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学位論文

Obstructive Sleep Apnea Syndrome as a Potential Cause of Nocturia in Younger Adults

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Obstructive Sleep Apnea Syndrome as a Potential Cause of Nocturia in Younger Adults

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OBJECTIVES To investigate the impact of age on the relationship between obstructive sleep apnea syndrome (OSAS), nocturia, and other lower urinary tract symptoms (LUTSs).

METHODS This was a secondary analysis study based on data derived from a previously conducted prospective observational cohort study on OSAS and nocturia. We analyzed 90 subjects who were suspected of having OSAS. Prior to polysomnography, we assessed International Prostate Symptom Score-Quality of Life scores, Overactive Bladder Symptom Scores, and International Consultation on Incontinence Modular Questionnaire-Nocturia Quality of Life scores to evaluate LUTSs. Nocturnal urine volume, night-time frequency, and night-time urine electrolyte content were measured during polysomnography. Patients were divided into groups according to age and OSAS severity determined using apnea-hypopnea index (AHI) scores. Young patients were those aged <65 years and elderly patients, ≥65 years. A multiple linear regression with multiple imputations was performed to examine the association of night-time frequency with demographic, polysomnographic, and clinical characteristics.

RESULTS In young patients, night-time frequency was significantly associated with nocturnal urine volume, AHI score, and total IPSS. However, night-time frequency in elderly subjects was not associated with demographic and polysomnographic characteristics. In order to compare the severity of OSAS, night-time frequency and urinary sodium content significantly increased only in young patients (P = .007 and .004, respectively).

CONCLUSION OSAS is a strong candidate of causative factor for nocturia in younger individuals. When a younger patient complains nocturia without any urological disorders, OSAS should be kept in mind as a potential cause of nocturia. UROLOGY 143: 42–47, 2020. © 2020 Elsevier Inc.

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive functional obstruction of the upper airway during sleep, resulting in frequent arousals and nocturnal hypoxemia.[1] Untreated OSAS is associated with hypertension and arrhythmia at a high rate in function of OSAS severity and has demonstrated a strong association with an increased risk of cardiovascular events such as ischemic heart disease, and even sudden death.[2,3] In this regard, early diagnosis and appropriate treatment intervention are undoubtedly beneficial. Although the major symptom associated with OSAS is daytime sleepiness, OSAS is also a contributor to lower urinary tract symptoms (LUTSs) including nocturia.[4,5] Nocturia in OSAS patients is thought to be caused by nocturnal polyuria associated with increased atrial natriuretic peptide secretion,[6,7] and night-time frequency has been reported to positively correlate with OSAS severity.[8-11] We previously reported in a prospective observational study that OSAS was associated with nocturia and deterioration of LUTS-related QOL, both of which were improved by continuous positive airway pressure (CPAP) treatment.[12]

Nocturia is caused by several factors, including overactive bladder (OAB), benign prostatic hypertrophy (BPH), and nocturnal polyuria. All of these factors are associated with aging. Nocturia severity therefore worsens with age. On the other hand, a substantial percentage of relatively young people without urological disorders suffer from nocturia which causes deterioration of QOL. The prevalence of nocturia in patients with OSAS has been reported to be 50%-70%.[9] The prevalence of OSAS in young-aged adults ranges from 2% to 4%.[13] It is possible that OSAS, rather than pathological LUTS such as OAB and BPH, is a potential cause of nocturia in young-aged adults. In this

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context, detection and early treatment intervention of OSAS for young adults who complain nocturia might be beneficial.

As a secondary analysis of previous study, we investigated the impact of OSAS on nocturia with particular interest in difference between younger and older age groups. The results obtained in this study suggest that OSAS is a potential cause in relatively young adults who complain of nocturnal urine frequency but lack any urological disorders.

PATIENTS AND METHODS

Study Design

This was a secondary analysis study that obtained data from a previous prospective observational cohort study.[12] Because this is a secondary analysis, no formal sample size calculations were performed for these analyses. The sample size calculation was performed on the primary objective and was determined to be 100 participants in prior study. The study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Research and was approved by the institutional review boards of KKR Takamatsu Hospital in Takamatsu, Japan (E40, Trial registration: University hospital Medical Information Network (UMIN) Center identifier UMIN 000008246). All patients provided written informed consent before participating in the study.

