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Contents:

Endocrine Aspect of Nocturia and Management

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The main contributing causes of nocturia include bladder storage problems, sleep disorders, advanced age, nocturnal and global polyuria, as well as mixed etiology (1,2).

Nocturnal and Global Polyuria

Nocturnal polyuria is defined as nocturnal urine volume/24-h urine volume (nocturnal polyuria index) ≥ 0.33 in elderly (> 65years old) and ≥ 0.2 in youth (3). Global Polyuria denoted by 24-h urine volume ≥ 40mL/kg bw (3). Polyuria can be the result of water diuresis (urine osmolality < 250mosmol/kg) or solute diuresis (urine osmolality > 300mosmol/kg) or combination.

Water diuresis happens in the setting of diabetes insipidus and primary polydipsia. Solute diuresis can occur due to the osmotic effects of excessive glucose in diabetes mellites, excessive sodium in relief of urinary tract obstruction, excessive urea in recovery from acute tubular necrosis or exogenous solute such as mannitol). Combined water and solute diuresis can take place in post-obstructive diuresis and recovery phase of acute tubular necrosis.

Nocturnal Polyuria

The underlying etiologies of nocturnal polyuria include age related change in circadian rhythm of urine output and ADH peripheral edema (when there is net transfer of fluid from the "third space" compartment back into the intravascular compartment at recumbent position), chronic heart failures (there is improved renal hemodynamics with sodium excretion at recumbent position), damage to renal tubules (due to diabetes, chronic kidney disease etc resulting in increased nocturnal solute excretion and loss of urinary concentrating ability), sleep apnea (with increased atrial natriuretic peptide), as well as excess fluid in the evening especially alcohol and caffeine.

Global Polyuria

The main causes of global polyuria include diabetes mellitus, diabetes insipidus, primary polydipsia, heavy alcohol drinking and usage of diuretics.

Diabetes insipidus (DI)

There are three forms of diabetes insipidus, namely cranial, nephrogenic and gestational. In all forms, there is reduced urine concentrating ability with resulting global polyuria, increased serum osmolality and reduced intravascular volume.

Central diabetes insipidus (CDI) is the result of decreased anti-diuretic hormone (ADH) secretion. CDI can either be acquired or congenital. Common acquired causes include trauma (surgery or head injury), vascular (stroke, anterior communicating artery aneurysm), neoplastic

(craniopharyngioma, meningioma, germinoma, pituitary tumor or metastases), lymphocytic hypophysitis, drugs/toxin (ethanol, snake venom) and idiopathic.

Nephrogenic diabetes insipidus (NDI), on the other hand, is the result of kidney resistance to the action of ADH. NDI can also be acquired or congenital. Common acquired causes include drug induced (lithium), infiltrating lesions (sarcoidosis, amyloidosis, myeloma), electrolyte imbalance (hypokalemia, hypercalcemia) and intrinsic renal diseases.

Gestational diabetes insipidus can occur during pregnancy and especially associated with multiple pregnancies, pre-clampsia, HELLP (hemolysis, elevated liver enzymes and low platelet count) and fatty liver of pregnancy.

Subjects with primary polydipsia can be differentiated from those with CDI or NDI by fluid deprivation. After fluid deprivation, urine osmolality in subjects with primary polydipsia will increase to > 750mosm/kg. However, in subjects with either complete CDI or NDI, urine osmolality remains as low as < 300 mOsm/kg. After desmopressin (DDAVP), subjects with complete CDI respond with increase in urine osmolality to > 750mOsm/kg while urine osmolality in subjects with NDI remain low. Subjects with partial CDI or NDI may have urine osmolality between 300-750mosm/kg after fluid deprivation with increase to < 750mosm/kg after DDAVP while those with chronic primary polydipsia may also display these figures due to medullary washout.

Diabetes Mellitus (DM)

Nocturia can occur in subjects with DM due to poor control leading to osmotic diuresis, obstructive sleep apnea (OSA), associated DM neuropathy or chronic renal failure and metabolic syndrome. Moderate or severe OSA can result in increased overnight urine production which is more evident in subjects with DM (4).

