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POTENTIAL BIOMARKERS FOR DIAGNOSIS AND PREDICTION OF TREATMENT EFFICACY IN OVERACTIVE BLADDER PATIENTS: URINARY NERVE GROWTH FACTOR, PROSTAGLANDIN E2, AND ADENOSINE TRIPHOSPHATE

Hypothesis / aims of study
Overactive bladder (OAB) is a complex clinical syndrome of urinary urgency, with or without urge incontinence, usually accompanied by frequency and nocturia. Its overall prevalence in women is 12.8 % in Europe and 16.9 % in the USA and the prevalence increases with age. The precise pathogenesis underlying OAB remains to be clarified and might be multifactorial. Although NGF, PGE2, and ATP may play a important role as a biomarker as proposed in several studies, there was no study that compared these biomarkers. Anticholinergic treatment for OAB is usually effective, but It is difficult to evaluate efficacy of anticholinergic treatment.
The aim of this study is to investigate appropriate urinary biomarkers for diagnosis, estimating therapeutic outcome, and prediction of recurrence in patients with OAB.

Study design, materials and methods
We enrolled 155 subjects over 18 years old with symptoms duration ≥3 months and ≥8 voids/24 h and ≥2 urgency/24 h reported in 3-day voiding diaries, who visited outpatient clinic from February 2010 to December 2013. Urinary urgency grade was classified according to the Urinary Sensation Scale. Of these, 81 subjects completed study. The control group included 30 healthy people who did not present any OAB symptom. All subjects with OAB received anticholinergic treatment (Fesoterodine 4mg). Change of urinary level of NGF, PGE2, ATP during treatment and after end of treatment were evaluated. Also urinary levels of biomarkers were evaluated in control group. Subjects with OAB visited outpatient clinic on 4, 12 weeks after beginning of treatment. The treatment success was defined when decrease of voids > 2 times/24 h and decrease of urgency times > 50%, and satisfaction on questionnaire assessing satisfaction with treatment, on 12 weeks or 24 weeks after treatment. After success of treatment, anticholinergic treatment was stopped. For subjects who did not meet the criteria, treatment was maintained.
All subjects with OAB recorded 3-day voiding diary, and determined Overactive Bladder Questionnaire-Short Form (OABQ-SF) and Overactive Bladder Symptom Score (OABSS). Urinary NGF and PGE2 levels were measured by the enzyme-linked immunosorbent assay (ELISA), and ATP level was measured using the luciferin-luciferase bioluminescence assay, and all these biomarkers were corrected by urinary creatinine (Cr).
After end of treatment, the recurrence was defined when subjects dissatisfied with treatment on questionnaire, and met at least one of following criteria; increase of voids > 2 times/24 h, or increase of urgency times > 50%.

Results
There was no difference between two groups regarding age and gender ratio (Table 1). The urinary levels of NGF normalized to urine Cr (NGF/Cr) was increased in subjects with OAB comparing with controls (Table 2). In the multivariate logistic regression analysis using urinary NGF/Cr, PGE2/Cr and ATP/Cr, urinary NGF/Cr was only significant predictor of OAB (Table 3). The urinary levels of NGF/Cr were significantly increased in subgroups of idiopathic OAB (n=71), OAB-dry (n=49), and OAB-wet (n=32) ($P<0.05$). Correlation analysis showed urinary frequency and urgency were significantly related to NGF/Cr level (Correlation coefficient: 0.197, 0.323, respectively).
In responder group (n=53), urinary level of NGF/Cr showed no significant difference, but there was strong tendency to decrease (Figure 1). Urinary NGF level was high in response group and no recurrence group at baseline comparing with non-response group and recurrence group, respectively ($P<0.05$). In no recurrence group (n=26), urinary NGF/Cr were decreased at the time of end of treatment comparing with baseline, and this decreasing tendency was maintained on 12 weeks after end of treatment (Figure 2). But in recurrence group (n=27), there were no significant change of biomarkers.

Interpretation of results
Urinary NGF was significant predictor of OAB, and correlated with urinary frequency and urgency. Urinary NGF showed tendency of decrease after anticholinergic treatment in responder group. Urinary NGF level was high in response group and no recurrence group at baseline. In no recurrence group, urinary NGF were decreased at the time of end of treatment comparing with baseline, and these decreasing tendency were sustained on 12 weeks after end of treatment.

