

Proportion of rapid eye movement sleep related obstructive sleep apnea (REM related OSA) in patients with sleep disordered breathing: A cross sectional study

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ABSTRACT

Background and Objectives: Obstructive sleep apnea (OSA) during rapid eye movement (REM) stage of sleep is gaining importance in recent years. This study was done to determine the proportion of REM-related OSA and its associated polysomnographic features. **Methods:** One hundred forty-two patients were included in the study. REM-related OSA was defined based on previously established broad and strict criteria (REM apnea–hypopnea index [AHI]/non-REM [NREM] AHI ratio ≥ 2 and REM AHI >5 with NREM AHI <5 , respectively), and its association with polysomnographic features was studied using appropriate statistical tools. **Results:** The proportion of REM-related OSA in the study was 56.3% and 25.3% as per broad and strict criterion, respectively. The REM-related OSA group had a mean younger age (47.4 ± 13.2 years) as compared to NREM-related OSA group (52.6 ± 15.8 years). Females (34 out of 45; 75.6%) were more likely to have REM-related OSA as compared to males (46 out of 107; 47.4%). Supine AHI, arousal index, oxygen desaturation index, length of the longest event, and the lowest oxygen saturation recorded during sleep had a significant association with REM-related OSA. 74% of patients with overall AHI <5 and 87% patients with overall AHI 5 to 15 satisfied the criteria for REM-related OSA as per broad criterion. **Conclusion:** REM-related OSA was quite prevalent in the study population (56.3%) and was more common in the mild and moderate severity subgroups of OSA.

KEY WORDS: Obstructive sleep apnea, polysomnography, rapid eye movement sleep, sleep apnea syndromes

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INTRODUCTION

Human sleep is divided into several stages which are defined primarily by electroencephalographic criteria and can be broadly divided into two main stages: rapid eye movement sleep (REM) and non-REM (NREM) sleep.^[1]

Obstructive sleep apnea (OSA) is a sleep disorder that involves complete cessation or a significant reduction in airflow in the presence of breathing effort, which occurs as a result of the inadequate motor tone of the upper airway dilator muscles. This results in recurrent episodes of partial (hypopnea) or complete (apnea) cessation of airflow through upper airway, leading to

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recurring episodes of hypoxemia and hypercapnia, and sleep fragmentation.^[2] The diagnostic strategy includes a sleep-oriented history and physical examination, followed by objective testing. Overnight, facility-based, and attended polysomnography (Level 1 PSG) remains the gold standard for the diagnosis of OSA. The apnea-hypopnea index (AHI) is the average number of apneic and hypopneic events per hour. This index derived from the PSG is used not only to diagnose OSA but also to determine its severity. OSA is classified according to AHI as mild, moderate, or severe. AHI ≥ 5 – <15 events per hour of sleep is graded as mild, AHI ≥ 15 – ≤ 30 events per hour of sleep as moderate, and severe OSA is AHI >30 events per hour of sleep.^[3,4]

Although upper airway collapse can occur in REM and NREM sleep, the loss of muscle tone during REM sleep further reduces pharyngeal muscle activity and this accentuates the chance for upper airway collapse in this stage of sleep. Thus, REM sleep in patients with OSA is associated with an increased risk and frequency of obstructive events as compared to NREM sleep. The term REM sleep-related OSA has been coined to denote the events that occur predominantly or exclusively during the REM stage of sleep.^[5]

There is a significant heterogeneity in defining REM-related OSA. The most commonly used and widely accepted criteria^[5-7] in several studies related to REM-related OSA are as follows.

Broad criterion

- (REM AHI)/(NREM AHI) ratio ≥ 2 .

Strict criterion

- REM AHI >5 with NREM AHI <5 ; and >10.5 min of REM sleep
- REM-AHI/NREM-AHI ratio ≥ 2 with NREM-AHI <15 , and >10.5 min of REM sleep.

Patients with REM-related OSA tend to have an overall low AHI and the relative contribution of sleep-disordered breathing (SDB) events during the REM stage to the overall AHI tends to be smaller, due to the disproportionately lower percentage of REM sleep as a function of total sleep duration. However, it is increasingly being recognized that SDB events during REM sleep are generally longer than those during NREM sleep. They are often associated with more significant hypoxemia and therefore they may have more adverse effects. Furthermore, REM sleep is also associated with increased sympathetic activation, which may further increase the physiologic consequences, and recent studies indicate that REM-related OSA may be “independently” associated with adverse cardiovascular, metabolic, and neurocognitive outcomes. Hence, it is critical to know the prevalence of REM-related OSA in our population and to study whether treating it will lead to better patient outcome.^[8]

MATERIALS AND METHODS

Objectives

The primary objective of the study was to determine the proportion of patients with REM-related OSA as defined as REM AHI/NREM AHI ratio ≥ 2 (broad criterion). The secondary objectives were to determine the proportion of patients with REM-related OSA in subgroups of overall AHI <5 (no OSA) and overall AHI 5–15 (mild OSA) and to determine the polysomnographic features associated with REM-related OSA as per both broad and strict criteria.