Early diabetic autonomic dysfunction of the urinary system can manifest as bladder instability and hypersensitivity with detrusor over activity leading to nocturia. With time, myopathy may set in, leading to reduced destrusor contractility, resulting in incomplete emptying. In the most severe form, bladder cystopathy, there is reduced bladder sensation and contractility with resulting increased postvoid residual urine.

Obesity, metabolic syndrome and DM are related to development of benign prostatic hyperplasia (BPH) and lower urinary tract syndrome (LUTS) in men (5,6). Worsen a1c was shown to be associated with increase chance of LUTS (7). Two recent meta-analysis confirmed higher prostatic growth rate and larger prostate volume in BPH subjects with metabolic syndrome (8,9). The mediators underlie metabolic syndrome and BPH include sex steroid as well as visceral adiposity and dyslipidemia leading to chronic low grade pro-inflammatory state.

Aging, sleep Disorder, testosterone deficiency and nocturia

Aging, sleep disorder, testosterone deficiency and nocturia are interrelated. Sleep disorders can be primary or secondary. Hormonal disorders, medications including steroid and thyroid hormones are potential secondary causes. Aging can lead to sleep disorders, testosterone deficiency as well as nocturia, with the later three conditions affecting each other. Endogenous testosterone production depends on the first three hours of uninterrupted sleep. Various sleep disorders (poor quality, short duration, circadian rhythm disruption with aging and sleep apnea) can result in low testosterone level. On the other hand, age-related change in neuroendocrine functions (growth hormones, cortisol, melatonin and sex hormones) can result in alterations of sleep quality and architecture.

Androgen receptors are found in the urothelium, urinary bladder, prostate and urethra. Testosterone can impact bladder smooth muscle differentiation, phosphodiesterase-5 activity and pelvic blood flow. Testosterone also has a physiological role in maintenance of ADH level. Gradual reduction in level of testosterone can be seen after 40 or even 30 years of old (11) due to lower number of leydig cells, decrease response to LH/FSH, lessen testicular blood flow or external factors (systemic diseases, drugs, environment and lifestyle). Testosterone deficiency can result in sleep disorder, lower urine concentration ability, metabolic syndrome, LUTS and overactive bladder. All these can lead to nocturia. Among men with BPH and LUTS, it was shown in multiple studies that nocturia correlated with lower level of testosterone (12). Moreover, when treated with DDAVP, testosterone level also increased (13). Short term study showed that testosterone replacement therapy (TRT) can improve sleep quality, LUTS and nocturia (14,15). However, systematic review showed that International Prostate Symptom Score did not change with TRT (16).

Treatment

Treatment for nocturia should address causative factors. We should screen for and optimize control of any underlying systemic diseases (diabetes insipidus, diabetes mellitus, congestive heart failure, sleep apnea etc), remove any offending drugs (e.g. lithium) and advise behavioral modification. Treatment for sleep disorders can also help to improve nocturia. Continuous positive airway pressure (cPAP) treatment for OSA helps to improve nocturia (17).

Behavioral modification with special attention to water and fluid intake is important although no RCT has been performed. The mean value for 24hour urine volume for healthy adults is around 23 ± 2 ml/kg. Intake of water <20ml/kg per day may result in dehydration while >30ml/kg can lead to hyponatremia and nocturnal polyuria. Excessive consumption of water, especially alcohol and caffeine, should be avoided starting from late afternoon. Exercise in the evening can be helpful because the pumping action of muscles will return interstitial fluid to blood vessels. Exercise on the whole reduces stress and excess water can also be lost as sweat. Multiple studies (18-22) and meta-analysis (23) showed that physical activities and weight loss can reduce occurrence and progression of BPH as well as LUTS. Consumption of fruits and vegetables especially those rich in β carotene, lutein and vitamin C, are also helpful (23-25). Daytime nap for a duration of shorter than half an hour with feet elevated is also helpful. For patients on diuretics, drugs should be taken at least six hours prior to bedtime.