Concluding message
These data suggest that urinary NGF level could serve as a basis for adjunct diagnosis of OAB, as a potential predictor of efficacy of anticholinergic treatment and recurrence.

Table 1. Baseline characteristics

	Controls (n=30)	*OAB (n=81)*	*P*
Age	52.7 ± 6.2	53.6 ± 14.5	0.641
Gender, female, n(%)	90.0%	82.7%	0.344
OABQ-SF			
Bother	-	20.4 ± 6.3	
HRQL	-	43.0 ± 12.2	
OABSS	-	8.7 ± 2.8	
Urinary frequency (24hr)	7.5 ± 2.0	11.7 ± 3.3	<0.001
Urinary urgency (24 hr)	0.0 ± 0.1	8.6 ± 5.3	<0.001

Table 2. Urinary biomarker between the OAB and control group at baseline

	Controls (n=30)	*OAB (n=81)*	*P*
Urine NGF/Cr (pg/mg)	0.1 ± 0.2	1.2 ± 2.2	<0.001
Urine PGE2/Cr (pg/mg)	19.1 ± 12.9	14.4 ± 13.2	0.097
Urine ATP/Cr (pmol/mg)	3.7 ± 5.2	30.6 ± 127.0	0.250

Table 3. Multivariate logistic regression analysis to predict overactive patients using urinary NGF, PGE2 and ATP levels

	OR (95% CI)	*P*
Urine NGF/Cr (pg/mg)	8.890 (1.854-46.623)	0.006
Urine PGE2/Cr (pg/mg)	0.000 (0.000-1.490)	0.053
Urine ATP/Cr (pmol/mg)	1.034 (0.988-1.082)	0.154

Figure 1. Change of urinary NGF levels after anticholinergic treatment

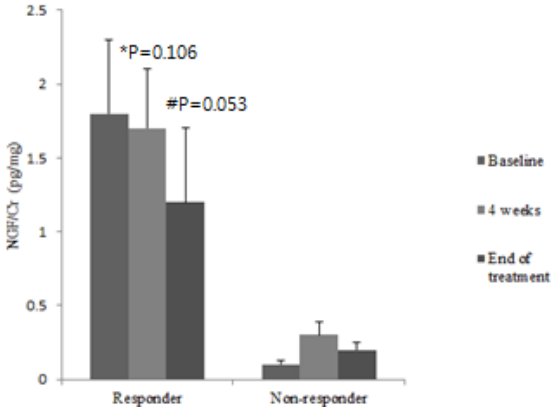
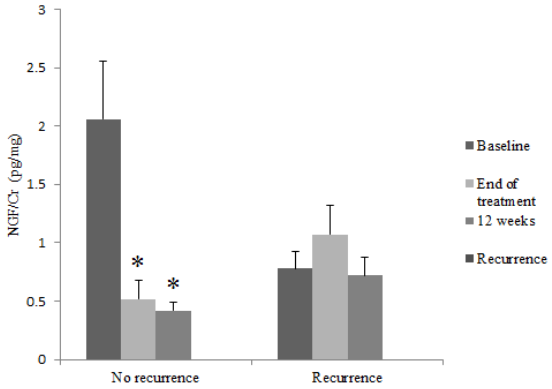


Figure 2. Change of urinary NGF levels after end of anticholinergic treatment



* Baseline vs 4 weeks
\# Baseline vs End of treatment

*P < 0.05

References

1. Antunes-Lopes T, Pinto R, Barros SC, Botelho F, Silva CM, Cruz CD, et al. Urinary neurotrophic factors in healthy individuals and patients with overactive bladder. J Urol 2013;189:359-65.
2. Liu HT, Tyagi P, Chancellor MB, Kuo HC. Urinary nerve growth factor but not prostaglandin E2 increases in patients with interstitial cystitis/bladder pain syndrome and detrusor overactivity. BJU Int 2010;106:1681-5.

Disclosures

Funding: Samsung Biomedical Research institute grant #SBRI C-B0-227-3 **Clinical Trial:** No **Subjects:** HUMAN **Ethics Committee:** Institutional Review Board of Samsung Medical Center **Helsinki:** Yes **Informed Consent:** Yes