Participants

Patients who were older than 20 years and underwent polysomnography between April and November 2012 at the Department of Sleep and Respiratory Center at KKR Takamatsu Hospital in Takamatsu, Japan, because of suspicion of OSAS, were enrolled in this study. OSAS was suspected when loud snoring, nocturnal choking, and daytime sleepiness was observed.

Our exclusion criteria were as follows: active urinary tract infection; urolithiasis; interstitial cystitis; serious complications such as cardiovascular disease, poorly controlled diabetes mellitus, liver disease, renal disease, immune system disease, lung disease, and malignant tumors. These included lesions of the bladder, prostate, and urethra that were to be treated or were previously treated with surgery, chemotherapy, or radiotherapy; patients requiring diuretics; pregnant and breastfeeding women; and women who intended to become pregnant during the study. Patients treated with any form of α1-blocker, 5α-reductase inhibitor, or anticholinergic agent within 4 weeks prior to enrollment were also excluded.

Study Protocol

All patients were screened using clinical interviews that obtained information regarding medical history and current medication use. The LUTSs include night-time frequency and LUTS-related QOL, evaluated using the following 3 questionnaires: the International Prostate Symptom Score-QOL questionnaire, OAB Symptom Score (OABSS) questionnaire, and International Consultation on Incontinence Modular Questionnaire-Nocturia Quality of Life (ICIQ-Nqol). These questionnaires were translated into Japanese, and the validity and reliability of the Japanese version were confirmed.[14-16]

Nocturnal urine volume and night-time frequency were measured simultaneously using polysomnography. We defined night-time frequency as the total number of times a patient urinated between going to sleep and rising in the morning. According to the definition of the International Continence Society, nocturia in this study was defined as the complaint by the individual requiring him to wake at night once or more times to void. Nocturnal urine volume was measured during this period as well. In our urine analyses, we excluded the last void before initially going to sleep and included their first void after rising in the morning.[17] Urinary electrolyte (sodium, chloride, and potassium) concentration in nocturnal urine was measured simultaneously when patients underwent polysomnography. Based on the measured urinary electrolyte concentrations and nocturnal urine volumes, the quantitative excretion of night-time urinary electrolytes was calculated. Biochemical profiles, including hemoglobin A1c percentage, serum blood urea nitrogen concentration, and serum creatinine concentration, were measured to identify and exclude subjects with poorly controlled diabetes mellitus or renal failure.

OSAS was diagnosed on the basis of full-night polysomnography findings obtained from a digital polysomnography system in our sleep laboratory (Sleep Watcher E series; Teijin Pharma Limited, Tokyo, Japan). Patients went to bed at their usual bedtime or by 22:00, and the recording device was removed at 6:00. Apnea was defined as a complete airflow cessation for at least 10 seconds, and hypopnea was defined as a 50% or more reduction in airflow for at least 10 seconds followed by 3% or more oxygen desaturation. The apnea/hypopnea index (AHI) was calculated as the total number of apnea and hypopnea events per hour of sleep. The severity of OSAS was evaluated in accordance with the guidelines provided by the American Academy of Sleep Medicine Task Force: OSAS severity was classified as none (AHI score < 5), mild ($5 \leq$ AHI score < 15), moderate ($15 \leq$ AHI score < 30), and severe ($30 \leq$ AHI score).[18]

Handling of Missing Data

A total of 100 patients were enrolled in this study. Two subsequently declined to participate in this study, one was then excluded due to hemoglobin A1c abnormally elevation, 7 were excluded due to incomplete data such as loss of nocturnal urine samples and/or failure to produce the questionnaire, and 23 were unexpected loss of accounts of only night-time frequency.

