W14: Nocturia, what about it?

Workshop Chair: Karel Everaert, Belgium

20 October 2014 14:00 - 18:00

Start	End	Topic	Speakers
14:00	14:30	Nocturia frequency, bother and quality of life: how often is too often?	• Kari Tikkinen
14:30	15:00	Causes, consequences and comorbidities?	• Jeffrey Weiss
15:00	15:30	What is the ideal diagnostic approach of nocturia/nocturnal polyuria?	• An-Sofie Goessaert
15:30	16:00	Break	None
16:00	16:30	How to address nocturia in patients with BPH?	• Matthias Oelke
16:30	17:00	How to address nocturia in patients with OAB?	• Alan Wein
17:00	17:30	How to address nocturia in older patients?	• Karel Everaert
17:30	18:00	Hormones and nocturia – guidelines for treatment?	• An-Sofie Goessaert

Aims of course/workshop

This workshop offers a comprehensive overview on the current knowledge on nocturia on an advanced level. In the first diagnostic part we will clarify the importance of nocturia and the effect on quality of life, sleep and general health. Based on patient characteristics a guidance for an advanced diagnostic approach will be set out.
In the second therapeutic part, nocturia in specific patient groups and the implications on treatment will be discussed. Besides, an overview on the different hormones involved in diuresis will be set forth as a guidance for treatment.

An interactive session at the end will give the audience the possibility to get a practical feeling with the new knowledge.

Nocturia: Causes, Consequences and Comorbidities

J. Weiss, Urology Dept. SUNY Downstate College of Medicine, Brooklyn, NY, USA

- Nocturia can be divided into upper vs. lower tract causes:
    - Medical/Renal
        - Nocturnal polyuria
        - Global (24 hour) polyuria
    - Urological/Lower tract dysfunction
        - Diminished global/nocturnal bladder capacity
- Nocturnal polyuria
    - Congestive heart failure
    - Diabetes mellitus
    - Obstructive sleep apnea
    - Peripheral edema
    - Excessive nighttime fluid intake
- Diminished global/NBC
    - Prostatic obstruction
    - Nocturnal detrusor overactivity
    - Neurogenic bladder
    - Cancer of bladder, prostate, or urethra
    - Learned voiding dysfunction
    - Anxiety disorders
    - Pharmacologic agents
        - Ketamine (street drug: “Special K”)
        - Tiaprofenic acid
        - cyclophosphamide
    - Bladder calculi
    - Ureteral calculi
- Polyuria (global)
    - Diabetes mellitus
    - Diabetes insipidus
        - Idiopathic
        - Trauma
        - Primary pituitary tumors (craniopharyngioma)
        - Metastatic disease (lung, breast)
        - Infiltrative disease (sarcoid, Wegener’s)
        - Infarction (Sheehan’s post partum)
        - Infection (TB, meningitis)
    - Primary polydipsia
        - Dipsogenic
        - Psychogenic
- Classification of nocturia through use of the voiding diary “unlocks” up to 17 significant underlying medical conditions which potentially contribute to its genesis
- Nocturnal polyuria (NP) may be defined as excessive urine production in comparison with:
    - 24 hour output
    - bladder capacity
    - neither (absolute diuresis rate during sleep)
- NP: Causes
    - Obstructive sleep apnea

    - Pharmaceuticals
        - Diuretics
        - SSRIs
        - Calcium channel blockers
        - Lithium
- Nocturia related to
    - Hypertension
    - Sleep disruption
    - Reduced immunity
    - Impaired glucose metabolism
    - Reduced vasopressin levels
- Relationship between N3 (Slow wave) sleep and nocturia
- Nocturia, sleep disruption and the metabolic syndrome
- Nocturia related to early mortality
    - Risk of coronary heart disease in younger patients
    - Mortality in the elderly
- Nocturia is a risk factor for falls, fractures
- Impaired physical and mental health
    - Proportionate to nocturia severity
- Nocturia in overactive bladder population
    - Related to nocturnal urine overproduction in older men and women
    - Related to low nocturnal bladder capacity in younger men and women
- Nocturia index (NUV/MVV) single diary-based parameter most closely determining nocturia severity
- Low bladder compliance, low bladder capacity are risk factors in nocturia severity

What is the ideal diagnostic approach of nocturia/NP?

