14.04±11.36	11.54±9.63	0.2226
PSQI mean global score	11.1±4.1	8.9±4.0	0.001	8.4±3.6	5.2±3.1	<0.0001	3.30±2.66	2.24±2.03	0.0168
PSQI ≥6 n (%)				28(77.8)	93(41.2)	<0.0001	4(14.81)	4(8.1%)	0.2572
Family history of migraine n (%)				27(75.0)	163(72.1)	0.915	4(14.8)	20(11.56)	0.6284
Depression	12 (13.6%)	68(9.9%)	0.28				1(3.7%)	4(2.31%)	0.6955

In this study anxiety was present in 16 patients of migraine without aura, which constitutes frequency of 8%. Presence of anxiety was associated with higher mean MIDAS score (17.06±10.42 versus 11.43±9.74, p=0.0286) and poor sleep quality (25% versus 7.61%, p=0.0197).

In this study depression was present in 5(2.5%) patients of migraine without aura. Presence of depression was associated with poor sleep quality (40% versus 8.2%, p=0.0197). Lampl et al, in their study regarding psychiatric co-morbidities in migraine patients reported anxiety in 19.1% and depression in 6.9% of the patients.[10] Patients with migraine frequently exhibit anxiety and depressive disorders; and sleep disturbance is one diagnostic criterion of depression and anxiety disorders. This study highlights the complex association of sleep impairment, anxiety and depression in patients of migraine. The positive association between RLS and migraine has been hypothesized to be due to a shared dopaminergic dysfunction in the hypothalamic A11 nucleus. By binding to D2-like receptors, the A11 nucleus inhibits firing in the Trigemino Cervical Complex (TCC), which is a key region for migraine information transmission from the head and or facial structures to the hypothalamus and brain; the A11 nucleus also sends direct inhibitory projections to preganglionic sympathetic neurons and the dorsal horn as well as anterior horn in the spinal cord, which innervates skeletal muscle.[11] Therefore, dysfunction of the A11 dopaminergic nucleus facilitates firing in the TCC, increases sympathetic activity in the spinal cord, and irritates the muscle spindles, causing or worsening migraine and RLS.

Strengths of the study were the following: ICHD 3 criteria were used to diagnose migraine, IRLSSG criteria was used to diagnose RLS. While diagnosing anxiety and depression HADS scoring ≥11 is considered to increase the specificity of anxiety or depression. All the patients were interviewed in person.

Limitations of the study were selection bias as the study population was not stratified; controls were not included in the study, so the internal comparison is not possible.

CONCLUSION

This study demonstrated an association between migraine without aura and RLS. All the patients had primary RLS. Poor sleep quality is significantly associated with RLS. Higher frequency of anxiety and depression was found in patients of migraine without aura.

The therapeutic implication of this study is that while treating migraine without aura, one should enquire regarding RLS. As migraine is frequently associated with poor sleep quality, anxiety and depression these factors need to be taken into account while treating these patients.

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REFERENCES

1. Kulkarni G, Rao G, Gururaj G, Subbakrishna DK, Steiner T, Stovner LJ. The prevalence and burden of migraine in india: results of a population-based study in Karnataka state. J Headach pain. 2014 Dec;15(1):B18).
2. Panda S, Taly AB, Sinha S, Gururaj G, Girish N, Nagaraja D. Sleep-related disorders among a healthy population in South India. Neurol Ind. 2012 Jan 1;60(1):68.
3. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurol. 2008 Jan 1;70(1):35-42.
4. Headache Classification Committee of the International Headache Society. The international classification of headache disorders. 3rd ed. Cephalalgia. 2013;33:629-808.
5. Valente M, Janes F, Russo V, Fontana A, Travanut A, Sommaro M, et al. Prevalence of Restless Legs Syndrome in Migraine Patients: A Case-Control Study. Analysis of Risk Factors for Restless Legs Syndrome in Migraine Patients. Headache: J Head Face Pain. 2017 Jul;57(7):1088-95.
6. Yang X, Liu B, Yang B, Li S, Wang F, Li K, et al. Prevalence of restless legs syndrome in individuals with migraine: a systematic review and meta-analysis of observational studies. Neurol Sci. 2018 Nov 1;39(11):1927-34.
7. Landy S, Kaniecki R, Taylor F. Chen PK, Fuh JL, Chen SP, et al. Association between restless legs syndrome and migraine. J Neurol Neurosurg Psychiatry. 2010;81:524-8.
8. Suzuki S, Suzuki K, Miyamoto M, Miyamoto T, Watanabe Y, Takashima R, et al. Evaluation of contributing factors to restless legs syndrome in migraine patients. J Neurol. 2011 Nov 1;258(11):2026-35.
9. Karthik N, Kulkarni GB, Taly AB, Rao S, Sinha S. Sleep disturbances in 'migraine without aura'-a questionnaire-based study. J Neurol Sci. 2012 Oct 15;321(1-2):73-6.
10. Lampl C, Thomas H, Tassorelli C, Katsarava Z, Laínez JM, Lantéri-Minet M, et al. Headache, depression and anxiety: associations in the Eurolight project. J head pain. 2016 Dec;17(1):59.
11. Charbit AR, Akerman S, Goadsby PJ. Dopamine: what's new in migraine? Curr Opin Neurol. 2010 Jun 1;23(3):275-81.

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