

Recent Investigations of Urinary Nerve Growth Factor as a Biomarker for Overactive Bladder Syndrome

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Purpose: Overactive bladder (OAB) is a symptom syndrome and is usually diagnosed by subjective symptoms of urgency with or without urgency incontinence. However, because urgency symptoms are so subjective, it is difficult to objectively grade symptoms of urgency. Although urodynamic study can detect detrusor overactivity (DO) objectively, not all patients with OAB are found to have DO. Therefore, recent research interests have focused on urinary and image biomarkers in the assessment of OAB.

Materials and Methods: Investigating articles from the literature and recent published works were reviewed.

Results: The urinary nerve growth factor (NGF) level is found to increase in patients with OAB-wet, bladder outlet obstruction, mixed urinary incontinence, and urodynamic DO. NGF levels are correlated with OAB symptoms and return to normal after treatment. However, urinary NGF is not increased only in patients with OAB and DO. It also increases in patients with interstitial cystitis/painful bladder syndrome (IC/PBS) and other lower urinary tract diseases such as urinary tract stones, bacterial infection, and urothelial tumor. Thirty percent of OAB patients have a low urinary NGF level. Nevertheless, antimuscarinic or botulinum toxin treatment can decrease the urinary NGF level, and changes in the NGF level are correlated with the urgency severity scale.

Conclusions: It is therefore possible to use urinary NGF levels as a biomarker for assessment of therapeutic outcome in patients with OAB. Further research on combined multiple biomarkers to differentiate OAB and IC/PBS is necessary. (**Korean J Urol 2009;50:831-835**)

Key Words: Overactive urinary bladder, Nerve growth factor, Urodynamics

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INTRODUCTION

The overactive bladder (OAB) syndrome is a condition of urinary urgency with or without urgency incontinence and is usually accompanied by frequency and nocturia [1]. Urgency-frequency symptoms can be due to psychological factors, increased urine production, uninhibited urge to void due to central nervous system (CNS) lesions, or having detrusor overactivity (DO) [2]. Multiple treatment modalities have been developed to treat OAB, but none can achieve complete relief of this syndrome [3]. Recent studies have postulated that

urothelial dysfunction, abnormal expression of sensory receptors, increased excitability of the detrusor muscles, and CNS sensitization may contribute to the development of OAB [4]. Down-regulation of both BK and SK2 and upregulation of Cx26 in the bladder mucosa in patients with mixed urinary incontinence have been found to contribute to urothelial instability and are correlated with the severity of OAB symptoms in these patients [5]. Although urodynamic study is a well-established method for diagnosing the presence of DO, not all patients with OAB are found to have DO [6]. A better way to diagnose OAB and to assess therapeutic outcome in patients with OAB seems mandatory.

NERVE GROWTH FACTOR IN THE URINARY BLADDER

Nerve growth factor (NGF) is a small secreted protein that induces the differentiation and survival of particular target neurons (nerve cells). NGF has been implicated as a chemical mediator of pathology-induced changes in C-fiber afferent nerve excitability and reflex bladder activity [7,8]. The levels of neurotrophic factors including NGF increase in the bladder after spinal cord injury (SCI) [7,9], and increased levels of NGF have been detected in the lumbosacral spinal cord and dorsal root ganglia of rats after SCI [10]. Endogenous NGF contributes to lower urinary tract dysfunction after SCI. Intrathecal application of NGF antibodies suppresses detrusor hyperreflexia and detrusor-sphincter-dyssynergia in rats with SCI [10,11]. Intrathecal administration of NGF antibodies also blocks autonomic dysreflexia induced by bladder or distal bowel distension in rats with SCI [12].

NGF is also considered to be a link between inflammation and altered pain signaling. In patients with interstitial cystitis/painful bladder syndrome (IC/PBS), neurotrophins, including NGF, neurotrophin-3, and glial cell line-derived neurotrophic factor, have been detected in the urine [13]. Increased expression of NGF is also present in bladder biopsies from women with IC/PBS [14]. Patients with IC/PBS who responded to intravesical botulinum toxin (BoNT-A) injection have been found to have reduced bladder tissue NGF expression [15].