A. Goessaert, Urology Dept. Ghent University Hospital, Belgium

A complete diagnostic evaluation is invaluable to initiate an adapted and individualised treatment. All patients with bothersome nocturia need to complete a frequency volume chart (FVC) and a questionnaire on sleep quality to diagnose the underlying cause(s) of nocturia: NP, 24h-polyuria, RFBC and sleep disorders. Patients with NP should have an additional evaluation with a renal function profile to evaluate abnormalities in glomerular filtration, osmotic diuresis and water diuresis.

1) Frequency volume chart (FVC)

Table 1: Information deducted from a FVC

	Unit
Diurnal voiding frequency Daytime voiding frequency Nighttime voiding frequency	number
Diurnal urine production Nocturnal urine production (NUP)	ml
Diurnal diuresis rate Nocturnal diuresis rate	ml/min
Functional bladder capacity (FBC) = maximal voided volume in 24h Mean FBC daytime = mean of voided volumes during daytime Mean FBC nighttime = mean of voided volumes during nighttime	ml
Mean hours of sleep	h
Diurnal fluid intake	ml
Frequency of diurnal incontinence episodes Frequency of nocturnal incontinence episodes	number
Mean volume of incontinence	g
Nocturia index (NI) = NUP/FBC → Nocturia if >1	/
NP33 definition: NP index (NPi) = NUP/24h-diuresis → NP if >33%	%
NUP90 definition = NUP/hours of sleep → NP if >90ml/h	ml/h
Nocturnal bladder capacity index (NBCI) = actual – predicted number of voids (= NI-1) → RFBC if >1.3	/

- **Nocturnal polyuria**

Various definitions for NP can be used when analysing a FVC (e.g. NPi33 or NUP90). In order to adapt treatment according to the underlying cause, we suggest to perform a renal function in all patients with NP.

- **24h-polyuria**

In patients with a 24h-diuresis exceeding 40ml/kg bodyweight, the most common disorders should be considered by evaluating: fluid intake (polydipsia), glucose or HbA1c (diabetes mellitus), low urinary osmolality on RFP (diabetes insipidus)

- **Reduced functional bladder capacity**

Because there are no cut-off values for a normal bladder capacity, the diagnosis of a RFBC is based on the NBCi (table 1). Further urological investigation with uroflowmetry, ultrasonography and urodynamics are recommended to explore the cause of the RBC.

2) Questionnaires on sleep quality

The Pittsburgh Sleep Quality Index (PSQI) contains 19 self-rated questions used to measure sleep quality over the past month in the following 7 domains:

- subjective sleep quality
- sleep latency
- sleep duration
- habitual sleep efficiency
- sleep disturbances
- use of sleeping medication
- daytime dysfunction

A polysomnography is recommended when a sleep disorder (e.g. obstructive sleep apnea syndrome) is suspected.

3) Renal function profile (RFP)

A renal function profile is a 24 hour test based on the collection of a urine sample every 3 hours to analyse diuresis rate, osmolality, sodium, urea and creatinine concentrations (figure 3). The voided volume at the time of sample collection has to be registered, as well as volumes of any interim micturition. This test starts in the morning with the first sample 3 hours after the first morning micturition. Urinary sample U1 is collected between 9 and 11am, U2 between 12 and 2pm, U3 between 3 and 5pm, U4 between 6 and 8pm, U5 between 9 and 11pm, U6 between 12 and 2am, U7 between 3 and 5am and U8 between 6 and 8am. A blood sample is taken to determine plasma osmolality, sodium, urea and creatinine.

The RFP makes it possible to identify the pathophysiological mechanism(s) of NP. Since there are no cut-off values, circadian rhythms are analysed by comparing the individual values of the 8 urine samples or by comparing the mean daytime and nighttime results.

Table 2: Information deducted from a RFP

Parameter	Formula	Pathophysiologic
Creatinine clearance	$C_{Cr} = (U_{Cr} * V) / P_{Cr}$	Glomerular hyperfiltration
Sodium clearance	$C_{Na+} = (U_{Na+} * V) / P_{Na+}$	Sodium diuresis
Free water clearance	$C_{H2O} = V - (U_{osm} / P_{osm}) * V$	Water diuresis

How to address nocturia in patients with OAB?

