New Aspects of the Classification of Nocturia

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Current Urology Reports 2008, **9:**362–367
Current Medicine Group LLC ISSN 1527-2737

Nocturia, one of the most bothersome urologic symptoms, has been poorly classified and understood. Multiple factors may cause nocturia, such as behavioral or environmental factors and pathologic conditions, including cardiovascular disease, diabetes mellitus, lower urinary tract obstruction, anxiety or primary sleep disorders, and sleep apnea. Nocturia caused by any combination of these and other conditions may be attributed to nocturnal polyuria, diminished nocturnal or global bladder capacity, global 24-hour polyuria, or a combination of these factors. Distinction among these classes of nocturia is made by a simple arithmetic analysis of the 24-hour voiding diary. Nocturia has been poorly studied and only recently classified according to its etiology and pathogenesis. After reviewing the current state of knowledge, we present a scheme for rational diagnosis of patients suffering from loss of sleep due to nocturnal micturition. This article reviews the current state of knowledge and presents algorithms for the diagnosis and classification of nocturia.

Introduction

One of the most common reasons for interrupted sleep in the general adult population is nocturia (ie, waking at least once during the night to urinate) [1]. Sleep is important for physical and mental well being. It is generally thought that adults need about 7–8 hours sleep per night, and that adequate sleep has a restorative effect. Insufficient or disrupted sleep has commonly been linked with excessive daytime sleepiness leading to poor motivation, poor job performance, and physical and mental disorders, particularly depression and mood alterations [2–5].

A Danish study evaluated patients with nocturia and found that two-thirds of patients in their study blamed an urge to void for their sleep interruption [6]; a Dutch study reported that nocturia was the commonest cause of disturbed sleep among 705 male participants surveyed [7]. A study of pre- and postmenopausal women indicated that daytime sleepiness was three times more common in those women who woke three or more times per night to urinate compared with those who did not wake [8].

Studies have shown that patients with nocturia are more likely to have depression and anxiety and require more sick days from work [8,9]. They also have a lower overall satisfaction with daily life, a worse general state of health, and an increase in mortality compared with those having fewer episodes of nocturia [7,8,10].

Pathologic conditions causing nocturia include cardiovascular disease, diabetes mellitus and insipidus, lower urinary tract obstruction, and waking to void for other reasons, such as anxiety or primary sleep disorders [2,11,12]. Behavioral and environmental factors contributing to nocturia include consumption of diuretic medication, caffeine, alcohol, or excessive fluid shortly before retiring for the night [13]. Commonly prescribed medications, such as β-blockers and selective serotonin reuptake inhibitors, are associated with an increase in nocturia [14,15]. Prostate disease and neurogenic bladder have been reported to lead to frequent nocturnal rising [12,13,16]. Nocturia may additionally result from stroke, congestive heart failure, peripheral edema (eg, owing to venous insufficiency or nephrotic syndrome), and myeloneuropathy secondary to vertebral disc disease or spondylosis [17].

Epidemiology and Bothersomeness

The prevalence of two or more nocturnal voids ranges from 11%–28% in various population studies, including adults of all ages [12,18–20], and 38%–60% of men and 36%–55% of women are estimated to void at least once per night [18–20].

Several studies found that women are more likely to have nocturia than men [19], whereas other studies found no gender difference in the prevalence of nocturia [20,21]. A Finnish study found the prevalence of nocturia in young women to be greater than that in similarly aged men. Conversely, older men are more likely than older women to have nocturia [21]. A recent study of 1872 Bostonians demonstrated a difference among racial and ethnic