URINARY NERVE GROWTH FACTOR

Increased levels of NGF have also been reported in the bladder tissue and urine of patients with sensory urgency and DO [16,17]. Previous studies on NGF in OAB or DO usually measured the bladder tissue level. Evidence has shown that visceral epithelia are a major source of NGF production and that NGF may regulate the function of adult visceral sensory and motor neurons [18]. The level of NGF in urine could increase bladder sensation or cause DO through some undetermined pathways [19]. Kim et al found that urinary NGF levels are increased in both men and women with OAB syndrome [20]. Yokoyama et al and associates evaluated urinary NGF in OAB patients and found that urinary NGF levels were elevated in neurogenic DO, spinal disease, and

sensory urgency; however, urinary NGF was not found to be elevated in idiopathic DO [21]. It is rational to hypothesize that NGF produced in the urothelium and suburothelium can be secreted into the bladder lumen. Stretching of the urothelium might induce production of NGF in the bladder tissue and secretion into the urine. Measurement of NGF in the urine is likely to be a more relevant and sensitive biomarker for OAB than bladder tissue NGF levels.

URINARY NGF LEVELS IN LOWER URINARY TRACT DYSFUNCTIONS

1. Overactive bladder

Measurement of urinary NGF levels in patients with increased bladder sensation, OAB dry and OAB wet, and control subjects revealed that patients with OAB dry and OAB wet had significantly higher urinary NGF levels than did the control group and patients with increased bladder sensation, suggesting that elevated urinary NGF levels play an important role in mediating the sensation of urgency in OAB [22].

2. Bladder outlet obstruction

In a recent study of urinary NGF/creatinine (Cr) levels in men with bladder outlet obstruction (BOO), urinary NGF levels were very low in the control group and in patients with BOO/non-OAB and were significantly elevated in patients with BOO/OAB and BOO/DO. Urinary NGF/Cr levels were not significantly different between the BOO/OAB and BOO/DO groups; however, the urinary NGF/Cr levels returned to normal after successful relief of OAB symptoms by medical treatment [23]. These results suggest that urinary NGF might be a potential biomarker for BOO with symptoms of OAB.

3. Detrusor overactivity

A cross-sectional study was performed in 143 patients with idiopathic DO and 100 with neurogenic DO who were untreated, well-treated, or failed-treated by antimuscarinics. The mean urinary NGF/Cr levels were significantly higher in the 66 patients with untreated IDO and the 59 patients with untreated NDO than in the controls [24]. Detrusor injection of BoNT-A (100 U for IDO, 200 U for NDO) decreased urinary NGF levels in patients who responded to BoNT-A treatment but not in those with failed treatment outcome at 3 months. The results of this study suggested that BoNT-A can reduce

NGF production in association with a decrease in detrusor overactivity and urgency severity.

4. Mixed urinary incontinence

Urinary NGF levels were measured in 38 women with urodynamic stress urinary incontinence (USI) with OAB, in 26 women with urodynamic DO but not stress urinary incontinence, in 21 women with persistent USI after anti-incontinence surgery, in 15 women with *de novo* DO, and in 31 normal controls [25]. Urinary NGF/Cr levels were low both in controls and in women with pure USI. NGF/Cr levels were significantly higher in women with mixed USI and DO than in controls and in pure USI patients, but were similar to the levels in women with pure DO. NGF/Cr levels were significantly higher in those with *de novo* DO after anti-incontinence surgery than in the controls and USI patients. The urinary NGF level may play a role in detecting DO in women with OAB and stress urinary incontinence.

5. Antimuscarinic treatment of OAB

In OAB patients treated with antimuscarinics, urinary NGF levels were significantly reduced at 3 months in 50 responders but not in 20 nonresponders [26]. After discontinuing antimuscarinic treatment for 1 month, however, urinary NGF/Cr levels were elevated in 23 responders and in 5 nonresponders. The urgency severity scale significantly changed with the change in urinary NGF/Cr levels in responders at different time points. The change in urinary NGF levels was associated with the change in the urgency severity scale after antimuscarinic treatment and discontinued medication. It is thus rational to continue antimuscarinic treatment for OAB patients if their urinary NGF levels remain higher than the control.

6. Cerebrovascular accident

In a recent study of urinary NGF levels in patients with cerebrovascular accident (CVA), NGF/Cr levels were found to be significantly higher in CVA patients than in normal subjects [27]. Urinary NGF/Cr levels correlated well with the severity of neurological impairment. However, urinary NGF/Cr levels were not correlated with age, location of CVA, multiplicity of CVA, duration of CVA, urodynamic findings, or the presence of urge urinary incontinence. This study suggests that urinary NGF might be a result of a neurologic lesion rather than a cause of bladder dysfunction in CVA.

