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Urinary Nerve Growth Factor Could Predict the Impact of Overactive Bladder on Female Sexual Function

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Abstract

Objectives: Estimation of Urinary Nerve Growth Factor (uNGF) and heparin-binding epidermal growth factor (uHB-EGF) for diagnosis of Overactive Bladder (OAB) in adult females and its relationship with female sexual dysfunction (FSD) and Quality Of Life (QOL).

Patients and methods: Women with both FSD and OAB were evaluated subjectively using FSF Index (FSFI), OAB symptom score (OABSS), OAB q and QOL scale. Women had FSFI ≤ 29 and OABSS>8 were enrolled as Study group and 20 women free of OAB and SD as Control group. Urinary NGF and HB-EGF levels were ELISA estimated and the ratio to urinary creatinine was calculated.

Results: Levels and ratios of urinary NGF and HB-EGF were significantly higher in study women especially with wet OAB. Urinary HB-EGF levels showed negative and positive correlation with FSFI and OABSS, respectively. Urinary NGF/Cr was correlated positively with OABSS and negatively with FSFI and QOL scores and a ratio of 8-15 pg/mg is suggestive, but at ≥ 15 is indicative for FSD. Urinary NGF level at 420 pg/ml is predictive of FSFI at<30.

Conclusion: OAB especially wet type affects female's QOL and SF. Urinary NGF is significantly correlated with impact of OAB on QOL and SF and could predict FSD.

Keywords: Urinary nerve growth factors; Heparin-binding epidermal growth factor; Overactive bladder; Female sexual dysfunction; Quality of life

Introduction

Overactive bladder (OAB) is defined as urgency, with or without urge incontinence, usually with frequency and nocturia [1]. OAB syndrome is a chronic medical condition with an estimated prevalence of 16.5%, affects performance of daily activities with a major influence on quality of life (QOL) [2]. Female Sexual Dysfunction (FSD) is prevalent and causes distress, particularly among women at midlife [3]. FSD has negative impact on female's QOL and is often multifactorial problem necessitating a multidisciplinary evaluation [4]. The lack of objective diagnostic methods for OAB syndrome has spurred research into its potential biomarkers which can constitute useful diagnostic tools [5].

Nerve Growth Factor (NGF) is a neurotrophin [6] that is able, after binding and activating its receptors [7], to promote nerve cell survival [8]. NGF, a small secretory protein produced and released by smooth muscle and urothelium as a chemical mediator in the bladder [9] and experimentally was found to induce sensitization of afferent nerve pathways leading bladder hypersensitivity without inflammation [10].

Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is an activating ligand for EGF receptor tyrosine kinase [11] and at least one of its isoform is synthesized by the smooth muscle of the human bladder wall [12]. HB-EGF may act as autocrine/paracrine GF involved in proliferation of tubular epithelial cells and kidney repair [13]. HB-EGF is synthesized as a membrane-anchored precursor which stimulates adjacent cells in a juxtacrine manner and is cleaved in a protein kinase C-dependent process, to yield its soluble form [14].

Objectives

Evaluation of the impact of OAB on female sexual function (FSF) and quality of life (QOL) and to determine the relationship between estimated urinary NGF and HB-EGF levels and these variables in adult females

Design

Observational multicenter diagnostic study

Setting

University hospitals, Tanta, Menoufia and Benha, Egypt

Patients and Methods

The protocol of this two-arm observational study as approved by the Local Ethical Committee intended to collect women attending Gynecology outpatient clinic complaining of FSD and those attending Urology outpatient clinic complaining of OAB manifestations. Both of these women were eligible for clinical evaluation for pathologies inducing either OAB or FSD and women older than 35 years or had

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organic lesions or psychological states predisposing to these complain were excluded from the study. Only women signed fully informed written consent were enrolled in the study.