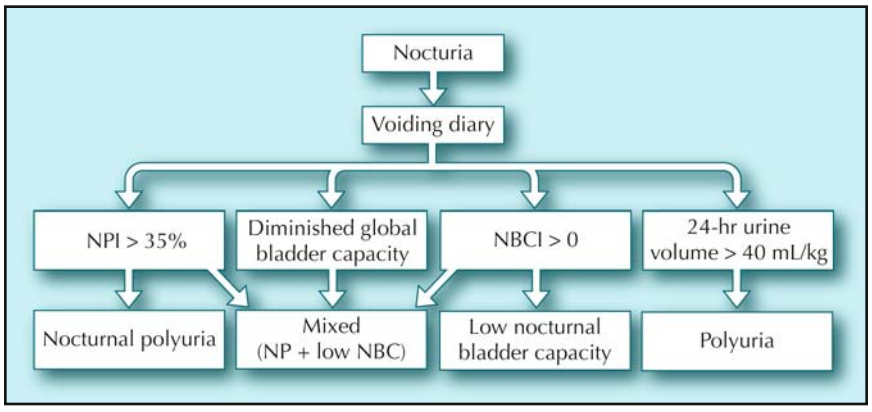

Figure 1. Flowchart of the evaluation of nocturia. NBCI—nocturnal bladder capacity index; NPI—nocturnal polyuria index.

groups, with the highest prevalence of nocturia in African Americans and the lowest in whites (38.5% vs 23.2%; $P < 0.001$) [9]. Regardless of gender, ethnicity, and race, the prevalence of nocturia increases with age [12,18–20].

A recent population study evaluated the effect of seasonal temperature change on nocturia. Yoshimura et al. [22] reported that nocturia was more common in the winter than summer (OR, 1.40; 95% CI, 1.14–1.73; $P = 0.0012$). They theorize that vasoconstriction of the extremities leads to increased free water clearance during winter months [22].

Definition

Nocturia is defined as waking during the night at least once to urinate. It has additionally been suggested that a nocturia-related void is preceded and followed by sleep [1]. Whether sleep must follow a nocturia-related void is not entirely clear. Thus, for example, if one rises an hour earlier than planned with the urge to void but cannot return to sleep, nocturia seems evident but would not be considered as such if one rigidly adheres to the notion that a nocturia-related void must be followed by sleep. Voiding during hours of sleep that results from wakening for reasons other than the urge to void is not considered nocturia, although from a practical standpoint it is difficult to keep track of "convenience voids" at night compared with true nocturia-related voids. Thus, most studies of nocturia in the literature include voiding for all reasons during sleep.

There are numerous scientific questions related to this definition. For example, how should sleep time be defined? Sleep time varies by individual, but on average it is eight hours per night [23]. This definition can affect the evaluation of nocturia, as the number of nocturnal voids depends partly on how many hours an individual actually sleeps. Another question concerns whether the patient is awakened by the need to void or the patient voids after being awakened for other reasons. Though most patients in one study with nocturia were awakened by the need to void, the rest were awakened by thirst, uncomfortable temperature, noises, worry, pain, or other stimuli [6].

Etiology

The etiology of nocturia falls into five broad categories: 1) nocturnal polyuria (NP); 2) low nocturnal bladder capacity (NBC) despite normal global bladder capacity; 3) diminished global bladder capacity; 4) mixed (a combination of NP and low bladder capacity); and 5) global polyuria. These categories derive from the 24-hour voiding diary, wherein each voided volume and its corresponding time is entered. Figure 1 presents an algorithm for evaluation analysis of nocturia.

Evaluation

Patients are likely to present to the clinician with either nocturia or indirect symptoms of nocturia, such as insomnia, daytime tiredness, or related somatic disease. Evaluation of nocturia begins with a focused history and physical examination considering aspects such as sleep, urinary complaints, fluid intake, cardiac problems, medication, prior lower urologic tract surgery, and other comorbidities that might account for excessive nocturnal urine output, detrusor overactivity, or sensory urgency. Of paramount importance is a frequency/volume chart, also known as a voiding diary. The voiding diary includes the volume and time of each voided urine, the time of retiring for sleep, and the time of rising during a 24-hour period. The patient is instructed to record the diary on a typical day and inform the doctor whether the night measured was representative of a normal sleep cycle [1,24].

