

Nocturia

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ABSTRACT

Nocturia, voiding at night, is a bothersome disorder known to have a negative impact on quality of life. The prevalence of nocturia increases with age and it affects men and women equally. A voiding diary is the principal tool in the assessment of nocturia. The underlying pathophysiologic process of nocturia comprises four main conditions: (1) 24-h polyuria, (2) nocturnal polyuria, (3) bladder storage problems, and (4) mixed entities. Effective management should aim at establishing the diagnosis and identifying the underlying causes. A detailed history and physical examination are required for diagnosis. Behavioral and lifestyle changes can be the first step in therapy and can provide some relief. However, pharmacologic treatment such as desmopressin and antimuscarinic agents are often required. This paper outlines the epidemiology, impact, underlying etiologies and diagnostic approach associated with nocturia and reviews current strategies of management.

Key words: nocturia, voiding diary, polyuria

DEFINITION AND EPIDEMIOLOGY

According to the definition of the International Continence Society (ICS), nocturia is a complaint that an individual wakes one or more times to void urine at night [1]. This definition covers any number of voids and each episode is preceded and followed by sleep. Proper assessment of this condition should consider the number of voids per night and the volume of nocturnal urine, which requires that the physician attempt to ascribe a cause to the nocturnal voiding.

It is difficult to get a precise figure for the prevalence of nocturia because epidemiological studies have varied in their definition of this disorder. The overall incidence of nocturia tends to increase with age and occurs almost equally in men and women. However, there is a tendency for young women to have this sole symptom more often than young men. On the contrary, it occurs more often in very old men than very old women [2,3].

In a nationwide telephone survey of 5,204 community-based adults with an average age of 45.8 years, 31% vs 14.2% of respondents reported at least one void vs two voids per night [4].

Studies in Japan and Austria, in which nocturia was defined as ≥ 2 voids per night, found prevalence rates of 28.5% and 11.3%, respectively [2,5]. Generally, the prevalence of nocturia ≥ 2 episodes / night typically varies from 5% to 15% for those 20-50 years old, 20%-30% for those 50-70 years old and 10%-50% for those aged ≥ 70 years [6].

IMPACT

Nocturia is often quoted as the most bothersome of lower urinary tract symptoms, and there is an association between the extent of impact and the frequency of nocturnal voiding [7]. For those rising twice or more at night, the impaired health related quality of life was similar to that of Type II diabetes [4].

An uninterrupted 7-8 hours sleep is necessary for most adults to maintain physical, mental, and emotional well-being. Sleep disturbance caused by nocturnal urinary frequency may result in decreased cognitive performance during daytime, decreased working performance and depression [8]. An evaluation of the Swedish population 40 to 64 years old revealed that nighttime disturbances caused by micturition were associated with sleep disorders, daytime fatigue, poorer quality of sleep and impaired well-being [6].

Quality of life is also negatively affected in the majority who experience nocturia. A number of studies have demonstrated that a high proportion of patients (63%-75%) with nocturia perceive it to be troublesome [6-8]. Schatzl et al found that $>60\%$ of men and women reported that nocturia had a negative effect on their quality of life [2].

Nocturia has also been associated with an increased risk of falling, bone fracture, excessive daytime somnolence and nocturnal enuresis [9]. A study of 1,500 ambulatory patients with an average age of 80 years found that individuals who voided ≥ 2 times per night were significantly more likely to fall than those who did not (odds ratio 1.84; $P=0.03$). Falls significantly increased among patients who voided ≥ 3 times per night (odds ratio 2.15; $P=0.04$) [10].

ETIOLOGY

Because the ICS definition of nocturia does not suggest causation, it is necessary to consider the reasons why an individual might awake at night to empty the bladder. Nocturia is associated with a number of putative conditions or circumstances. Some are clearly common sense and we can rapidly exclude any abnormal pathology in cases of sleep disturbance, fluid intake at night or during the day and medications (including diuretics and analgesics). Other causes include diabetes mellitus (DM), diabetes insipidus (DI), congestive cardiac failure (CHF), overactive bladder (OAB) and benign prostate hyperplasia (BPH).

