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ASSOCIATIONS BETWEEN URINARY BRAIN DERIVED NEUROTROPHIC FACTOR AND INDIVIDUAL LOWER URINARY TRACT SYMPTOMS IN WOMEN

Hypothesis / aims of study

Urothelial inflammation may be an important driver of overactive bladder symptoms, with previous investigations having demonstrated a range of inflammatory markers in urine of patients with overactive bladder. Recent reports have explored a role for brain derived neutrophic factor (BDNF) as a biomarker of overactive bladder symptom severity and treatment response. Although significant differences between overactive bladder patients and healthy controls are noted [1], no further validation of the role of BDNF as a biomarker has been reported. In this study we aimed to test the relationships between BDNF and individual lower urinary tract symptoms (LUTS), and measure the formal properties of BDNF as a diagnostic tool in a typical heterogenous clinical sample.

Study design, materials and methods

Women were recruited from urogynaecology and general gynaecology hospital clinics. After informed consent each participant provided a mid-stream urine, and completed the ICIQ-Female Lower Urinary Tract Symptom (ICIQ-FLUTS) questionnaire. One aliquot of urine was sent for microscopy and culture to exclude women with acute UTI, and a further aliquot was used to measure urinary creatinine. Urine was kept refridgerated, and centrifuged within 30 minutes, with supernatant stored at -80c, before testing for BDNF using the Emax® ImmunoAssay System. Urinary BDNF was log transformed for analysis. Multivariable logistic regression, adjusting for age, parity and BMI was used to assess symptom associations. Receiver operator characteristics (ROC) were used to assess diagnostic performance.

Results

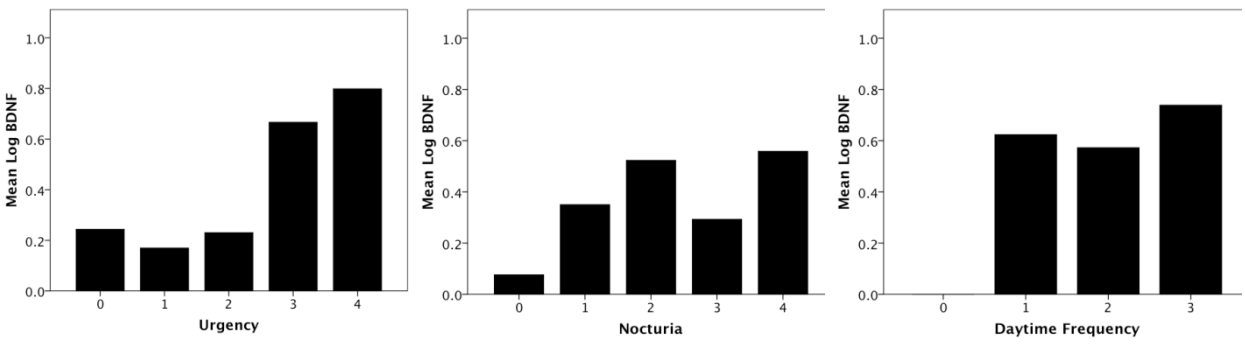
After exclusions for acute UTI, we recruited 104 women between April 2012 and January 2013. Mean age was 45, mean BMI was 24.9, and median parity was 1. Urinary BDNF ranged from the lower limit of detection of the ELISA kit (approximately 0 pg/ml) to 504 pg/ml, median 3.4 pg.ml, with highly significant skewness (Kolmogorov-Smirnov Z=4.1 p<.0001, Skewness 8.9). We found no evidence of an association between urinary creatinine and BDNF (rho = 0.07), consistent with its putative release from the urothelium, and therefore report BDNF concentrations without creatinine normalisation. The figure below charts mean log BDNF, for nine items from the ICIQ-FLUTS, demonstrating broadly increased levels of BDNF for all storage and incontinence symptoms, and bladder pain. In unadjusted analyses, statistically significant associations were found for urgency incontinence, daytime frequency, nocturnal enuresis, and overall incontinence episode frequency (see Table). These results were not improved by creatinine normalisation. Corresponding areas under the curve (AUC) in ROC analysis suggested very modest test performance.

Interpretation of results

Although statistically significant associations with urgency incontinence, daytime frequency and nocturnal enuresis were found, urinary BDNF has poor performance as diagnostic test, and does not discriminate well between important competing diagnoses for overactive bladder including bladder pain, and stress incontinence. Previous reports of good discriminant validity may be explained by either spectrum bias, or failure to adjust for relevant confounders.