On the basis of the voiding diary, the patient is categorized as having NP, low nocturnal or global bladder capacity, a mixed disorder, or polyuria using a few simple equations (Table 1). Nocturnal urine volume (NUV) is the volume of urine voided during sleep hours. However, the first morning void is considered a normal diurnal voiding episode and should not be included with the tally of actual nightly voids. Maximum voided volume (MVV) is defined as the largest volume of urine voided throughout the 24-hour period. Nocturia index (NI) is calculated by dividing NUV by MVV [25]. When the NI is > 1, the nocturnal urine volume exceeds the bladder maximal storage capacity and nocturia occurs (enuresis if the patient does not wake).

Table 1. Formulas for evaluation of nocturia

Formula	Analysis
NI = NUV/MVV	If NI is > 1, nocturia is due to NUV exceeding MVV
NPI = NUV/24-h V	If NPI is > 25%, the diagnosis is nocturnal polyuria
NBCI: ANV – PNV (PNV* = NI – 1)	If NBCI is > 0, nocturia occurs at volumes < MVV

*Round up to nearest integer if not already an integer.
24-h V—24-hour urine volume; ANV—actual number of nightly voids; MVV—maximum voided volume; NBCI—nocturnal bladder capacity index; NI—nocturnal index; NPI—nocturnal polyuria index; NUV—nocturnal urine volume; PNV—predicted number of nightly voids.

Table 2. Causes of nocturia

Nocturia category	Causes
Nocturnal polyuria	Congestive heart failure
	Diabetes mellitus
	Obstructive sleep apnea
	Peripheral edema
	Venous stasis
	Nephrotic syndrome
	Hepatic failure
	Hypoalbuminemia
	Excessive nighttime fluid intake
Diminished nocturnal bladder capacity and/or global bladder capacity	Prostatic obstruction
	Nocturnal detrusor overactivity
	Neurogenic bladder
	Cancer of bladder, prostate, or urethra
	Learned voiding dysfunction
	Anxiety disorders
	Pharmacologic agents
	Bladder calculi
	Ureteral calculi
Global polyuria	Diabetes mellitus
	Diabetes insipidus
	Primary polydipsia

Rembratt et al. [26] performed an analysis of the nocturia index in nocturics and nonnocturics. They reported that NI = 2.1 for nocturics and 1.0 for nonnocturics. These results imply that the most significant reason for nocturia is a mismatch between nocturnal bladder capacity and the volume of urine excreted during the hours of sleep [26]. An increased NI may be due to either NP, low bladder capacity, or both. Of course, patients with low nocturnal bladder capacity may also have low global bladder capacity. Thus, a patient with low voided volumes both day and night is likely to produce more urine at night than the bladder can possibly hold, regardless of the time in bed; nocturia is inevitable in these patients.

Nocturnal Polyuria

NP is an increased production of urine at night that is offset by lowered daytime urine production creating a normal 24-hour urine volume [27]. The nocturnal polyuria index (NPI) is defined as NUV divided by the 24-hour urine volume. Normally, urine is produced in a circadian pattern that is age-dependent. In young people (< 25 y), mean NPI = 14% compared with older people (> 65 y) whose mean NPI = 34% [28]. Therefore, NP exists when 24-hour urine production is within normal limits and NPI is ≥ 0.35 at any age. Several other definitions of nocturnal polyuria have been used, including NUV > 6.4 mL/kg and nocturnal urine output ≥ 0.9 mL/min [29].

Nocturnal polyuria may be secondary to various factors including congestive heart failure, diabetes mellitus, obstructive sleep apnea (OSA), cerebrovascular accident (CVA), peripheral edema, or late-evening diuretic or fluid intake (Table 2). The workup of NP includes history, physical examination, and laboratory studies designed to evaluate the patient for symptoms and signs of these conditions. Unfortunately, despite appropriate workup, in many patients, clearly identifiable remediable conditions are not found.