Study design, setting, and population

This was a cross-sectional study conducted in a tertiary care hospital in Thiruvananthapuram, Kerala, from October 2019 to June 2020. All consecutive outpatients and inpatients aged ≥ 15 years, who underwent a Level 1 PSG during this period, and who were willing to give consent for the study were included. Patients with no recorded REM sleep and patients who were diagnosed with sleep disorders other than OSA at the end of Level 1 PSG were excluded.

Clearance was obtained from the institutional human ethics committee and confidentiality of the participants was maintained.

Methodology

The sample size calculated was 140 based on previous studies on the prevalence of REM-related OSA.^[9] 142 patients who satisfied the inclusion and exclusion criteria were enrolled into the study after obtaining informed consent. Data on age, gender, body mass index, neck circumference, presence of comorbidities, and Epworth sleepiness scale score were obtained by personally interviewing the patients. All the patients underwent PSG in the in-house quality-controlled Level 1 sleep lab, using the PSG system by XLTEK BRAIN MONITOR (Natus Medical Inc., Pleasanton, CA, USA). Data on polysomnographic variables were overall AHI, REM AHI, NREM AHI, REM AHI/NREM AHI ratio, supine AHI, longest recorded event in REM and NREM sleep, sleep latency, sleep efficiency, snoring index, oxygen desaturation index, arousal index, lowest recorded oxygen saturation (SpO_2), limb movement index, and length of REM sleep as a percentage of total sleep. These were obtained from the PSG report data generated at the end of the Level 1 PSG. All the data were collected in a structured pro forma and were analyzed at the end of the study.

Statistical analysis

All the collected data were entered into MS Excel and analyzed using Epi Info version 7.2.2.6, Centers for Disease Control and Prevention (CDC) Atlanta, Georgia (US). Categorical variables were summarized as number (%) and continuous variables as mean and standard deviation. Proportion and 95% confidence limits were determined for REM-related OSA in the entire study cohort and in

subgroups of overall AHI <5 (no OSA) and overall AHI 5–15 (mild OSA). The association of qualitative variables with REM-related OSA was assessed using Chi-square test. The association with quantitative variables with normal and nonnormal distribution of data was assessed using the Student's *t*-test and Mann–Whitney U-test, respectively. *P* <0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

The age of the patients ranged from 15 to 83 years with a mean age of 49.7 (+14.6) years. The highest percentage (28.2%) of patients belonged to the age group of 40–49 years. Out of 142 patients enrolled in study, 97 (68.3%) were male and 45 (31.7%) were female. 56 (39%) of patients in our study population did not have any comorbidity. The most common comorbidity was systemic hypertension (33.8%), followed by diabetes mellitus (19%) and hypothyroidism (7%). The mean Epworth sleepiness score was 9.1 (+4.9) in the study population.

27 (19%) patients were found to have no OSA (overall AHI <5) and 115 (81%) patients had OSA (overall AHI >5). Among these 115 patients with OSA, 22% had mild OSA, 26% had moderate OSA, and 33% had severe OSA.

Outcomes of the study

The proportion of for REM-related OSA in our study population was 80 out of 142 patients (56.3%, 95% confidence interval [CI]: 48.1–64.5) as per the broad criteria of REM AHI/NREM AH ratio ≥2. This was the primary outcome of this study. The proportion of REM-related OSA as per broad criterion in the no OSA, mild OSA, and moderate OSA as per overall AHI was 74%, 87%, and 73%, respectively, and was reduced to 12.8% in the severe OSA group. The distribution of REM AHI in each severity subgroup of overall AHI and NREM AHI was also studied [Figures 1-3].

The REM-related OSA group had a mean younger age (47.4 ± 13.2 years) as compared to NREM-related OSA group (52.6 ± 15.8 years), and females (34 out of 45; 75.6%) were more likely to have REM-related OSA as compared to males (46 out of 107; 47.4%) in the study (*P* < 0.05). Among the polysomnographic variables that were studied, supine AHI, arousal index, oxygen desaturation index, lowest SpO₂, and length of longest event in REM and NREM sleep showed a significant association with REM-related OSA. There was no significant difference between the mean BMI, neck circumference, or the Epworth sleepiness score between the REM-related OSA and the NREM-related OSA groups as defined by the broad criterion [Table 1].

