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ORIGINAL ARTICLE

Prevalence of obstructive sleep apnea detected by the Berlin Questionnaire in patients with nocturia attending a urogynecology unit

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Abstract
Introduction and hypothesis Nocturia has been associated with several chronic conditions including obstructive sleep apnea (OSA). The pathophysiological link between nocturia and OSA has been well delineated, but the prevalence of this condition in patients with nocturia is unknown. The aim of this study was to determine the prevalence of sleep apnea in patients with nocturia compared with patients without nocturia in a group of women referred to a urogynecology unit.
Methods After ethics approval, a cross-sectional case control study including 81 cases and 79 controls was conducted. The sample size of 72 patients was required for each arm to detect a 23 % difference in the prevalence of OSA with a 95 % confident interval (CI) and statistical power of 80 %. All patients completed the Nocturia, Nocturia Enuresis and Sleep Interruption Questionnaire (NNES-Q) and the Berlin OSA Questionnaire. The NNES-Q was used to define cases and controls. The Berlin Questionnaire was used to classify patients as being at a high or a low risk of having OSA. Univariate analysis was first performed, followed by logistic regression to assess the association between nocturia and OSA, as well as other possible variables associated with nocturia.
Results Fifty of the cases (61.7 %) were classified as being at a high risk of having OSA compared with only 19 (24.1 %) in the control group (OR 2.9, 95 % CI 1.29–6.52, p=0.01). Other variables found to be statistically significant by logistic regression were high BMI, overactive bladder, and low bladder capacity (<300 cc).
Conclusion Patients with nocturia showed a significantly higher risk of having OSA. Patients with nocturia should be screened for OSA.

Keywords Nocturia · Obstructive sleep apnea · Prevalence

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Introduction

Nocturia is defined as a complaint that the individual has to wake at night one or more times to void [1]. It has been recognized as a frustrating symptom for patients and a common cause of consultation and referral to the urogynecology clinic. It is the most bothersome of all urinary complaints and the most frequently reported because of sleep disturbance [2]. It has also been associated with a decrease in the general state of health, a greater risk of falls in the elderly, and in those who void three or more times nightly, a greater mortality rate from all causes [3–5]. Nocturia is known to rise in prevalence with aging, occurring in 51 % of women over 80 years of age [6].

Nocturia is a symptom of many etiologies, and it has been associated with several chronic conditions, including obstructive sleep apnea (OSA) [7, 8]. OSA is a disorder that is characterized by repetitive episodes of complete or partial upper airway obstruction, which gives rise to negative intra-thoracic pressures [9]. The increased negative intra-thoracic pressure results in increased venous return and atrial stretch [10]. These produce a false symptom of fluid volume overload and trigger the secretion of atrial natriuretic peptide, causing the kidneys to increase urine production, with an increased loss of water and sodium [10]. This process results in an increased

production of urine at night-time in addition to an increase in nocturnal voiding.

Despite the recognition of the pathophysiological link between OSA and nocturia, the prevalence of OSA in patients with nocturia is still unknown. Some pilot studies suggest that it might be extremely high [11].

The objective of the current study was to characterize the prevalence of sleep apnea in patients with nocturia compared with patients without nocturia attending a urogynecology unit.

Materials and methods

After research ethics board approval, a cross-sectional case control study was conducted from June 2013 to December 2013 at the urogynecology clinic, Mount Sinai Hospital, Toronto, Canada.

The sample size of 72 patients was required for each arm to detect a 23 % difference in the prevalence of OSA with a 95 % confident interval (CI) Statistical power of 80 % was computed for the study based on previous published studies that showed that the prevalence of OSA in the general population was 26 % and the rate of nocturia in patients with OSA was 48.7 % [12, 13].

All consecutive patients referred de novo for all indications who were scheduled for urodynamics were eligible and were asked to take part in the study. Patients were excluded if they refused to participate in the study, if English was not spoken or comprehended well, or if patients had cognitive impairment. All patients who consented to participate completed the Nocturia, Nocturia Enuresis and Sleep Interruption Questionnaire (NNES-Q) and the Berlin Questionnaire.

