EXPRESSION OF NERVE GROWTH FACTOR, VASCULAR ENDOTELIAL GROWTH FACTOR AND CONNECTIVE TISSUE GROWTH FACTOR IN THE DETRUSOR OF PATIENTS WITH BLADDER OUTLET OBSTRUCTION DUE TO BENIGN PROSTATIC HYPERPLASIA

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Introduction

Bladder outlet obstruction (BOO) due to benign prostatic hyperplasia (BPH) may lead to functional and morphological alterations in the bladder. Bladder function may be severely affected due to low compliance, detrusor overactivity (DO) or impaired detrusor contractility, which may be persistent even after the surgical relief of BOO. [1] Different mechanisms involved in bladdder dysfunction due to BOO have been studied, mostly in animal models, [2] The influence of growth factors such as the nerve growth factors (NGF), vascular endotelial growth factor (VEGF) and connective tissue growth factor (CTGF) has been evaluated in experimental studies. NGF levels increase in urine and in the hypertrophied bladders in rats with partial urethral ligation and its increased NGF expression has been linked to changes in afferent excitability in cats and to mechanical stretch in rats. The CTGF has been associated with fibrosis in different organs, including liver and biliary fibrosis. In rats, the expression of CTGF has been shown to increase after partial urethral ligation. In experimental studies, VEGF is upregulated in response to mechanical strain in cultured detrusor cells and also after partial bladder outlet obstruction in rats. Although extensively studied in animal models the expression of NGF, CTGF and VEGF in the normal human bladder and in obstructed bladders of patients with BPH have not been characterized. Our study aims to evaluate the expression of NGF, CTGF and VEGF in the detrusor of men with BOO due to BPH.

Methods

Twenty nine consecutive patients undergoing open prostatectomy for BOO due to BPH were evaluated. All subjects provided written informed consent and the study was approved by the Institutional Board of Ethics. Urodynamic was performed in all patients. A bladder specimen from the dome was obtained during prostatectomy. Nine cadaveric organ donors composed the control group. The detrusor biopsies were prepared for relative gene expression analysis with quantitative real-time polymerase chain reaction (RT-PCR) of NGF, CTGF and VEGF. Data were expressed as medians and interquartile ranges or absolute values and fractions. Confidence intervals were calculated with natural logarithm transformation.

Results

Fourteen (48.2%) patients were operated due to lower urinary tract symptoms (LUTS) and fifteen (51.8%) were in urinary retention. Mean age was 68.7 ± 7.1 years old and mean prostate volume was 130.8 ± 47.2 cm3. Mean International Prostatic Symptom Score for patients not in retention was 24.0 ± 6.4. Mean cystometric maximum capacity was 350.5 ± 104.9 mL, mean bladder compliance 34.9 ± 25.7 mL/cmH2O and mean bladder outlet obstruction index of 80.7 ± 34.1. Fifteen (51.8%) patients had detrusor overactivity. Patients with BOO had significant underexpression of NGF and VEGF genes in comparison with controls while CTGF expression was heterogeneous, with no significant difference (Table 1).

Table 1 - Relative gene expression of NGF, CTG and VEGF in patients with BPH as compared to controls

	Median Fold Change	95% Confidence Interval	Significantly Predominant Pattern	Subjects with predominant pattern	p value
NGF	0.38	0.28 – 0.67	Underexpressed	75.9%	0.0017
CTGF	0.73	0.35 – 1.67	Heterogeneous	62.8%	0.8480
VEGF	0.42	0.30 – 0.58	Underexpressed	89.7%	0.0002

Conclusions

We investigated the expression of the NGF, CTGF and VEGF genes in men with BOO due to BPH. They have been shown to be overexpressed in animal models of bladder outlet obstruction. In our series, however, these genes were either underexpressed (NGF or VEGF) or had a heterogeneous expression pattern (CTGF). These discrepant results may be a reflection of differences in the duration of obstruction and consequent activation/deactivation of molecular pathways involved in detrusor remodeling. Animal models of BOO are based on acute partial urethral ligation and studies are usually performed with short term obstruction (months). In contrast, BOO due to BPH is slowly progressive and of very long duration. Consistent with this, our series includes patients with long term LUTS, very large prostates, severe obstruction based on the high BOOI and high frequency of patients with urinary retention. On the contrary, this temporal difference between the BOO onset in the animal models and the patients included in our series may explain the gene expression differences observed. We reinforce that caution should be used when extrapolating the results from studies with animals to applications with humans.

Counteracting what was previous demonstrated in BOO animal models, NGF, CTGF and VEGF were not overexpressed in the detrusor layer of men with BOO due to BPH.

References

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