The proportion of REM-related OSA in our study upon using the strict definition criterion of REM AHI >5, NREM AHI <5, and REM sleep duration as a percentage

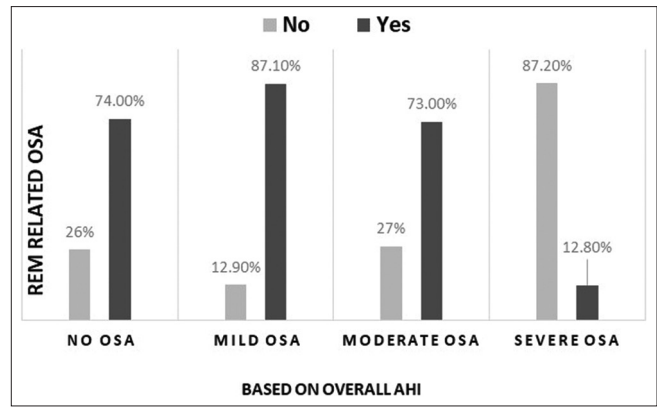


Figure 1: Proportion of patients with rapid eye movement-related obstructive sleep apnea (as per broad criterion) in each severity subgroup of overall apnea–hypopnea index

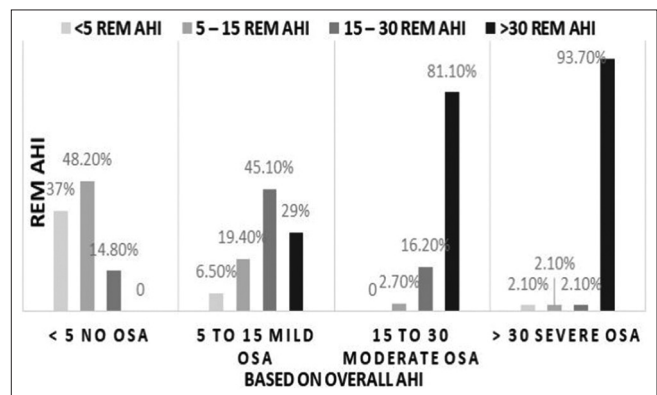


Figure 2: Distribution of rapid eye movement apnea–hypopnea index in each severity subgroup of overall apnea–hypopnea index

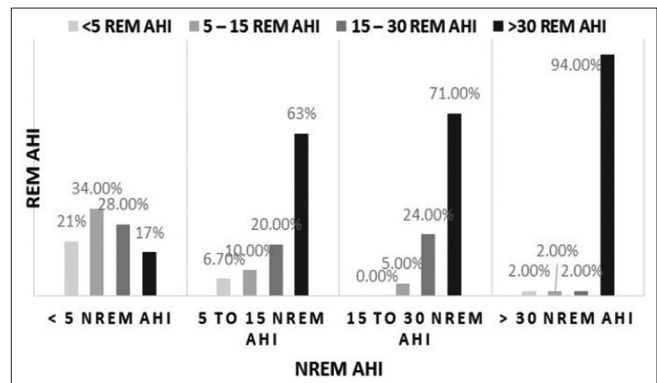


Figure 3: Distribution of rapid eye movement apnea–hypopnea index in each severity subgroup of nonrapid eye movement apnea–hypopnea index

of total sleep >5% was 25.4% (95% CI: 18.4–33.3). The proportion of REM-related OSA as per strict criterion in the no OSA, mild OSA, and moderate OSA category as per overall AHI was 62.9% (17 out of 27), 54.9% (17 out of 31), and 5.4% (2 out of 34), respectively. None of the patients in severe OSA category as per overall AHI satisfied criteria for REM-related OSA as per the strict definition criterion. The association of polysomnographic variables

Table 1: Association of variables with rapid eye movement-related obstructive sleep apnea (as per broad criterion)