Urine output usually decreases during the night. This circadian pattern appears to be closely related to a corresponding increase in secretion of antidiuretic hormone (ADH) during the hours of sleep. Because ADH increases the resorption of water from the renal tubule, higher concentrations of ADH occurring at night result in the production of lower volumes of concentrated urine. Plasma ADH levels are often undetectable during the night in elderly subjects with nocturia, implying a cause and effect relationship between ADH secretion and NP [30]. ADH secretion may also be altered by CVA. Central nervous system lesions due to CVA can affect the hypothalamic–pituitary axis, causing a loss of ADH circadian rhythmicity [31]. Diuresis occasioned by inhibition of ADH action at the renal level may also be induced by prostaglandin E-2, atrial natriuretic peptide, hypercalcemia, hypokalemia, lithium, and tetracyclines [32].

Graugaard-Jensen et al. [33•] provide a clinical study of variables accounting for nocturia in 18 healthy older (age 55–73 y; mean, 61 y) male volunteers. The study population was unusual in that men had only occasional nocturia that was not their presenting symptom or chief complaint. Thus, data derived therein provided a look at the etiology of nocturia in men free of fixed underlying

cardiovascular, renal, endocrine, or urologic diseases. Bladder diary data were correlated with changes in serum aldosterone, angiotensin II, atrial natriuretic peptide, and ADH levels in both settings. Key findings were that NUV was 9.6 mL/kg body weight on nocturic nights (NPI = 0.37) versus 5.2 mL/kg body weight on nonnocturic nights (NPI = 0.24). In the clinic setting, day/night urine output ratio was 1.8 on nocturic nights versus 2.8 on nonnocturic nights. On nocturic nights, the NUV exceeded maximal bladder capacity by 48%, whereas on nonnocturic nights the NUV was only 80% of the maximal bladder capacity. Thus, sporadic nocturia in this healthy male population was attributable to nocturnal urine overproduction in excess of bladder capacity [33].

In this study, the authors suggested that the underlying pathophysiology of nocturia is related to increased mean arterial blood pressure and blunted circadian variation (slower rate of secretion) in ADH on nocturic nights than on nonnocturic nights. Interestingly, the other hormones studied demonstrated normal circadian variation whether or not nocturia was experienced, a finding not consistently demonstrated previously [29]. A study of patients with NP and severe nocturia confirms these findings. The nocturia polyuria indices in these patients were significantly correlated with the overall mean arterial blood pressure, and 86% of the patients studied showed a blunting of the nocturnal ADH surge [26].

OSA is a sudden cessation of respiration due to airway obstruction during sleep. Endeshaw et al. [34] showed elderly patients with severe sleep disordered breathing have a greater number of nocturia episodes. Other studies also reveal that increased severity of OSA predicts greater nocturia [35•,36]. The mechanism for nocturia in these patients is an elevation in atrial natriuretic peptide levels due to increased right atrial transmural pressure resulting from hypoxia-induced pulmonary vasoconstriction [37]. Risk factors for OSA include morbid obesity, acromegaly, asthma, hypertension, adult onset diabetes mellitus, and craniofacial abnormalities. Nocturic patients at increased risk for OSA should be submitted for polysomnographic sleep studies owing to their 30%–40% chances of having OSA [38].

Decreased Nocturnal Bladder Capacity

Nocturia due to diminished bladder capacity is of two types: a global decrease in bladder capacity as expressed by low MVV, or decreased nocturnal bladder capacity. In both conditions, nocturnal urinary volume exceeds bladder capacity and the patient is awakened by the need to void because the bladder does not hold enough. Urologic causes of low nocturnal and global bladder capacity include infravesical obstruction, idiopathic nocturnal detrusor overactivity, neurogenic bladder, cystitis, bladder calculi, ureteral calculi, and neoplasms of the bladder, prostate, or urethra. A urologic workup for etiology of diminished NBC includes cystoscopic and urodynamic techniques for diagnosing these disorders (Table 2). A significant association between patients with severe nocturia and NBC > 2 has been demonstrated; thus, we use the latter as a cutpoint to define nocturia related to diminished nocturnal bladder capacity [25].