Regarding the 23 participants that had most of the data available for analysis but only night-time frequency was missing, in order to account for missing data for night time-frequency, we used multiple imputations as a statistical plan. In the present study, we replaced each missing value with a set of substituted plausible values by creating 20 filled-in complete data sets using a multiple imputation by chained equation method. In the imputation process, the following covariates were used to create 20 complete data sets: age, sex, body mass index, AHI, nadir oxygen saturation during polysomnography, nocturnal urine volume, night-time frequency, urinary sodium content, urinary chloride content, urinary potassium content, total IPSS score, QOL score, total OABSS score, total ICIQ-Nqol score. Ultimately, 90 patients were analyzed, with 67 complete data and 23 missing data with multiple imputation data.

Statistical Analyses

Patients were divided into 2 groups based on age. Young patients were those below 65 and elderly patients 65 or more years of age according to World Health Organization definition of the elderly. We compared the characteristics of both groups using the Mann-Whitney test for continuous data, and the Chi-squared test for categorical data. A multiple linear regression with multiple imputation was performed to examine the

association of night-time frequency and demographic, polysomnographic, and clinical characteristics.

Patients were also divided into three groups based on OSAS severity, which was determined via the AHI, in order to compare OSAS severity with baseline characteristics in terms of age. These were the none to mild, moderate, and severe OSAS groups. The Kruskal-Wallis analysis of variance was used to compare continuous data, and the Chi-squared test was applied to analyze categorical data.

Data were presented as median ± standard deviation. All *P* values less than .05 were considered statistically significant. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL) version 26 software for Windows.

RESULTS

Association between Night-Time Frequency and Demographic, Polysomnographic, and Clinical Characteristics

Table 1 shows the patient's demographic and polysomnographic characteristics in all patients with and without missing data (n = 90) and patients in the young (n = 65) and elderly (n = 25) groups.

Overall, patients comprised 71 men and 19 women with a median age of 56.0 ± 12.0 years (range, 25-79 years), median AHI score was 26.5 ± 26.3 events/h (range, 2.1-121.2 events/h), and median night-time frequency was 2.0 ± 1.4 (range, 0.0-7.0 times). Sixty-five young patients consisting of 54 men and 11 women with a median age of 51.0 ± 8.8 years (range, 25-64 years), median AHI score was 29.1 ± 4.0 events/h (range, 2.1-112.2 events/h), and median night-time frequency was 1.0 ± 1.1 (range, 0.0-5.0 times). The remaining 25 elderly patients consisted of 17 men and 8 women with a median age of 70.0 ± 4.5 years (range, 65-79 years), median AHI score was 25.8 ± 26.7 events/h (range, 4.8-121.2 events/h), and median night-time frequency was 2.0 ± 1.9 (range, 1.0-7.0 times). In the young group, night time frequency and total OABSS score were significantly lower in comparison to the elderly group.

A multiple linear regression with multiple imputations was calculated to predict night-time frequency based on age, AHI, nocturnal urine volume, total IPSS score, total OABSS score, and total ICIQ-Nqol score.

For all patients, night-time frequency was significantly associated with nocturnal urine volume and total IPSS score: a significant regression equation was found ($F(6, 60) = 8.900$, $P < .000$), with an R^2 of 0.511. The patients' predicted night-time frequency was equal to −0.759 + 0.002 (nocturnal urine volume) + 0.065 (total IPSS score). Both nocturnal urine volume and total IPSS score were significant predictors of night time frequency.

In young patients, night-time frequency was significantly associated with AHI, nocturnal urine volume, and total IPSS score: a significant regression equation was found ($F(6,45) = 10.305$, $P < .000$), with an R^2 of 0.579. Patients' predicted night-time frequency was equal to −0.386 + 0.010 (AHI) + 0.002 (nocturnal urine volume) + 0.082 (total IPSS score). AHI, nocturnal urine volume, and total IPSS score were significant predictors of night-time frequency.

In elderly patients, night-time frequency was not associated with demographic and polysomnographic characteristics. The full results regarding our association of night-time frequency, demographic and polysomnographic characteristics are shown in Table 2.