Concluding message

In a mixed gynaecological population, urinary BDNF is elevated in association with a range of storage and incontinence LUTS. Although it is unlikely to have a useful clinical role a diagnostic biomarker, this should not preclude further investigation of its role in the pathogenesis of LUTS.



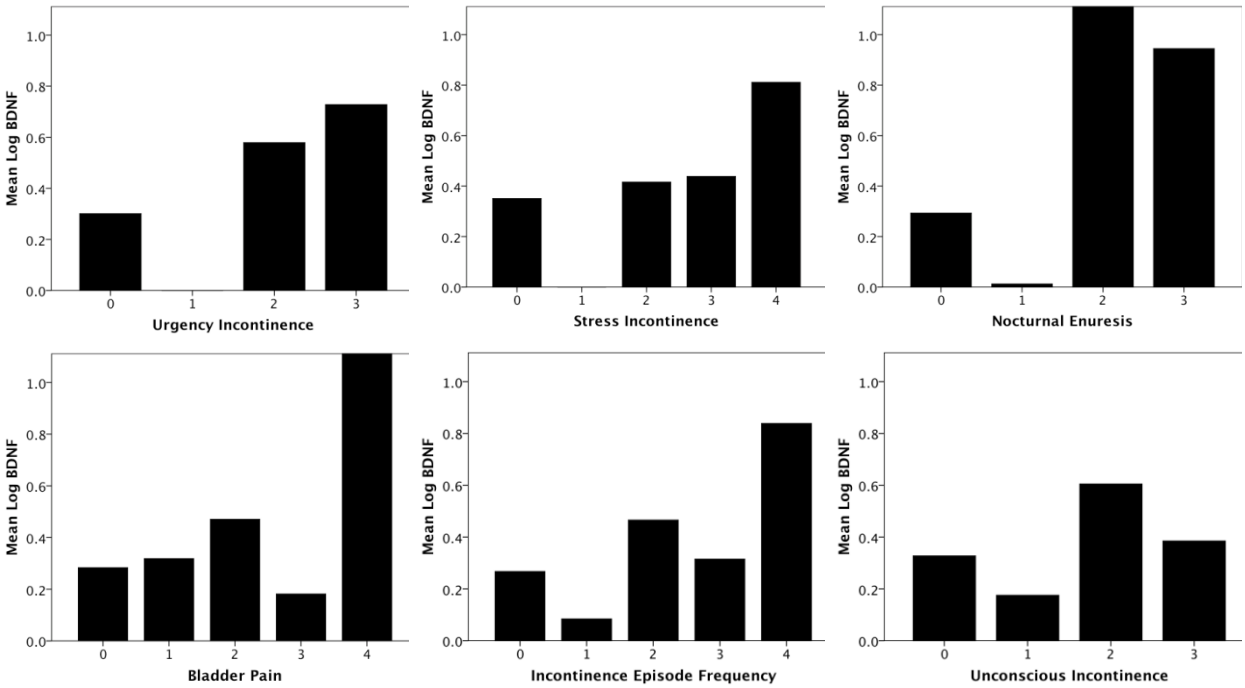


Figure: Mean log urinary BDNF plotted against ICIQ-FLUTS symptom scores.

	OR (95%CI)	Adjusted OR (95%CI)	AUC
Stress Incontinence	1.5 (0.9-2.5)	1.6 (0.9-2.8)	0.60
Urgency Incontinence	2.3 (1.1-4.4)	2.3 (1.1-4.4)	0.63
Urinary Urgency	1.3 (0.9-2.1)	1.4 (0.8-2.3)	0.55
Daytime Frequency (≥8 / day)	1.8 (1.1-3.0)	2.2 (1.2-4.2)	0.63
Nocturia (≥2 / night)	1.4 (0.9-2.2)	1.7 (1.0-3.0)	0.56
Unconscious Incontinence	1.3 (0.7-2.7)	1.1 (0.5-2.3)	0.56
Nocturnal Enuresis	4.1 (1.4-12.2)	2.5 (0.8-8.3)	0.74
Bladder Pain	1.2 (0.7-2.2)	1.2 (0.6-2.4)	0.52
Incontinence Episode Frequency	1.7 (1.0-2.7)	1.7 (0.9-3.2)	0.59

Table: Unadjusted and adjusted associations between BDNF and symptoms, with corresponding Area Under the Curve statistics

References
1. J Urol 2013 Jan;189(1):359-65

Disclosures
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