Demopressin (DDAVP) is the only recommended treatment for nocturnal polyuria according to both the European and American guidelines (level of evidence 1, grade of recommendation A). DDAVP is a synthetic analogue of anti-diuretic hormone (ADH) with antiduretic action 3-10 times the parent hormone. It binds to V2 receptor at the renal collecting ducts and ascending limb of Henle's loop to increase intracellular adenylate cyclase with resulting increase in water resorption. It is proven to reduce number of nocturnal voids, increase time to first void and improve quality of life in nocturia subjects. Adverse drug reactions (ADRs) tend to occur early and predominantly affect subjects ≥ 65 years old and mostly related to dosage. The most common ADRs include headache, lower limb edema, nausea, dizziness and hyponatremia. ADRs tend to be mild to moderate in severity and resolved with discontinuation of drugs or limit water intake. The effective dose is lower for women (25mcg) compared to men (50mcg) since women are more sensitive to the effect of DDAVP while also more prone to hyponatremia (26). This is because the gene coding for V2 receptor is located on X chromosome with female expressing higher level of transcripts compared to males. In 2017, FDA approved DDAVP nasal spray for the treatment of nocturia in adults awaken ≥ two times per night to urinate. In June 2018, oral disintegrating tablet (ODT) form of DDAVP

(Nocdurna) was approved. It is a sublingual tablet with shorter duration of action while higher bioavailability. It is recommended to be taken one hour before sleep without water and will reduce nocturnal voids 52% in women and 43% in men compared to baseline. Symptoms of hyponatremia may be non-specific. If hyponatremia develops, we should withdraw DDAVP, institute fluid restriction and consider diuretics. Patient should be re-examined within 3 days for presence of edema, body weight and sodium level.

In order to prevent hyponatremia, FDA recommended that sodium level be checked before starting of DDAVP, recheck one week and one month later then periodically. Closer monitoring is required if patient is ≥65 years old or taking other drugs which post them at increased risk. These drugs include psychotropic drugs (tricyclic anti-depressants, selective serotonin reuptake inhibitors, chlorpromazine), anti-convulsants (lamotrigine, carbamazepine), opiate, thiazide, sulfonylureas and NSAIDs. Patients should be warned to limit fluid intake one hour before and eight hours after dosing. The following situations posted a patient at heightened risk of hyponatremia and are contraindications for usage of DDAVP: history of hyponatremia, polydipsia, eGFR < 50ml/min, currently taking loop diuretics or steroid, illness associated with fluid or electrolytes imbalance (gastroenteritis, salt losing nephropathies, systemic infection), syndrome of inappropriate ADH. DDAVP should also be avoid in patients with congestive heart failure and uncontrolled hypertension because of risk of worsening of these two conditions.

Conclusions

Main causes for nocturia include local problems, sleep disorders and polyuria (global or nocturnal). Causes for nocturnal polyuria include age related change in circadian rhythm, peripheral edema, damage to renal tubules, sleep apnea, excess fluid intake etc. Main causes for global polyuria include DI, DM, diuretic usage and primary polydipsia. Treatment of nocturia should address causative factors. Behavioral changes, screen for and optimize control of underlying systemic diseases, remove offending drugs, treat sleep disorders are all useful. DDAVP is the only recommended drug treatment for nocturnal polyuria. Hyponatremia is the most important side effect of DDAVP. Recent data on relationship between metabolic syndrome, late onset hypogonadism, BPH/LUTS and nocturia may have therapeutic implications and worth further studies.

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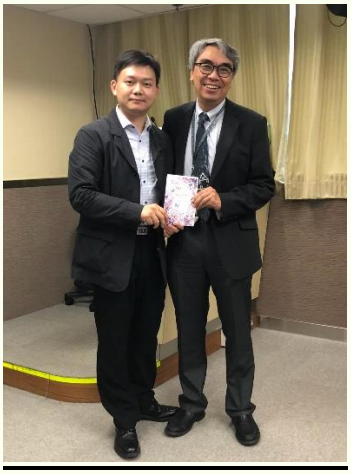
Dr. Leung Man Fuk presents gift to Dr. Greg Mak

Dr. Leung Man Fuk presents gift to Dr. Mak Siu King



Dr. Tong Bing Chung presents gift to Dr. Tony Chan

Dr. Tong Bing Chung presents gift to Dr. Elaine Cheung

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