Impact of Age on the Relationship between OSAS Severity and Demographic, Polysomnographic, and Clinical Characteristics

Of the 90 patients with and without missing baseline data, 22 were in the none-to-mild OSAS group (17 young and five elderly patients), 26 were in the moderate OSAS group (16 young and 10 elderly patients), and 42 were in the severe OSAS group (32 young and 10 elderly patients). In overall patients, urinary sodium content significantly increased according to the severity of OSAS. In 65 young patients, night-time frequency and urinary sodium content significantly increased ($P = .007$ and .004, respectively) with OSAS severity as shown in Table 3, alternatively in elderly patients, no significant difference was

Table 1. Patients' demographic and polysomnographic characteristics

Characteristics	All Patients n = 90	Age < 65 Years n = 65	Age ≥ 65 Years n = 25	*P* Value
Age (years)	56.0 ± 12.0	51.0 ± 8.8	70.0 ± 4.5	.000*
% male	78.9	83.1	68.0	.116
BMI (kg/m^2)	25.5 ± 4.0	26.1 ± 4.0	23.9 ± 3.6	.072
AHI score (events/h)	26.5 ± 26.3	29.1 ± 26.3	25.8 ± 26.7	.636
Nadir SpO_2 (%)	83.0 ± 9.4	82.0 ± 8.9	85.0 ± 10.6	.181
Night-time urine volume (ml)	420.0 ± 340.0	400.0 ± 304.4	480.0 ± 407.5	.107
Night-time frequency (number of urination times during sleep)	2.0 ± 1.4	1.0 ± 1.1	2.0 ± 1.9	.008*
u-Na (mEq)	60.0 ± 39.7	59.1 ± 41.7	62.2 ± 34.7	.982
u-Cl (mEq)	52.0 ± 39.4	50.2 ± 41.6	60.9 ± 33.6	.698
u-K (mEq)	9.9 ± 6.2	9.6 ± 6.7	11.0 ± 4.6	.508
Total IPSS score	5.0 ± 5.4	4.0 ± 4.8	6.0 ± 6.7	.149
QOL score	3.0 ± 1.5	2.0 ± 1.5	3.0 ± 1.7	.340
Total OABSS score	2.0 ± 2.3	2.0 ± 1.7	4.0 ± 3.0	.002*
Total ICIQ-Nqol score	91.7 ± 14.8	93.8 ± 13.9	89.6 ± 16.9	.121

AHI, apnea-hypopnea index; BMI, body mass index; ICIQ-Nqol, international consultation on incontinence modular questionnaire-nocturia quality of life; IPSS, international prostate symptom score; Nadir SpO_2, nadir oxygen saturation during polysomnography; OABSS, overactive bladder symptom score; u-Na, urinary sodium content; u-Cl, urinary chloride content; u-K, urinary potassium content.
Data are presented as median ± standard deviation.
* Mann-Whitney test for comparison of a group of age < 65 years and a group of age ≥65 years.

Table 2. Multiple linear regression analysis with multiple imputation for correlation between night-time frequency and obstructive sleep apnea syndrome patients' demographic and polysomnographic characteristics

Variable	All Patients			Age < 65 Years			Age ≥ 65 Years		
	B	SE B	β	B	SE B	β	B	SE B	β
Age	0.02	0.01	0.22	0.00	0.01	0.03	−0.12	0.37	0.23
AHI	0.01	0.01	0.13	0.01	0.00	0.24*	−0.01	0.12	−0.16
Nocturnal urine volume	0.00	0.00	0.45†	0.00	0.00	0.50†	0.00	0.01	0.45
Total IPSS score	0.07	0.03	0.24*	0.08	0.03	0.36†	−0.03	0.51	0.09
Total OABSS score	0.00	0.08	0.01	0.10	0.08	0.13	0.10	1.14	−0.10
Total ICIQ-Nqol score	−0.01	0.01	−0.07	−.0.00	0.01	−0.01	−0.02	0.10	−0.17
R2	.51			.58			.54		
F	8.90†			10.31†			3.57*		

Data were obtained via multiple linear regression analysis.
AHI, apnea-hypopnea index; ICIQ-Nqol, international consultation on incontinence modular questionnaire-nocturia quality of life; IPSS, international prostate symptom score; OABSS, overactive bladder symptom score.
* $P < .05$.
† $P < .001$.

