Incont Pelvic Floor Dysfunct 2009; 3(1):28-29

Assessment of Nerve Growth Factor Levels Suggests that Overactive Bladder is a Systemic Disease in Patients who are Refractory to Antimuscarinic Therapy -Hypothesis

Hann-Chorng Kuo, M.D.
Department of Urology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan; E-mail: hck@tzuchi.com.tw

Overactive bladder (OAB) is a condition of urinary urgency with or without urge incontinence, and is usually accompanied by frequency and nocturia. Urgency is the core symptom for OAB [1]. The degree of urgency is usually measured subjectively using an urgency severity scale [2]. However, the method of measuring urgency leads to a wide variation in different grades of severity. Urgency-frequency symptoms could be due to psychological factors, increased urine production, or uninhibited urge because of central nervous lesions or detrusor overactivity (DO) [3]. Urodynamics is a well-established method for diagnosing DO. A better method to diagnose OAB and assess therapeutic outcome in patients with OAB needs to be found.

Diagnosis of OAB should exclude diseases such as neurogenic lesions (cerebrovascular accident [CVA], spinal cord lesion, multiple sclerosis) and local pathologies (bladder outlet obstruction, bladder tumor, bladder inflammation) [1]. Recent investigations have proposed that urothelial dysfunction, abnormal expression of sensory receptors, abnormal function of suburothelial interstitial cells, and increased excitability of detrusor muscles could be etiologies for OAB [4-6].

Antimuscarinic therapy is the first line treatment for OAB [7]. About 70% of patients with OAB can be well treated with antimuscarinics, however, there is a certain percentage of patients whose OAB symptoms cannot be adequately relieved [8]. Many novel treatment modalities have been discovered in recent years, such as intravesical instillation of vanilloids and intravesical injection of botulinum toxin [9]. These therapies treat OAB locally at the urinary bladder level. However, symptoms usually recur after a period of therapeutic effect. Furthermore, OAB symptoms fluctuate with time. Many patients have symptoms which wax and wane. Patients with OAB often have several co-morbidities such as diabetes, congestive heart failure, and depression [10]. These conditions may exacerbate the severity of OAB. It is possible that some unknown circulating factors might affect bladder function and cause OAB symptoms.

Nerve growth factor (NGF) is produced from the urothelium and bladder muscles. Patients with idiopathic DO (IDO), neurogenic bladder or inflammatory bladder diseases such as in interstitial cystitis were reported to have increased urinary and bladder NGF levels [11,12]. In the diagnosis of patients with urgency frequency symptoms, determination of the NGF level in a urine sample may allow a more objective diagnosis than one based on subjective symptoms alone [13,14]. NGF is responsible for the growth and maintenance of sensory neurons and appears to have a role in neuroimmune interactions, in tissue inflammation, and in neuroplasticity for neuronal events leading to OAB [15]. Increased NGF in urine can induce hyperactivity of the urinary bladder in rats [16]. Infusion of NGF into the bladder can induce a nociceptive fos expression and increased calcitonin gene-related peptide-immunoreactivity (CGRP-IR) in the spinal cord in response to a bladder stimulus [17].

A rise in bladder NGF in the muscle or urothelium initiates signals that are transported along the afferent nerves of the bladder to the dorsal root ganglion or spinal cord. Sensitization of sensory pathways by viral vectors encoding NGF contributes to the development of hypersensitivity in neighboring organs and cutaneous referred sites [18]. Inflammation increases NGF and transient receptor potential vanilloid receptor subfamily-1 (TRPV1) expression and the increased TRPV1 expression within trk-A positive neurons is prevented by anti-NGF treatment [19]. Although the NGF in bladder tissue was not found to be significantly associated with IDO [20], patients with neruogenic detrusor overactivity (NDO) who were successfully treated with detrusor BoNT-A injections had a reduced NGF bladder tissue level as well as decreased levels of sensory purinergic receptors $P2X_3$ and TRPV1 [5, 21]. This evidence suggests that NGF is associated with activation of sensory receptors which leads to OAB symptoms. Urinary NGF levels are elevated both in IDO and NDO and have a similar trend after treatment, suggesting NGF production is involved in a common pathway in the pathogenesis of DO.

Previous studies have found increased NGF mRNA production in OAB bladders [20]. Urinary NGF levels were also found to elevate significantly in 70% of patients with OAB [14]. In patients with CVA, the urinary NGF levels increase in accordance with the severity of neurological impairment [22]. Serum NGF levels are also found to increase in some patients with CVA and urinary incontinence [23]. The plasticity of bladder afferents after CVA might be due to increased circulating NGF levels after stroke. In addition, NGF is involved in the development and maintenance of specific peripheral and central populations of neuronal cells. NGF may operate through multiple pathways to ultimately regulate physiological homeostasis and behavioral coping [24]. Increased plasma NGF levels have been found in vernal keratoconjunctivitis, allergic diseases and asthma [25]. Increased serum NGF levels might reduce the excitatory threshold of the bladder to dorsal root ganglia, resulting in increased mechanosensitivity of the bladder wall. Put together, it is possible that circulating serum NGF elevates with changes in systemic conditions. Increased bladder NGF levels have been demonstrated to potentiate the expression of TRPV1 in rats. Elevated circulating NGF might act on the bladder and cause an increased excitability or susceptibility of sensory receptors such as $P2X_3$ and TRPV1 through intrinsic enhancement [26]. Therefore, the bladder becomes more excitable and urgency with or without urge incontinence ensues.