Variable	REM-related OSA				P
	No (n=62)		Yes (n=80)		
	Mean±SD	Median (IQR)	Mean±SD*	Median (IQR) [#]	
Age	52.6±15.8	51 (39.75-65)	47.4±13.2	47 (40-58)	0.33*
BMI	30.7±6	29.7 (25.8-34.93)	29.8±4.9	29 (26-32.23)	0.32
Neck circumference	38.7±4.4	39 (35.75-42)	37.6±3.9	38 (34-40)	0.12
Epworth score	9.7±5.2	9 (7-13)	8.7±4.7	9 (4.75-12)	0.42
Supine AHI	47.7±34.3	44 (22.25-70.5)	14.7±14.1	10.4 (4.9-20)	<0.001 [#]
Longest REM event	43.8±20.3	46 (29-56)	38.9±17.2	36.5 (29-46.75)	0.06
Longest NREM event	49.1±43.1	42 (28.25-55)	32.9±20.9	30 (21-38)	<0.001 [#]
Snoring index	383.3±206.2	393 (210-541.75)	385±210.9	406 (203-531.75)	0.98
Arousal index	38.3±28.2	33.3 (12.98-55.95)	18.5±15.7	14.75 (7.45-21)	<0.001 [#]
Desaturation index	38.2±32.4	28.7 (10.13-61.15)	10.2±9.4	6.85 (3.73-14)	<0.001 [#]
Sleep efficiency	88.1±10	90.5 (83.75-96)	88.3±11	90 (84.8-97)	0.61
Sleep latency	5.6±6.3	2.9 (1.2-8.78)	9±14.1	4.1 (1.5-13)	0.28
Lowest SpO ₂	75.9±14	79 (65.75-88)	81.7±9.6	84.2 (78-89)	0.01 [#]
Limb movement index	18.4±19.2	11.8 (5.35-25.8)	13.1±17.3	7.5 (4.05-14.58)	0.04 [#]

*Student's *t*-test, significant at 0.05 level, [#]Mann-Whitney U-test, significant at 0.05 level. SD: Standard deviation, IQR: Interquartile range, OSA: Obstructive sleep apnea, REM: Rapid eye movement, BMI: Body mass index, AHI: Apnea-hypopnea index, NREM: Non-REM

Table 2: Association of variables with rapid eye movement-related obstructive sleep apnea (as per strict definition)

Variable	REM-related OSA strict definition				P
	No (n=106)		Yes (n=36)		
	Mean±SD	Median (IQR)	Mean±SD*	Median (IQR) [#]	
Age	50.2±15.6	50 (39-61)	48.2±10.8	46 (40-57)	0.47
BMI	30.7±5.7	30 (26.15-34.6)	28.5±3.9	28.45 (25.08-31.38)	0.03*
Neck circumference	38.5±4.2	39 (35-41)	36.8±3.9	37.5 (34-40)	0.03*
Epworth score	9.4±4.8	9 (7-12)	8.3±5.3	8 (3-11)	0.17
Supine AHI	36.9±31.1	27 (14-55)	6.9±4.7	6.1 (4-8.8)	<0.001 [#]
Longest REM event	42.9±19.9	41 (30-54)	35.2±12.8	33 (27.25-43)	0.03 [#]
Longest NREM event	44.3±36.7	39 (28-51)	26±10.8	24 (19-34)	<0.001 [#]
Snoring index	402±209.6	411.5 (246.75-564.5)	331.9±197.1	313.5 (154.75-499.5)	0.08
Arousal index	31.3±25.4	24.5 (12.55-44.25)	14.8±13.7	11.15 (7.33-16.83)	<0.001 [#]
Desaturation index	28.1±28.3	18.3 (6.35-41.25)	5.5±4.2	4.75 (2.3-8.73)	<0.001 [#]
Sleep efficiency	88.2±10.2	90 (83-96)	88.2±11.7	90.5 (87-96)	0.77
Sleep latency	7.1±11.2	3.65 (1.35-8.9)	8.9±12.2	4.2 (1.28-14)	0.65
Lowest SpO ₂	77.5±12.8	81 (70.8-87.25)	84.4±7.3	88 (81-89)	0.002 [#]
Limb movement index	15.6±17.6	9.9 (4.68-20.58)	15.3±20.7	7.3 (3.65-14.3)	0.35

*Student's *t*-test, significant at 0.05 level, [#]Mann-Whitney U test, significant at 0.05 level. SD: Standard deviation, IQR: Interquartile range, OSA: Obstructive sleep apnea, REM: Rapid eye movement, BMI: Body mass index, AHI: Apnea-hypopnea index, NREM: Non-REM

with REM-related OSA as per the strict definition criterion was also studied [Table 2].

DISCUSSION

The prevalence of REM-related OSA varies in literature between 10% and 40% based on the definition criteria used and population characteristics.^[6,10] The proportion of REM-related OSA in this study population was 56.3% (80 out of 142 patients) as per the broad criterion: REM AHI/NREM AHI ratio >2.