7. Interstitial cystitis/painful bladder syndrome

Patients with IC/PBS have increased urinary NGF/Cr levels compared with controls. Urinary NGF/Cr levels are very low when the bladder is not distended and are significantly elevated at full bladder in patients with IC/PBS. Patients who responded to treatment and had an improved visual analogue scale (VAS) pain score of ≥ 2 had significantly decreased NGF/Cr levels compared with nonresponders who had a VAS improvement of < 2 . However, urinary NGF/Cr levels were not correlated with VAS or cystometric bladder capacity at diagnosis or with maximal bladder capacity during hydrodistention [28].

8. Bacterial cystitis

Patients with acute bacterial cystitis with or without OAB symptoms had elevated urinary NGF levels compared with the controls. The urinary NGF level in patients with bacterial cystitis was not significantly different from that in patients with OAB or IC/PBS. However, there was no significant difference between patients with and without OAB symptoms associated with cystitis. The urinary NGF levels decreased significantly after treatment with antibiotics compared with baseline. Interestingly, among the patients who had resolved cystitis after treatment, a significantly greater reduction in the urinary NGF/Cr level was noted in patients with disappearance of OAB symptom compared with that in patients who had residual OAB

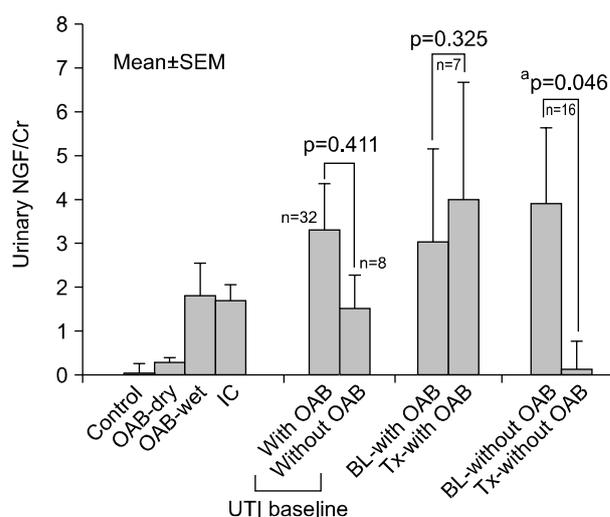


Fig. 1. Urinary NGF/Cr levels in patients with bacterial cystitis at baseline (BL) and after treatment (Tx). NGF: nerve growth factor, Cr: creatinine, OAB: overactive bladder, UTI: urinary tract infection.

symptoms after cystitis (Fig. 1).

9. Ureteral stone or bladder tumor

An elevated urinary NGF level was noted in patients with ureteral stones with or without associated OAB symptoms compared with controls, but no significant difference was noted between subgroups with and without OAB symptoms. Patients with urothelial cancer also had an elevated urinary NGF/Cr level compared with the controls. The urinary NGF levels in patients with ureteral stone or bladder tumor were not significantly different from those of patients with OAB wet.

CONCLUSIONS

Measurement of urinary NGF levels in patients with OAB and different conditions has provided insight to the underlying pathophysiology of this sensory disorder. Any inflammation in the urinary tract can cause an elevation of the urinary NGF level. Therefore, it can be suggested that OAB could be an inflammatory disorder of the bladder. The results of recent investigations suggest that the urinary NGF level is a promising biomarker for the diagnosis of OAB. Measurement of urinary NGF levels may serve as a useful objective test to evaluate treatment outcome of OAB. However, the high percentage of patients having low NGF levels limits the wide application of the urinary NGF level as a biomarker for diagnosis of OAB or DO. Therefore, it is rational to hypothesize that NGF might be a downstream protein produced as a result of several bladder dysfunction or systemic disorders. Nevertheless, in patients with OAB who are treated with antimuscarinics or botulinum toxin injection, urinary NGF levels have been shown to decrease significantly in association with reduction of urgency severity. Thus, it may be possible to use urinary NGF levels as a biomarker for assessment of therapeutic outcome in patients with OAB.