The NNES-Q is a validated questionnaire designed to identify and evaluate patients with nocturia, nocturnal enuresis, and sleep interruption [14]. This questionnaire was used to define cases and controls. Cases were defined as sleep interruption due to an urge to void twice or more per night. We used the cutoff of >1 night time voids or what is known in the literature as pathological nocturia because it has been shown to be clinically relevant and it has a significant effect on quality of life [1].

The Berlin Questionnaire is an accepted sleep apnea screening tool proven to effectively classify patients as being at a low or high risk of having OSA by calculating BMI and asking questions regarding snoring behavior, daytime somnolence, and history of hypertension [15]. This ten-question test is well known for its accuracy in predicting the presence of sleep apnea.

A medical history was taken including demographic data (age, BMI, parity, menopause status, smoking), surgical history (previous pelvic/bladder or incontinence surgery), medical history (diabetes mellitus, diabetes insipidus, congestive heart failure, interstitial cystitis, bladder cancer, diagnosis of obstructive sleep apnea proven by polysomnography, others), medications (hormone replacement, anticholinergics, antidepressives, diuretics, neurological drugs, others), and socials habits (alcohol, smoking, caffeine intake). Also, the medical history included specific questions regarding urogynecological conditions including overactive bladder. Overactive bladder was defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathological condition [16].

A urogynecological examination was also performed including a bimanual examination and objective assessment for pelvic organ prolapse in each compartment (anterior, apical, and posterior), and assessment of vaginal epithelium appearance and the presence or absence of urogenital atrophy. Vaginal epithelial atrophy was graded as none, mild, moderate, or severe, depending on the characteristics of the vaginal epithelium including pallor, petechiae, friability, and vaginal dryness.

Urodynamic testing was performed for all patients, including multichannel cystometry, urethral pressure profile, uroflowmetry, and postvoid residual.

With regard to statistical analysis, descriptive and inferential analysis was used for variables in each group using SPSS version 22 (IBM, Armonk, NY, USA). All inferential tests were done using 0.05 as the level of significance.

For continuous measure we reported mean and standard deviation. The comparison between case and control groups was conducted using independent samples *t* tests. For discrete variables we reported median and range. The inferential analysis was conducted using the Mann–Whitney test.

Categorical variables have been summarized using counts and percentages. The comparison between two groups was done using the Chi-squared test. Univariate analysis was first performed, followed by binary logistic regression to assess the association between nocturia and OSA, as well as other possible variables associated with nocturia. Three logistic regression models were used: first, with only OSA as a predictor of nocturia; second, with all factors; and third, using a stepwise method to keep only statistically significant predictors.

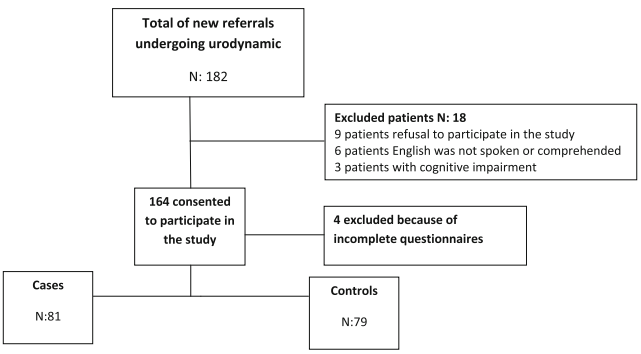

Fig. 1 Patient flow chart

Table 1 Demographics and characteristics (univariate analysis)