Table 3. Demographic, polysomnographic, and clinical characteristics of younger group (< 65 years old) according to obstructive sleep apnea syndrome severity

Characteristics	None to Mild OSAS (0 < AHI Score < 15) n = 17	Moderate OSAS (15 ≤ AHI Score < 30) n = 16	Severe OSAS (30 ≤ AHI Score) n = 32	P Value
Age (years)	51.0 ± 9.9	51.0 ± 9.9	52.5 ± 7.9	.875
% Male	64.7	81.3	93.8	.034†
BMI (kg/m^2)	23.9 ± 4.9	27.9 ± 4.0	26.0 ± 3.4	.134
AHI score (events/h)	10.4 ± 3.9	22.0 ± 4.6	48.6 ± 22.7	.000*
Nadir SpO_2 (%)	87.0 ± 3.9	83.0 ± 7.7	74.5 ± 8.3	.000*
Night-time urine volume (ml)	330.0 ± 317.7	430.0 ± 323.9	425.0 ± 294.8	.519
Night-time frequency (number of urination times during sleep)	1.0 ± 0.9	2.0 ± 0.9	2.0 ± 1.1	.007*
u-Na (mEq)	39.2 ± 40.3	45.7 ± 49.2	77.0 ± 35.3	.004*
u-Cl (mEq)	35.6 ± 40.4	42.8 ± 43.6	66.9 ± 38.1	.469
u-K (mEq)	7.6 ± 7.4	8.7 ± 5.9	10.4 ± 6.8	.006*
Total IPSS score	4.0 ± 4.4	5.0 ± 5.2	4.0 ± 4.9	.867
QOL score	2.0 ± 1.6	2.0 ± 1.6	2.0 ± 1.4	.988
Total OABSS score	2.0 ± 1.6	1.5 ± 1.3	2.0 ± 1.9	.542
Total ICIQ-Nqol score	97.9 ± 12.1	97.9 ± 12.5	91.7 ± 15.5	.592

AHI, apnea-hypopnea index; BMI, body mass index; ICIQ-Nqol, international consultation on incontinence modular questionnaire-nocturia quality of life; IPSS, international prostate symptom score; Nadir SpO_2, nadir oxygen saturation during polysomnography; OABSS, overactive bladder symptom score; OSAS, obstructive sleep apnea syndrome; u-Na, urinary sodium content; u-Cl, urinary chloride content; u-K, urinary potassium content.
Data are presented as median ± standard deviation.
* Kruskal-Wallis analysis of variance.
† Chi-squared test.

observed in OSAS severity with respect to these parameters, as shown in Table 4.

DISCUSSION

Epidemiologic survey of LUTS for randomly selected men and women aged 40 years or older in Japan showed that the prevalence of nocturia ranged from 40% to 60% in younger age of 40-59 years and increased with age. Moreover, among LUTSs, nocturia affects most harmfully on QOL.[19] Although the prevalence of nocturia varies among survey in other countries, it is consistently common that nocturia is a major cause of deterioration of QOL.[20] In this study, night-time frequency in younger age group (<65 years old) was significantly associated with nocturnal urine volume, AHI score, and LUTS-related QOL, although such clear association was not found in older age group (≥65 years old). Our results suggest that OSAS has more straightforward influence on nocturnal urine frequency and urine volume in younger population, which results in deterioration of their QOL. The reported prevalence of OSAS in young-aged adults is not so high ranging from 2% to 4%,[13] although it might have been underestimated. Anyhow, our findings as to the association of OSAS with nocturia in younger population is considered clinically important because early detection and treatment with CPAP can relieve not only night time voiding complaint but also future cardiovascular events and even sudden death. On the other hand, there was no such straightforward association of nocturia with OSAS in elderly population. This does not necessarily mean low clinical importance of nocturia as a primary symptom of