The proportion of REM-related OSA in the no OSA, mild OSA, and moderate OSA groups as per overall AHI was 74%, 87%, and 73%, respectively, and was reduced to 12.8% in the severe OSA group. Several studies have also shown that REM-related OSA is more common in patients with mild or moderate OSA (overall AHI 5–30), who represent more than 80% of individuals with OSA in the community-based samples.^[10-12] In the Wisconsin

Sleep Cohort, 18% of the sleep studies with no evidence of OSA (overall AHI <5) demonstrated moderate or severe OSA during REM sleep (REM AHI ≥15).^[13]

This may be because the overall AHI is more influenced by the NREM AHI in view of the longer duration of NREM sleep as compared to REM sleep. It is also well established in literature that as the severity of OSA increases, the duration of REM sleep reduces. This is another important reason for the reduced proportion of REM-related OSA in the severe OSA group.^[14] Furthermore, in patients with severe OSA, since the pretest probability is high, it is likely that they may undergo a split night study, thereby reducing the chances of truly capturing the entire REM sleep.^[11]

When NREM AHI and REM AHI were compared with each other, it was noted that there were several patients who had a low NREM AHI and had a higher REM AHI. This may be explained by the increased loss of muscle tone

and greater upper airway collapse in REM sleep stage and, consequently, an increased AHI in this stage of sleep.^[5]

It was noted that the mean age was lower in the REM-related OSA cohort and that females were more prone to develop REM-related OSA in our study. Mokhlesi and Punjabi.^[5,8] also observed that REM-related OSA was more common in younger individuals, women, and children.

There was no significant difference between the mean BMI, neck circumference, or Epworth sleepiness scale score between the REM-related OSA group and the NREM-related OSA groups as per broad criterion. Al Oweidat *et al.*^[7] and Chami *et al.*^[12] also observed the same. It is important to note here that despite having a lower overall AHI, patients with REM-related OSA present with a similar daytime sleepiness as those with NREM-related OSA. Hence, excessive daytime sleepiness may be stronger associated with apneas/hypopneas occurring in REM than NEM sleep based on this finding.^[15]

Among the polysomnographic variables studied, snoring index, sleep efficiency, and sleep latency were comparable and did not vary significantly between the REM-related OSA and NREM-related OSA groups. Supine AHI, arousal index, oxygen desaturation index, and length of the longest event in NREM sleep stage had a significant association with REM-related OSA and were lower in the REM-related OSA group. The mean lowest SpO₂ was, however, lower in the NREM-related OSA group. Several studies on REM-related OSA prevalence have made observations similar to our findings.^[7,11,16]

Furthermore, to study if there are any differences between the broad definition and strict definition criteria for REM-related OSA, we found the proportion of REM-related OSA in our study cohort upon using the strict definition criterion also and it was found to be 25.4% (36 out of 142 patients). The proportion of REM-related OSA strict definition was also more in the mild/moderate OSA groups and the proportion decreased as the overall AHI increased. The mean age was lower and females were more prone to REM-related OSA as per strict criterion also. Additional significant association was found between REM-related OSA as per strict criterion and BMI, Epworth sleepiness scale score, and length of the longest event in REM sleep stage.

Strength of the study

Very few studies have been done in India to ascertain the prevalence of REM-related OSA and its associated polysomnographic features, and this is the first study of its kind from Kerala.

Almost all the previous studies on REM-related OSA, studied its prevalence only in patients with overall AHI >5. In our study, we found out that a significant number of patients satisfy the criteria for REM-related OSA even when the overall AHI <5 and also showed that these

patients have a significantly high REM AHI as compared to overall AHI. In fact, these patients have to be treated as having OSA itself.

Both the broad and strict criteria were used to define REM-related OSA and to study the association of polysomnographic variables with REM-related OSA, which reiterates the significant association of REM-related OSA with the studied variables.

Limitations of the study

This was a cross-sectional study and follow-up needed to know the treatment effect of CPAP on REM-related OSA and whether it is similar to the NREM-related OSA group was not done in our study.

This study did not analyze the independent association of REM-related OSA with cardiovascular/metabolic/cognitive dysfunction.

CONCLUSION

REM-related OSA is quite prevalent in our study population with a proportion of 56.3% as per broad criterion and 25.4% as per strict criterion and was found to be more common in the mild and moderate severity subgroups of OSA.

Clinical implications

REM-related OSA may represent an important early part of the spectrum of SDB, and it may be missed unless specifically looked for when doing a PSG. The presence of REM-related OSA in patients with overall AHI <5 will alter their diagnosis and upstage them as having OSA, which needs to be managed appropriately. It is also to be emphasized that REM AHI should be considered as an important parameter in future clinical research studies done in patients with SDB.

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Conflicts of interest

There are no conflicts of interest.

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