REFERENCES

- Abrams P, Kelleher CJ, Kerr LA, Rogers RG. Overactive bladder significantly affects quality of life. *Am J Manag Care* 2000;6(11 Suppl):S580-90.
- Romanzi LJ, Groutz A, Heritz DM, Blaivas JG. Involuntary detrusor contractions: correlation of urodynamic data to clinical categories. *Neurourol Urodyn* 2001;20:249-57.
- Lee KS, Lee YS. Overactive bladder. *Korean J Urol* 2007;48:1191-208.
- 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;49:644-50.
- Kim DY, Kim JW, Yang EK. Altered expressions of calcium-activated potassium channel and connexin in bladder mucosae of stress urinary incontinence patients with overactive bladder symptoms. *Korean J Urol* 2006;47:722-8.
- Hashim H, Abrams P. Is the bladder a reliable witness for predicting detrusor overactivity? *J Urol* 2006;175:191-4.
- Vizzard MA. Changes in urinary bladder neurotrophic factor mRNA and NGF protein following urinary bladder dysfunction. *Exp Neurol* 2000;161:273-84.
- Yoshimura N. Bladder afferent pathway and spinal cord injury: possible mechanisms inducing hyperreflexia of the urinary bladder. *Prog Neurobiol* 1999;57:583-606.
- Vizzard MA. Neurochemical plasticity and the role of neurotrophic factors in bladder reflex pathways after spinal cord injury. *Prog Brain Res* 2006;152:97-115.
- Seki S, Sasaki K, Fraser MO, Igawa Y, Nishizawa O, Chancellor MB, et al. Immunoneutralization of nerve growth factor in lumbosacral spinal cord reduces bladder hyperreflexia in spinal cord injured rats. *J Urol* 2002;168:2269-74.
- Seki S, Sasaki K, Igawa Y, Nishizawa O, Chancellor MB, De Groat WC, et al. Suppression of detrusor-sphincter dyssynergia by immunoneutralization of nerve growth factor in lumbosacral spinal cord in spinal cord injured rats. *J Urol* 2004;171:478-82.
- Weaver LC, Marsh DR, Gris D, Brown A, Dekaban GA. Autonomic dysreflexia after spinal cord injury: central mechanisms and strategies for prevention. *Prog Brain Res* 2006;152:245-63.
- Okragly AJ, Niles AL, Saban R, Schmidt D, Hoffman RL, Warner TF, 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;161:438-41.
- 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;79:572-7.
- Liu HT, Kuo HC. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. *Urology* 2007;70:463-8.
- Tuttle JB, Steers WD, Albo M, Nataluk E. Neural input regulates tissue NGF and growth of the adult urinary bladder. *J Auton Nerv Syst* 1994;49:147-58.
- Dupont MC, Spitsbergen JM, Kim KB, Tuttle JB, Steers WD. Histological and neurotrophic changes triggered by varying models of bladder inflammation. *J Urol* 2000;166:1111-8.
- Lommatzsch M, Braun A, Mannsfeldt A, Botchkarev VA,

- Botchkareva NV, Paus R, et al. Abundant production of brain-derived neurotrophic factor by adult visceral epithelia. Implications for paracrine and target-derived Neurotrophic functions. *Am J Pathol* 1999;155:1183-93.
19. Lamb K, Gebhart GF, Bielefeldt K. Increased nerve growth factor expression triggers bladder overactivity. *J Pain* 2004;5: 150-6.
 20. 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;175:1773-6.
 21. Yokoyama T, Kumon H, Nagai A. Correlation of urinary nerve growth factor level with pathogenesis of overactive bladder. *Neurourol Urodyn* 2008;27:417-20.
 22. Liu HT, Kuo HC. Urinary nerve growth factor level could be a potential biomarker for diagnosis of overactive bladder. *J Urol* 2008;179:2270-4.
 23. Liu HT, Kuo HC. Urinary nerve growth factor levels are increased in patients with bladder outlet obstruction with overactive bladder symptoms and reduced after successful medical treatment. *Urology* 2008;72:104-8.
 24. Liu HT, Chancellor MB, Kuo HC. Urinary nerve growth factor levels are elevated in patients with detrusor overactivity and decreased in responders to detrusor botulinum toxin-A injection. *Eur Urol* 2008;Epub ahead of print
 25. Liu HT, Chancellor MB, Kuo HC. Urinary nerve growth factor level could be a biomarker in the differential diagnosis of mixed urinary incontinence in women. *BJU Int* 2008;102: 1440-4.
 26. Liu HT, Chancellor MB, Kuo HC. Decrease of urinary nerve growth factor levels after antimuscarinic therapy in patients with overactive bladder. *BJU Int* 2009;103:1668-72.
 27. 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;Epub ahead of print
 28. Liu HT, Tyagi P, Chancellor MB, Kuo HC. Urinary nerve growth factor level is increased in patients with interstitial cystitis/bladder pain syndrome and decreased in responders to treatment. *BJU Int* 2009;Epub ahead of print