The underlying pathophysiologic process in nocturia comprises four main conditions: (1) 24-h polyuria (overproduction of urine during a 24-h period), (2) nocturnal polyuria (NP) (overproduction of nocturnal urine), (3) problems with bladder storage, and (4) mixed entities, a combination of NP and bladder storage problems.

24-h polyuria

The condition of 24-h polyuria is recognized when an individual produces more than 40 mL/kg urine over a 24-h period [1]. Affected

individuals have both increased daytime and nighttime urinary volume. The causes of 24-h polyuria include primary thirst disorders, DM, and DI of both central and nephrogenic origin [11]. Central DI results from a dysfunction in the production of antidiuretic hormone (ADH). Nephrogenic DI occurs when kidneys fail to respond to ADH. These conditions can be distinguished with a renal concentrating capacity test (RCCT). Following the administration of oral or intranasal desmopressin combined with water restriction, a urine osmolality of >800 mOsm/kg represents normal renal concentrating ability; thus the patient has central DI. If the RCCT yields low urinary osmolality (<500 mOsm/kg), polyuria is due to nephrogenic DI [12].

Nocturnal polyuria

Nocturnal polyuria refers to a condition with excessive urine production only at night, but the total daily urine output is within normal limits. Healthy young adults between the age of 21 and 35 years old excrete $14 \pm 4\%$ of their total urine volume between 23:00 and 07:00, whereas more elderly people excrete $34 \pm 15\%$ [13]. An appropriate description of nocturnal polyuria from the ICS is a nocturnal urine volume (NUV) of at least one-third of the total daily urine production [1].

Primary nocturnal polyuria may result from abnormality in secretion of ADH at nighttime. Patients with a history of a cerebrovascular accident that affects the hypothalamic-pituitary axis may have an alteration in ADH. ADH secretion normally increases during sleep. If this pattern is altered, water resorption in the collecting duct of the glomerulus is inhibited, which causing nocturnal polyuria [14].

Secondary causes of nocturnal polyuria include lifestyle and dietary factors such as increased consumption of nighttime liquids, caffeine and alcohol. Other causes include right-sided CHF, renal insufficiency, lower extremity edema due to venous stasis or lymphostasis, nephrotic syndrome, hypoalbuminemia and high intake of salt, which may result in third space fluid accumulation, possibly explaining the fluid retention associated with nocturnal polyuria [15].

Nocturnal polyuria has also been associated with obstructive sleep apnea. In this condition, hypoxia of the lungs can lead to pulmonary vasoconstriction and raised concentrations of plasma atrial natriuretic peptide (ANP) which is responsible for elimination of sodium in the urine, resulting in elevated secretion of water while the patient is asleep [16].

Bladder storage problems

This condition is usually secondary to a urological disorder resulting in reduced nocturnal bladder capacity (NBC) or lower urinary tract dysfunction. Urological causes of reduced NBC include bladder outlet obstruction (BOO), idiopathic nocturnal detrusor overactivity, neurogenic bladder, cystitis, learned voiding dysfunction, anxiety disorders, certain pharmacological agents or stones and neoplasms of the lower urinary tract [17].

Mixed nocturia

"Mixed" nocturia is a combination of nocturnal polyuria and decreased NBC. Most patients with nocturia have more than one etiology. In a study of 194 patients in whom nocturia was a chief or significant complaint, 7% had simple nocturnal polyuria, 57% had decreased NBC, and 36% had a mixed etiology [18]. Mixed nocturia is diagnosed through the maintenance and analysis of voiding diaries. In these patients, treatment should be directed at all relevant conditions.

ASSESSMENT AND DIAGNOSIS

In order to diagnose nocturia properly, it is necessary to establish whether the individual is awakening at night to void, or voids because he or she has already awakened. A careful review of etiologies of sleep interruption must include an analysis of sleep-related disorders.

