The Association between Overactive Bladder and Lower Urinary Tract Symptoms/Benign Prostate Hyperplasia

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INTRODUCTION

Overactive bladder (OAB) affects both young and old adults, and the prevalence increases with age [1]. The symptoms of OAB, such as frequency, urgency, and/or urge incontinence, overlap with those attributed to the irritated symptoms of bladder outlet obstruction (BOO). Thus, the association of OAB and lower urinary tract symptoms/benign prostate hyperplasia (LUTS/BPH) should be taken into consideration in care and discussion.

OAB IN MALE PATIENTS: BLADDER, OUTLET OR BOTH?

Urinary urgency and frequency cannot easily be explained directly by obstruction; the secondary effects of obstruction on the bladder are identified as causative factors. The possible causative factors of urinary urgency and frequency include infravesical obstruction and primary bladder abnormality [2].

DIAGNOSIS OF BOO

The prevalence of OAB increases with age. The symptoms of OAB are similar to the irritated symptoms of BOO. Therefore, diagnosis of BOO seems to be important. Clinically, uroflowmetry can be used as a screening tool due to its ease of performance and low cost. However, uroflowmetry cannot differentiate between urinary bladder problems and bladder outlet problems. A low flow rate may be due to BOO or poor contractility of the urinary bladder. Although pressure-flow study is an invasive diagnostic tool, it can be used to identify the presence and severity of BOO. Obstructive symptoms, such as weak stream, terminal dribble, hesitancy, incomplete emptying and intermittency, are the most prevalent symptoms in patients with BOO. However, irritative symptoms, such as frequency, urgency, urge incontinence and nocturia, are the most bothersome symptoms for patients with BOO.

MALE BLADDER CONTROL PROBLEMS: A GUIDE TO ASSESSMENT

In men presenting with symptoms of urgency and frequency, a differential diagnosis between OAB and benign prostatic disease must be made because their cause and treatment are different. Empiric treatment of urgency symptoms may cause them to worsen if the diagnosis is not correct [3]. In men with BOO, it is difficult to identify the etiology of LUTS. OAB occurs in 52% to 80% of men with BOO [4].

Up to 38% of men with BOO continue to suffer from OAB after surgical relief of the obstruction [5]. Twelve elderly patients with bladder instability were included in a study and only 1 became stable after prostatectomy. Is the bladder instability due to age, bladder related changes or the irreversible changes in the bladder due to BOO [6]? OAB symptoms affect male patients. Many men suffer from storage symptoms that may be more related to bladder dysfunction than to BOO [7].

MECHANISMS OF BLADDER DISEASE

(1) The role of nerve growth factor (NGF) in the pathophysiology of bladder disorders: (A) clinically, NGF levels are elevated in the bladders of men with BPH, women with interstitial cystitis and in patients with idiopathic OAB. Blockade of NGF, using either an endogenous antibody or an antibody against the NGF receptor, prevents bladder overactivity in experimental models [8]; (B) the ability of NGF to trigger bladder overactivity might rely on altering the properties of sodium or potassium channels (or their expression) in bladder afferent fibers [8].

(2) Gap junction in a rat model of bladder overactivity following partial BOO: increased connexin43-mediated intercellular communication in a rat model of bladder overactivity following partial BOO in rats. Partial BOO produces an OAB that may be more dependent on intercellular communication through gap junctions for modulation of contractile responses than its normal counterpart [9].

WHAT HAPPENS IN THE BLADDER AFTER BOO?

Bladder changes in BOO mice: non-voiding bladder activity was consistently recorded in BOO mice; both frequency and amplitude increased significantly ($p<0.01$). BOO bladders showed bladder wall hypertrophy [10]. Strength of the detrusor contraction in normal and BOO micturition: strong contraction is maintained until the bladder is empty in non-BOO cases but the contraction fades away prematurely in BOO cases, which results in a large residual urine volume of more than 100 mL.

The possible causes of premature fade away of strength of the detrusor contraction in BOO include: (A) a biochemical factor due to exhaustion of the energy reserve; (B) a mechanical factor due to the thickened bladder wall preventing complete lumen collapse; (C) a temporal factor due to the effect of a myogenic detrusor rhythm; and (D) a

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neurological factor due to the abnormal operation of voiding reflexes.

According to the results of our previous study on the morphological and morphometric analysis of human detrusor mitochondria with urodynamic correlation after partial BOO [11], the volume at initial urge and bladder capacity decreased as the severity of BOO increased. Also, the detrusor mitochondria damage increased as the severity of BOO increased. In another study, we found the presence of mitochondrial DNA deletion in the human detrusor after partial BOO and the proportion of mitochondrial DNA deletion increased as the severity of BOO increased [12].

Partial BOO is an established way to produce bladder overactivity in experimental animals, causing significant changes in micturition pattern. In BOO mice, detrusor overactivity may develop without significant changes in smooth muscle function (in vitro investigation). Major disturbances caused by BOO may be due to changes in the afferent pathway [13].