Clinical evaluation

1. Evaluation questionnaires– All enrolled women were asked to complete the following questionnaires in presence and assistance of a clinic female assistant not included in the study and was blinded about the main complaint and the referral clinic:

a. Female Sexual Function Index (FSFI) which includes 6 domains; desire, arousal, lubrication, orgasm, satisfaction and pain [15]. Principal components of each domain were scored and summed. Sexual activity was graded as good (FSFI=30), intermediate (FSFI=22-29) or poor (FSFI<22).

b. The OAB symptom score (OABSS) that evaluated four symptoms: daytime frequency (score: 0-2), nighttime frequency (score: 0-3), urgency (score: 0-5), and urgency urinary incontinence (score: 0-5). The simple sum of the four symptom scores was obtained and sums score>8 were suggestive of OAB [16].

c. The OAB q comprises an eight-item Symptom Bother scale (SBS) and 25-item health-related quality of life (HRQL) scale with four domains (concern, coping, sleep, and social interaction). Scores range from 0 to 100; higher SBS score indicates greater symptom severity while higher HRQL scores indicate better HRQL [17].

2. All women gave FSFI ≤ 29, OABSS>8, high SBS and/or low HRQL were enrolled as Study group. Twenty women of cross-matched age and were free of manifestations of OAB (OABSS<8, low SBS) and sexual problems with FSFI>30 and high HRQL were selected from those attending family planning unit and were included as Control group for comparative purposes. All study and control women were asked to give urine sample for laboratory investigations.

Patient selection

During the study period, 537 women had attended Gynecology clinic complaining of SD; 117 women had evident gynecological pathologies inducing SD and were excluded, while 420 women had no definite pathology and were eligible for evaluation for presence of OAB using OABSS that defined 51 women with scores suggestive of OAB and were included in the study. On the other arm, 171 women attended Urology clinic complaining of symptoms suggestive of OAB; 129 women had non-neurogenic OAB and were eligible for evaluation for SD, and FSFI score was suggestive of SD in 23 women who were also included in the study. These 74 women gave urine samples for laboratory investigations (Figure 1).

Laboratory Investigations

Sample collection

Random mid-stream urine sample was collected as described by Sussman [18] as follows: patient was advised to wash her hands, cleans urethral meatus with 0.9% NaCl soaked cotton wool balls in a downwards motion front-to-back, pass first part of urine stream, catch midstream specimen in sterile specimen container and ensure lid is tightened on container.

Sample processing

The obtained mid-stream urine sample was immediately centrifuged at 3,000 rpm for 20 minutes. The supernatants were carefully separated into two parts:

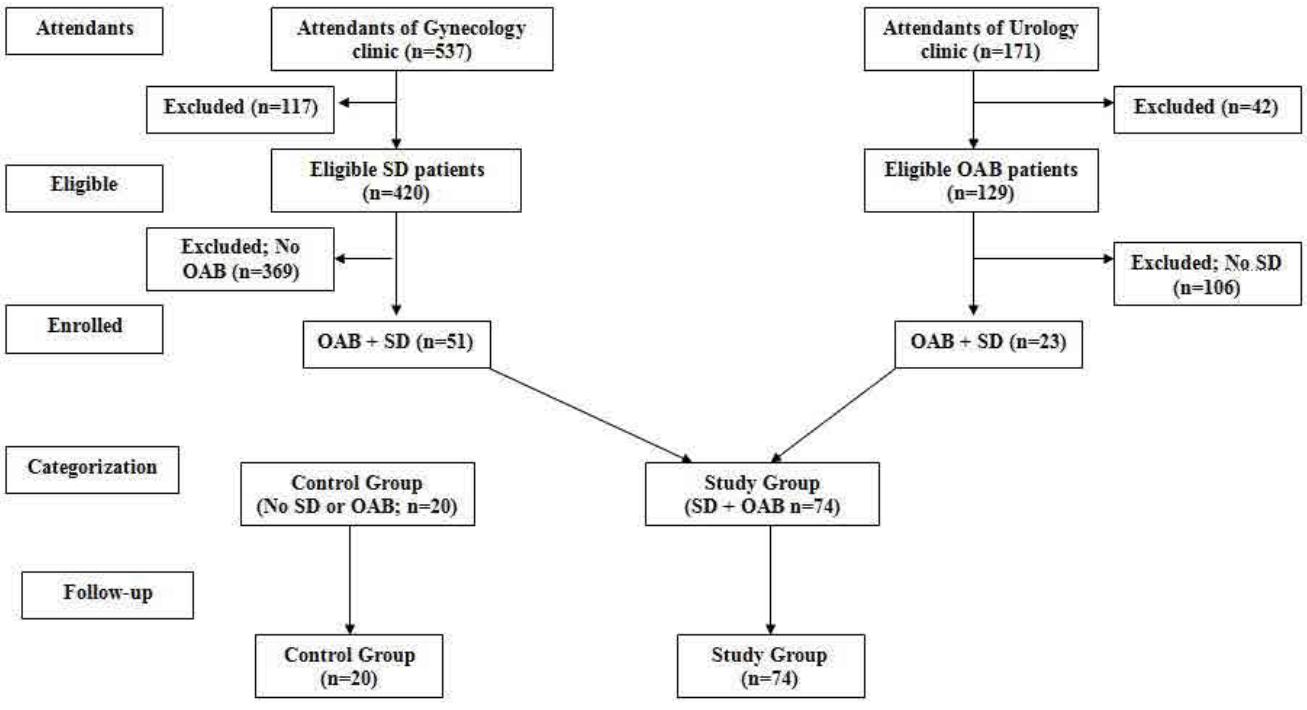

Figure 1: Flow chart of the study.

1. The first part: 1-ml of supernatant was collected in 1.5-ml sterile dry tubes and preserved at-20˚C till be assayed.

2. The second part: 3-ml of supernatant was collected in a clean dry tube for measurement of urinary creatinine (uCr).

Investigation

1. The urinary nerve growth factor was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. MBS010772, My BioSource, Inc., San Diego, USA) by sandwich ELISA technique according to the manufacturer's instructions, as previously reported [19].

2. Urinary heparin binding epidermal growth factor (uHB-EGF) was measured with the enzyme linked immunoassay (ELISA) kit (catalog no. DY259B, R and D Systems, Minneapolis, Minnesota 55413, United States) by Solid Phase Sandwich ELISA technique [20].

3. Urinary creatinine (uCr) was measured with creatinine (urinary) colorimetric assay kit (catalog no. 500701, Cayman Chemical, Ann Arbar, MI. USA) by Jaffe's reaction method [21]. The total urinary NGF and HB-EGF levels were normalized to the estimated uCr concentration to determine urinary NGF/Cr and HB-EGF/Cr (pg/g) ratios.

Statistical analysis

Obtained data were presented as median with inter-quartile range and mean ± SD. Data were analyzed using Mann-Whitney U Test and One-way ANOVA test. Possible relationships were investigated using Pearson linear regression analysis. Sensitivity and specificity of estimated parameters and ratios as predictors for the impact of OAB on FSF were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) that was compared versus null hypothesis that AUC=0.5. Kaplan-Meier regression analysis was used to determine a cutoff point for urinary NGF/Cr ratio above which OAB affects FSF. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015) for Windows statistical package. P value<0.05 was considered statistically significant.

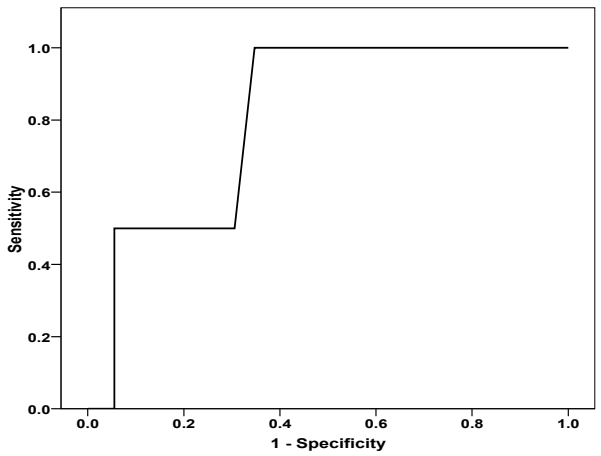

Figure 2: AUC defined by ROC curve analysis of urinary NGF level at 420 (pg/ml) as cutoff point for prediction of the impact of OAB on FSD.