History and physical examination

A detailed history of the problem is required for any patients. These conditions include neurologic disorders, cardiac problems, DM, hypertension, lower urinary tract surgery, sleep disorders, and medications such as diuretics, cardiac glycosides, lithium, phenytoin and calcium antagonists [15]. The usual consumption of alcohol and caffeine should also be ascertained.

During physical examination, obesity should be noted because it increases the risk for sleep apnea. Patients should be screened for lower limb edema to rule out cardiac or renal disease as contributory factors. For female patients, a pelvic examination should be performed to exclude a pelvic mass and significant urogenital prolapse or meatal atrophy. In additions, examination of the pelvic floor muscles should be performed. Pelvic floor muscles are just like other muscles. Exercise can make them stronger. Women with bladder control problems can regain control through pelvic muscle exercises, also called Kegel exercises. Digital rectal examination is important to assess an enlarged prostate for male patients. Neurologic examination should include evaluation of anal tone, the bulbo-cavernous reflex and sensation in the sacral dermatomes.

Urinalysis can exclude the possibility of a lower urinary tract infection and may also be used to screen for DM. Urine osmolality measurement may be useful to exclude DI.

Voiding diary

A voiding diary is the most important diagnostic process for nocturia. Diurnal changes in voiding should include any episodes of incontinence, fluid intake and volume of voided urine. It is important to note that the first morning void is not considered a nocturnal void, although the voided volume from that voiding is counted within the NUV.

A diary provides important data about patterns of micturition, the 24-h total voided volume (TVV) and the maximum voided volume (MVV) which is the largest single recorded volume voided during a 24 hour period. Data from the voiding diary can help a specialist calculate the nocturnal polyuria index (NPI), nocturia index (Ni) and nocturnal bladder capacity index (NBCi), which together assist in establishing the individual's etiology of nocturia [19].

The *NPI* is the NUV divided by the 24-h urine output (NUV/TVV). The *Ni* is the NUV divided by the MVV (NUV/MVV). The predicted number of night time voids (PNV) is derived by subtracting 1 from the *Ni* ($Ni-1$). The *NBCi* is the difference between the actual number of nocturnal voids and the PNV ($ANV-PNV$).

The condition of 24-h polyuria is impressed when an individual produces >40 mL/kg urine over a 24 hour period. An *NPI* $>33\%$ implies nocturnal polyuria. An *NBCi* greater than 0 indicates that nocturia occurs at volumes less than the MVV, implying substantial bladder storage problems. A significant association between severe nocturia and an *NBCi* greater than 2 has been demonstrated [19]. Therefore, urological referral is recommended for these patients.

MANAGEMENT

Searching for the underlying causes of nocturia is the first step in treatment. Particular attention should be given to excluding and treating any underlying medical comorbidities such as DM, DI, CHF and sleep apnea syndrome. Control of blood sugar may improve symptoms in patients with DM. On the contrary, treatment of DI requires an accurate evaluation of the etiology. The use of nasal continuous positive airway pressure can be used to treat sleep apnea, and therefore, reduce nocturia associated with this respiratory and sleep disorder. Urological causes should be treated according to the underlying etiologies including BPH, detrusor overactivity, neurogenic bladder, cystitis, stones and neoplasms. Any infections should be treated and current medications evaluated and even altered. Psychiatric referral and treatment are advised for patients with primary polydipsia.

Behavior therapy

In patients with nocturnal polyuria, the first treatment step is lifestyle and behavioral modification. Fluid intake including alcohol and caffeine consumption in the evening should be eliminated. If nocturia is the result of gravity-induced third space fluid accumulation in the lower extremities, compression stockings may be used. Patients can elevate their legs during the late afternoon to simulate sleep which increases venous return to increase urine output at dusk and diminish the fluid burden during nighttime sleep. Diuretics given during the late afternoon or early evening may also help to decrease third space fluid accumulation [15].