	Case nocturia 2 or more *N*=81 (%)	Control nocturia (0–1) *N*=79 (%)	*p* value*
Age	56.94±15.13	51±16	0.02
Body mass index (BMI)	28.85±6.18	24.75±4.77	< 0.001
Gravity	2 (0–8)	2 (0–9)	0.79
Vaginal delivery	65 (80.2)	65 (82.3)	0.74
Previous pelvic surgery	17 (21.0)	17 (21.5)	0.94
Postmenopausal	57 (70.4)	43 (54.4)	0.04
Smokers	6 (7.4)	7 (8.9)	0.58
Medical conditions			
Diabetic	11 (13.6)	4 (5.1)	0.07
Overactive bladder	20 (24.7)	5 (6.3)	0.001
Congestive heart failure	1 (1.2)	1 (1.3)	0.99
POP > stage 2	24 (29.6)	18 (22.8)	0.33
Anterior > stage 2	14 (17.3)	14 (17.7)	0.82
Urogenital atrophy (moderate or severe)	30 (37.0)	18 (22.8)	0.049
High risk of OSA	50 (61.7)	19 (24.1)	0.001

*p values are calculated using t test for continuous variables or Chi-squared or Fisher's exact test for categorical data (univariate alalysis)

Results

One hundred and sixty subjects were included in the study. A total of 22 patients were excluded for the following reasons: refusal to participate in the study (9 patients), English was not spoken or comprehended well (6 patients), cognitive impairment (3 patients), and incomplete questionnaires (4 patients; Fig. 1). Using the NNES-Q, 81 subjects were classified as cases (nocturia two or more voids per night), and 79 were classified as control (0–1 voids per night). Table 1 shows demographics and characteristics of the two groups, with univariate analysis. As shown in Table 1, patients with nocturia were older and had a higher BMI. Also, a greater number of patients with nocturia were postmenopausal, had a diagnosis of overactive bladder and a clinical diagnosis of moderate to severe urogenital atrophy.

As shown in Table 2 patients with nocturia had a smaller bladder capacity and a greater number of patients had a low bladder capacity (<300 cc) on urodynamics findings.

Table 2 Urodynamics findings

	Case *N*=81 (%)	Control *N*=79 (%)	*p* value*
Bladder capacity	367.62±168.71	422.27±160.93	0.04
Low bladder capacity (<300 cc)	25 (31.6)	10 (13.0)	0.01
Detrusor overactivity	5 (6.2)	2 (2.5)	0.26
Post-void residual>100	10 (12.7)	8 (10.4)	0.66

*p values are calculated using t test for continuous variables or Chi-squared or Fisher's exact test for categorical data (univariate analysis)

Using the Berlin Questionnaire 50 cases (61.7 %) were classified as being at a high risk of having OSA compared with only 19 (24.1 %) in the control group. Binary logistic regression with only OSA being a predictor of nocturia (model 1) showed a statistically significant association (OR 4.99, 95 % CI 2.49–10.00, $p<0.001$). Then, we added all the variables that were found to be significant in the univariate analysis (model 2) and used a stepwise method to build model 3, where only significant predictors remained. Model 3 results are presented in Table 3. We found OSA to be still statistically significant (OR 2.9, 95 % CI 1.29–6.52, $p=0.01$). Other variables found to be statistically significant by logistic regression were high BMI, overactive bladder, and low bladder capacity (<300 cc). Age, menopausal status, urogenital atrophy, parity, prolapse stage, previous pelvic surgery, and diabetes were found not to be significant in the logistic regression analysis. Of the cases, 10 (12.3 %) reported having a positive history of OSA proven by polysomnography compared with none in the control group. NNES-Q showed that in patients

Table 3 Multivariate logistic regression model

Association with nocturia	OR (95 % CI for OR)	*p* value
High risk of OSA according to the Berlin Questionnaire	2.90 (1.29–6.52)	0.01
Age	1.00 (0.96–1.05)	0.86
BMI	1.10 (1.02–1.18)	0.02
Postmenopausal	0.97 (0.25–3.75)	0.97
Overactive bladder	5.26 (1.69–16.41)	< 0.01
Urogenital atrophy	1.11 (0.39–3.13)	0.85
Low bladder capacity	2.92 (1.13–7.53	0.03

with nocturia, sleep was interrupted more commonly (81 [100 %] vs 46 [58.2 %], $p<0.001$) and they were more bothered by being woken up compared with the control group (6.86±2.31 vs 2.81±3.06, $p<0.001$). Enuresis was also more common in the cases: 35 (43.2 %) vs 9 (11.4 %, $p<0.001$).