Results

The study included 74 study and 20 control women; all women were multipara with median parity of 2 (IQR: 1-3) and had mean age of 27.9 ± 3.5 with non-significant (p>0.05) difference between women of both groups. Nineteen study women (25.7%) had intermediate and 55 women (74.3%) had poor SF with median FSFI score of 20 (IQR: 19-23). Thirty-two study women (43.2%) had dry OAB with mean OABSS of 9.3 ± 0.5, while 42 women (56.8%) complained of wet OAB with mean OABSS of 9.7 ± 1.1 and significant difference (p=0.045) in favor of dry OAB. Enrolled women assured that both OAB and SF affected their quality of life with a median HRQL score of 38 (IQR: 34-56) and OAB q of 68 (IQR: 57-70).

Estimated urinary NGF and HB-EGF levels and its ratios to uCr were significantly higher in study than control women and in women had wet than women had dry OAB (Table 1).

Pearson correlation analysis showed a positive significant (r=0.601, p=0.0001) correlation between FSFI and HRQL scores, while showed negative significant correlations between FSFI and OABSS (r=-0.357, p=0.002), OAB q (r=-0.354, p=0.002) scores, NGF/Cr (r=-0.676, p<0.001) and uHB-EGF (r=-0.325, p=0.005). Moreover, severity of OAB as judged by OABSS and OABq showed positive significant correlation with NGF/Cr ratio (r=0.476, p=0.001 and r=0.267, p=0.022, respectively) and uHB-EGF (r=0.265, p=0.022 and r=0.252, p=0.047, respectively). Subsequently, HRQL scoring showed negative significant correlation with NGF/Cr ratio (r=-0.907, p=0.0001), but showed positive non-significant correlation (r=0.029, p=0.804) with uHB-EGF levels.

Regression analysis defined deterioration of HRQL score (β: 0.555, p=0.0009) and high urinary NGF/Cr level (β: 0.637, p=0.0004) as the significant predictors for the impact of OAB on sexual function. ROC curve analysis assured the sensitivity of high urinary NGF/Cr level (AUC: 0.096, p=0.018) and the specificity of low HRQL score (AUC: 0.869, p=0.031) as the significant predictors for the impact of OAB on sexual function. Kaplan-Meier regression analysis defined urinary NGF/Cr ratio ranging between 8 and 14 pg/mg as suggestive levels for the risk of FSD and at level of ≥15 the ratio indicates the risk of sexual dysfunction. ROC curve analysis defined NGF level at 420 pg/ml (AUC: 0.809, p=0.038) as the cutoff point for prediction of FSFI at<30 (Figure 2).

Group		Control	Study				
Variables			Total	P	Wet	Dry	P
Urinary Cr (mg/dl)		61.5 ± 16.2	59.6 ± 14	0.489	59.3 ± 12.7	60 ± 15.2	0.798
Urinary NGF	Level (pg/ml)	90.2 ± 24.7	797 ± 348	<0.001	1091 ± 99	410 ± 31.3	<0.001
	Ratio (pg/mg)	7.23 ± 1.7	14 ± 6.8	<0.001	19.2 ± 4	7.2 ± 1.7	<0.001
Urinary HB-EGF	Level (pg/ml)	297.6 ± 144.5	399 ± 149	0.008	436.2 ± 148	351 ± 138	0.014
	Ratio (pg/mg)	5.12 ± 2.33	7.28 ± 3.72	0.016	7.7 ± 3.2	6.1 ± 2.4	0.021
Data are presented as mean ± SD **Abbreviations:** Cr: Creatinine; NGF: Nerve Growth Factor; HB-EGF: Heparin-Binding Epidermal Growth Factor-Like Growth Factor							

Table 1: Mean levels of studied laboratory parameters.