A. Wein, Urology Dept. University of Pennsylvania, USA

Nocturia used to be attributed to BPH or OAB or a combination, and the assumption was that treatment directed towards OAB or residual urine volume would correct the nocturia. Unfortunately, in most circumstances, this has not proven to be the case. The treatment options for OAB will be reviewed and the results updated with respect to nocturia with emphasis on the difference between statistically and clinically significant outcomes. With respect to pharmacologic therapy directed specifically towards OAB, the inclusion criteria are clearly those of OAB, with respect to other types of therapy, the inclusion criteria are not so clear with respect to the presence of "urgency", the hallmark symptom.

Simple Logic: to decrease nocturia

1. Decrease bladder activation on the motor or sensory side
2. Decrease nocturnal urine production
3. Decrease significant residual urine volume and thereby increase functional bladder capacity

What are the outcome indicators for "success" and what represents a significant improvement or goal ?

Therapies to be reviewed:

1. Obstructive sleep apnea
2. Obstructive benign prostatic enlargement
    a. Alpha adrenergic blocking agents
    b. Outlet reduction
3. Antimuscarinics
4. Combined therapy(2a + 3)
5. Lifestyle modifications
6. DDAVP medication

How to address nocturia and nocturnal polyuria in older patients??

K. Everaert, Urology Dept. Ghent University Hospital, Belgium

Introduction

Although the problem of nocturnal polyuria has been recognized, its pathophysiological mechanism remain unclear. Since urine output depends on water intake, distribution and excretion, it is evident that abnormalities in each of these components could affect urinary output (1). First, it is considered that the circadian rhythm in the secretion of the anti-diuretic hormone, arginine vasopressin (AVP), is disturbed in the same way as in children with enuresis and aged persons with nocturnal polyuria. Healthy individuals produce smaller volumes of concentrated urine during the night due to the increased nocturnal vasopressin secretion but this would be inadequate or even absent in elderly and therefore contribute to an increased water diuresis (2;4). Second, it is known that elderly like patients with spinal cord lesions experience fluid retention in the lower extremities during daytime because of the absence of the pumping action of the leg muscles and the vessel tone loss that is attributed to the chronic autonomic failure. Changing position during the night to a recumbent position, increases intravascular volume and causes a surplus of fluid that is presented to the kidney and leads to a higher nocturnal diuresis (2-4). This increased intravascular volume also stimulates secretion of the atrial natriuretic peptide (ANP) which contributes to an increased solute diuresis by increasing natriuresis (1;5).

Nocturnal polyuria in elderly people

Nocturnal polyuria is a highly age-dependent condition, affecting up to 85% of the elderly population (>65 years old).(6) A decrease in renal concentrating ability appears to be a normal ageing process, which might already lead to a higher nocturnal urine production, but a decrease of nocturnal ADH secretion with an increased diuresis at one hand and/or an increase of nocturnal ANP secretion with an increased natriuresis at the other hand seem to lay at the base of excessive nocturnal urine production.(7,8) Anyhow, it is a multifactorial condition, especially in the elderly, who often have an extended medical history and accompanying medical therapy list.

Nocturnal polyuria and incontinence

A review from 2007 published that 44% of women and 29% of men suffer from UI once they are older than 65 years. Over 80 years, the prevalence rates are respectively 57% and 42%. For elderly who are institutionalized, the prevalence rates increases up to 77%. It affects more women and is an important indicator of institutionalization (9,10). With the global population aging, the absolute numbers of elderly people, also those who suffer from UI, will increase exponentially in the future.

In our study, 84% of the institutionalised elderly have nocturnal polyuria and 40% of the subjects with nocturnal polyuria present with nocturia, whereas 52% presents with incontinence; the latter group has significantly higher nocturnal urine volumes and experiences a more pronounced influence on quality of life

compared to those who can get up at night to void. And although the need for incontinence material might not only depend on bladder related problems, it seems that reducing the nocturnal urine volume might improve quality of life within the subgroup of patients wearing incontinence material because of nocturnal enuresis by reducing the need for incontinence material. Our analysis shows that a nocturnal volume of ≥625 mL is a risk factor for the need of incontinence material . This suggests that nocturnal overdistension of the bladder beyond this point leads to incontinence rather than nocturia. Combining this incidental overflow incontinence with lower urethral resistance, overactivity of the bladder and obstruction/detrusor underactivity results in complex forms of incontinence explaining our feelings that elderly with incontinence are therapy resistant and have a lot of side effects. Often only urinary diversionsor diapers are successful options.