Discussion

A primary conclusion of our study is that those patients with nocturia are more likely to have OSA. Our study supports the findings of Lowenstein et al. in a pilot study in which they suggest that the prevalence of OSA in patients with nocturia is particularly high [11].

Nocturia is classified according to its underlying pathophysiology. It is mainly divided into four groups: 24-h polyuria, nocturia polyuria (NP), low bladder capacity, and sleep disorders. Nocturia caused by OSA is categorized as NP because of the excess production of atrial natriuretic peptide (notably occurring during sleep) [17]. NP has been recognized as the most frequent cause of nocturia in adults, especially those in the elderly age group [18]. Because of this, and the high prevalence of OSA in patients with nocturia shown in our research, we strongly support the proposal that all patients with nocturia should be screened for OSA. By doing this we will be able to direct the treatment toward the underlying disorder. It has been well documented that by treating patients with OSA with C-PAP, nocturia improves dramatically [7, 19–21]. In our study, we chose the Berlin Questionnaire as our screening tool because it has the highest sensitivity and specificity of all the questionnaires designed to screen for OSA [22]. In primary care patients, the sensitivity and specificity were 86 and 77 % respectively [23]. This questionnaire has many of the characteristics of a good screening test including a high sensitivity and specificity, and it is easy to administer, inexpensive, reproducible, and valid.

It is important to highlight that multiple etiologies of nocturia may coexist in the individual. Low bladder capacity including overactive bladder syndrome is a known cause of nocturia per se. In our study 31.6 % of the patients with nocturia had a low bladder capacity (<300 cc) and 24.7 % had a clinical diagnosis of OAB. Both of these were also associated with an increased risk of nocturia. These findings are important specifically to guide the most appropriate pharmacotherapy. It is likely that patients with OAB or lower bladder capacity are the only groups to benefit from antimuscarinic drugs. This may also explain why most of the clinical trials assessing pharmacotherapy options for the treatment of nocturia often report statistically significant results that do not translate to clinically significant reductions in night-time voids [24].

Nocturia has been identified as an independent predictor for severe OSA [25, 26]. Because of this, we believe that the urogynecological evaluation is a golden opportunity to identify patients at a high risk of OSA and refer them for complete evaluation and proper treatment. By doing this we improve not only the urinary symptoms, but we may also reduce the risk of other complications linked to OSA such as sleep deprivation, cardiovascular disease, high blood pressure, stroke, diabetes, clinical depression, weight gain, and obesity [27–29].

Our study has several strengths, including the methodological design. This is also one of the first studies in which the sample of patients is taken from a urogynecology specialty clinic and not from the sleep clinics where the sample may be biased. Some authors have suggested that all patients with nocturia should be referred for sleep studies [11]. We agree that this may be ideal, but it is impractical and virtually impossible, knowing that nocturia and OSA are far more prevalent than can be handled by the available sleep laboratories. Because of this, we believe that a screening tool such as the Berlin Questionnaire may help us to select the patients who should undergo complete sleep studies.

A limitation of our study was that most patients did not undergo a full polysomnography test in our study, limiting our knowledge of the specific sensitivity and specificity in addition to the positive and negative predictive values of the Berlin Questionnaire in our specific population (patients with nocturia). More research is needed to obtain this information and to create specific guidelines on how patients should be screened.

Conclusion

Patients with nocturia are at an increased risk of OSA and should be screened for it. The Berlin Questionnaire may be a good screening tool in this population.

Conflicts of interest None.

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