Discussion

The current observational screening study aimed for evaluation of the impact imposed by OAB on the couple sexual relationship; to standardize the study outcome only women younger than 35 years were included in the study. Such group of women was considered at their highest emotional warmness and desire for sexual relationship and on the other side their male partners most probably will be around the same age group and mostly had competent ability to do an act as regards potency, ejaculatory function and sexual interest. The study relied on FSFI questionnaire which is a widely used instrument, applicable as a multidimensional measurement of FSF in sexually active or inactive women as previously documented in literature [22-25].

The outcome of the study could be summarized in the following points; firstly there was a relation between OAB and female sexual dysfunction (FSD), where 17.8% of women presenting by OAB had FSD and 12.1% women complaining of FSD had OAB for a total co-incidence rate of 13.5%. Moreover, the negative impact of OAB on FSF and female QOL was evident as FSFI scores showed negative significant correlation with OABSS and positive significant correlation between HRQL that showed a negative significant correlation with OABSS.

In line with these findings, Lai et al. [26] detected the presence of widespread systemic symptoms among OAB patients that was correlated with OAB symptoms and is associated with poorer quality of life and more psychosocial difficulties especially loss of sexual interest. Also Juliato et al. [27] reported worse scores in FSFI domains in women with greater OAB severity, especially in those had urge incontinence. Moreover, Chughtai et al. [28] found combination of anti-muscarinic medication and topical vaginal estrogen significantly improved OAB symptom severity, HRQL and sexual QOL especially in older women.

Secondly, estimated levels of urinary NGF and HB-EGF standardized in relation to uCr levels were significantly higher in women with OAB than controls and with wet than dry OAB. These results supported that previously reported in literature concerning the detection of higher levels of uNGF and high ratio in relation to uCr levels in OAB patients [29-31]. Furthermore, estimated levels of uNGF were positively correlated with OABSS and OAB q scores but negatively with FSFI and HROL scores; a finding that points to a possible relationship between disturbed levels of growth factors and development, persistence or aggravation of OAB and go in hand with Suh et al. [32] who demonstrated that urinary urgency was significantly related to urinary NGF/Cr level.

Thirdly, the reported statistical findings assured the relation between estimated urinary markers and OAB on one side and OAB and FSD on the other side. Moreover, statistical analyses defined NGF/Cr levels at range of 8-15 pg/mg as suggestive indicator for FSD and at 15 pg/mg as indicative predictor for FSD with uNGF level at 420 pg/ml as the cutoff point for prediction of FSFI at<30 in women with OAB with high specificity (AUC=0.809).

In line with these findings, Ozdemir et al. [29] found urine NGF/Cr at a cut-off level of>360 had sensitivity of 87.5%, specificity of 100% and positive and negative predictive values of 100% and 90.9% for OAB diagnosis. Also, Vijaya et al. [33] assured the reliability of urinary NGF as a good predictor of patients having OAB or not and using a cut off of 13 ng NGF/g creatinine provides a sensitivity of 81%, but a specificity of only 39% for OAB. Moreover, Suh et al. [32] demonstrated that OAB manifestations were significantly related to urinary NGF/Cr level and urinary NGF/Cr was a sensitive biomarker for discriminating OAB patients with significant AUC. Recently, Dagdeviren and Cengiz [34] found that NGF threshold of>380 ng/ml had a sensitivity of 81.7% and a specificity of 100% to discriminate between women with both OAB and metabolic syndrome and healthy women free of both conditions.

In support of the assumption that urinary NGF is a potential biomarker that could be used to aid for diagnosis of presence of and severity of OAB; both Ciftci et al. and Suh et al. found urinary levels of NGF/Cr tended to decrease in patients who responded to OAB treatment and in those who did not experience recurrence and concluded that urinary NGF is a potential biomarker for predicting the outcome of OAB treatment and may help for deciding to stop treatment in responders.

Conclusion

OAB especially wet type affects female's QOL and SF. Urinary NGF is significantly correlated with impact of OAB on QOL and SF and could predict FSD. However, wider scale comparative studies using objective parameters were mandatory to document these subjectively obtained results and to assure the diagnostic value of the assumed level of uNGF as a diagnostic cutoff point for identification of women affected sexually secondary to OAB manifestations.

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