Nocturnal polyuria and retention

Besides incontinence, nocturnal polyuria can lead to urinary retention due to the combination of the mismatch between the bladder capacity and the increased nocturnal urine production rate together with a decreasing bladder sensation and decreasing detrusor contractility. Depending of the time of the day, there is a significant variability in the post-voided residual urine volume measurements with highest volume ocurring in the morning.

Reduced bladder capacity due to nocturnal retention, OAB, obstruction or detrusor underactivity is together with nocturnal polyuria a major cause of invalidating nocturia in elderly patients with preserved bladder sensation.

Redefining the concept of LUTS in elderly

We currently recognize 3 ethiopathogenetic causes for UI that can exist as a solitary condition or co-exist with each other:

1. LUTS associated with disorders of the emptying faze of the bladder (obstruction, detrusor underactivity).
2. LUTS associated with disorders of the filling faze of the bladder (overactive bladder syndrome, decreased urethral resistance).
3. LUTS associated with overdistention of the bladder (related to polyuria, loss in bladder sensation).

Conclusion:

Nocturnal polyuria is more than nocturnal enuresis and nocturia but can cause important decrease in quality of life due to nocturnal incontinence and urinary retention and can be highly invalidating, sometimes demanding for major surgery like urinary diversion.

Hormones and nocturia – guidelines for treatment?

A. Goessaert, Urology Dept. Ghent University Hospital, Belgium

	Antidiuresis			Diuresis
What?	**Arginine-vasopressine or antidiuretic hormone**	**Angiotensine II**	**Aldosterone**	**Atrial natriuretic peptie**
Site of synthesis?	Neurohypophysis	Lungs	Adrenal glands	Atria
Site of effect in kidney?	Cortical and medullary collecting tubule	Proximal tubule	Cortical collecting tubule (epithelial sodium channels)	Glomeruli & inner medullary collecting duct
Receptors?	V2-receptor	AT1-receptor	MR-receptor	NPR-A
Main effect in kidney?	Antidiuresis through water reabsorption by fusion of aquaporin-2 channels with luminal membrane	Antidiuresis through: - Sodium reabsorption, both directly and indirectly (stimulation of aldosterone secretion) - Water reabsorption, indirectly (sodium reabsorption and stimulation of ADH)	Antidiuresis through sodium reabsorption	Natriuresis through: - inhibition of sodium reabsorption directly and indirectly (inhibition of RAAS) - inhibition of water reabsorption indirectly (diminish response to ADH)
Stimulating factors?	- Hyperosmolality - Hypovolemia - stress e.g. pain - hypoglycemia	Increase in renin due to: - Low blood volume - Low Na+ concentration in distal tubule - Drop in blood pressure	- Ang II - Plasma K+ concentration - ACTH	- Volume expansion with atrial stretch - Aldosterone escape
Role in nocturnal polyuria?	Reduced e.g. in nocturnal enuresis	Reduced e.g. in hypertension	Reduced e.g. sleep apnea syndrome	Increased e.g. in heart failure
V = vasopressin; AT = angiotensin; MR = mineralocorticoid; NPR = natriuretic peptide receptor; ADH = antidiuretic hormone; RAAS = renin-angiotensin-aldosteron system; Ang = angiotensin; ACTH = adrenocorticotropic hormone				

Hormones	**Main effect**	**Consequence**	**Therapeutical implication for NP**
Prostaglandins: - PGE2 - PGI2	→ antagonizes ADH → antagonizes RAAS	Diuresis	NSAIDs
Melatonin	stimulates ADH stimulates RAAS	Antidiuresis	Melatonin
Sex hormones: - estrogens - progesterone - testosterone	→ stimulates ADH, Renin, Ang II, ANP; inhibits Aldosteron → stimulates Aldosteron; antagonizes ADH, ANP → stimulates ADH, Renin, Ang II	Antidiuresis	Replacement therapy if necessary
PGE2: Prostaglandin E2; PGI2: Prostaglandin I2; ADH: antidiuretic hormone; RAAS: renin-angiotensin-aldosterone system; ANP: atrial natriuretic peptide; NSAIDs: non-steroidal anti-inflammatory drugs			