Table 4. Demographic, polysomnographic, and clinical characteristics of the elderly group of patients (≥ 65 years old) according to obstructive sleep apnea syndrome severity

Characteristics	None to Mild OSAS (0 < AHI score < 15) n = 5	Moderate OSAS (15 ≤ AHI Score < 30) n = 10	Severe OSAS (30 ≤ AHI Score) n = 10	P Value
Age (years)	71.0 ± 5.2	70.0 ± 3.5	69.5 ± 4.8	.402
% male	80.0	50.0	80.0	.289†
BMI (kg/m^2)	22.7 ± 2.3	24.0 ± 3.6	25.5 ± 3.9	.210
AHI score (events/h)	5.8 ± 2.4	18.2 ± 4.6	48.3 ± 25.5	.000*
Nadir SpO_2 (%)	90.0 ± 2.2	86.5 ± 4.8	78.0 ± 13.7	.014*
Night-time urine volume (ml)	480.0 ± 246.0	430.0 ± 182.5	887.5 ± 542.1	.207
Night-time frequency (number of urination times during sleep)	3.0 ± 2.3	2.0 ± 0.8	5.0 ± 2.2	.065
u-Na (mEq)	48.7 ± 23.0	56.5 ± 22.0	69.0 ± 46.4	.674
u-Cl (mEq)	45.8 ± 20.2	61.1 ± 21.8	62.1 ± 44.7	.574
u-K (mEq)	9.2 ± 6.7	11.2 ± 4.5	11.7 ± 4.0	.596
Total IPSS score	5.0 ± 3.0	6.0 ± 7.8	5.0 ± 6.5	.484
QOL score	2.0 ± 1.8	3.0 ± 1.8	3.0 ± 1.6	.345
Total OABSS score	4.0 ± 1.7	4.5 ± 3.9	3.5 ± 2.1	.323
Total ICIQ-Nqol score	89.6 ± 15.6	90.6 ± 20.3	89.6 ± 15.4	.926

AHI, apnea-hypopnea index; BMI, body mass index; ICIQ-Nqol, international consultation on incontinence modular questionnaire-nocturia quality of life; IPSS, international prostate symptom score; Nadir SpO_2, nadir oxygen saturation during polysomnography; OABSS, overactive bladder symptom score; OSAS, obstructive sleep apnea syndrome; u-Na, urinary sodium content; u-Cl, urinary chloride content; u-K, urinary potassium content.
Data are presented as median ± standard deviation.
* Kruskal-Wallis analysis of variance.
† Chi-squared test.

OSAS at the time of diagnosis for the elderly. Rather, nocturia in elderly population is caused by multiple factors including BPH, OAB, and other age-related structural changes in urinary organs.

When patients were grouped according to OSAS severity, night-time frequency and urinary electrolyte content significantly associated with OSAS severity in the younger group of patients. It is particularly interesting that natriuresis in younger patients was remarkable, which may indicate that the quantity of natriuretic peptide secretion depends on OSAS severity whereas such association was not found in the elderly group. These results correspond with our biochemical analyses in the previous study in which OSAS contributes to night-time frequency in young people more than in the elderly.[21-24] In the elderly, there are several causes that affect night-time urination characteristics, for example, light sleep or decreasing antidiuretic hormone levels.

There are several limitations to the present study. First, we did not perform further clinical evaluation at the time of enrollment for those who suspiciously suffer BPH or OAB although those who were medically treated with any form of α1-blocker, 5α-reductase inhibitor, or anticholinergic agent were excluded. Therefore, individuals with undetected BPH and OAB may have been included especially in the elderly group. Second, when patients slept in the sleep laboratory during polysomnography, many monitors were attached to their body that may have impaired quality of sleep and affected night-time frequency. It would be ideal to assess urinary data using frequency-volume chart analysis while in a natural state of sleep, since this may provide the most reliable results for assessing the relationship between OSAS and nocturnal polyuria.

CONCLUSION

OSAS is a strong candidate of causative factor for nocturia in younger individuals. When a younger patient complains nocturia without any urological disorders, OSAS should be kept in mind as a potential cause of nocturia.

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