Pharmacotherapy

At present, the first-line medications for nocturia are desmopressin acetate and several different antimuscarinic agents. When treating elderly patients with comorbidity, it is important to consider potential adverse interactions between the nocturia therapy and other medications that they are taking.

Desmopressin is effective and well tolerated in children and adults with DI or nocturnal enuresis. It is available in nasal, oral, and parenteral formulations [15]. In general, desmopressin increases the sleep time until the first nocturnal void and decreases the number of nocturnal voids, NUV voided and the NPI [20-24]. Central DI can be treated with desmopressin, but nephrogenic DI may be caused by certain medications such as tetracycline and lithium. Primary renal disease is possible and a nephrological referral is recommended for these patients.

The main side-effects of desmopressin are headache, nausea and significant hyponatremia which may develop in 7% patients [24]. The risk of hyponatremia with desmopressin, appears to increase with age. It is therefore advised that desmopressin be given to elderly patients only with careful monitoring of plasma sodium [21]. However, desmopressin should be avoided in patients with primary polydipsia-related polyuria and liver cirrhosis [25]. Patients with CHF who receive desmopressin should be reminded to restrict evening fluid intake to minimize fluid retention. Which may be associated with the development of acute CHF [26].

Antimuscarinic agents, including trospium chloride, oxybutynin chloride, tolterodine tartrate, darifenacin hydrobromide and solifenacin succinate are the first-line drugs for OAB and other bladder-related symptoms. However, there is no data to support which agent is best. Historically, antidepressant drugs such as imipramine have also been

used in the treatment of OAB and nocturnal enuresis. However, it should not be considered a first-line medication because of concerns about prolongation of the Q-T interval which may cause cardiac arrhythmias [27].

In addition to direct inhibition of muscarinic receptors within the detrusor muscle, antimuscarinics also work via afferent pathways, mitigating the sensation of urgency [28-30]. Some clinical trials have revealed improvement in nocturia associated with OAB, providing further evidence for this application [31-33].

Adverse events from antimuscarinics include dry mouth, constipation, headache, and dizziness [28]. Despite these adverse effects, antimuscarinic therapy appears to offer a positive benefit risk ratio for many highly selected patients with OAB. However, antimuscarinics should be cautiously prescribed in patients with risks for urinary retention. They are contraindicated in patients with untreated closed-angle glaucoma and those with delayed gastric emptying [26].

Botulinum toxin is a presynaptic neuromuscular blocking agent which has been extensively studied for bladder-related dysfunction. It has been shown to reduce nocturia in patients with OAB without detrusor overactivity [34]. Botulinum toxin therapy is limited by its expense and short durability of efficacy, and repeated injections are necessary to sustain its effectiveness [35-37]. It may be useful in patients who are refractory to antimuscarinic treatment [38-40].

Surgery

Surgical correction, such as transurethral prostatectomy and pelvic organ prolapse repair, may be appropriate when obstruction is suspected to be a significant causative factor in nocturia, especially for those with post voiding residual urine due to bladder outlet obstruction or bladder irritation due to vaginal mass (prolapse) effect. Sacral nerve neuromodulation [41], detrusor myectomy and clam cystoplasty [42,43] are options for the treatment of patients with intractable nocturia associated with OAB.

CONCLUSIONS

Nocturia is a bothersome symptom which is known to adversely affect quality of life, cause sleep deprivation and reduce daily productivity. It is present equally in men and women and the prevalence increases with age. The causes of nocturia are often multifactorial and a thorough investigation is essential to find and treat underlying causes.

A detailed history and physical examination are required for diagnosis of nocturia. A voiding diary is the principal diagnostic tool for assessing nocturia. Behavioral and lifestyle modification can be the first therapeutic step and may provide some relief, but medications such as desmopressin and antimuscarinic agents are often required. However, the risks of adverse events associated with available medications require careful selection and monitoring to optimize the therapeutic index.

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