Mixed Nocturia

Many patients with nocturia are found to have a combination of NP and low NBC. A recent evaluation of 850 patients with overactive bladder showed that diminished NBC plays a greater role in the pathogenesis of nocturia in younger patients, whereas in older patients NP assumes relatively greater importance [39•]. In a study of 194 nocturic patients, nocturia was due to NP in 7%, low NBC in 57%, global polyuria in 23%, and a mixture of NP and low NBC in 36% [40]. Treatment options may be tailored to predominance of one or several etiologies of nocturia as gleaned by arithmetic analysis of the voiding diary.

Global Polyuria

Polyuria is defined as a 24-hour urine output > 40 mL/kg and causes both daytime urinary frequency and nocturia owing to a general increase in urine output, outstripping even normal bladder capacity. This contrasts with nocturnal polyuria in which the 24-hour urine production remains normal, but there is an increased production of urine throughout the night. Inappropriate excretion of water in polyuria leads to polydipsia to prevent circulatory collapse. Common causes of global polyuria are diabetes mellitus, diabetes insipidus (DI), and primary polydipsia.

Uncontrolled diabetes mellitus leads to hyperglycemia and an osmotic diuresis predisposing patients to nocturia. Treatment for this etiology of nocturia is directed at treating diabetes mellitus and decreasing the serum levels of glucose with diet, oral hypoglycemics, and insulin where indicated.

DI is a disorder of water balance. Central DI is caused by deficient synthesis of antidiuretic hormone secondary to the loss of neurosecretory neurons in the hypothalamus or posterior hypophysis. Nephrogenic DI is due to an inability of the kidneys to respond to ADH. When polyuria is demonstrated using the voiding diary, a water deprivation test (WDT) may be used to distinguish between DI and polydipsia [41]. Water deprivation testing involves the patient refraining from drinking throughout the night. If the patient usually drinks during the night, the test should be done in a monitored setting to prevent dehydration. The first morning void is checked for osmolality. Osmolality > 800 mOsm/kg H_2O indicates that there is normal ADH secretion and normal renal response to ADH. Thus, a normal WDT means that polyuria is due to primary polydipsia. Primary polydipsia is either dipsogenic or psychogenic.

Dipsogenic polydipsia is associated with a history of central neurologic abnormality, such as prior brain trauma, radiation, or surgery. Psychogenic polydipsia is long-term behavioral or psychiatric disorder, treated with behavioral modification to reduce fluid intake, although unfortunately many patients are resistant to such changes. There is no known treatment for dipsogenic polydipsia.

If the water deprivation test is abnormal, a renal concentrating capacity test (RCCT) may be done to distinguish between central and nephrogenic DI. In adults, 40 μg of desmopressin is administered intranasally or 0.4 mg orally. The bladder is emptied and a urine sample for osmolality obtained 3–5 hours later. Water intake is restricted for the first 12 hours after drug administration. The reference level for normal urine osmolality after desmopressin administration is > 800 mOsm/kg for most patients. If RCCT is normal, the patient has central DI that can be treated with desmopressin itself. Considerably reduced concentrating capacity following desmopressin (urine osmolalities < 550 mOsm/kg) indicates nephrogenic DI.

Conclusions

Nocturia, a common disorder in men and women, increases with age. Nocturia can be caused by NP, low nocturnal and/or global bladder capacity, mixed etiology, or global polyuria. Thus, the etiology of nocturia is multifactorial and often unrelated to an underlying urologic condition. A voiding diary is the principal tool for accurate diagnosis, leading to cause-specific treatment of nocturia.

Disclosures

Dr. Weiss is a consultant for Pfizer and Ferring. No further conflicts of interest relevant to this article were reported.

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