

## URINARY NERVE GROWTH FACTOR IN WOMEN WITH OVERACTIVE BLADDER SYNDROME

### Hypothesis / aims of study

Overactive bladder (OAB) is highly prevalent in women. Chronic inflammation has been considered as a possible pathophysiology of OAB. Menopause and obesity have been found to increase the risk of OAB in women. We measured urinary nerve growth factor (NGF) in women with OAB-dry and OAB-wet and investigated the association of urinary NGF expression with these factors.

### Study design, materials and methods

Women with frequency urgency and/or urgency incontinence who visited our out patient clinic were enrolled prospectively for analysis. A group of women without lower urinary tract symptoms (LUTS) served as the controls. Differentiation between OAB-wet and OAB-dry was based on symptoms and a 3-day voiding diary. All subjects were requested to maintain a 3-day voiding diary to verify the occurrence of OAB-dry (urgency at least once per day without urgency incontinence) or OAB-wet (at least one episode of urgency incontinence per 3 days). The control women were the employee of the hospital and the patients who had disorders other than lower urinary tract and were free of LUTS. Urinary NGF levels were measured by ELISA according to previously reported methods. The total urinary NGF and NGF/Cr levels were compared among the controls, patients with OAB-dry and OAB-wet subgroups using one-way ANOVA test. The NGF levels were also compared between OAB patients with age  $\geq 55$  (postmenopause) and  $< 55$  years (premenopause), as well as between patients with a BMI of  $< 20$ , 20-30 and  $> 30$ . Mann-Whitney U-test was used for statistical analysis between subgroups without making the assumption of normality and univariate nature. Pearson's correlation was used for analysis the association between urinary NGF levels and age as well as BMI. Receiver operating characteristics (ROC) curves were used for calculation of areas below curves and analysis the sensitivity and specificity of cut-off values of urinary NGF or NGF/Cr in differentiation of OAB subgroups. A p value of less than 0.05 was considered statistically significant.

### Results

A total of 113 women with OAB-dry, 106 with OAB-wet and 84 controls were enrolled in this study. The mean age was  $61.5 \pm 14.3$  and  $42.6 \pm 16.9$  years for the OAB and control group, respectively ( $p < 0.001$ ). The urinary NGF and NGF/Cr levels were significantly highest in OAB-wet and second highest in OAB-dry than that of the controls. (**Table 1**) Using the ROC analysis, the area below curve was highest in urinary NGF/Cr (0.901) as well as NGF levels (0.897) between OAB-wet and the controls. A cut-off urinary NGF value of 1.265 pg/ml provided a sensitivity of 87.7% and specificity of 80%, while a cut-off value of urinary NGF/Cr level of 0.085 provided a sensitivity of 84.9% and specificity of 84.5% in differentiation OAB-wet and controls. The areas below curve were 0.766 and 0.765 for urinary NGF/Cr and NGF levels in differentiation between overall OAB patients and the controls, respectively. Age significantly correlated with BMI in the controls ( $r = 0.593$ ,  $p < 0.001$ ) and OAB women ( $r = 0.146$ ,  $p = 0.037$ ). Analysis of urinary NGF or NGF/Cr levels in the controls, OAB-dry and OAB-wet women by age  $> 55$  or  $< 55$  years, BMI  $< 20$ , 20-30 and  $> 30$  revealed no significant different in subgroups within group, except for OAB-dry. A significantly higher urinary NGF/Cr level was noted in women with OAB-dry and age  $< 55$  years ( $p = 0.038$ ). However, this result was not observed in women with OAB wet. Using Pearson's correlation, the urinary NGF/Cr levels was significantly correlated with age ( $p = 0.002$ ) but not with BMI ( $p = 0.441$ ) in the controls and women with OAB. The urinary NGF /Cr levels was not significantly correlated with age ( $p = 0.088$ ) or BMI ( $p = 0.886$ ) in women with OAB-dry and OAB-wet.

### Interpretation of results

More and more evidence have shown that OAB might be an inflammatory disorder. Patients with increased bladder sensation without symptoms of urgency had a urinary NGF level similar to that in the controls but patients with OAB-dry or OAB-wet had significantly higher urinary NGF levels. Our results show that patients with OAB-wet had significantly higher urinary NGF levels than those in OAB-dry. The possible reason for the difference of NGF levels between OAB-dry and OAB-wet might be the different degree of inflammation and higher percentage of DO in patients with OAB-wet. These clinical observations suggest that urinary NGF level is strongly associated with the severe urgency symptom and a higher urinary NGF level might have impact on the occurrence of DO. Although the prevalence of OAB in women is associated with ageing and obesity, risk factors of OAB such as menopause and BMI, however, are not found to correlate well with urinary NGF expression in this study. This observation might be resulted from multiple etiologies such as neurogenic inflammation, urothelial dysfunction, or myogenic instability in the pathogenesis of OAB.

### Concluding message

Urinary NGF levels were significantly elevated in women with OAB-dry and further elevated in OAB-wet. The urinary NGF level was not associated with ageing, menopause or increased BMI in the controls or OAB patients.

Table 1. The urinary NGF and NGF/Cr levels in the controls and women with OAB of different age and BMI subgroups

		Control (n=84)	OAB dry (n=113)	OAB wet (n=106)	P value
Urine	NGF	2.45±6.57	10.6±23.2	66.8±94.9	$p = 0.000$
	NGF/Cr	0.07±0.21	0.265±0.59	2.13±3.87	$p = 0.000$

Age	<55	0.07±0.21 (60)	0.46±0.68 * (34)	1.54±1.71 * (30)	* $p=0.002$
	≥55	0.07±0.23 (24) $p=0.905$	0.18±0.48 * (79) $p=0.038$	2.37±4.43 * (76) $p=0.170$	* $p=0.000$
BMI	<20	0.02±0.06 (19)	0.00 (4)	1.96±3.00 (14)	
	20-30	0.07±0.23 (53)	0.27 ±0.59 (91)	2.26±4.15 (71)	
	>30	0.069±0.17 (11) $p=0.603$	0.40 ± 0.52 (11) $p=0.491$	2.52±4.37 (13) $p=0.938$	

( ) : number of subjects

<b>Specify source of funding or grant</b>	<b>None</b>
<b>Is this a clinical trial?</b>	<b>No</b>
<b>What were the subjects in the study?</b>	<b>HUMAN</b>
<b>Was this study approved by an ethics committee?</b>	<b>Yes</b>
<b>Specify Name of Ethics Committee</b>	<b>Institutional Review Board of Tzu Chi University and Tzu Chi General Hospital</b>
<b>Was the Declaration of Helsinki followed?</b>	<b>Yes</b>
<b>Was informed consent obtained from the patients?</b>	<b>Yes</b>