Therefore, we hypothesize that OAB refractory to antimuscarinics might have a systemic pathogenesis. Investigation of serum NGF levels, urinary NGF levels and bladder NGF mRNA levels in patients with OAB before and after antimuscarinic therapy might clarify whether OAB refractory to antimuscarinic therapy is a systemic disease. Although patients with OAB can be treated with antimuscarinics, their OAB symptoms might not be completely eliminated if the underlying factors are not resolved. Circulating serum NGF can be a consequence of systemic disease or a local lesion, and the effect of serum NGF on bladder function can only be eliminated when these diseases have been cured.

REFERENCES

1. Abrams P, Kelleher CJ, Kerr LA, Rogers RG: Overactive bladder significantly affects quality of life. Am J Manag Care 2000; **6(Suppl 11)**:S580-S590.
2. Nixon A, Colman S, Sabounjian L, et al: A validated patient reported measure of urinary urgency severity in overactive bladder for use in clinical trials. J Urol 2005; **174**:604-607.
3. Temml C, Heidler S, Ponholzer A, Madersbacher S: Prevalence of the overactive bladder syndrome by applying the International Continence Society definition. Eur Urol 2005; **48**:622-627.
4. Yiangou Y, Facer P, Ford A, et al: Capsaicin receptor VR1 and ATP-gated ion channel P2X3 in human urinary bladder. BJU Int 2001; **87**:774-779.
5. Apostolidis A, Popat R, Yiangou Y, et al: Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol 2005; **174**:977-982.
6. Powell DW, Mifflin RC, Valentich JD, Crowe SE, Saada JI, West AB: Myofibroblasts. II. Intestinal subepithelial myofibroblasts. Am J Physiol 1999; **277**:C183-C201.
7. Chapple CR: Muscarinic receptor antagonist in the treatment of overactive bladder. Urology 2000; **55(Suppl 3)**:33-46.
8. Abrams P, Kelleher CJ, Kerr LA, Rogers RG: Overactive bladder significantly affects quality of life. Am J Manag Care 2000; **6(Suppl 11)**:S580-C590.
9. Ouslander JG: Mangement of overactive bladder. N Eng J Med 2004; **350:**786-799.
10. Melville JL, Walker E, Katon W, Lentz G, Miller J, Fenner D: Prevalence of comorbid psychiatric illness and its impact on symptom perception, quality of life, and functional status in women with urinary incontinence. Am J Obstet Gynecol 2002; **187**:80-87.
11. Lowe EM, Anand P, Terenghi G, Williams-Chestnut RE, Sinicropi DV, Osborne JL: Increased nerve growth factor levels in the urinary bladder of women with idiopathic sensory urgency and interstitial cystitis. Br J Urol 1997; **79**:572-577.
12. Okragly AJ, Niles AL, Saban R, et al: Elevated tryptase, nerve growth factor, neurotrophin-3 and glial cell line-derived neurotrophic factor levels in the urine of interstitial cystitis and bladder cancer patients. J Urol 1999; **161**:438-442.
13. Kim JC, Park EY, Seo SI, Park YH, Hwang TK: Nerve growth factor and prostaglandins in the urine of female patients with overactive bladder. J Urol 2006; **175**:1773-1776.
14. Liu HT, Kuo HC: Urinary nerve growth factor level could be a potential biomarker for diagnosis of overactive bladder. J Urol 2008; **179**: 2270-2274.
15. Steers WD: Pathophysiology of overactive bladder and urge urinary incontinence. Rev Urol 2002; **4**:S7-S18.
16. Chung YC, Fraser MO, Yu Y, Chancellor MB, de Groat WC, Yoshimura N: The role of bladder afferent pathways in bladder hyperactivity induced by the intravesical administration of nerve growth factor. J Urol 2001; **165**:975-979.
17. Zvara P, Vizzard MA: Exogenous overexpression of nerve growth factor in the urinary bladder produce bladder overactivity and altered micturition circuity in the lumbosacral spinal cord. BMC Physiol 2007; **7**:9-19.
18. Bielefeldt K, Lamb K, Gebhart GF: Covergence of sensory pathways in the development of somatic and visceral hypersensitivity. Am J Physiol Gastrointest Liver Physiol 2006; **291**:G658-G665.
19. Amaya F, Schimosato G, Nagano M, et al: NGF and GDNF differentially regulate TRPV1 expression that contributes to development of inflammatory thermal hyperalgesia. Eur J Neurosci 2004; **20**:2303-2310.
20. Birder LA, Wolf-Johnston A, Griffiths D, Resnick NM: Role of urothelial nerve growth factor in human bladder function. Neurourol Urodyn 2007; **26**:405-409.
21. Apostolidis A, Dasgupta P, Fowler CJ: Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. Eur Urol 2006; **49**:644-650.
22. Liu HT, Liu AB, Chancellor MB, Kuo HC: Urinary nerve growth factor levels is correlated with severity of neurological impairment in patients with cerebrovascular accident. BJU Int 2009, In press.
23. Stanzani L, Zoia C, Sala G, et al: Nerve growth factor and transforming growth factor-beta serum levels in acute stroke patients. Possible involvement of neurotrophins in cerebrovascular disease. Cerebrovasc Dis 2001; **12**:240-244.
24. Alleva E, Santucci D: Psychosocial vs. "physical" stress situations in rodents and humans: Role of neurotrophins. Physiol Behav 2001; **73**:313-320.
25. Bonini S, Lambiase A, Bonini S, Levi-Schaffer F, Aloe L: Nerve growth factor: An important molecule in allergic inflammation and tissue remodeling. Int Arch Allergy Immunol 1999; **118**:159-162.
26. Steers WD, Tuttle JB: Mechanisms of diseases: The role of nerve growth factor in the pathophysiology of bladder disorders. Nature Clin Pract Urol 2006; **3**:101-110.