BLADDER AFFERENT PATHWAY, DETRUSOR OVERACTIVITY AND BOO

Involuntary detrusor contractions in patients with BOO might be C-fiber afferent mediated [14]. C-fiber hyperactivity has been identified in idiopathic detrusor overactivity after BOO and BPH [15]. Intravesical resiniferatoxin was effective in treating refractory detrusor overactivity in 51.2% of non-spinal cord injury (SCI) patients and was effective in 61.1% of patients with detrusor overactivity due to previous BOO [16].

Detrusor instability occurs in association with BOO. The increase of afferent activity is one of the possible mechanisms for this detrusor instability. The alpha-ENaC, beta-ENaC and gamma-ENaC proteins were expressed in human urinary bladder epithelium with BOO, and the alpha-ENaC and gamma-ENaC proteins were virtually unstained in the control bladders [17]. Each ENaC mRNA in the obstructed bladders was significantly greater than those in the controls. The quantified ENaC expression correlated significantly with the storage symptom score. The ENaC expressed in the bladder epithelium might be implicated in the mechanosensory transduction in the bladder afferent pathways, thereby inducing detrusor instability by BOO [17].

We conducted a study in a rat model using a putative afferent nerve inhibitor, KW-7158, to study the effect of this novel drug on bladder and vesico-vascular reflexes (VV-R) [18]. The drug is an ATP-sensitive K^+ channels opener (KCO). We found that the ATP-sensitive KCO plays important roles in the regulation of excitability in urinary bladder smooth muscle cells to produce membrane hyperpolarization. KCO can suppress bladder overactivity induced by xylene and suppressed VV-R induced by reflex bladder contractions or bladder distension in normal and irritated bladders. We found that this KCO depresses VV-R and bladder hyperactivity without altering the amplitude and duration of reflex bladder contractions. This is consistent with the view that the drug affects reflex bladder activity by depressing afferent pathways [18].

We conducted another study to evaluate the voiding dysfunction and purinergic mechanism in awake long-term SCI rats using metabolism cage and cystometrogram (CMG) measurements [19]. We found that the mean voided interval and mean volume per void in long-term SCI rats increased after the application of $P2X_3$ antagonist (30 mol/kg, s.c.) in a metabolism cage. The interval of effective contraction increased, the number of non-voiding contractions decreased and the pressure threshold increased after the application of $P2X_3$ receptor antagonist in a CMG study [19]. However, the amplitude and duration of effective bladder contraction showed no significant change before and after $P2X_3$ receptor antagonist administration in the CMG study. The $P2X_3$ receptor antagonist suppressed non-voiding contractions and increased bladder capacity without altering amplitude or duration of bladder contraction. Thus, $P2X_3$ receptors are involved in the bladder afferent pathway. The drugs that block $P2X_3$ receptors might be useful for the treatment of bladder overactivity [19].

Unpublished data from our group revealed that TRPV1 antagonist may selectively block the effect of capsaicin on the bladder afferent pathway. This drug may be used for the management of bladder overactivity.

Urodynamic studies evaluating young men presenting with LUTS showed that they have different underlying etiologies. Clinical diagnosis and treatment are often empiric and inaccurate. Urodynamic study is useful in the evaluation of this group of patients [20].

COMBINATION THERAPY FOR BPH

About half of men with symptomatic BOO had an OAB. About three-quarters of men with symptomatic BOO and no OAB improved with doxazosin but only a third with BOO and OAB were helped with doxazosin alone. Combining tolterodine with doxazosin was effective in three-quarters of men with BOO and OAB [21].

In a clinical study, patients were divided into group I: doxazosin controlled release gastrointestinal therapeutic system formulation (4 mg once daily) only, and group II: propiverine hydrochloride (20 mg once daily) plus doxazosin controlled release gastrointestinal therapeutic system formulation, for an 8-week treatment regimen [22]. This study showed that the combination therapy provided greater improvement in mean daytime frequency, nocturia, number of voids per 24 hours, voided volume, urgency severity and patient global satisfaction. Treatment side effects showed no significant difference between the groups but more dry mouth symptoms were noted in the combination therapy group.

The combinations of tamsulosin with propiverine or tolterodine, and doxazosin with tolterodine for BPH have been shown to cause a significant improvement in LUTS when compared with alpha 1-blocker monotherapy [23].

TREATMENT OF BOO AND OAB

Similar to BOO, OAB symptoms are very common and increase in prevalence as men age. The goal of treatment should be an improved quality of life and, ultimately, prevention of clinical deterioration. A common dilemma when treating men with BOO and OAB is the risk of acute urinary retention or morbidities related to increasing postvoid residual volume. In men with OAB without evidence of BOO (including OAB after treatment for BOO), first-line medical therapy with anticholinergics is indicated. Men with significant BOO should be appropriately treated to decrease bladder outlet resistance before adding anticholinergics for treatment of OAB [24].

CONCLUSIONS

Irritative symptoms are the most bothersome components of BOO, not obstructive symptoms. There is a strong association between OAB and LUTS/BPH. The bladder afferent pathway might play an important role in the pathogenesis and management of OAB.

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